Washington State Health Care Authority

Health Technology Assessment

Autologous Blood or Platelet-Rich Plasma Injections

Final Evidence Report

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Autologous Blood or Platelet-Rich Plasma Injections

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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ABBREVIATIONS

ABI:	autologous blood injection
ADL:	activities of daily life
AOFAS:	American Orthopaedic Foot and Ankle Society
ASES:	American Shoulder and Elbow Surgeons (standardized shoulder assessment)
CI:	confidence interval
CMS:	Constant-Murley score (functional assessment of the shoulder)
DASH:	Disabilities of the Arm, Shoulder, and Hand
DN:	dry needling
EQ-5D:	EuroQoL 5-Dimension Questionnaire
EQ-VAS:	EuroQoL Visual Analog Scale
ESWT:	extracorporeal shock wave therapy
F/U:	follow-up
FADI:	Foot and Ankle Disability Index
FFI:	Foot Function Index
HA:	hyaluronic acid
HHS:	Harris Hip Score
HOS:	Hamstring Outcome Score
HR:	hazards ratio
HR-QoL:	Health-Related Quality of LIfe
IKDC:	International Knee Documentation Committee
IQR:	inter-quartile range
KOOS:	Knee Injury and Osteoarthritis Outcome Score
LA:	local anesthetic
LEFS:	Lower Extremity Function Scale
LP-PRP:	leukocyte-poor platelet-rich plasma
LR-PRP:	leukocyte-rich platelet-rich plasma
MCPIE:	Mayo Clinic Performance Index of the Elbow
MD:	mean difference
NC:	not calculable
NR:	not reported
NRS:	Numerical Rating Scale
NS:	not statistically significant
NSAID:	nonsteroidal anti-inflammatory drug
OA:	osteoarthritis
OMERCAT-OARSI:	Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative
PRP:	platelet-rich plasma
PRTEE:	Patient-Rated Tennis Elbow Evaluation
QoL:	quality of life
RCT:	randomized controlled trial

RR:	risk ratio
SD:	standard deviation
SF-36:	Short Form-36
SMD:	standardized mean difference
SPADI:	Shoulder Pain and Disability Index
TENS:	transcutaneous electrical nerve stimulation
TMJ:	temporomandibular joint
VAS:	Visual Analog Scale
VISA-A:	Victorian Institute of Sports Assessment-Achilles
WMD:	weighted mean difference
WOMAC:	Western Ontario and McMaster Osteoarthritis Index
WORC:	Western Ontario Rotator Cuff Index

Executive Summary

Introduction

Platelet-rich Plasma (PRP) injections and Autologous Blood Injections (ABI) are treatments utilized for a variety of healing applications in sports medicine[16] and orthopedic medicine.[27] Conditions where PRP or whole blood injections are commonly utilized include refractory acute or chronic ligament injuries, muscle strain injuries, cartilage injuries, osteoarthritis, and tendinopathies. In particular, the use of PRP and blood injections in sports medicine have seen a recent increase in public exposure, as many professional athletes have elected to receive these treatments, especially PRP, for sports-related injuries.

The rationale behind ABI and PRP injections is to increase the concentration of growth-factor rich platelets around the injured area. In general, PRP formulations contain an increase of platelets from baseline count. Platelets contain over 30 growth factors that aid in angiogenesis, cell growth and division, and cell regeneration.[45] Both of these therapies utilize the patient's own blood to obtain the PRP or ABI samples used in the injection; as a result, there is little risk of transmissible diseases or hypersensitivity reactions.[42] Although the method of preparation can greatly vary, PRP preparation involves at least one centrifugation step to isolate a platelet-rich buffy coat that can then be injected or spun down again. Platelet-activating factors like 10% calcium chloride or batroxobin[41] may be added to PRP to stimulate platelets to release growth factors and increase recruitment of tissue repair factors. No additional processing occurs for whole blood injections after venipuncture. Injection is usually performed under ultrasound guidance,[61] and can be repeated if needed. PRP and ABI outpatient procedures. Systematic reviews have indicated low incidence of PRP and ABI-related adverse events for the treatment of musculoskeletal disorders.[33,47]

Despite the use of PRP and whole blood injections for healing applications, the efficacy and safety for PRP and whole blood injection treatments are not well established, as there is a lack of standardization for PRP and ABI preparation. Additionally, while the technology to obtain PRP is FDA-approved, PRP itself is currently not indicated for direct injection.[6]

Policy Context

Platelet-rich plasma (PRP) and whole blood injections are proposed for a variety of healing applications. Concerns are considered medium for safety, medium/high for efficacy and medium for cost-effectiveness.

Objectives

To systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of PRP in adults for treating musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain. The differential effectiveness and safety of PRP for subpopulations will be evaluated, as will the cost effectiveness.

Key Questions

In patients with musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain (evaluated separately):

1. What is the evidence of the short- and long-term efficacy and effectiveness of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?
2. What is the evidence regarding short- and long-term harms and complications of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?
3. Is there evidence of differential efficacy, effectiveness, or safety of autologous PRP or whole blood injections compared with alternative treatment options no treatment/placebo? Include consideration of age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation?
4. What is the evidence of cost-effectiveness of autologous PRP or whole blood injections compared with alternative treatment options?

Inclusion and exclusion criteria are summarized as follows:

- **Population**: Patients with musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain.
- **Intervention:** Autologous PRP or whole blood injections (injections used in conjunction with other procedures such as surgery will be excluded)
- **Comparators:** Alternative treatment(s), placebo, or no treatment
- **Outcomes:** Function (primary), pain (primary), time to recovery, return to normal activities (sports, work, or activity level), quality of life, patient satisfaction, recurrence, medication use, secondary procedures (e.g., surgery), adverse events (primary), cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcomes
- **Study design**: Eligible studies compared autologous PRP or whole blood injections with an included comparator treatment utilizing a randomized or cohort study design. Case series specifically designed to evaluate harms/adverse events that enrolled at least 100 patients and that had follow-up of at least 70% of patients were considered for Key Question 2. Only RCTs that stratified results by patient characteristics of interest so that statistical interaction (effect modification) could be evaluated were considered for Key Question 3; subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. For Key question 4, formal economic analyses were eligible for inclusion (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies).

Methods

The scope of this report and final key questions were refined based on input from clinical experts from a variety of disciplines and public comments received on draft key questions. Clinical expert input was sought to confirm critical outcomes on which to focus.

A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed to identify relevant peer reviewed literature as well as other sources (National Guideline Clearinghouse, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments.

Studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature.

Pertinent studies were critically appraised independently by two reviewers based on Spectrum's Class of Evidence (CoE) system which evaluates the methodological quality and potential for bias based on study design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results

Overall, 54 randomized trials (in 56 publications) and 8 cohort studies were included. No case series focused on harms or full economic analyses were identified that met the inclusion criteria. The comparisons evaluated and their respective studies are listed in the table below; comparisons of interest not listed in the table below had no comparative evidence available that met the inclusion criteria. Diagnoses for which comparative evidence was identified include tendinopathies (elbow epicondylitis, Achilles tendinopathy, patellar tendinopathy, rotator cuff tendinosis and/or partial tears), plantar fasciitis, acute injuries (acute muscle injuries, Achilles tendon rupture, ankle sprain), osteochondral lesions of the talus, temporomandibular joint (TMJ) dislocation, and osteoarthritis (OA) (knee OA, hip OA, and TMJ OA). No comparative studies were identified that met the inclusion criteria for any other diagnosis of interest.

Number of studies for each comparison of efficacy for included conditions of the lumbar and cervical spine.

Comparisons	Studies
TENDINOPATHIES	
Elbow Epicondylitis	
PRP vs. ABI	4 RCTs[11,54,55,71]
PRP vs. Conservative Control	8 RCTs (9 publications)[5,20,22,38,39,44,52,69,77], 2 cohort studies[70,73]
PRP vs. Surgery	1 cohort study[18]
ABI vs. Conservative Control	6 RCTs[3,14,29,32,49,67]
Achilles Tendinopathy	
PRP vs. Conservative Control	2 RCTs (in three publications)[12,13,33]
ABI vs. Conservative Control	2 RCTs[7,51]
Patellar Tendinopathy	
PRP vs. Conservative Control	2 RCTs[15,75]
Rotator Cuff Tendinosis and/or partial tears	
PRP vs. Conservative Control	2 RCTs[34,59], 1 cohort study[76]
PLANTAR FASCIITIS	
PRP vs. Conservative Control	5 RCTs[10,28,35,46,72], 3 cohort studies[1,64,66]

Comparisons	Studies
ABI vs. Conservative Control	3 RCTs[30,36,40]
ACUTE INJURIES	
Acute Muscle Injuries	
PRP vs. Conservative Control	4 RCTs[8,24,48,57]
Achilles Tendon Rupture	
PRP vs. Conservative Control	1 cohort study[31]
Ankle Sprain	
PRP vs. Conservative Control	1 RCT[60]
OSTEOCHONDRAL LESIONS OF THE TALUS	
PRP vs. Hyaluronic Acid (HA)	1 RCT[43]
TEMPOROMANDIBULAR JOINT (TMJ) DISLOCATION	
ABI vs. Surgery	1 RCT[25]
OSTEOARTHRITIS (OA)	
Knee OA	
PRP vs. HA	6 RCTs[9,17,21,53,63,74], 4 cohort studies[37,62,65,68]
PRP vs. Corticosteroid	1 RCT[19]
PRP vs. Saline	2 RCTs[21,50]
PRP vs. Exercise ± TENS	2 RCTs[2,56]
Hip OA	
PRP vs. HA	1 RCT[4]
TMJ OA	
PRP vs. HA	1 RCT[26]

ABI: autologous blood injection; HA: hyaluronic acid; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized control trial; TENS: transcutaneous electrical nerve stimulation; TMJ: temporomandibular joint

KQ1 Summary of Results:

Tendinopathies: More detailed summaries for each tendinopathy can be found in the text and tables below. In general, PRP and ABI resulted in outcomes that were the same or better than that of the control treatment. Of the tendinopathies for which studies were identified, elbow epicondylitis had the most evidence for benefit with PRP. For PRP versus ABI, there was evidence of greater benefit with PRP in the short-term for both pain and function, and in the intermediate-term for function (but pain was similar between groups); otherwise, no differences were found between groups in any other outcome reported although the evidence for primary outcomes was of insufficient quality. For PRP versus conservative control interventions, pain and function (scores and success) results were similar between groups in the short-term, but by the intermediate-term PRP was associated with better results than the control group in terms of pain scores, pain success, and function (but there was no difference between groups in function success). In the long-term, treatment with PRP led to better function scores, pain scores, pain success, and fewer additional procedures. However, there was evidence from one trial that

found that the PRP group was less likely to achieve full recovery/no symptoms than the steroid injection group in the short-, intermediate, and long-term. For ABI versus conservative control interventions, PRP yielded better short-term results with respect to pain and function scores, and similar results were seen for pain scores in the intermediate-term; otherwise, the quality of the evidence available was insufficient to draw conclusions for this comparison. For rotator cuff tendinopathy, there was evidence of short- and intermediate-term benefit with PRP versus conservative control in terms of function; pain scores were also better with PRP but the quality of evidence was insufficient for both time points. By the long-term, function was similar between groups. For Achilles tendinopathy, there were no differences between PRP (or ABI) and conservative control groups in any outcome reported. For patellar tendinopathy, there was no difference between groups in pain or function in the short-term; the evidence for intermediate- and long-term pain and function was insufficient to draw conclusions.

Elbow Epicondylitis

PRP vs. ABI: Four RCTs[11,54,55,71] (and no cohort studies) were included which enrolled between 28 and 150 patients; the trials were found to be at moderately low (3 RCTs) or moderately high (1 RCT) risk of bias. With respect to primary outcomes, the report concluded that in the short-term, there was greater improvement with PRP versus ABI in function (4 RCTs) and pain (3 RCTs) scores based on low quality evidence. In the intermediate-term, while there was greater improvement with PRP versus ABI in function (3 RCT), there was no difference between groups in pain (2 RCTs) based on low quality evidence. There was insufficient quality evidence for the following primary outcomes: no difference between groups in long-term function and pain (1 RCT for each), and no difference between groups in the percentage of patients who achieved pain success at any time point (1 RCT). There was no evidence on function success. With respect to secondary outcomes, there was no difference between groups in the intermediate-term risk of surgery or the composite outcome of function success and no surgery (1 RCT).

PRP vs. Control: Eight RCTs (in nine publications)[20,22,52,38,77,39,5,44,69] and two prospective cohort studies[70,73] were included. The trials enrolled between 25 and 240 patients and were found to be at moderately high (6 RCTs) or moderately low (2 RCTs) risk of bias. The RCTs compared PRP to steroid injections (5 RCTs) or anesthetic injections (2 RCTs); one RCT compared PRP plus dry needling (DN) to DN alone. With respect to primary outcomes, in the short-term, there were no differences between PRP and control groups in any primary outcomes, including pain scores (7 RCTs, moderate quality evidence), pain or function success (1 RCT for each, low quality evidence), or in function scores (7 RCTs, insufficient quality evidence). In the intermediate term, low quality evidence suggested that PRP (versus control) resulted in significantly better function scores (5 RCTs), pain scores (3 RCTs), and pain success (1 RCT- for PRP vs. steroid or anesthetic only), while there was low quality evidence of no difference between groups in function success (1 RCT). In the long-term, there was low quality evidence of better function scores (3 RCTs), pain scores (2 RCTs), and pain success (1 RCT) with PRP versus control; there was insufficient quality evidence for long-term function success with inconsistent results between the 2 RCTs reporting. With respect to secondary outcomes, results were mixed, with one RCT reporting that fewer additional procedures with PRP versus steroid through the long-term, while another RCT found that PRP patients were less likely than steroid patients to achieve full recovery/no symptoms in the short-, intermediate-, and long-term. The cohort studies were at moderately high risk of bias and enrolled 52 and 81 patients; both compared PRP to low level laser radiation therapy. While one study reported no difference between groups in short-, intermediate-, and long-term pain and function, the other found better pain scores in the PRP group at these same time points.

PRP vs. Surgery: One moderately high risk of bias retrospective cohort study[18] (N=78) (and no RCTs) was included and found no differences between groups in function, pain, symptoms, and secondary outcomes through the intermediate-term (mean 10-12 months follow-up).

ABI vs. Control: Six moderately high risk of bias RCTs[3,14,29,32,49,67] (three of which were quasi-randomized) and no cohort studies were included that compared ABI to a conservative control treatment (steroid in all 6 trials, one of which also compared ABI to extracorporeal shock wave therapy (ESWT)). Trial size ranged from 50 to 80 patients. With respect to primary outcomes, in the short-term, there was low quality evidence of better function and pain scores (3 RCTs + 1 quasiRCT each) with ABI. In the intermediate-term, while pain scores were better with ABI versus steroid (2 RCTs, low quality evidence), there was insufficient evidence regarding any difference between groups in function scores (1 quasiRCT). In addition, there was insufficient quality evidence and unclear results for the following: long-term function (1 quasiRCT), short-term pain success (1 RCT + 1 quasiRCT), and intermediate-term pain success (better with ABI, 1 RCT). There was no evidence on function success for any time point or for long-term pain or pain success. No secondary outcomes were reported.

Achilles Tendinopathy

PRP vs. Control: Two RCTs (in three publications)[12,13,33] (and no cohort studies) were included that compared PRP to a conservative control (saline injection or exercise); the trials were found to be at moderately low (1 RCT) or moderately high (1 RCT) risk of bias. Trial size was 20 and 54 patients. With respect to primary outcomes, there were no differences between groups in function scores as measured in the short-term (2 RCTs, moderate quality evidence), intermediate-term (2 RCTs, low quality evidence), or long-term (1 RCT, low quality evidence). No other primary outcomes were reported. With respect to secondary outcomes, there were no differences between the PRP and exercise groups in short- or intermediate-term health-related quality of life or overall health state in one RCT; the other trial reported no differences between the PRP and saline groups in short-, intermediate-, or long-term patient satisfaction or return to sport as well as a similar risk of secondary procedures through the intermediate-term.

ABI vs. Control: Two RCTs[7,51] (and no cohort studies) were included that compared ABI to a conservative control: one trial compared ABI to DN (N=53) and the other trial compared ABI plus exercise to exercise alone (40 tendons). The trials were found to be at moderately low (1 RCT) or moderately high (1 RCT) risk of bias. With respect to primary outcomes, there was insufficient quality evidence regarding function scores in the short- (2 RCTs) and intermediate-term (1 RCT). No other primary outcomes were reported. With respect to secondary outcomes, one trial reported no differences between ABI and DN groups in intermediate-term patient-reported recovery or return to sport.

Patellar Tendinopathy

PRP vs. Control: Two RCTs[15,75] (and no cohort studies) were included that compared PRP to a conservative control: one trial compared PRP plus DN to DN alone (N=20) and the other trial compared PRP to ESWT (N=46). The trials were found to be at moderately low (1 RCT) and moderately high (1 RCT) risk of bias. With respect to primary outcomes, in the short-term, there was no difference between groups in function (2 RCTs) or pain scores (2 RCTs) based on low quality evidence. In the intermediate- and long-term, the quality of evidence was insufficient for both pain and function scores. No other primary outcomes were reported. With respect to secondary outcomes, results were mixed, with one trial reporting no differences between PRP and ESWT in

short- or intermediate-term health-related quality of life, and the other trial reporting better long-term outcomes for pain during sports with PRP plus DN (although there were no differences between groups in the short- or intermediate-term).

Rotator Cuff Tendinopathy

PRP vs. Control: Two RCTs[34,59] and one retrospective cohort study[76] were included that compared PRP to a conservative control; the trials compared PRP to DN (both groups used same technique, N=39) or to saline injections (N=40). The trials were found to be at low (1 RCT) and moderately low (1 RCT) risk of bias. With respect to primary outcomes in the short- and intermediate term, function scores were better with PRP versus control based on moderate quality evidence (2 RCTs); pain scores were also better with PRP but the quality of evidence was insufficient for both time points (1 RCT). In the long-term, there were no differences between groups in function scores based on low quality evidence (1 RCT). No other primary outcomes were reported. With respect to secondary outcomes, one trial found no differences between PRP and saline groups in short-, intermediate-, or long-term health-related quality of life. The cohort study (N=50) was found to be at moderately high risk of bias and reported better short-term function with PRP but no difference between groups by the intermediate term. Both groups had a similar risk of surgery through six months.

Plantar Fasciitis: More detailed summaries for each tendinopathy can be found in the text and tables below. In general, PRP and ABI resulted in outcomes that were the same as that of the control treatment. For PRP compared with conservative control treatments, short- and intermediate-term pain and function results were similar between groups, although long-term function scores were better with PRP than steroid injections. Results for secondary outcomes were mixed: there was no benefit with PRP in short- or intermediate-term disability but long-term symptoms were better with PRP versus steroid. For ABI compared with conservative control treatments, short-term pain was worse with ABI versus steroid, though intermediate-term pain was similar between groups (as was short- and intermediate-term function, but the quality of the evidence was insufficient). While one trial found no differences between groups in intermediate-term symptoms, results were mixed regarding repeat injections, with one trial showing no difference between ABI and steroid groups in the short-term and another finding that more ABI patients required additional injections than steroid patients through the intermediate-term; the latter trial found no difference between ABI and anesthetic plus DN in the need for additional injections through the intermediate-term.

Plantar Fasciitis

PRP vs. Control: Five moderately high risk of bias RCTs[28,46,72,10,35] and three prospective cohort studies[1,64,66] were included. The trials compared PRP to steroid injection (3 RCTs), prolotherapy (1 RCT), ESWT or conservative care (1 trial with both control groups) and enrolled between 21 and 60 patients each. With respect to primary outcomes in both the short- and intermediate-term, there was no difference between groups in function or pain scores based on low quality evidence (4 RCTs for each). In the long-term, low quality evidence suggested better function scores with PRP versus steroid (2 RCTs), while there was insufficient quality evidence of more PRP patients achieving function success (1 RCT) and better pain scores with PRP versus steroid (1 RCT). No other primary outcomes were reported. With respect to secondary outcomes, results were mixed, with one trial reporting no differences between PRP and prolotherapy in short- or intermediate-term disability, and the other trial reporting better long-term symptoms with PRP versus steroid (although there were no differences between groups in the short- or intermediate-term). *The cohort studies were all at moderately high risk of bias and compared PRP to steroid injections, with 50 to 60 patients per study. Function was better in PRP patients in the short- (2 studies) and intermediate-term (1 study), while*

results for pain were mixed (some studies showed no difference and some favored PRP) in both the short- (3 studies) and intermediate-term (2 studies). One study reported no difference between groups in short- and intermediate-term symptoms.

ABI vs. Control: Three small moderately high risk of bias RCTs[30,36,40] (and no cohort studies) were included and compared PRP to steroid injections; two of the trials also compared ABI to anesthetic plus DN. With respect to primary outcomes in the short-term, the ABI group had worse pain scores than the steroid group (2 RCTs, low quality evidence), while there was no difference between the ABI and anesthetic plus DN group (1 RCT, insufficient quality evidence). In the intermediate-term, there was no difference between ABI and either control group in pain scores (3 RCTs, low quality evidence) or in function scores (1 RCT, insufficient quality evidence). No other primary outcomes were reported. With respect to secondary outcomes, one trial found no differences between ABI and both comparator groups in intermediate-term symptoms. Results were mixed regarding repeat injections, with one trial showing no difference between ABI and steroid groups in the short-term and another finding that more ABI patients required additional injections than steroid patients through the intermediate-term; the latter trial found no difference between ABI and anesthetic plus DN in the need for additional injections through the intermediate-term.

Acute Injury: More detailed summaries for each acute injury can be found in the text and tables below. In general, there were no differences between PRP and conservative control groups, and for the primary outcomes, any evidence of benefit with PRP was of insufficient quality.

Acute Muscle Injury

PRP + Conservative Care (CC) vs. Control: Four RCTs[8,23,24,58] were included; trial size ranged from 28 to 80 patients each. One trial was found to be at low risk of bias, two at moderately low risk of bias, and one at moderately high risk of bias. The trials compared PRP plus CC to either CC alone (2 RCTs) or plus saline injection (1 RCT). With respect to primary outcomes, there was low quality evidence of no difference in pain scores between groups (3 RCTs); short-term function was better with PRP plus CC compared with CC alone (1 RCT), however the quality of evidence was insufficient. In the intermediate-term, there was low quality evidence of no difference between PRP plus CC versus saline plus CC in function and pain scores (1 RCT each). No other primary outcomes were reported. With respect to secondary outcomes, short-term return to sport results were mixed, with two studies finding better results with PRP plus CC and one finding no difference between groups. One trial reported no difference between groups in short-term recovery and patient satisfaction as well as in intermediate-term symptoms, health-related quality of life, and return to sport. There were no differences between groups in re-injury rates in the short- (2 RCTs), intermediate- (1 RCT), or long-term (1 RCT).

Acute Achilles Tendon Rupture

PRP + CC vs. CC: One moderately high risk of bias retrospective cohort study[31] was included (N=145). The only outcome reported was long-term function, for which there was insufficient quality evidence of no difference in function scores between PRP plus CC compared with CC alone.

Ankle Sprain

PRP vs. Placebo: One moderately high risk of bias RCT[60] was included that compared PRP injection with saline injection (N=33). Only short-term pain and function were reported, for which there was insufficient quality evidence of no difference between groups.

Other injuries:

Temporomandibular Joint Dislocation

ABI vs. Intermaxillary Fixation (IMF): One moderately high risk of bias RCT[25] was included (N=32). The only outcome reported was long-term recurrent dislocation, for which there was insufficient quality evidence for a greater risk of recurrence of dislocation following PRP compared with IMF.

Osteochondral Lesions of the Talus

PRP vs. Hyaluronic Acid (HA): One moderately high risk of bias quasi-RCT[43] was included (N=29). With respect to primary outcomes in both the short- and intermediate-term, PRP resulted in significantly better function and pain scores compared with HA, though the quality of evidence was insufficient. No other primary outcomes were reported. With respect to secondary outcomes, the PRP group had marginally better stiffness scores in the short-term, and the difference reached significance for the intermediate-term.

Osteoarthritis: More detailed summaries for each osteoarthritis can be found in the text and tables below. Of the types of osteoarthritis for which studies were identified (knee, hip, and temporomandibular joint (TMJ)), only knee osteoarthritis had evidence of benefit with PRP. For PRP versus HA injections, although there were no short-term differences between groups in pain or function, by the intermediate-term, function scores were better and pain success more common in the PRP (although there were no differences between groups in function success or pain scores). In the long-term, pain and function success was more common and function scores were better with PRP (but there were no differences between groups in pain scores). There was also evidence of better intermediate- and long-term health-related quality of life with PRP, although there were no differences between groups in terms of patient satisfaction for these time periods. For PRP versus steroid injections, there was evidence of better short- and intermediate-term pain and function scores, however the quality of evidence was insufficient to draw firm conclusions. For the comparison of PRP to saline injections, short- and intermediate-term pain and function scores were better with PRP, as was intermediate-term patient satisfaction and health-related quality of life. For PRP versus exercise (with or without TENS), there were no differences between groups in any primary outcomes. For hip and TMJ osteoarthritis, outcomes were similar between PRP and HA injection groups.

Knee Osteoarthritis

PRP vs. HA: Six RCTs[9,17,74,63,21,53] and four cohort studies (3 prospective[37,65,68] and 1 retrospective[62]) were included. The RCTs enrolled between 96 and 192 patients; trials were found to be at low (2 RCTs), moderately low (2 RCTs), or moderately high (2 RCTs) risk of bias. With respect to primary outcomes, in the short-term, there was no difference between groups in function (4 RCTs, moderate quality evidence) or pain (1 RCT, low quality evidence) scores. In the intermediate-term, function scores were better with PRP (5 RCTs, moderate quality evidence), however it was unclear whether functional success was more common following PRP versus HA (2 RCTs, low quality evidence); intermediate-term pain scores were similar between groups (3 RCTs, moderate quality evidence) while pain success was more common following PRP (2 RCTs, moderate quality evidence). In the long-term, function success was more common following PRP (1 RCT, low quality evidence), and function scores were slightly better with PRP (3 RCTs, low quality evidence); long-term pain success was more common following PRP (1 RCT, low quality evidence), although long-term pain scores were similar between groups (3 RCTs, low quality evidence). No other primary outcomes were reported. With respect to secondary outcomes, health-related quality of life was similar between groups in the short-term (1 RCT), the same or better (varying by outcome measure) with PRP across in the

intermediate-term (2 RCTs), and better with PRP in the long-term (2 RCTs). Patient satisfaction was similar between groups in the intermediate- and long-term (1 RCT each), and medication use was similar between groups through six months (1 RCT). The cohort studies enrolled between 60 and 150 patients each; all were considered to be at moderately high risk of bias. Function scores were better in the PRP group in in the short-term (in 3 of the 4 studies and similar between groups in the 4th) and intermediate-term (3 studies). Pain was better in both the short- (3 studies) and intermediate-term (2 studies). One study also reported better intermediate-term health-related quality of life and patient satisfaction with PRP.

LR-PRP vs. Steroid: One moderately low risk of bias RCT[19] was included (N=48) that found better short- and intermediate-term pain and function scores with LR-PRP versus corticosteroid injection, although the quality of evidence was insufficient. No other primary outcomes were reported. With respect to secondary outcomes, there was no difference between groups in health-related quality of life in the short-term, but by the intermediate-term, this outcome was better in the PRP group. There was no difference between groups in medication use through six months.

PRP vs. Saline: Two moderately low risk of bias RCTs[50,21] (and no cohort studies) were included; trial size was 78 and 136 patients. With respect to primary outcomes, in the short-term, function and pain scores were better in the PRP versus saline groups (1 RCT each, low quality evidence). Similarly, in the intermediate-term, function (2 RCTs) and pain (1 RCT) scores were better in the PRP versus saline groups based on low quality evidence. No other primary outcomes were reported. With respect to secondary outcomes, in the intermediate-term, both trials reported that patient satisfaction was more common in the PRP group, and one trial found better health-related quality of life with PRP.

PRP vs. Exercise ± TENS: Two moderately low risk of bias RCTs[56,2] (and no cohort studies) were included; one compared LR-PRP plus exercise to exercise alone (N=65), the other compared PRP to exercise plus transcutaneous electrical nerve stimulation (TENS) (N=54). With respect to primary outcomes, in the short- and intermediate term, there were no clear differences between groups in function or pain scores (1 RCT for each) based on insufficient quality evidence. No other primary outcomes were reported. With respect to secondary outcomes, there was no difference between groups in short- or intermediate-term quality of life (1 RCT each); in addition, acetaminophen use was higher in the PRP plus exercise group than the exercise alone group through six months.

Hip Osteoarthritis

PRP vs. HA: One moderately low risk of bias RCT[4] was included (N=104). With respect to primary outcomes, there were no differences between PRP and HA groups in short-, intermediate-, or long-term function or pain scores based on low quality evidence. No other primary outcomes were reported. The only primary outcome reported was medication use, which was similar between groups at all three time points.

TMJ Osteoarthritis

PRP vs. HA: One moderately high risk of bias RCT[26] was included (N=50). There were no clear differences between PRP and HA groups in short-, intermediate-, or long-term function or pain scores based on insufficient quality evidence. No other outcomes were reported.

KQ2: Summary of Results

More detailed summaries can be found in the text and tables below. All included comparative studies were evaluated for harms and complications. In addition, case series specifically designed to evaluate harms were considered for inclusion, however none were identified that met the inclusion criteria. Across all included studies there was no evidence of any serious adverse events with any intervention or control treatment. The most common no-serious adverse events was injection-site pain (both during and after the injection), which may be more common following PRP or ABI injection than other injections.

KQ3: Summary of Results

More detailed summaries can be found in the text and tables below. For this key question, RCTs that stratified on patient characteristics of interest, permitting evaluation of effect modification were considered for inclusion. Subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. All RCTs included to evaluate the efficacy or safety of PRP or ABI versus comparators of interest were assessed. In general, there was very little reporting of differential efficacy and safety; all evidence that was identified was of insufficient quality to draw firm conclusions.

KQ4: Summary of Results

No formal economic analyses were identified that met the inclusion criteria.

Strength of Evidence Summaries

The following summaries of evidence have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by comparator. Details of other outcomes are available in the report.

Key Question 1 Strength of Evidence Summary: Elbow Epicondylitis Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Elbow Epicondylitis: PRP vs. ABI						
Function success	Any	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	4 RCTs (Creaney, Raeissadat 2014a, Raeissadat 2014b, Thanasas)	N= 260	RoB[1] (-1), Imprecision[3] (-1)	SMD 0.31 (95% CI 0.06, 0.56) Conclusion: Significantly greater improvement with PRP vs. ABI as evaluated by PRTEE, MMCPIE, and Liverpool elbow score.	⊕⊕◯◯ LOW
	Intermediate-term	3 RCTs (Creaney, Raeissadat 2014a, Thanasas)	N= 220	RoB[1] (-1), Imprecision[3] (-1)	SMD 0.48 (95% CI 0.21, 0.75) Conclusion: Significantly greater improvement with PRP vs. ABI as evaluated by PRTEE, MMCPIE, and Liverpool elbow score.	⊕⊕◯◯ LOW
	Long-term	1 RCT	N=	RoB[1] (-1),	MD 5.0 (95% CI -4.2, 14.2)	⊕◯◯◯

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
		(Raeissadat 2014a)	61	Imprecision[3,6] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions.	INSUFFICIENT
Pain success (≥25 VAS improve-ment)	Short-term	1 RCT (Raeissadat 2014a)	N= 61	RoB[1] (-1), Imprecision[3,6] (-2)	RR 1.0 (95% CI 0.7, 1.4) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Raeissadat 2014a)	N= 61	RoB[1] (-1), Imprecision[3,6] (-2)	RR 1.1 (95% CI 0.8, 1.4) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Raeissadat 2014a)	N= 61	RoB[1] (-1), Imprecision[3,6] (-2)	RR 1.2 (95% CI 0.9, 1.8) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain (VAS (0-10) worst))	Short-term	3 RCTs (Raeissadat 2014a, Raeissadat 2014b, Thanasas)	N= 130	RoB[1] (-1), Imprecision[3] (-1)	WMD -0.8 (95% CI -1.3, -0.2) Conclusion: Significantly greater improvement with PRP vs. ABI in VAS pain.	⊕⊕◯◯ LOW
	Intermediate-term	2 RCTs (Raeissadat 2014a, Thanasas)	N= 90	RoB[1] (-1), Imprecision[3] (-1)	WMD -0.6 (95% CI -1.4, 0.1) Conclusion: No difference between groups.	⊕⊕◯◯ LOW
	Long-term	1 RCT (Raeissadat 2014a)	N= 61	RoB[1] (-1), Imprecision[3,6] (-2)	MD -0.6 (95% CI -1.8, 0.6) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Elbow Epicondylitis: PRP vs. Control*						
Function Success (various measures)	Short-term	1 RCT (Lebiedzinski)	N=99	RoB[1] (-1), Imprecision[3] (-1)	RR 1.0 (95% CI 0.7, 1.4) Conclusion: No difference between PRP and steroid groups in the achievement of "very good" DASH scores (i.e., scores 0-25 on 0-100 scale).	⊕⊕◯◯ LOW
	Intermediate-term	1 RCT (Lebiedzinski)	N=99	RoB[1] (-1), Imprecision[3] (-1)	RR 1.0 (95% CI 0.8, 1.3) Conclusion: No difference between PRP and steroid groups in the achievement of "very good" DASH scores (i.e., scores 0-25 on 0-100 scale).	⊕⊕◯◯ LOW
	Long-term	2 RCTs (Gosens, Lebiedzinski)	N=199	RoB[1] (-1), Inconsistency[2] (-1), Imprecision[3] (-1)	Conclusion: Insufficient results preclude firm conclusions: • ≥25% reduction in DASH scores + no re-intervention: 73% vs. 39% (RR 1.9 (95% CI 1.3, 2.8), 1 RCT (N=100) (Lebiedzinski) • "Very good" DASH scores (i.e., scores 0-25 on 0-100 scale): 81% vs. 78% (RR 1.0 (95% CI 0.8, 1.3)),	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					1 RCT (N=99) (Gosens)	
Function (various measures)	Short-term	7 RCTs (Gautam, Krogh, Gosens, Lebiedzinski, Yadav, Behera, Mishra)	N=545	RoB[1] (-1), Inconsistency[2] (-1), Imprecision[3] (-1)	Conclusion: Insufficient strength of evidence precludes firm conclusions: • DASH, MMCPIE, ΔPRTEE disability: WMD -2.35 (95% CI -6.27, 1.58), 7 RCTs (N=545) (Gautam, Krogh, Gosens, Lebiedzinski, Yadav, Behera, Mishra) One trial included in the pooled analysis reported two additional functional outcomes: • No difference in MMCPIE: MD 0.6 (95% CI -1.6, 2.8), 1 RCT (N=30) (Gautam); • Better Oxford Elbow Scores in control (steroid) group: MD -2.4 (95% CI -4.6, -0.2), 1 RCT (N=30) (Gautam)	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	5 RCTs (Gautam, Gosens, Lebiedzinski, Behera, Mishra)	N=372	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Significantly greater improvement with PRP vs. control as evaluated by: • DASH, MMCPIE, PRTEE: WMD -7.67 (95% CI –11.67, -3.67), 5 RCTs (N=372) (Gautam, Gosens, Lebiedzinski, Behera, Mishra) One trial included in the pooled analysis reported similar results with two additional functional outcomes: • Oxford Elbow Score: MD 4.9 (95% CI 1.5, 8.4), 1 RCT (N=30) (Gautam) • MMCPIE: MD 9.2 (95% CI 5.2, 12.7), 1 RCT (N=30) (Gautam)	⊕⊕◯◯ LOW
	Long-term	3 RCTs (Gosens, Lebiedzinski, Beher)	N=223	RoB[1] (-1), Imprecision[3] (-1)	WMD -14.1 (95% CI -22.8, -12.3) Conclusion: Significantly greater improvement with PRP vs. control as evaluated by the DASH and MMCPIE outcome measures.	⊕⊕◯◯ LOW
Pain Success (various measures)	Short-term	1 RCT (Mishra)	N=192	RoB[1] (-1), Imprecision[4] (-1)	RR 1.1 (95% CI 0.9, 1.4) Conclusion: No difference between groups in the percentage of patients achieving a ≥25% decrease in VAS scores (75% vs. 66%).	⊕⊕◯◯ LOW
	Intermediate-term	1 RCT (Mishra)	N=119	RoB[1] (-1), Imprecision[4] (-1)	RR 1.2 (95% CI 1.2, 2.6) Conclusion: Significantly more PRP vs. steroid patients achieved a ≥50% decrease in VAS scores (82% vs. 60%).	⊕⊕◯◯ LOW
	Long-term	1 RCT (Gosens)	N=100	RoB[1] (-1), Imprecision[4] (-1)	RR 0.2 (95% CI 0.05, 0.9) Conclusion: Significantly more PRP	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
				(-1)	vs. steroid patients achieved a ≥25% decrease in VAS scores without re-intervention (77% vs. 43%).	
Pain (various measures)	Short-term	7 RCTs (Gautam, Gosens, Krogh, Behera, Stenhouse, Mishra, Yadav)	N=471	RoB[1] (-1)	Conclusion: No difference between groups (regardless of control treatment) as evaluated by: • VAS or PRTEE pain: SMD 0.02 (95% CI -0.22, 0.25), 6 RCTs (N=279) (Gautam, Gosens, Krogh, Yadav, Behera, Stenhouse) • VAS pain (% improvement): 55% vs. 47% (MD NR/NC, p=NS‡), 1 RCT (N=192) (Mishra) • Activity-related pain (Nirschl): SMD -0.29 (95% CI -0.86, 0.29), 2 RCTs (N=49) (Behera, Stenhouse)	⊕⊕⊕◯ MODERATE
	Intermediate-term (PRP vs. steroid or LA)	3 RCTs (Gautam, Gosens, Behera)	N=154	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Overall, there was significantly greater improvement with PRP vs. steroid or LA: • VAS pain: SMD -1.17 (95% CI -1.71, -0.62), 3 RCTs (N=154) (Gautam, Gosens, Behera) • VAS pain (% improvement) (for PRP vs. steroid): 72% vs. 56% (MD NR/NC, p=NS‡), 1 RCT (N=119) (Mishra) • Activity-related pain (Nirschl): SMD -2.06 (95% CI -3.10, -1.02), 1 RCT (N=24) (Behera)	⊕⊕◯◯ LOW
	Intermediate-term (PRP + DN vs. DN)	1 RCT (Behera)	N=25	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusion: • VAS pain: SMD -0.09 (95% CI -0.88, 0.69) • Activity-related pain (Nirschl): SMD -0.22 (95% CI -1.01, 0.57)	⊕◯◯◯ INSUFFICIENT
	Long-term	2 RCTs (Gosens, Behera)	N=124	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Significantly greater improvement with PRP: • vs. steroid as evaluated by VAS: SMD -0.76 (95% CI -1.17, -0.36), 1 RCT, (N=100) (Gosens) • vs. LA as evaluated by VAS: SMD -2.09 (95% CI -3.14, -1.04), 1 RCT (N=24) (Behera) • vs. LA as evaluated by activity-related pain (Nirschl): SMD -1.66 (95% CI -2.64, -0.69), 1 RCT (N=24) (Behera)	⊕⊕◯◯ LOW
Elbow Epicondylitis: ABI vs. Control†						

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Function success	Any	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	3 RCTs (Arik, Singh, Kazemi), 1 quasi-RCT (Ozturan)	N= 238	RoB[1] (-1), Imprecision[3] (-1)	SMD -0.87 (95% CI -1.41, -0.33), I^2 = 74% Conclusion: Significantly greater improvement with ABI vs. steroid as evaluated by PRTEE, qDASH, and Upper Extremity Functional Scale.	⊕⊕◯◯ LOW
	Intermediate-term	1 quasi-RCT (Ozturan)	N= 37-38	RoB[1,5] (-2), Imprecision[3,6] (-2)	ABI vs. steroid: MD -6.4 (95% CI -11.9, -0.9) ABI vs. ESWT: MD 1.5 (95% CI -4.4, 7.4) Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 quasi-RCT (Ozturan)	N= 37-38	RoB[1,5] (-2), Imprecision[3,6] (-2)	ABI vs. steroid: MD -8.9 (95% CI -15.1, -2.7) ABI vs. ESWT: MD -0.9 (95% CI -6.1, 4.3) Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain (various measures)	Short-term	3 RCTs (Arik, Singh, Kazemi), 1 quasi-RCT (Ozturan)	N= 250	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Significantly greater improvement with ABI vs. steroid as evaluated by: • VAS pain: SMD -0.8 (95% CI -1.2, -0.5), 4 RCTs (N=250) • Activity-related pain (Nirschl): SMD -0.8 (95% CI -1.2, -0.1), 3 RCTs (N=170) (Dojode, Jindal, Kazemi)	⊕⊕◯◯ LOW
	Intermediate-term	2 RCTs (Dojode, Arik)	N= 140	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Significantly greater improvement with ABI vs. steroid as evaluated by: • VAS pain: SMD -0.8 (95% CI -1.2, -0.5), 2 RCTs (N=140) • Activity-related pain (Nirschl): SMD -0.6 (95% CI -1.13, -0.1), 1 RCT (N=60) (Dojode)	⊕⊕◯◯ LOW
	Long-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
Pain Success	Short-term	1 RCT (Dojode), 1 quasi-RCT (Jindal)	N= 110	RoB[1,5] (-2), Inconsistency[2] (-1), Imprecision[4] (-1)	Conclusion: Insufficient strength of evidence prevents firm conclusion: • VAS improvement ≥7 points: RR 3.0 (95% CI 0.3, 27), 1 RCT (N=50) (no difference between groups) (Dojode) • Patient-reported "complete pain relief": RR 0.3 (95% CI 0.1, 0.6), 1 RCT (N=60) (better in steroid	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					group) (Jindal)	
	Intermediate-term	1 RCT (Dojode)	N= 60	RoB[1] (-1), Imprecision[3,6] (-2)	RR 1.9 (95% CI 1.3, 2.9) Conclusion: Insufficient strength of evidence precludes firm conclusions	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT

* PRP vs. control comparators:
- Gautam, Gosens, Krogh, Yadav, Lebiedzinski: PRP vs. steroid injection
- Mishra, Behera: PRP vs. LA
- Stenhouse: PRP + DN vs. DN

†ABI vs. control comparators:
- Arik, Dojode, Jindal, Kazemi, Ozturan, Singh: ABI vs. steroid injection
- Ozturan: ABI vs. ESWT

‡p-values were reported by the trial; Spectrum was unable to confirm due to missing SDs.

Reasons for downgrading:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
5. Risk of bias downgraded an additional level (so -2) due to quasi-randomized nature of the majority of studies (patients "randomized" by alternate allocation).
6. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

Key Question 1 Strength of Evidence Summary: Achilles Tendinopathy Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Achilles Tendinopathy: PRP vs. Control*						
Function success, Pain success, Pain	Any	0 RCTs			No evidence.	⊕○○○ INSUFFICIENT
Function (VISA-A (0-100 (best))	Short-term	2 RCTs (de Jonge, Kearney)	N= 73	Imprecision[3] (-1)	WMD -1.5 (95% CI -11.3, 8.4) Conclusion: No difference between groups.	⊕⊕⊕○ MODERATE
	Intermediate-term	2 RCTs (de Jonge, Kearney)	N= 73	Inconsistency[2] (-1), Imprecision[3] (-1)	WMD -6.5 (95% CI -25.7, 12.7) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Long-term	1 RCT (de Jonge)	N= 54	Imprecision[3,4] (-2)	MD 6.6 (95% CI -5.1, 18.3) Conclusion: No difference between groups.	⊕⊕○○ LOW
Achilles Tendinopathy: ABI vs. Control†						
Function success, Pain success, Pain	Any	0 RCTs			• No evidence.	⊕○○○ INSUFFICIENT
Function (VISA-A (0-100 (best))	Short-term (ABI vs. exercise)	1 RCT (Pearson)	N=28 tendons	RoB[1] (-1), Imprecision[3,4] (-2)	MD 9.3 (95% CI 2.1, 16.5) Conclusion: Greater improvement with ABI; insufficient strength of evidence prevents firm conclusion.	⊕○○○ INSUFFICIENT
	Short-term (ABI vs. DN)	1 RCT (Bell)	N=50	RoB[1] (-1), Imprecision[3,4] (-2)	MD 0.3 (95% CI -8.1, 8.7) Conclusion: No difference between groups; insufficient strength of evidence prevents firm conclusion.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Bell)	N= 50	RoB[1] (-1), Imprecision[3,4] (-2)	MD -1.2 (95% CI -10.2, 7.8) Conclusion: Insufficient strength of evidence prevents firm conclusion	⊕○○○ INSUFFICIENT
	Long-term	0 RCTs			No evidence.	⊕○○○ INSUFFICIENT

* PRP vs. control comparators:
- De Jonge: PRP vs. saline injection
- Kearney: PRP vs. exercise

†ABI vs. control comparators:
- Bell: ABI vs. DN
- Pearson: ABI + exercise vs. exercise (results reported per tendon)

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

Key Question 1 Strength of Evidence Summary: Patellar Tendinopathy Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Patellar Tendinopathy: PRP vs. Control*						
Function success, Pain success	Any	0 RCTs			No evidence.	⊕○○○ INSUFFICIENT
Function (various measures)	Short-term	2 RCTs (Dragoo, Vetrano)	N= 67	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups as evaluated by: • VISA-P: WMD 7.4 (95% CI -1.5, 16.2), 2 RCTs, N=67 • ΔLysholm: MD 2.7 (95% CI -25.4, 20.0), 1 RCT, N=21 (Dragoo) • Tegner: MD 0.9 (95% CI 0.7, 2.5), 1 RCT, N=21 (Dragoo)	⊕⊕○○ LOW
	Intermediate-term (PRP vs. ESWT)	1 RCT (Vetrano)	N= 46	RoB[1] (-1), Imprecision[3,4] (-2)	MD 13.0 (3.0, 23.0)) (VISA-P) • Conclusion: Significantly greater improvement with PRP vs. ESWT; insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
	Intermediate-term (PRP + DN vs. DN)	1 RCT (Dragoo)	N= 17	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: No difference between groups; insufficient strength of evidence prevents firm conclusions: • VISA-P: MD -4.3 (-24.0, 15.4) • Lysholm: MD -15.5 (95% CI -33.3, 2.3), 1 RCT, N=17 (NOTE: Due to baseline imbalances, ΔLysholm was also evaluated and favored the DN group (MD -30.7 (95% CI -50.3, -11.1)). (Dragoo) Tegner: MD -0.6 (95% CI -2.6, 1.4), 1 RCT, N=17 (Dragoo)	⊕○○○ INSUFFICIENT
	Long-term	1 RCT (Vetrano)	N= 46	RoB[1] (-1), Imprecision[3,4] (-2)	MD 13.7 (95% CI 4.6, 22.8) (on VISA-P) Conclusion: Insufficient strength of evidence prevents firm conclusions	⊕○○○ INSUFFICIENT
Pain	Short-term	2 RCTs	N=	RoB[1] (-1),	WMD -0.7 (95% CI -1.8, 0.4)	⊕⊕○○

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
(VAS (0-10) (worst))		(Dragoo, Vetrano)	67	Imprecision[3] (-1)	Conclusion: No difference between groups.	LOW
	Intermediate-term (PRP vs. ESWT)	1 RCT (Vetrano)	N= 46	RoB[1] (-1), Imprecision[3,4] (-2)	MD -1.5 (-2.7, -0.3) Conclusion: Significantly greater improvement with PRP vs. ESWT; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Intermediate-term (PRP + DN vs. DN)	1 RCT (Dragoo)	N= 17	RoB[1] (-1), Imprecision[3,4] (-2)	MD -0.1 (-2.2, 2.0) Conclusion: No difference between groups; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Vetrano)	N= 46	RoB[1] (-1), Imprecision[3,4] (-2)	MD -1.7 (-2.9, -0.5) Conclusion: Insufficient strength of evidence prevents firm conclusions:	⊕◯◯◯ INSUFFICIENT

DN: dry needling; ESWT: extracorporeal shock wave therapy
* Comparators:
- Dragoo: PRP + DN vs. DN alone
- Vetrano: PRP vs. ESWT

Reasons for downgrading:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

Key Question 1 Strength of Evidence Summary: Rotator Cuff Tendinosis and/or Partial Tear Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Rotator Cuff Tendinosis and/or partial tear: PRP vs. Control*						
Function or pain success	Any	0 RCTs			• No evidence.	⊕◯◯◯ INSUFFICIENT
Function SPADI (0-100 (worst))	Short-term	2 RCTs (Kesikburun, Rha)	N= 72	Imprecision[3] (-1)	• MD -13.5 (95% CI -24.8, -2.2) (Rha) • Median 27.6 vs. 45.3, p=NS (Kesikburun) Conclusion: Greater functional improvement with PRP vs. control.	⊕⊕⊕◯ MODERATE
	Intermediate-term	2 RCTs (Kesikburun, Rha)	N= 70	Imprecision[3] (-1)	• MD -11.8 (95% CI -22.5, -1.1) (Rha) • Median 21.7 vs. 40.9, p=NS (Kesikburun) Conclusion: Greater functional	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					improvement with PRP vs. control.	
	Long-term	1 RCT (Kesikburun)	N= 40	Imprecision[3,4] (-2)	Median 14.6 vs. 15.4, p=NS Conclusion: No difference between groups.	⊕⊕◯◯ LOW
Pain (VAS (0-100) (worst))	Short-term	1 RCT (Rha)	N= 32	RoB[1] (-1), Imprecision[3,4] (-2)	MD -5.2 (95% CI -9.5, -0.9) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Rha)	N= 30	RoB[1] (-1), Imprecision[3,4] (-2)	MD -4.7 (95% CI -8.9, -0.5) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT

DN: dry needling; ESWT: extracorporeal shock wave therapy
* Comparators:
- Rha: PRP vs. DN alone (both used same technique)
- Kesikburun: PRP vs. saline injection

Reasons for downgrading:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

Key Question 1 Strength of Evidence Summary: Plantar Fasciitis Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Plantar Fasciitis: PRP vs. Conservative Control*						
Function success	Short-, intermediate-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Jain)	N=46 (60 heels)	RoB[1] (-1), Imprecision[4,5] (-2)	RR 1.8 (95% CI 1.0, 3.2), p=0.04 Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	4 RCTs (Jain, Kim, Chew, Monto)	N= 134	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups. However: Three trials reported no difference between groups (regardless of control treatment) as evaluated by: • AOFAS Ankle and Hindfoot scale: • MD -2.7 (95% CI -11.1, 5.7), 1 RCT	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					(N=46, 60 heels) (Jain) • Median: 86 vs. 80 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT)) • Median: 86 vs. 80 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC)) • FFI total score: MD 0.1 (95% CI -44, 44), 1 RCT (N=20) (Kim) • FFI activity limitation subscale score: MD 2.3 (95% CI -7.8, 12), 1 RCT (N=20) (Kim) In contrast, one trial reported a better outcome following PRP vs. steroid: • AOFAS Ankle and Hindfoot scale: median 95 vs. 81, MD NR/NC†, p<0.01‡, 1 RCT (N=40) (Monto)	
	Intermediate-term	4 RCTs (Jain, Kim, Chew, Monto)	N= 134	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups. However: Three trials reported no difference between groups (regardless of control treatment) as evaluated by: • AOFAS Ankle and Hindfoot scale: • MD 4.7 (95% CI -3.3, 12.7), 1 RCT (N=46, 60 heels) (Jain) • Median: 90 vs. 90 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT)) • Median: 90 vs. 87 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC)) • FFI total score: MD -16.1 (95% CI -67, 35), 1 RCT (N=20) (Kim) • FFI activity limitation subscale score: MD 0.9 (95% CI -10.8, 12.6), 1 RCT (N=20) (Kim) In contrast, one trial reported a better outcome following PRP vs. steroid: • AOFAS Ankle and Hindfoot scale: median 94 vs. 74, MD NR/NC†, p<0.01‡, 1 RCT (N=40) (Monto)	⊕⊕◯◯ LOW
	Long-term	2 RCTs (Jain, Monto)	N= 86	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Significantly greater improvement with PRP vs. steroid as evaluated by the AOFAS Ankle and Hindfoot scale: • MD 13.4 (95% CI 4.6, 22.3), 1 RCT (N=46, 60 heels) (Jain) • Median: 92 vs. 56 MD NR/NC†, p<0.01‡, 1 RCT (N=40) (Monto)	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Pain success	Any	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT

Pain (VAS (0-100) (worst))	Short-term	4 RCTs (Jain, Kim, Chew, Tiwari)	N= 174	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups. However:
					
					Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
					• VAS pain:
					  • MD 0.7 (95% CI -1.0, 2.4), 1 RCT (N=46, 60 heels) (Jain)
					  • Median: 4 vs. 4 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT)
					  • Median: 4 vs. 4 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC)
					• FFI pain subscale score: MD -0.6 (95% CI –17, 16), 1 RCT (N=20) (Kim)
					
					In contrast, one trial reported a better outcome following PRP vs. steroid as evaluated by:
					• VAS pain: MD -0.8 (95% CI -1.1, -0.5), 1 RCT (N=60) (Tiwari)
						⊕⊕◯◯ LOW

	Intermediate-term	4 RCTs (Jain, Kim, Chew, Tiwari)	N= 174	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups. However:
					
					Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
					• VAS pain:
					  • MD 0.4 (95% CI -1.5, 2.3), 1 RCT (N=46, 60 heels) (Jain)
					  • Median: 2 vs. 3 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT)
					  • Median: 2 vs. 3 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC)
					• FFI pain subscale score: MD 7.7 (95% CI -29, 14), 1 RCT (N=20) (Kim)
					
					In contrast, one trial reported a better outcome following PRP vs. steroid as evaluated by:
					VAS pain: MD -0.8 (95% CI -1.1, -0.5), 1 RCT (N=60) (Tiwari)
						⊕⊕◯◯ LOW

	Long-term	1 RCT (Jain)	N=46 (60 heels)	RoB[1] (-1), Imprecision[3,5] (-2)	MD -2.0 (95% CI -3.9, -0.1), 1 RCT (N=46, 60 heels) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Plantar Fasciitis: ABI vs. Conservative Control[§]						
Function, Pain success	Any	0 RCTs			• No evidence.	⊕○○○ INSUFFICIENT
Function (AOFAS Ankle and Hindfoot)	Short-term	0 RCTs			• No evidence.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Kiter)	N= 29-30	RoB[1] (-1), Imprecision[3,5] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. • ABI vs. steroid: MD 0.8 (95% CI -11.2, 12.8), 1 RCT (N=29) • ABI vs. LA + DN: MD 2.7 (95% CI -7.2, 12.6), 1 RCT (N=30)	⊕○○○ INSUFFICIENT
	Long-term	0 RCTs			No evidence.	⊕○○○ INSUFFICIENT
Pain (VAS)	Short-term, ABI vs. steroid	2 RCTs (Kalaci, Lee)	N= 111	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Significantly worse improvement with PRP vs. steroid as evaluated by VAS pain: • WMD 1.68 (95% CI 0.70, 2.66)	⊕⊕○○ LOW
	Short-term, ABI vs. LA + DN	1 RCT (Kalaci)	N= 50	RoB[1] (-1), Imprecision[3,5] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. • MD -0.30 (95% CI -1.80, 1.20)	⊕○○○ INSUFFICIENT
	Intermediate-term, ABI vs. steroid	3 RCTs (Kalaci, Kiter, Lee)	N= 140	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups as evaluated by VAS pain: • WMD 1.09 (95% CI -0.09, 2.27)	⊕⊕○○ LOW
	Intermediate-term, ABI vs. LA + DN	2 RCTs (Kalaci, Kiter)	N= 80	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups as evaluated by VAS pain: • WMD 0.27 (95% CI -0.82, 1.36)	⊕⊕○○ LOW
	Long-term	0 RCTs			No evidence.	⊕○○○ INSUFFICIENT

DN: dry needling; ESWT: extracorporeal shock wave therapy; LA: local anesthetic

* Comparators:
  - Jain, Monto, Tiwari: PRP vs. steroid injection
  - Kim: PRP vs. prolotherapy
  - Chew: PRP vs. ESWT vs. CC

†Unable to calculate effect size (study reported median and range scores).

‡p-values were reported by the trial; Spectrum was unable to confirm due to missing SDs.

§Comparators:
  - Kalaci, Kiter, Lee: PRP vs. steroid injection
  - Kalaci, Kiter: PRP vs. LA + DN

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 1 Strength of Evidence Summary: Acute Muscle Injury Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Acute Muscle Injury: PRP vs. Control*						
Function success, Pain success	Any	0 RCTs			No evidence.	⊕○○○ INSUFFICIENT
Function (various)	Short-term	1 RCT (Bubnov)	N= 30	RoB[1] (-1), Imprecision[3,4] (-2)	Subjective global function scores (0-100 (best)), PRP + CC vs. CC: 92 vs. 74 (MD NR/NC, p<0.05†) Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Reurink)	N= 80	Imprecision[3,4] (-2)	MD -3 (95% CI -12, 7) Conclusion: No difference between groups as evaluated by HOS-Overall (0-100 (best)).	⊕⊕○○ LOW
	Long-term	0 RCTs			No evidence.	⊕○○○ INSUFFICIENT

Pain (various)	Short-term	3 RCTs (Bubnov, Reurink, Hamid)	N= 136	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between groups. However:
					
					Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
					• VAS pain:
					  • MD -0.1 (95% CI -0.5, 0.3), 1 RCT (N=78) (Reurink)
					  • Mean: 0.4 vs. 1.0 (MD NR/NC, p<0.05†), 1 RCT (n=30) (Bubnov)
					• BPI-SF pain interference as assessed over time: β ± SE = -0.185 ± 0.130 (95% CI -0.44, -0.07) (NOTE: p=NS as reported by trial even though the 95% CI suggests otherwise) (Hamid)
					
					In contrast, one trial reported a better outcome following PRP vs. steroid as evaluated by:
					• BPI-SF pain severity as assessed over time: β ± SE = -0.390 ± 0.142 (95% CI -
						⊕⊕○○ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					0.67, -0.11) (Hamid)	
	Intermediate-term	1 RCT (Reurink)	N= 80	Imprecision[3,4] (-2)	Conclusion: No difference between groups as evaluated the following HOS scales (0-100 (best)): • HOS-Soreness: MD -2 (95% CI -11, 7) (Reurink) • HOS-Pain: MD 1 (95% CI -9, 10) (Reurink)	⊕⊕◯◯ LOW
	Long-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT

BPI-SF: Brief Pain Inventory-Short Form; CC: conservative care; CI: confidence interval; HOS: Hamstring Outcome Score; MD: mean difference; NRS: numerical rating scale; PRP: platelet-rich plasma; QoL: Quality of Life; RCT: randomized controlled trial; VAS: visual analog scale.

* PRP vs. control comparators:
  - Bubnov, Hamid, Hamilton: PRP + CC vs. CC
  - Reurink: PRP + CC vs. Saline + CC

†p-values were reported by the trial; Spectrum was unable to confirm due to missing SDs.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

Key Question 1 Strength of Evidence Summary: Acute Achilles Tendon Rupture Effectiveness Results

Outcome	Follow-up	Studies	N	Reasons for Downgrading	Conclusion	Quality
Acute Achilles Tendon Rupture: PRP + CC vs. CC						
Function success, Pain success, Pain	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT
Function (Leppilahti score)	Short-, intermediate-term	0 studies			No evidence.	⊕○○○ INSUFFICIENT
	Long-term	1 retro. cohort study (Kaniki)	N= 100	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕○○○ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

Key Question 1 Strength of Evidence Summary: Ankle Sprain Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Ankle Sprain: PRP vs. placebo (saline)						
Function success, Pain success	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT
Function (LEFS (0-80 (best))	Short-term	1 RCT (Rowden 2015)	N= 33	RoB[1] (-1), Imprecision[3,4] (-2)	MD 3.9 (95% CI -4.4, 12.2) Conclusion: Insufficient strength of evidence prevents firm conclusions. (NOTE: Due to baseline imbalances, ΔLEFS was calculated and favored the PRP group (MD 9.6 (95% CI 4.5, 14.7))	⊕○○○ INSUFFICIENT
	Intermediate-, long-term	0 studies			No evidence.	⊕○○○ INSUFFICIENT
Pain (VAS (0-10 (worst))	Short-term	1 RCT (Rowden 2015)	N= 33	RoB[1] (-1), Imprecision[3,4] (-2)	MD -0.5 (95% CI -2.0, 1.0) Conclusion: Insufficient strength of evidence prevents firm conclusions. (NOTE: Due to baseline imbalances, ΔVAS was calculated and favored the PRP group (MD -1.6 (95% CI -2.6 to -0.6))	⊕○○○ INSUFFICIENT
	Intermediate-, long-term	0 studies			No evidence.	⊕○○○ INSUFFICIENT

CI: confidence interval; LEF: Lower Extremity Function Scale; MD: mean difference; PRP: platelet-rich plasma; RCT: randomized controlled trial; VAS: visual analog scale.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

Key Question 1 Strength of Evidence Summary: Osteochondral Lesions of the Talus Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Osteochondral lesions of the talus: PRP vs. HA						
Function success, Pain success	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT
Function (various)	Short-term	1 quasi-RCT (Mei-Dan 2012)	N= 29	RoB[1,4] (-2), Imprecision[3,5] (-2)	Conclusion: Insufficient strength of evidence precludes firm conclusions: • ΔVAS function (0-10 (worst)): MD -1.3 (95% CI -2.4, -0.2) (NOTE: Due to baseline imbalances, follow-up scores were also assessed and provided similar results (MD -2.4 (95% CI -3.9, -0.9)) • Subjective global function/disability (0-100 (best)): MD 19.0 (95% CI 6.5, 31.5) • AOFAS modified Ankle and Hindfoot Scale (0-100 (best)): MD 8.5 (95% CI -0.3, 17.0) (p=0.05)	⊕○○○ INSUFFICIENT
	Intermediate-term	1 quasi-RCT (Mei-Dan 2012)	N= 29	RoB[1,4] (-2), Imprecision[3,5] (-2)	Conclusion: Insufficient strength of evidence precludes firm conclusions: • ΔVAS function (0-10 (worst)): MD -1.6 (95% CI -2.7, -0.5) (NOTE: Due to baseline imbalances, follow-up scores were also assessed and provided similar results (MD -2.7 (95% CI -4.3, -1.1)) • Subjective global function/disability (0-100 (best)): MD 18.0 (95% CI 5.8, 30.2) • AOFAS modified Ankle and Hindfoot Scale (0-100 (best)): MD 14.2 (95% CI 5.4, 23.0)	⊕○○○ INSUFFICIENT
	Long-term	0 studies			No evidence.	⊕○○○ INSUFFICIENT
Pain (VAS (0-10 (worst))	Short-term	1 quasi-RCT (Mei-Dan 2012)	N= 29	RoB[1,4] (-2), Imprecision[3,5] (-2)	MD -2.1 (95% CI -3.4, -0.8) Conclusion: Insufficient strength of evidence prevents firm conclusions: (NOTE: Due to baseline imbalances, ΔVAS was also calculated and no difference was seen between groups (MD -0.6 (95% CI -1.6, 0.4)).	⊕○○○ INSUFFICIENT
	Intermediate-	1 quasi-	N=	RoB[1,4] (-2),	MD -2.2 (95% CI -3.6, -0.8)	⊕○○○

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
	term	RCT (Mei-Dan 2012)	29	Imprecision[3,5] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions: (NOTE: Due to baseline imbalances, ΔVAS was also calculated and no difference was seen between groups (MD -0.7 (95% CI -1.7, 0.3)).	INSUFFICIENT
	Long-term	0 studies			No evidence.	⊕◯◯◯ INSUFFICIENT

AOFAS: American Orthopaedic Foot and Ankle Society; CI: confidence interval; HA: Hyaluronic Acid; MD: mean difference; PRP: platelet-rich plasma; RCT: randomized controlled trial; VAS: visual analog scale.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Risk of bias downgraded an additional level (so -2) due to quasi-randomized nature of the majority of studies (patients "randomized" by alternate allocation)
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 1 Strength of Evidence Summary: Temporomandibular Joint Dislocation Efficacy Results

Outcome	Follow-up	RCT	N	Reasons for Downgrading	Conclusion	Quality
Temporomandibular Joint Dislocation: ABI vs. IMF						
Pain or function success, Pain or function scores	Any	0 studies			No evidence.	⊕◯◯◯ INSUFFICIENT
Recurrence of dislocation	Short-, intermediate-term	0 studies			No evidence.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Hegab)	N= 32	RoB[1] (-1), Imprecision[3,4] (-2)	RR 2.7 (95% CI 0.9, 8.3); ABI 50% vs. HA 19% Conclusion: Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT

ABI: autologous blood injection; IMF: intermaxillary fixation; RCT: randomized controlled trial; RR: relative risk.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 1 Strength of Evidence Summary: Knee Osteoarthritis Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Knee OA: PRP vs. HA						
Function Success (various measures)	Short-term	0 RCTs			No evidence	⊕◯◯◯ INSUFFICIENT
	Intermediate –term	2 RCTs (Vaquerizo, Sanchez 2012)	N = 272	Inconsistency[2] (-1), Imprecision[4] (-1)	Conclusion: It is unclear whether functional success is more common following PRP vs. HA. OMERACT-OSARSI responders*: The proportion of responders was statistically similar between groups based on pooled analysis, however: • One trial reported no difference between groups (RR 1.07 (95% CI 0.80, 1.43)) (Sanchez 2012) • The other trial reported significantly more responders with PRP (RR 3.08 (95% CI 1.90, 4.98)) (Vaquerizo); The same trial reporting significantly more responders also reported that more PRP than HA patients achieved functional success for the following (Vaquerizo): WOMAC Physical Function • ≥30% decrease: RR 4.1 (95% CI 2.0, 7.6) 60% vs. 17% • ≥50% decrease: RR 3.8 (95% CI 1.5, 9.3) 40% vs. 11% WOMAC Stiffness • ≥ 30% decrease: RR 2.2 (95% CI 1.2, 3.9), 52% vs. 27% • ≥ 50% decrease: RR 2.3 (95% CI 1.0, 5.1), 35% vs. 16% Lequesne Index • ≥ 30% decrease: RR 5.0 (95% CI 2.5, 10.1), 73% vs. 17% • ≥ 50% decrease: RR 7.0 (95% CI 1.7, 29.2), 29% vs. 4%,	⊕⊕◯◯ LOW
	Long-term	1 RCT (Vaquerizo)	N = 96	Imprecision[4,5] (-2)	Conclusion: Significantly more PRP than HA patients achieved 30% and 50% or more decrease in the following measures, however wide CIs suggest estimate instability:	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					WOMAC Physical Function • ≥30% decrease: RR 3.7 (95% CI 1.8, 7.7), 54% vs. 17% • ≥50% decrease: RR (NC) 31% vs. 0%, p<0.01 WOMAC Stiffness • ≥ 30% decrease: RR 4.8 (95% CI 2.0, 11.5), 52% vs. 12% • ≥ 50% decrease: RR 8.0 (95% CI 1.9, 32.9), 33% vs. 5% Lequesne Index • ≥ 30% decrease: RR 23.0 (3.2, 163.6), 48% vs. 2% • ≥ 50% decrease: RR 9.0 (1.2, 68.3), 19% vs. 2%	
Function (various)	Short-term	4 RCTs (Sanchez 2012, Vaquerizo, Cerza, Filardo)	N= 575	RoB[1] (-1)	Conclusion: No difference between groups based on the following: • Lequesne Index: MD -0.20 (95% CI -1.0, 0.60); 2 RCTs (N=272) (Sanchez 2012, Vaquerizo). • WOMAC, IKDC: SMD 0.57 (95% CI 0.60, 1.75), 2 RCTs (N=303) (Cerza, Filardo). • KOOS subscales or Tegner scores : no difference between groups in 1 trial (Filardo)	⊕⊕⊕◯ MODERATE
	Intermediate-term	5 RCTs (Cerza, Vaquerizo, Sanchez 2012, Filardo, Gormeli)	N= 747	RoB[1] (-1)	SMD 0.84 (95% CI 0.19 ,1.48) Conclusion: Significantly better function with PRP versus HA, based on WOMAC total and IKDC scores. Note that High statistical heterogeneity (I^2=94%), may in part be due to differences in the magnitude of effect estimates, failure of two trials (Sanchez, Vaquerizo) to reach statistical significance and limitations of the random effects model.	⊕⊕⊕◯ MODERATE
	Long-term	3 RCTS (Vaquerizo, Raeissadat 2015, Filardo)	N= 412	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Function may be improved following PRP as evaluated by: • WOMAC total and IKDC scores: SMD 0.66 (95% CI 0.01, 1.31), p = 0.05, 3 RCTs (N= 412) (Vaquerizo, Raeissadat, Filardo) • WOMAC Stiffness: SMD 0.90 (95 % CI 0.32, 1.49), 2 RCTs (N=229) (Vaquerizo, Raeissadat) • WOMAC Physical Function: SMD 0.93 (95% CI 0.19, 1.67), 2 RCTs (N=229) (Vaquerizo, Raeissadat)	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					However, One trial included in the pooled analysis reported no difference for any KOOS subscale or the Tegner Score. (Filardo)	
Pain Success (≥50% or ≥20% decrease in WOMAC pain score)	Short-, long-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	2 RCTs (Sanchez 2012, Filardo)	N = 272	Imprecision[4] (-1)	Conclusion: Significantly greater improvement with PRP vs. HA based on >50% decrease in WOMAC pain score: • Both trials reported significantly greater improvement with PRP: (RR 5.2 (95% CI 2.18, 12.41) in one trial (Vaquerizo) but results were marginally significant in the other (RR 1.58 (95% CI 1.0, 2.5) (Sanchez 2012). However, in one of these trials, there was no difference between treatments for ≥20% decrease in WOMAC pain score, RR 1.08 (95% CI 0.8, 1.4) (Sanchez 2012).	⊕⊕⊕◯ MODERATE
Pain Success (≥30% or ≥50% decrease in WOMAC pain score)	Short-, intermediate-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Vaquerizo)	N = 96	Imprecision[4,5] (-2)	Conclusion: Significantly more PRP than HA patients achieved pain success: • ≥30% decrease: RR 4.9 (95% CI 2.1, 11.5) • ≥50% decrease: RR 13.3 (95% CI 1.81, 95)	⊕⊕◯◯ LOW
Pain (various)	Short-term	1 RCTs (Filardo)	N= 192	RoB[1] (-1), Imprecision[3] (-1)	MD -0.1, 95% CI -5.63, 5.43 Conclusion: No difference between treatments in pain based on the KOOS Pain subscale.	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
	Intermediate-term	3 RCTs (Vaquerizo, Sanchez 2012, Filardo)	N= 455	Inconsistency[2] (-1)	SMD -0.45, 95% CI -1.14, 0.24 Conclusion: No difference between groups based on pooled WOMAC and KOOS pain subscales. Inconsistency and wide confidence intervals both likely stem from the smallest trial showing a significantly better results in the PRP group (Vaquerizo) while the other two trials s showed no difference between groups (Sanchez, Filardo).	⊕⊕⊕◯ MODERATE
	Long-term	3 RCTs (Vaquerizo, Raeissadat 2015, Filardo)	N= 412	RoB[1] (-1), Inconsistency[2] (-1)	SMD -0.49 (95% CI -1.16, 0.18) Conclusion: No difference between groups based on pooled WOMAC and KOOS pain subscales. Inconsistency and wide confidence intervals both likely stem from the smallest trial showing a significantly better results in the PRP group (Vaquerizo) while the other two trials showed no difference between groups (Raeissadat, Filardo).	⊕⊕◯◯ LOW
Knee OA: LR-PRP vs. Corticosteroid						
Function Success, Pain success	Any	0 RCTs			No evidence	⊕◯◯◯ INSUFFICIENT
Function (KOOS Symptoms, ADL, Sporting Subscales)	Short-term	1 RCT (Forogh)	N= 41	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions: • KOOS Symptoms: MD 14.7 (95% CI 3.4, 25.9) • KOOS ADL: MD 20.3 (95% CI 9.5, 31.1) • KOOS Sporting ability: MD 2.7 (95% CI -3.1, 8.5)	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Forogh)	N= 41	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions: • KOOS Symptoms: MD 19.8 (95% CI 11.8, 27.8) • KOOS ADL: MD 12.0 (95% CI 0.93, 23.1) • KOOS Sporting ability: MD -0.3 (95% CI -3.6, 5.7)	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
Pain (KOOS pain and VAS Pain Intensity)	Short-term	1 RCT (Forogh)	N= 41	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. • KOOS Pain relief: MD 13.5 (95% CI 3.2, 23.8)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					• VAS: MD -20.2 (95% CI -34.5, -5.8)	
	Intermediate-term	1 RCT (Forogh)	N= 41	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. • KOOS Pain relief: MD 23.6 (95% CI 13.5, 33.7) • VAS : MD -27.9 (95% CI -38.4, -17.4)	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTs			No evidence.	⊕◯◯◯ INSUFFICIENT
Knee OA: PRP vs. Saline						
Function Success, Pain Success	Any	0 RCTs			No evidence	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	1 RCT (Patel)	N= 78	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: PRP resulted in significantly improved function versus saline based on percent change from baseline in • WOMAC total score (-57% versus 12%), • WOMAC stiffness score (-47% versus 2.0%) • WOMAC physical function score (-56% versus 11%)	⊕⊕◯◯ LOW
	Intermediate-term	2 RCTs (Patel 2013, Gormeli 2015)	N= 204	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: PRP resulted in improved function based on evaluation of : Percent change from baseline in the following: • WOMAC total score: -47% versus 20%, p<0.05 (Patel) • WOMAC stiffness score: -47% versus 10%, p<0.05 (Patel) • WOMAC physical function score 46% versus 20%, p<0.05 (Patel) IKDC: MD 19.0 (95% CI 16.2, 21.8) (Gormeli)	⊕⊕◯◯ LOW
	Long-term	0 RCTS			No evidence	⊕◯◯◯ INSUFFICIENT
Pain	Short-term	1 RCT (Patel 2013)	N= 78	RoB[1] (-1), Imprecision[3] (-1)	Mean percent changes from baseline were -63% vs. 18% (p <0.05) Conclusion: LP-PRP resulted in significantly improved pain.	⊕⊕◯◯ LOW
	Intermediate-term	1 RCT (Patel 2013)	N= 78	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: LP-PRP resulted in significantly improved pain compared with saline based on:	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					• WOMAC pain (% change): -50% vs. 25%, p <0.05 • VAS (0-10): MD -2.3 (95% CI -2.7, -1.8)	
	Long-term	0 RCTS			No evidence	⊕◯◯◯ INSUFFICIENT
Knee OA: PRP vs. Exercise (conservative care) or Exercise with TENS						
Function Success, Pain Success	Any	0 RCTs			No evidence	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	1 RCT (Angoorani)	N= 54	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions: • KOOS Symptoms: MD 8.3 (95% CI -0.42, 17.90) • KOOS ADL: MD 4.3 (95% CI -6.91, 15.48) • KOOS Sports: MD 0.5 (95% CI -12.73, 13.68)	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Rayegani)	N= 62	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions: • WOMAC Total Score: MD -0.5 (95% CI -9.73, 8.73) • ΔWOMAC Stiffness: MD 0.0 (95% CI -0.7, 0.7) • ΔWOMAC Physical: MD 0.2 (95% CI -5.7, 5.9)	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTS			No evidence	⊕◯◯◯ INSUFFICIENT
Pain (various measures)	Short-term	1 RCT (Angoorani)	N= 54	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions: • KOOS Pain: Adjusted MD 2.9 (-7.7, 13.50) • VAS Pain Scores: 47 versus 53, p = 0.900	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Rayegani)	N= 62	RoB[1] (-1), Imprecision[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions: • ΔWOMAC Pain: MD -0.9 (95% CI -2.9, 0.9)	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTS			No evidence	⊕◯◯◯ INSUFFICIENT

* OMERACT-OSARSI responders are those who experienced a high improvement in pain or function ≥50% and absolute change ≥20; OR had improvement in 2 of the following: 1) Pain ≥20% and absolute change in ≥10; 2) Function ≥20% and absolute change in ≥10; 3) Patient's global assessment ≥20% and absolute change in ≥10.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
5. Imprecision downgraded an additional level (so -2) because the confidence intervals were extremely wide, bringing into question the stability of the estimate
6. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 1 Strength of Evidence Summary: Hip and TMJ Osteoarthritis Efficacy Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Hip Osteoarthritis : PRP vs. HA						
Function Success, Pain Success	Any	0 RCTS			No evidence	⊕○○○ INSUFFICIENT
Function (Harris Hip Score (0-100 (best))	Short-term	1 RCT (Battaglia)	N = 104	RoB[1] (-1), Imprecision[3] (-1)	MD -4.3 (95% CI -10.6, 1.99) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Intermediate-term	1 RCT (Battaglia)	N = 104	RoB[1] (-1), Imprecision[3] (-1)	MD -5.5 (95% CI -12.0, 0.92) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Long-term	1 RCT (Battaglia)	N = 104	RoB[1] (-1), Imprecision[3] (-1)	MD -6.8 (95% CI -14.1, 0.51) Conclusion: No difference between groups.	⊕⊕○○ LOW
Pain VAS (0-10 (worst))	Short-term	1 RCT (Battaglia)	N = 104	RoB[1] (-1), Imprecision[3] (-1)	MD 0.0 (95% CI -0.84, 0.84) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Intermediate-term	1 RCT (Battaglia)	N = 104	RoB[1] (-1), Imprecision[3] (-1)	MD 0.25 (95% CI -0.59, 1.09) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Long-term	1 RCT (Battaglia)	N = 104	RoB[1] (-1), Imprecision[3] (-1)	MD 0.16 (95% CI -0.78, 1.1) Conclusion: No difference between groups.	⊕⊕○○ LOW
TMJ Osteoarthritis: PRP vs. HA						
Function Success, Pain Success	Any	0 RCTS			No evidence	⊕○○○ INSUFFICIENT
Function Maximum voluntary	Short-term	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: Insufficient strength of evidence precludes firm conclusions (no data reported for control group).	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
mouth opening (MVMO)						
	Intermediate-term	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,4] (-2)	Median 39 vs. 40 mm Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,4] (-2)	MD 2.8 mm (95% CI 0.82 mm, 3.7 mm) Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain	Short-term	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: Insufficient strength of evidence precludes firm conclusions (inadequate data were provided to generate conclusions).	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: Insufficient strength of evidence precludes firm conclusions (inadequate data were provided to generate conclusions).	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,4] (-2)	VAS pain score: PRP 0.4 vs. HA 1.6, MD -1.24 (95% CI -1.83, -0.64) Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 2 Strength of Evidence Summary: Tendinopathy Harms and Complications Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Elbow Tendinopathy: PRP vs. ABI						
Serious adverse events	Any	1 RCT (Thanasas)	N= 28	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: No serious adverse events were reported to occur; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 RCT (Thanasas)	N= 28	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: Injection-site pain was reported for PRP vs. ABI (64% vs. 29%, RR 2.25 (95% CI 0.90, 5.6)); no other adverse events were reported. Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Elbow, Rotator Cuff, Achilles, or Patellar Tendinopathy: PRP vs. Conservative Control*						
Serious adverse events	Any	13 RCTs (Behera, de Jonge/de Vos, Dragoo, Gosens/Peerbooms, Kearney, Kesikburun, Krogh, Mishra, Rha, Stenhouse, Vetrano, von Wehren, Yadav) 3 cohort studies (Ford, Tetschke, Tonk)	N= 913	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	13 RCTs (Behera, de Jonge/de Vos, Dragoo, Gosens/Peerbooms, Kearney, Kesikburun, Krogh, Mishra, Rha, Stenhouse, Vetrano, von Wehren, Yadav) 3 cohort studies (Ford, Tetschke, Tonk)	N= 913	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Non-serious adverse events occurred relatively infrequently and similarly between treatment groups. More commonly reported events included: • Post-injection pain may be more common following PRP injection (2-13% patients in 3 RCTs) versus anesthetic injection (0% patients in 1 RCT). One trial reported significantly worse post-injection pain with PRP versus steroid when rated on a NRS pain scale (0-10 (worst)) (9.0 vs. 6.0, MD 3.0 (95% CI 1.5, 4.5)) (Krogh). • Adverse events (type not specified): while one trial reported than any such event occurred similarly between PRP and anesthetic injection groups (19% vs. 18%) (Krogh), 7 RCTs (Rha, Dragoo, Kearney, de Jonge/de Vos, Yadav, Behera, Stenhouse) and all three cohort studies (Ford, Tetschke, Tonk) reported that no complications or	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
					adverse events occurred.	
Elbow or Achilles Tendinopathy: ABI vs. Conservative Control†						
Serious adverse events	Any	6 RCTs (Arik, Bell, Dojode, Kazemi, Ozturan, Pearson)	N= 346	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	6 RCTs (Arik, Bell, Dojode, Kazemi, Ozturan, Pearson)	N= 346	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Non-serious adverse events occurred relatively infrequently and similarly between treatment groups. More commonly reported events included: • Post-injection pain may be more common following PRP vs. steroid injection (25-60% vs. 0-26%) as reported by 2 RCTs (Arik, Dojode). However, another trial reported 100% of ABI, steroid, and ESWT patients experienced such pain (Ozturan). Another reported post-injection pain occurred in 21% of ABI patients (and no exercise control patients) (Pearson). • One trial reported slightly fewer cases of local erythema, swelling, or nausea with PRP versus ESWT (0% vs. 16-21%) (Ozturan) (p=NS due to small sample size).	⊕⊕◯◯ LOW

*Control groups included dry needling (Rha, Dragoo, Stenhouse), saline injection (Kesikburun, de Jonge/de Vos), exercise (Kearney), steroid injection (Krogh, Gosens/Peerbooms, von Wehren, Yadav), anesthetic injection (Mishra, Behera), and extracorporeal shock wave therapy (ESWT) (Vetrano).

†Control groups included steroid injection (Kazemi, Arik, Dojode, Ozturan), extracorporeal shock wave therapy (ESWT) (Ozturan), exercise (Pearson), and dry needling (Bell).

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 2 Strength of Evidence Summary: Plantar Fasciitis Harms and Complications Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
PRP vs. Conservative Control*						
Serious adverse events	Any	4 RCTs (Chew, Jain, Kim, Tiwari) 2 cohort studies (Aksahin, Say)	N= 241 pts. & 60 heels	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	4 RCTs (Chew, Jain, Kim, Tiwari) 2 cohort studies (Aksahin, Say)	N= 241 pts. & 60 heels	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No non-serious adverse events were reported to occur, including soft tissue injection, osteomyelitis, loss of function, stiffness.	⊕⊕◯◯ LOW
ABI vs. Conservative Control†						
Serious adverse events	Any	2 RCTs (Kalaci, Lee)	N= 135	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	2 RCTs (Kalaci, Lee)	N= 135	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Post-injection pain was more common following ABI versus steroid injection (53% vs. 13%, RR 4.1 (95% CI 1.5, 11) (1 RCT) (Lee). Otherwise, no adverse events were reported to occur, including infection, plantar fascia rupture, fat pad atrophy, skin hypopigmentation, or hematoma.	⊕⊕◯◯ LOW

*Control groups included steroid injection (Jain, Tiwari, Aksahin, Say), conservative care (Chew), extracorporeal shock wave therapy (ESWT) (Chew), and prolotherapy (Kim)

†Control groups included steroid injection (Kalaci, Lee) and anesthetic injection plus dry needling (Kalaci).

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI

Key Question 2 Strength of Evidence Summary: Acute Injuries Harms and Complications Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Acute muscle injuries: PRP vs. Conservative Control*						
Serious adverse events	Any	3 RCTs (Hamid, Hamilton, Reurink)	N= 157	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	2 RCTs (Reurink, Hamid)	N= 102	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Painful dermal hyper aesthesia was reported in one PRP patient (3%) over 12 months in one trial. Pain during blood draw and PRP injection was reported by "most patients" in the other trial. No other adverse events were reported.	⊕⊕◯◯ LOW
Acute Achilles tendon rupture: PRP vs. Conservative Control*						
Serious adverse events	Any	1 cohort study (Kaniki)	N=145	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Insufficient strength of evidence precludes any firm conclusions. The incidence of repeat tendon rupture within 3 months was similar between the PRP and exercise groups: 3% vs. 4%, OR 0.65 (95% CI 0.1, 4.0). No other serious adverse events (i.e. superficial or deep infection, venous thrombosis, pulmonary embolus, numbness) were reported.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 cohort study (Kaniki)	N=145	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No non-serious adverse events were reported to occur; insufficient strength of evidence precludes any firm conclusions.	⊕◯◯◯ INSUFFICIENT

*All control groups included standardized physical therapy programs, either alone (Hamilton, Reurink); with acetaminophen 1000 mg as needed, max. 4 x daily (Hamid); or with removable below the knee arthrosis and 2 weeks non-weight-bearing prior to commencement of exercises (Kaniki).

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI

Key Question 2 Strength of Evidence Summary: Osteochondral Lesions of the Talus Harms and Complications Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Osteochondral Lesions of the Talus: PRP vs. HA						
Serious adverse events	Any	1 quasi-RCT (Mei-Dan 2012)	N= 29	RoB[1,4] (-2), Imprecision[3,5] (-2)	Conclusion: No serious adverse events were reported to have occurred; insufficient evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 quasi-RCT (Mei-Dan 2012)	N= 29	RoB[1,4] (-2), Imprecision[3,5] (-2)	Conclusion: Insufficient evidence prevents firm conclusions. However, no infections occurred in either group. Acute mild pain following injection and new symptoms of mild plantar fasciitis (timing not reported) and Achilles tendinopathy (through 7 months) were reported in 7%, 29% and 7% of PRP patients, respectively, compared with no patients in the HA group (p=0.03 between groups for new plantar fasciitis symptoms).	⊕◯◯◯ INSUFFICIENT

HA: hyaluronic acid; PRP: platelet-rich plasma.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Risk of bias downgraded an additional level (so -2) due to quasi-randomized nature of the majority of studies (patients "randomized" by alternate allocation)
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 2 Strength of Evidence Summary: Temporomandibular Joint Dislocation Harms and Complications Results

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
TMJ Dislocation: ABI vs. IMF						
Serious adverse events	Any	1 RCT (Hegab)	N=32	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. However, no serious adverse events were reported to occur following ABI; no information was provided for the IMF group.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 RCT (Hegab)	N=32	RoB[1] (-1), Imprecision[3,4] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. However, in the IMF group, patients complained of weight loss due to restricted diet and those who received eyelet wiring (vs. orthodontic braces) developed marginal gingivitis; no information on non-serious adverse events was provided for the ABI group.	⊕◯◯◯ INSUFFICIENT

ABI: autologous blood injection; IMF: intermaxillary fixation; TMJ: temporomandibular joint.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 2 Strength of Evidence Summary: Osteoarthritis Treatment-Related Harms and Complications Results

Outcome	Follow-up	Studies	N	Reasons for Downgrading	Conclusion	Quality
Knee Osteoarthritis: PRP vs. HA						
Serious adverse events	Any	4 RCTS (Filardo, Sanchez 2012, Vaquerizo, Cerza) 3 Cohort Studies (Say, Spakova, Kon)	N=944	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious treatment-related adverse events were reported to have occurred.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	2 RCTs (Filardo, Vaquerizo)	N= 288	Inconsistency[2] (-1), Imprecision[3] (-1)	Conclusion: Non-serious treatment-related events appear to be similar for PRP and HA, but data are limited. Injection-site pain and/or swelling were the most commonly reported and may be similar between treatments. • Post-injective pain reaction was similar between treatments, 16.6% vs. 14.2%, RR 1.2 (95% CI 0.4 to 3.1) (Vaquerizo) • Severe pain, swelling leading to withdrawal occurred only in the HA group; 0% vs. 2.1% (Filardo) Conclusions regarding pain and swelling intensity are not possible; no statistical evaluation was performed. • Pain (VAS 0-100) x duration; Median 9 (0 to 20) vs. 1 (0 to 7) (Filardo) • Swelling (VAS 0-100) x duration; Median 6 (0 to 16) vs. 1 (0 to 4) (Filardo) Pseudoseptic reaction, reported in one trial may be similar for both treatments PRP (0%) vs. HA (4.7%) (Filardo)	⊕⊕◯◯ LOW
Knee Osteoarthritis: PRP vs. Saline						
Serious adverse events	Intermediate-term	1 RCT (Patel)	N =78	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious treatment-related adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Intermediate-term	1 RCT (Patel)	N =78	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: Non-serious events were fairly common following PRP; systemic events were significantly more common following PRP: • Systemic effects (syncope,	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	N	Reasons for Downgrading	Conclusion	Quality
					headache, nausea, gastritis, sweating, tachycardia) occurred more frequently following PRP; PRP 32.6% vs. Saline 0% (RR not calculable); p<0.01 • Post-injection pain or stiffness lasting ≥2 days were only reported for the PRP group (13.5%); no comparative safety conclusions are possible.	
Knee Osteoarthritis: PRP vs. Exercise + TENS						
Serious adverse events	Short-term	1 RCT (Angoorani)	N= 54	RoB[1] (-1), Imprecision[3,5] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. However, no serious treatment-related adverse events were reported to occur.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Short-term	1 RCT (Angoorani)	N= 54	RoB[1] (-1), Imprecision[3,5] (-2)	Conclusion: Mild pain and swelling following PRP vs. exercise + TENS: 11% vs. 4% (RR 3.0 (95% CI 0.3, 27.1)). Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Hip Osteoarthritis: PRP vs. HA						
Serious adverse events	Any	1 RCT (Battaglia)	N= 100	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No serious treatment-related adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	1 RCT (Battaglia)	N= 100	RoB[1] (-1), Imprecision[3] (-1)	Conclusion: No difference between treatment groups was observed for moderate pain during or after treatment (20% vs. 12%, RR 1.6 (95% CI 0.65, 4.23).	⊕⊕◯◯ LOW
TMJ Osteoarthritis: PRP vs. HA						
Serious adverse events	Any	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,5] (-2)	Conclusion: No serious treatment-related adverse events were reported to occur, however, insufficient strength of evidence precludes drawing firm conclusions.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 RCT (Hegab)	N = 50	RoB[1] (-1), Imprecision[3,5] (-2)	Conclusion: Insufficient strength of evidence precludes drawing firm conclusions; however non-serious adverse events appear to be more common following PRP versus HA • More PRP vs. HA patients had pain during injection, RR 1.46 (95% CI 1.03, 2.08) • More PRP vs. HA patients had pain post-intervention, RR 2.37 (95% CI 1.28, 4.38)	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

Key Question 3 Strength of Evidence Summary: Knee Osteoarthritis Differential Effectiveness

Outcome	Follow-up	RCTs	N	Reasons for Downgrading	Conclusion	Quality
Knee OA : PRP vs. HA						
Differential Efficacy or Safety	Intermediate-term	1 RCT (Gormeli)	N= 122	RoB[1, 2] (-2), Imprecision[3] (-1)	Conclusion: Insufficient evidence precludes firm conclusions. Patients with early OA reported better function (IKDC) and better quality of life (EQ VAS) than those with advanced OA with PRP injection. Authors do not stated if subgroup analysis was planned a priori or conducted post hoc. Outcome: IKDC (PRP vs. HA) Early OA: MD = 9/6 (95% CI 6.8, 12.4) Advanced OA: MD = 2.7 (95% CI -0.5, 5.8) Outcome: EQ-VAS (PRP vs. HA) Early OA: MD = 7.45 (95% CI 4.8, 10.1) Advanced OA: MD = 2.0 (95% CI 1.3, 5.3)	⊕◯◯◯ INSUFFICIENT
Knee OA: PRP vs. Saline						
Differential Efficacy or Safety	Intermediate-term	1 RCT (Gormeli)	N= 123	RoB[1, 2] (-2), Imprecision[3] (-1)	Conclusion: Insufficient evidence precludes firm conclusions. Patients with early OA reported better function (IKDC) and better quality of life (EQ VAS) than those with advanced OA with PRP injection. Authors do not stated if subgroup analysis was planned a priori or conducted post hoc. Outcome: IKDC (PRP vs. Saline) Early OA: MD = 23.1 (95% CI 20.4, 27.7) Advanced OA: MD = 10.8 (95% CI 7.9, 13.6) Outcome: EQ-VAS (PRP vs. Saline) Early OA: MD = 23.1 (95% CI 20.6, 25.5) Advanced OA: MD = 9.9 (95% CI 6.6, 13.2)	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Serious risk of bias in evaluation of HTE failure to specify subgroup analysis *a priori*; the subgroup hypothesis was not one of a smaller number tested no formal test for interaction was done
3. Imprecise effect estimate for a dichotomous outcome: small sample size

Key Question 4 Evidence Summary Cost Effectiveness

No evidence.

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1. Appraisal

1.1 Background and Rationale

Platelet-rich Plasma (PRP) injections and Autologous Blood Injections (ABI) are treatments utilized for a variety of healing applications in sports medicine[74] and orthopedic medicine.[110] Conditions where PRP or whole blood injections are commonly utilized include refractory acute or chronic ligament injuries, muscle strain injuries, cartilage injuries, osteoarthritis, and tendinopathies. In particular, the use of PRP and blood injections in sports medicine have seen a recent increase in public exposure, as many professional athletes have elected to receive these treatments, especially PRP, for sports-related injuries.

The rationale behind ABI and PRP injections is to increase the concentration of growth-factor rich platelets around the injured area. In general, PRP formulations usually contain platelet levels that are increased from baseline counts. Platelets contain over 30 growth factors that aid in angiogenesis, cell growth and division, and cell regeneration.[185] Both of these therapies utilize the patient's own blood to obtain the PRP or ABI samples used in the injection; as a result, there is little risk of transmissible diseases or hypersensitivity reactions.[172] Although the method of preparation can greatly vary, PRP preparation involves at least one centrifugation step to isolate a platelet-rich buffy coat layer that can then be injected or spun down again. Platelet-activating factors like 10% calcium chloride or batroxobin[170] may be added to PRP to stimulate platelets to release growth factors and increase recruitment of tissue repair factors. No additional processing occurs for whole blood injections after venipuncture. Local anesthetic can be added to PRP and ABI to reduce pain at the injection site, although it may reduce some of the cell proliferation induced by PRP. Injection is usually performed under ultrasound guidance,[38,240] and can be repeated if needed. PRP and ABI outpatient procedures. Systematic reviews have indicated low incidence of PRP and ABI-related adverse events for the treatment of musculoskeletal disorders.[130,189]

Despite the use of PRP and whole blood injections for healing applications, the efficacy and safety for PRP and whole blood injection treatments are not well established, as there is a lack of standardization for PRP and ABI preparation. Given the multitude of PRP preparation kits available on the market, the mode of preparation, the concentration of platelets and/or leukocytes, and platelet activation methods can vary greatly, making direct comparison for effectiveness studies difficult. Additionally, while the technology to obtain PRP is FDA-approved, PRP itself is currently not indicated for direct injection.[19]

Policy Context

Platelet-rich plasma (PRP) and whole blood injections are proposed for a variety of healing applications. Concerns are considered medium for safety, medium/high for efficacy and medium for cost-effectiveness.

Objectives

To systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of PRP in adults for treating musculoskeletal soft tissue

injuries, tendinopathies, osteoarthritis, or low back pain. The differential effectiveness and safety of PRP for subpopulations will be evaluated, as will the cost effectiveness.

1.2 Key Questions

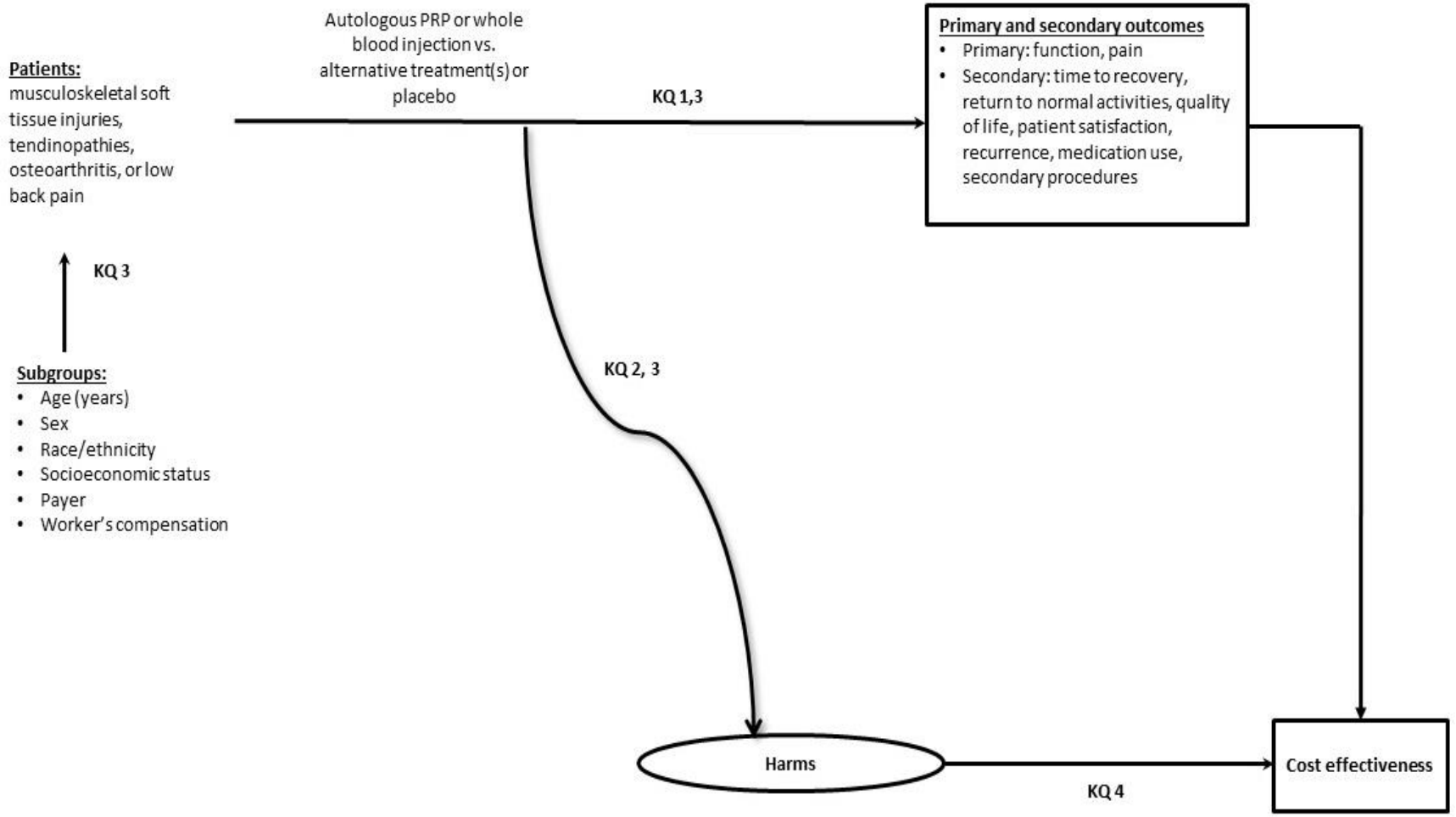
In patients with musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain (evaluated separately):

1. What is the evidence of the short- and long-term efficacy and effectiveness of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?
2. What is the evidence regarding short- and long-term harms and complications of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?
3. Is there evidence of differential efficacy, effectiveness, or safety of autologous PRP or whole blood injections compared with alternative treatment options no treatment/placebo? Include consideration of age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation?
4. What is the evidence of cost-effectiveness of autologous PRP or whole blood injections compared with alternative treatment options?

Inclusion and exclusion criteria are summarized as follows:

- **Population**: Patients with musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain.
- **Intervention:** Autologous PRP or whole blood injections (injections used in conjunction with other procedures such as surgery will be excluded)
- **Comparators:** Alternative treatment(s), placebo, or no treatment
- **Outcomes:** Function (primary), pain (primary), time to recovery, return to normal activities (sports, work, or activity level), quality of life, patient satisfaction, recurrence, medication use, secondary procedures (e.g., surgery), adverse events (primary), cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcomes
- **Study design**: Eligible studies compared autologous PRP or whole blood injections with an included comparator treatment utilizing a randomized or cohort study design. Case series specifically designed to evaluate harms/adverse events that enrolled at least 100 patients and that had follow-up of at least 70% of patients were considered for Key Question 2. Only RCTs that stratified results by patient characteristics of interest so that statistical interaction (effect modification) could be evaluated were considered for Key Question 3; subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. For Key question 4, formal economic analyses were eligible for inclusion (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies).

Figure 1. Analytic framework



1.3 Outcomes Assessed

The studies included in this assessment used a variety of measures to evaluate treatment outcomes, which are outlined in Table 1. The primary outcome measures were those which measured function and pain; these were designated primary outcomes a priori based on clinical expert input. Information on the minimal clinically important difference (MCID) was obtained for the population being evaluated whenever statistical differences were found between groups.

Table 1. Outcome measures used in included studies

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
20 meter walk test[84]†	Clinician	Patient asked to jog a straight 20 meter line. Clinician uses a chronometer to time how long the patient takes to complete test. Two trials are completed, and mean time is calculated.	0 to variable maximum	The lower the mean time, the greater the walking ability.	For knee OA: NR
American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment Form [223]	Patient, clinician	Patient Self-Evaluation: Pain (7 items) Instability (1 item) Activities of daily living (10 items) Clinician Assessment: Strength (4 items) Instability (8 items) Range of motion (5 items) Tenderness, crepitus, impingement (11 items)	Items that are scored on a 0 to variable maximum 3 or 10 point scale and normalized to 100; total score ranges from 0 to 100	The lower the score, the greater pain and disability.	For Rotator cuff tear: 6.4[182] 12-17 (depending on 15-item function, 15 item pain, or 4 item improvement questionnaires; which are 12.01, 16.92, and 16.72 respectively)[269] 7[283]
Ankle-Hindfoot Scale of the American Orthopaedic Foot and Ankle Society (AOFAS)[139]	Clinician	3 subscales (9 items): Pain (40 points) Function (50 points) Alignment (10 points)	0 to 100 (total score)	The lower the score, the greater the disability. Score 100-91: excellent Score 90-81: good Score 80-71: fair Score <70: poor	For osteochondral lesions: NR[135] (source says MCID calculated, but value was NR) For unspecified ankle etiology:

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
					8.90[58,60]
Blazina Scale [30]	Patient	4 phases/stages: Phase 1: pain after activity only Phase 2: pain/discomfort during and after activity does not interfere with participation Phase 3: Pain during and after activity interferes with competition Phase 4: complete tendon disruption	Phase 1 to phase 4	The higher the phase, the greater the disruption	
Brief Pain Inventory-Short From (BPI-SF)[46]	Patient	2 subscales: Pain severity (4 items) Pain interference (7 items)	No scoring algorithm	The lower the score, the greater the pain severity and interference.	For acute hamstring muscle injury: NR
Constant-Murley functional assessment of the shoulder (CMS)[49]	Clinician	4 subscales (10 items): Pain (15 points) Activities of daily living (20 points) Range of motion (40 points) Strength (25 points) Modified score: strength assessed with sling over upper arm Abbreviated score: excludes strength assessment	0 to 100 (total score)	The higher the score, the higher the function.	For Rotator cuff tears treated with arthroscopic surgery: 10.4[146] For rotator cuff (no specific pathology): NR[11]
Disabilities of the Arm, Shoulder and Hand (DASH)[111]	Patient	3 modules (one required, two optional) Module 1: ability to perform (required); 6 subscales Activities of daily living (105 points) Social activities (5 points)	Scores normalized to 100; total score ranges from 0 to 100.	The higher the score, the lower the function.	For musculoskeletal upper extremities: 10.2[247]

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		Work activities (5 points) Symptoms (25 points) Sleeping (5 points) Confidence (5 points) Module 2: ability to perform sports/performing arts (optional) (20 points) Module 3: ability to perform work (optional) (20 points)			
EuroQol 5-Dimension Questionnaire (EQ5D)[75]	Patient	5 dimensions of health: Mobility Self-care Usual activities Pain/discomfort Anxiety depression Each dimension is rated on a scale from 1 (no problems) to 3 (extreme problems)	A 5-digit number is produced to represent level of problems in each dimension.	The higher the digit for each dimension, the greater the problems.	
EuroQol Visual Analog Scale (EQ-VAS)[280]	Patient	One item, asks the individual to select a number from a scale indicating their health state of the day.	0 to 100 (total score)	The higher the score, the lower the health impairment.	For Knee OA: MCID: NR[162]
Foot and Ankle Disability Index (FADI)[171]	Patient	2 subscales (26 items): Pain subscale Activity subscale	0 to 4 (items score) 0 to 100 (total score)	The higher the score, the greater the function.	
Foot Function Index (FFI)[36]	Patient	3 subscales (23 items): Foot pain Disability Activity limitation	0 to 10 (item score) 0 to 100 (subscale score) 0 to 230 (total score)	The higher the score, the greater the disability/functional impairment.	For plantar fasciitis: Total: 6.5 Pain: 12.3 Disability: 6.7 Activity limitation: 0.5 [148]
Hamstring Outcome Score (HaOS)[73]	Patient	5 subscales: Symptoms (1 item) Soreness (4 items)	0 to 100 (total score)	The higher the score, the better the hamstring function.	

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		Pain (8 items) Function, daily living and sports (4 items) Quality of life (2 items)			
Harris Hip Score (HHS)[103]	Clinician	4 subscales (16 items): Pain (44 points) Function (47 points) Deformity (4 points) Range of motion (5 points) Items scored on a 0 to variable maximum 1 to 44 point score	0 to 100 (total score)	The higher the score, the better the hip function. Score 100-90: excellent Score 89-80: good Score 79-70: fair Score <70: poor	
International Knee Documentation Committee (IKDC) Subjective Knee Form[113]	Patient	3 subscales (45 items): Symptoms Sports activities Function	Scores summed and normalized to 100; total score ranges from 0 to 100.	The higher the score, the greater the knee function.	For Knee OA: NR
Knee Injury and Osteoarthritis Outcome Score (KOOS)[233]	Patient	5 subscales (42 items): Pain Symptoms Activities of daily living Sports and recreation Quality of life	Scores normalized to 100 for each subscale and each subscale scored separately	The higher the score, the greater the knee function.	For Knee OA: KOOS, KOOS PS, KOOS ADL: NR[48] KOOS PS: 2.2 KOOS QOL: 8.0 [255]
Leppilahti Achilles Tendon Rupture Score[155]	Clinician	7 subscales (7 items): Pain Stiffness Subjective calf weakness Footwear restrictions Range of motion Subjective assessment Isokinetic muscle strength	0 to variable maximum 10 or 15 (item score)	The higher the score, the greater the Achilles tendon function. Excellent: 90 to 100 Good: 75 to 85 Fair: 60 to 70 Poor: <55	
Lequesne Index[156]	Patient	3 subscales (11 items): Pain	0 to variable maximum (item score)	The higher the score, the greater the impairment.	For knee OA: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		Walking distance Activities of daily living Two indices available: hip and knee. Both scored the same, have identical subscales, etc. The 1997 update made minor changes to morning stiffness items and added "algofunctional index" to the name.	0 to 24 (total score)	Extremely severe: >14 Very severe: 11 to 13 Severe: 8 to 10 Moderate: 5 to 7 Minor: 1 to 4 No severity: 0	
Liverpool Elbow Score[244]	Clinician, patient	Clinician assessment: 3 subscales (6 items) Strength Range of motion Ulna nerve involvement Patient assessment: 2 subscales (9 items) Pain Activities of daily living	0 to 100 (total score)	All responses are transformed to a scale of 0-10 and equally weighted for summation by averaging	For elbow epicondylitis: NR
Lower Extremity Functional Scale (LEFS)[26]	Patient	Functional activities (20 questions)	0 to 80 (total score)	The lower the score, the greater the disability.	For musculoskeletal injury: 9 (patient assessed) scale points (Binkley 1999)
Lysholm Knee Function Scoring Scale[164]	Patient	8 subscales (8 items): Instability (25 points) Pain (25 points) Catching, locking (15 points) Swelling (10 points) Stair climb (10 points) Squat (5 points) Limp (5 points) Support (5 points)	0 to 100 (total score)	The lower the score, the greater the disability. Score 100-95: excellent Score 94-84: good Score 83- 65: fair Score <65: poor	For general knee problems: Traumatic: 20.5 Non-traumatic: 13.0 Combined: 18.0 (Heintjes 2003)
Mayo Clinic Performance	Clinician	4 subscales (8 items):	0 to 100 (total score)	The lower the score, the greater the	For elbow epicondylitis: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
Index for the Elbow (MCPIE)[190]		Pain (45 points) Range of motion (20 points) Stability (10 points) Daily function (25 points)		disability. Score 100-90: excellent Score 89-75: good Score 74-60: fair Score <60: Poor	
Mental Component Summary Score of the SF-36 (MCS-36)[292]	Patient	6 subscales (35 items): Physical functioning Role-physical Bodily pain General health Vitality Social functioning Role-emotional Mental health	0 to 100 (total score)	The lower the score, the greater the mental ailment.	
Neer Impingement Sign (using 0-100 VAS)[193]	Patient	Clinician conducts the Neer test by internally rotating the patient's arm and forcefully moving the arm through the full range of forward flexion or until reports of pain; patient then rates pain along the VAS.	0 to 100 (total score)	The higher the score, the greater the pain.	
Nirschl Staging System[195]	Clinician and patient	3 subscales: Observed histology Patient's described pain duration Patient's described pain intensity	<u>Pathologic Stages</u> Stage 1: temporary irritation Stage 2: permanent tendinosis – less than 50% tendon cross-section Stage 3: permanent tendinosis – greater than 50% tendon cross-section Stage 4: partial or total rupture <u>Phases of Pain</u> Phase 1: mild pain with exercise, resolves within 24 hours Phase 2: pain after exercise, exceeds 48	The higher the stage and/or phase, the greater the disability.	<u>For elbow epicondylitis:</u> NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
			hours Phase 3: pain with exercise, does not alter activity Phase 4: pain with exercise, alters activity Phase 5: Pain with heavy activities of daily living Phase 6: pain with light activities of daily living, intermittent pain at rest Phase 7: constant pain at rest, disrupts sleep		
Modified Nirschl[261]	Patient	Patient asked to rate their pain level/ intensity according to the level of activity using the 5-point phase scoring system.	0 to 4 (item score) Phases of Pain Phase 1: Full activity, no pain Phase 2: No pain during normal daily activity, moderate pain during sports/ occupational activity Phase 3: Occasional pain during normal daily activities, moderate pain during sports/ occupational activity Phase 4: Mild to moderate pain during normal daily activities, severe pain during sports/ occupational activity Phase 5: Pain at rest	The higher the score/pain phase, the greater the disability.	For elbow epicondylitis: NR
Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for	Patient	3 subscales (item number variable by study)‡: Pain Function Patient's global assessment	Patient considered a "responder" if: experienced a high improvement in pain or function ≥50% and absolute change ≥20; OR improvement in 2 of the following Pain ≥20% and	If patient is considered a "responder", they have experienced high improvement in pain or function.	

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
Clinical Trials Response Criteria Initiative (OMERACT-OARSI) Responder Index[69,207]			absolute change in ≥10 Function ≥20% and absolute change in ≥10 Patient's global assessment ≥20% and absolute change in ≥10 Failure to meet the above criteria indicates that the patient is a "non-responder".		
Oxford Elbow Score (OES)[59]	Patient	3 subscales (12 items): Elbow pain Elbow function Social-psychological impact	0 to 4 (item score) 0 to 100 (total score	The higher the score, the greater the elbow disability.	
Pain-Free Function Questionnaire (PFFQ)[266]	Patient	Questionnaire assesses 10 activities frequently affected in patients with tennis elbow	0 to 4 (item score) 0 to 40 converted into 0 to 100 (total score)	The higher the score, the greater the discomfort.	
Pain in Maximum Grip[275]	Clinician and patient	A hand-held dynamometer is used to measure the maximum grip a participant can exert. Pain is measured before and after the grip test using a visual analog scale.	Change in VAS scores (before and after grip test) calculated	The higher the score change, the greater the pain.	
11-point Pain Intensity Numerical Rating Scale (PI-NRS)[77]	Patient	One item, asks the individual to select a number from a scale indicating their neuropathic pain of the day.	0 to 10 (item score)	The higher the score, the greater the pain.	<u>For chronic musculoskeletal pain</u>: 15% [239] <u>MCII for knee OA</u>: NRS (not PI-NRS) Global: 2.72 Function: 2.79 Physician NRS Global: 2.50 Function MCII: 2.55 [201]

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
Pain Pressure Threshold (PPT)[81]	Clinician	A pressure algometer is used to measure the minimum pressure that induces pain or discomfort in the individual.	"Normal" control point is determined by clinicians (typically 2 kg/cm^2) and pain threshold deviation from this point is measured.	The lower the threshold, the greater the pain and/or discomfort impairment. Critical level of abnormality: 2 kg/cm^2 lower threshold relative to a normal control point	
Patient-Related Tennis Elbow Evaluation (PRTEE)[232]	Patient	2 subscales (15 items): Pain Function (further divided into specific activities and usual activities)	0 to 100 (total score)	The higher the score, the greater the pain and functional impairment.	For elbow epicondylitis: MCID defined as "a little better" Total PRTEE: 7/100, 22% of baseline score MCID defined as "much better" or "completely recovered" Total PRTEE: 11/100 or 37% of baseline score MCID for subgroups <40/100 at baseline: 7/100 or 35% MCID for subgroups for ≥40/100: 21 or 40%: 21 or 40%[210]
Physical Component Summary Score of the SF-36 (PCS-36)[292]	Patient	6 subscales (35 items): Physical functioning Role-physical Bodily pain General health Vitality Social functioning	0 to 100 (total score)	The lower the score, the greater the physical disability.	
Disabilities of the Arm, Shoulder, and Hand Quick	NR	5 subscales (11 items): Activities of daily	Total score = [(Sum of responses divided by number of correct	The higher the score, the lower the arm/ shoulder/ hand	For shoulder pain: 8.0[183]

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
Questionnaire (Quick DASH)[137]		living Social activities Work activities Symptoms Sleeping	responses) subtracted from one] multiplied by 25; can range from 0 to 100	function.	For elbow epicondylitis: 15.8[256]
Roles and Maudsley Outcome Score[230]	Patient	Pain scale where: 1 = excellent, no pain, full movement, full activity 2 = good, occasional discomfort, full movement, and full activity 3 = fair, some discomfort after prolonged activity 4 = poor, pain limiting activities	1 to 4 (total score)	The higher the score, the greater the pain.	
Short Form-12 (SF-12)[290]	Patient	8 subscales (12 items): Physical functioning Role-physical Bodily pain General health Vitality Social functioning Role-emotional Mental health	0 to 100 (total score)	The higher the score, the lower the disability.	
Short Form-36 (SF-36)[291,292]	Patient	8 subscales (36 items): Role-functioning Role limitations due to physical health problems Bodily pain General health Vitality Social functioning Role limitations due to emotional problems Mental health The Mental Component Score of the SF-36 (MCS-36) contains the subscales listed as 4-8 and includes 35	0 to 100 (subscale score) 0 to 100 (component score) Total score not used	The higher the score, the greater the function.	For Knee OA: 4.3 General health: -7.3 (-11.3 to -3.3) Vitality: 3.44 (-2.2 to 9.1) Social functioning: 6.15 (-1.7 to 14.0) Role emotional: 2.42 (-9.2 to 14.1) Mental health: 4.02 (-1.7 to 9.7)[265]

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		items. The Physical Component Score of the SF-36 (PCS-36) contains the subscales listed as 1-5 and includes 35 items.			
Shoulder Pain and Disability Index[228]	Patient	2 subscales (13 items): Pain Disability	Item scores for subscale divided by maximum score for subscale deemed applicable to subject (subscale score) Total score = average of pain and disability subscale scores, can range from 0 to 100	The higher the score, the lower the shoulder function and pain.	For rotator cuff disease: 15.4 at 2 weeks, 23.1 at 6 weeks[71] For nonspecific shoulder etiology: 10[173] 8[54] 13.2[247]
Simple Shoulder Test (SST)[159]	Patient	12 yes or no questions concerning the ability to perform 12 activities of daily living.	0 to 100 (total score) Reported as a percentage of questions answered in the affirmative.	The higher the score, the greater the shoulder function.	For rotator cuff disease: range 0-12: 2.05 (fifteen item function) or 2.33 (4 item assessment), 2 point overall[269] For asymptomatic rotator cuff tear: For range 0-100, 17 to 19[132]
Subjective global function[180]	Patient	Patients are asked to assess their function during activities of daily living and subjective wellbeing compared to prior function.	1% to 100% (total score)	The higher the score, the greater the function. 100% = pre-injury function	For osteochondral lesions: NR
Tegner Score[271]	Patient	10 activity levels within 3 activities: Competitive sports Recreational sports Work	0 to 10 (total score)	The lower the score, the greater the function.	For ACL etiology: 1[32,70]
Upper Extremity Functional Scale[211]	Patient	8 items representing common activities affecting upper extremity function.	1 to 10 (per item) 8 to 80 (total score)	The higher the score, the lower the upper extremity function.	For elbow epicondylitis: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
Victorian Institute of Sports Assessment-Achilles (VISA-A)[229]	Patient	3 subscales (8 items): Pain Activity Functional status	0 to 100 (total score)	The lower the score, the greater the Achilles disability.	For Achilles tendinopathy: 6.5[174] 15[264]
Victorian Institute of Sports Assessment Patella (VISA-P)[286]	Patient	3 subscales (8 items): Symptoms Function Ability to perform sports	0 to variable maximum (item score) 0 to 100 (total score)	The higher the score the lower the patellar disability.	For patellar tendinopathy: 13 points[107]
Visual Analog Scale (VAS)§	Patient	Patients are asked to indicate on a scale line (100 mm in length) where they rate their pain level of the day. One variation of this measure includes changing the length of the line.	0 to variable maximum typically of 10 or 100 (total score)	The higher the score, the greater the pain. No pain: 0 to 4 mm Mild pain: 5 to 44 mm Moderate pain: 45 to 74 mm Severe pain: 74 to 100 mm	For elbow epicondylitis: NR For patellar tendinopathy: VAS-Usual = 2 (1-10 scale.), VAS-Worst = 2 (1-10 scale)[56] For rotator cuff disease: 1.37 mm[270] For plantar fasciitis: 9 mm[148]
Visual Analog Scale function[180]	Patient	Patients are asked to evaluate functional impairment during activities of daily living including climbing up and down stairs, walking on a flat surface, going out for a long walk, or performing household work on a scale of 1 to 10. Item scores are averaged to produce a function score.	0 to 10 (item score and total score)	The higher the score, the greater the functional impairment.	For osteochondral lesions of the talus: NR
Visual Analog Scale stiffness[180]	Patient	Patients are asked to evaluate joint stiffness experienced in the morning and	0 to 10 (item score and total score)	The higher the score, the greater the stiffness	For osteochondral lesions of the talus: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		throughout the day on a scale of 1 to 10. Item scores are averaged to produce a stiffness score.			
Western Ontario and McMaster OA index (WOMAC)[21]	Patient	3 subscales: Pain (5 items) Stiffness (2 items) Physical function (17 items)	Likert Scale: 0 to 4 (item score) 0 to 96 (total score) **	The higher the score, the greater the pain, stiffness, and functional limitations.	<u>For Knee OA, 0-100 scale</u>: Pain: 9.7 Stiffness: 9.3 Function: 10 (Babul 2004) Global: 17.13 Function: 17.02[201] Total WOMAC: 10.1 Pain: 2.1 Stiffness: 2.1 Function: 6.5[265] <u>For general knee problems (0-100)</u>: *Traumatic* Pain: 10.9 Stiffness: 16.8 Function: 21.0 Overall: 18.6 *Non-Traumatic* Pain: 15.4 Stiffness: 13.8 Function: 12.0 Overall: 12.9 *Combined* Pain: 16.8 Stiffness: 20.3 Function: 23.0 Overall: 19.1[106]
Western Ontario Rotator Cuff (WORC) Index[138]	Patient	5 subscales (21 items): Physical symptoms Sports/recreation Work Lifestyle Emotions	Scores normalized to 100% and reported as percentage of normal. Total score ranges from 0 to 2100	The higher the score, the greater the rotator cuff disability. The higher the normalized score, the lower the rotator cuff disability.	

*MCIDs were only found if an outcome was significant in any of the results of this report. Those that are significant in the results, but not found searching the literature, then the MCID is reported as NR.

†Note that 20 meter walk test in Forogh is jogging, while other studies use walking within the same outcome measure

‡The measures used for the three subscales vary depending on the study.

§ Multiple versions and modifications to this outcome measure were reported in the studies included in this report.

**One study (Sanchez 2012) utilized a non-standard “normalized” WOMAC scoring system for each subscale, where each subscale was 0-100(worst).

1.4 Washington State Utilization and Cost Data

No data are available for this technology

2. Background

2.1.1. Epidemiology and Burden of Disease

Musculoskeletal disorders describe a range of conditions involving muscle, bone, and connective tissues, and are a common cause of long-term pain and disability.[295] Musculoskeletal injuries present across a broad spectrum of ages and can be acute or chronic in nature: acute injuries are characterized by tearing and hematoma formation after trauma,[189] while chronic injuries result from overuse and aging, as the body loses its ability to heal microtears induced by repeated use. In the United States alone, soft tissue injuries represent 45% of all musculoskeletal injuries.[12]

The burden of musculoskeletal disease is great. A study in over 14,000 Austrian subjects indicated that two-fifths of the population suffered from some type of musculoskeletal disease,[282] while in the United States at least one-third of adults are affected by joint pain, swelling, or limitation of movement.[295] In general, musculoskeletal disorders have low mortality rates but are associated with high morbidity rates, which commonly translate to long-term disability and subsequent lack of physical activity.[181] In one epidemiologic study evaluating musculoskeletal injuries in over 6,000 sedentary and physically active adults, nearly one-third of the population permanently stopped their exercise regimen after injury.[109] Musculoskeletal disorders represent a burden on society in both direct costs to the health care system and indirect costs through loss of work and productivity, including forced early retirement, as well as their impact on the psychosocial status of affected people.[53,181,295]

2.1.2. Tendinopathies

While the etiology of tendinopathies are not well-understood,[160] tendinopathy disorders can arise from repetitive motions and overuse of tendons.[9] Tendons are responsible for facilitating movement by connecting bone and muscle, and result in disrupted tissue healing.[166] The pathogenesis of tendinopathies includes a defective healing response, and histologically manifests as tendon enlargement, neovascularization, calcium deposits, and the presence of calfcification.[160] Tendinopathies, also described as tendinosis or tendonitis, can be inflammatory (tendinitis) or non-inflammatory and degenerative in nature (tendinosis).[76] Tendinopathies result in reduced activities of daily living and reduced sports participation;[167] and are estimated to account for 30-50% of all sports-related injuries.[118,126] Additionally, tendinopathy-related pain is not necessarily connected to evident tissue damage.[227] Treatment of tendinopathies can be difficult due to the heterogeneity of cases; tendinopathies are a result of both extrinsic (e.g., work load) and intrinsic (e.g., biomechanics, age) factors, and as such, it has been proposed that tendinopathies exist on a continuum upon which treatment should be based.[51] Further, according to clinical expert input, success of treatment largely depends on the stage of the tendinopathy, with end-stage tendinopathies unlikely to respond to any treatment while earlier stages may be highly responsive to a variety of appropriate treatments.

Tendinopathies included in this report and described in more detail below include lateral epicondylitis, Achilles tendinopathy, patellar tendinopathy, and rotator cuff tendinopathy.

Lateral Epicondylitis (Tennis Elbow)

Lateral epicondylitis, colloquially known as tennis elbow, stems from overuse of the extensor carpi radialis muscle and associated tendons through repetitive microtrauma.[62] The term epicondylitis describes chronic tendinosis with little inflammation.[195] Symptoms of elbow epicondylitis include pain and burning lateral to the elbow that radiates to the extensor muscle, weak grip strength, and painful resistance against dorsiflexion of the wrist.[62] A 1998 study in Washington State regarding the incidence

of work-related disorders found that the claims rate for elbow epicondylitis was 11.7 claims per 10,000 full-time workers.[252] Several factors have been shown to be associated with an increased risk for lateral epicondylitis. Recreational tennis players develop tennis elbow more frequently than experienced players, due primarily to faulty stroke biomechanics and the use of improper equipment.[62] A study in a Finnish population indicated that smoking, type 2 diabetes, repetitive work tasks involving use of the hands or wrists, and work tasks involving the use of vibrating tools were found to be associated with lateral epicondylitis.[249] Additionally, increased age is a risk factor for lateral epicondylitis, with incidence being highest among those aged 30 to 55.[101]

Achilles Tendinopathy

Achilles tendinopathy can from microtears stemming from overuse of the Achilles tendon,[251] although one study has indicated that approximately 2% of cases are caused by chronic diseases such as a rheumatoid arthritis or other inflammatory joint diseases[119] and another study indicated that 30% of their patient population had Achilles tendinopathy not directly associated with activity.[231] Symptoms include pain during and after physical activity, tenderness upon touch, swelling, and stiffness after long periods of inactivity, such as when first waking in the morning.[251] It most commonly affects elite endurance athletes, [145] particularly those involved in track and field, volleyball, badminton, and basketball.[167] It disproportionately affects more men than women (prior to menopause),[50] and is more common in older athletes than younger athletes.[117] Additionally, high body mass index (BMI)[85] and floroquinone use is associated with greater risk of Achilles tendinopathy.[136] It is frequently diagnosed with magnetic resonance imaging (MRI) and ultrasound, although X-rays can be helpful for determining Achilles calcification.[97]

Patellar Tendinopathy

Patellar tendinopathy, or Jumper's Knee, is another condition resulting from overuse that describes inflammation or injury to the tendon that attaches either the thigh or lower leg bones to the kneecap.[217] Common among athletes in sports that require repeated jumping, such as volleyball or basketball,[79] it is estimated to have an incidence of around 20% in this population.[117] Ultrasound is more accurate than MRI for diagnosing patellar tendinopathy.[289]

Rotator Cuff Tendinopathy

The etiology of rotator cuff tendinopathy is unclear, but is caused by a combination of intrinsic and extrinsic factors.[179] It can be caused by shoulder impingement, which leads to a diminished vascular supply resulting in inflammation and degeneration of the tendon.[25,279] Symptoms of a rotator cuff tendinopathy are dull, increasing pain the area of the four rotator cuff tendons and tenderness in the shoulder-joint, especially when reaching overhead (person is unable to reach higher than 90 degrees abduction) and behind the back, lifting and sleeping on the affected side; the pain is often associated with growing weakness of the shoulder. It is common in swimmers,[128] elderly athletes,[128] patients who are wheelchair-bound,[127] and patients with high BMI.[85] Conservative methods, such as rest, ice, medication and physical therapy, are often sufficient to treat rotator cuff tendinopathies; however, some injuries may be severe enough that surgery is required.

Plantar Fasciitis

Plantar fasciitis describes typically bilateral inflammation or irritation in the fascia covering the heel due to repetitive strain and microtears[268,304] from activities such as long periods of standing or a sudden increase in exercise. Symptoms include severe morning plantar heel pain that eases with activity but then increases throughout the day, as well as tenderness upon palpitation.[254] Risk factors include spending large amounts of time on one's feet, unaccustomed running,[254] limited ankle mobility, obesity,

and diabetes mellitus.[57,225] Plantar fasciitis accounts for over 800,000 hospital visits annually in the United States.[226] Most cases respond to conventional treatment,[116] which includes pain medication, stretching, and orthotics.

2.1.3. Traumatic Musculoskeletal Injuries

Traumatic musculoskeletal disorders included in this report are acute local muscle injury, ankle sprain, talus osteochondral lesions, Achilles tendon tears, and temporomandibular joint dislocation.

Acute Local Muscle Injury
Acute local muscle injury is a common occurrence among elite athletes and accounts for about a third of time-loss injuries, with approximately 40% of cases experiencing re-injury.[99] Hamstring injuries are especially frequent in elite athletes, primarily those who's sport requires constant running, jumping, and kicking;[121] they are the most common acute muscle injury in professional European football.[72] Hamstring injuries occur when there is overload during the eccentric phase of hamstring contraction, and symptoms include tenderness and pain.[121] Usually, with proper treatment, most people recover completely from acute muscle injuries.

Ankle Sprains
Another common traumatic musculoskeletal injury is ankle sprains, which are estimated to affect over 2 million people each year in the United States.[234] Ankle sprains occur when forces greater cause strain on the ankle joint and surrounding ligaments. Lack of physical activity and obesity are risk factors. Symptoms of ankle sprains include swelling, pain, paresthesia, and muscle spasms.[305]

Osteochondral Lesions to the Talus
Osteochondral lesions to the talus are structural injuries to the cartilage and bone in the ankle joint.[259] The majority are caused by trauma, and symptoms include deep ankle pain upon weight bearing, as well as swelling and instability of the ankle.[94,259]

Achilles Tendon Rupture
Rupture of the Achilles tendon is a common tendon injury in adults.[125] Experienced as acute, severe pain, acute Achilles tendon ruptures are complete breaks in the tendon resulting in swelling, reduced range of motion, and inability to walk. Especially prevalent in those aged 30 to 50, the cause of Achilles tendon ruptures is multifactorial and can be caused by excessive and repetitive strain in addition to degeneration of the tendon.[147] Achilles ruptures occur more frequently in males and among recreational athletes.[238]

Temporomandibular Joint (TMJ) Dislocation
The temporomandibular joint (TMJ) is located where the mandibular condyle and temporal bone connect; TMJ dislocation occurs when these two bones detach.[42] Acute TMJ dislocation usually occurs during extreme opening of the mouth, and less frequently from trauma or as a result of neurologic disorders. Other factors contributing to TMJ dislocation include weakness of the TMJ ligaments, muscle spasms, and abnormal chewing movements.[165]

2.1.4. Osteoarthritis

Osteoarthritis (OA) describes chronic degenerative joint disease that results from the breakdown of cartilage and bone. At the molecular level, cytokines and inflammatory mediators are released and chondrocytes are activated during osteoarthritis, releasing a multitude of signaling molecules causing restructuring of the surrounding tissue and bone.[267] As of 2010, osteoarthritis was ranked as the 11th

leading cause in the world for years lived with disability (YLDs) and overall is the third most prevalent musculoskeletal disorder, accounting for an estimated 17.1 million YLDs.[288]

Osteoarthritis of the Knee

Osteoarthritis of the knee is the most common presentation of OA. Symptoms include knee pain, stiffness, swelling, and decreased range of motion.[157] The 2010 Global Burden of Disease project indicated that 3.64% of the world population has knee OA, with the disease being more prevalent in women (4.75%) than men (2.56%); this gender differential was confirmed in a 2010 systematic review.[29] In 2000, it was estimated that 40% of people over 70 have osteoarthritis of the knee.[200] Additional risk factors include age, obesity, prior injury, and repetitive use.[29,224]

Osteoarthritis of the Hip

Hip osteoarthritis can be characterized by sharp or dull hip pain, stiffness, joint deformity, and reduced range of motion.[154,236] Risk factors include previous hip disorders, trauma, or obesity.[154] Hip osteoarthritis is the second most prevalent manifestation of osteoarthritis after the knee.[17]

Osteoarthritis of the Temporomandibular Joint

Temporomandibular joint (TMJ) osteoarthritis symptoms include pain, stiffness, presence of joint clicking, and limited range of motion in the joint connecting the cranium and the mandible.[78,105] Circumstances that can lead to TMJ osteoarthritis are tooth grinding during sleep, functional overload, and trauma. Prevalence in the literature varies greatly, ranging from 1% to 84% depending on the diagnostic method used.[63]

Osteoarthritis Severity Grading Systems

The Kellgren-Lawrence system,[133] developed in 1957, classifies the severity of knee osteoarthritis. This system utilizes X-ray assessments to establish evidence of osteoarthritis through visualization of aberrant bony growths/osteophytes and reduction in joint space. Similar to the Kellgren-Lawrence system, the Ahlback knee OA grading system[206] utilizes radiological assessments of the knee to establish evidence of OA through visualization of reductions in the tibio-femoral joint space.

Osteoarthritis grading systems do not necessarily correlate with pain, function, or disability; this is due to the multifactorial nature of these symptoms, which are not necessarily reflected in radiographic features.[23] As such, it is possible to have asymptomatic Kellgren-Lawrence Grade 3 osteoarthritis patients and highly disabled Kellgren-Lawrence Grade 1 osteoarthritis patients.

Ahlback and Kellgren-Lawrence grades and definitions are below:

<u>Kellgren-Lawrence Knee OA Grading System</u>:

- Grade 0: Minute osteophytes with doubtful significance
- Grade 1: Definite osteophytes but unimpaired joint space
- Grade 2: Moderate diminution of joint space
- Grade 3: Moderate osteoarthritis, with joint space greatly impaired with sclerosis of subchondral bone
- Grade 4: Severe osteoarthritis, with joint space greatly impaired with sclerosis of subchondral bone

<u>Ahlback Knee OA Grading System</u>:

- Grade 1: Joint space narrowing (joint space < 3 mm)
- Grade 2: Joint space obliteration
- Grade 3: Minor bone attrition (0-5 mm)
- Grade 4: Moderate bone attrition (5-10 mm)
- Grade 5: Severe bone attrition (>10 mm)

2.2. Technology: Platelet Rich Plasma and Autologous Blood Injections

Platelet rich plasma (PRP) and autologous blood injection (ABI) are blood-derived autologous biologics used to promote tissue healing and regeneration by inducing a supra-physiological concentration of growth factor-rich platelets into an injured area. PRP preparations contain a platelet concentration that is greater than baseline platelet count. PRP and ABI therapies are commonly used in orthopedics, sports medicine, and dentistry. Although intramuscular PRP injections were previously a prohibited substance by the World Anti-Doping Agency (WADA) in 2010, they were removed from the list one year later. Subsequently, PRP is no longer banned for use by the International Olympic Committee.[74]

PRP products are not standardized—the mode of preparation, the concentration of platelets and/or leukocytes, and platelet activation methods can vary greatly from system to system, making direct comparison for effectiveness studies difficult. While PRP and ABI are under the purview of the FDA's Center for Biologics Evaluation and Research, they are considered minimally manipulated and are exempt from regulatory code 21 CFR 1271, which calls for regulation of more than "minimally manipulated" human cells, tissues, cellular and tissue-based products.[19] Additionally, although there are a number of PRP-preparation systems on the market that are FDA-approved, PRP itself is not FDA regulated for direct injection; PRP preparations from these systems are intended for combination with bone graft materials for orthopedic use.[19] As such, direct injection of PRP can be considered "off label" usage.

2.2.1. Mechanism of Action

PRP therapy increases the concentration of platelets which then release growth factors upon activation through the coagulation cascade. Platelets, the crux of PRP treatment, are the primary constituents in blood-clotting (hemostasis) and contain over 30 growth factors that aid in angiogenesis, cell growth/division, and cell regeneration.[185] It is this coagulation cascade that PRP and ABI therapy takes advantage of to induce tissue repair and growth. ABI therapy is based on creating a new injury in a chronically non-healing location in order to initiate the wound repair and healing process.[52,196]

As ABI and PRP injections aim to induce a healing cascade in the injured area, the mode of injury repair after injection likely mimics the four phases of the wound healing cascade: inflammation, proliferation, repair, and remodeling.[185] During inflammation the first battery of growth factors— IGF-I and TGFβ[209]—are released, inducing the migration of macrophages and neutrophils to clear away cellular debris left over from tissue injury; during the wound healing process, inflammation occurs from the time of injury to approximately 2 days post-injury.[185] The fibroblast proliferation phase is then induced by a second influx of growth factors such as IFG-I,[5,163] VEGF,[31] PDGF,[209] and bFGF;[40,82] during the wound healing process, this normally occurs between 2 to 4 days post-injury.[185] Afterwards, repair of the injured area occurs—in the wound healing process, this happens anywhere from 4 days to 2 weeks post-injury. Finally, remodeling and organization of the collagen occurs[185] via PDGF[303] and bFGF[40] signaling, which induces collagen fiber I and III expression; during the wound healing process, this occurs from 2 to 3 weeks post-injury. However, because of the variability in PRP preparation, not all preparations may be able to induce the pathways associated with the different phases of repair and growth.[243]
Additionally, some PRP formulations include leukocytes in addition to platelets. Leukocyte-rich PRP (LR-PRP) contains supra-physiologic concentrations of leukocytes, while leukocyte-poor PRP (LP-PRP) has leukocyte concentrations below that of whole blood.[222] Some possible benefits of LR-PRP include antimicrobial activity,[65,187] greater platelet recruitment to the healing site, and thus, increased recruitment of growth factors.[170] However, a recent network meta-analysis indicated that LP-PRP may

confer an increased benefit on functional outcome scores compared to LR-PRP, although the confidence interval was wide due to the small sample size analyzed.[222]

2.2.2. Injection procedure

The process of obtaining PRP begins by drawing 9 to 60 mL of blood from the patient. Common veins used to harvest autologous blood for PRP include the antecubital fossa, cephalic vein, basilica vein, and the median antecubital vein.[172] After venipuncture, anticoagulants such as ACD-A (Anticoagulant Citrate Dextrose Solution Formula A) may be added to the autologous blood. PRP can be produced via blood filtration and plateletphoresis or centrifugation.[170] With centrifugation methods, the force, length of time, and number of times centrifugation occurs can vary,[67] but PRP preparation involves at least one centrifugation step to separate the blood into an erythrocyte layer at the bottom, a buffy coat layer in the middle, and an acellular plasma layer at the top. The middle platelet-rich buffy coat layer can then be harvested and prepared for injection, or can be spun down again to increase platelet concentration. ABI requires no additional processing after venipuncture.

To prepare the patient for ABI or PRP injection, the area to be injected is sterilized, and local anesthetic can be applied prior to injection to ease post-injection pain. Activating agents, such as 10% calcium chloride or batroxobin,[170] can be added to the PRP mixture as a clot activator to speed the activation of thrombin,[12] which in turn aids the release of growth-factors from platelets. Studies included in this report injected anywhere from 2 to 5 mL of PRP in the affected area. Dry needling, which is the repeated passing of a needle through the tissue in the affected area, is sometimes done in conjunction with ABI or PRP injections—this is thought to stimulate inflammation and promote the wound healing cascade.[115] Dry needling can be done in conjunction with injections for tendinopathies and plantar fasciitis. If treatment is for osteoarthritis, PRP will generally be injected intra-articularly. ABI and PRP injection are outpatient procedures.

After injection, it is typically recommended that patients decrease activity for several days to several weeks. Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually prohibited post-injection, as they interfere with the inflammatory process necessary for the PRP-induced healing cascade; paracetamol/acetaminophen and ice therapy are usually prescribed for any post-injection pain. Because ABI and PRP injection utilize the body's immune response to promote healing and regeneration, there may be a temporary worsening of symptoms post-injection.[240]

2.2.3. Guidance and Imaging

During the injection procedure, imaging can be useful in ensuring that the application of PRP or ABI is as close to the site of injury as possible. Ultrasound is a common imaging technique during PRP and ABI therapy.[240] It is thought that ultrasound aids in visualization in two particular ways: 1) real-time tracking, so clinicians know exactly when and where needle placement is occurring, and 2) optimization of visualization, such as enhancing contrast between needle and tissues, thus providing better image clarity and distinction between structures.[257,258] Color Doppler ultrasound is especially useful for imaging areas of neovascularization and inflammation,[152] as it is designed to image moving fluids such as blood.[102]

2.2.4. Proposed Benefits

ABI and PRP injections aim to promote tissue healing and repair by enhancing the biocellular environment with an infusion of growth factors.[189] However, unlike other similar therapies, ABI and PRP have the added benefit of being derived from the patients' own blood, so there is little risk of

transmissible diseases or hypersensitivity reactions.[172] Intended outcomes are improvement in function, pain, and quality of life, all while minimizing adverse effects.

2.2.5. Consequences and adverse events

Common side effects of PRP and ABI are post-injection pain, and systematic reviews have indicated low incidences of adverse events for treatment of musculoskeletal disorders.[131,189] Contraindications against PRP injections include pregnancy or active breastfeeding; patients with a tumor or metastatic disease; active infections; or low platelet or hemoglobin count. No studies have indicated that PRP contributes to tumorigenesis.[240]

2.3. Comparator Treatments

Common comparator treatments for PRP and ABI in musculoskeletal disorders include dry needling or peppering, various injections, conservative care, and surgery.

2.3.1. Dry needling

Dry needling and peppering are often used in the treatment of tendinopathies as placebo injections or in conjunction with other injection types. Dry needling, peppering, and needling are terms used somewhat interchangeably to denote the process of repeatedly passing a needle through the tendon to disrupt collagen fibers and induce bleeding without injecting any substance.[76,115] Dry needling encompasses a heterogeneous group of treatments that range from procedures done with small acupuncture needles without anesthesia to treatments performed with large bore hypodermic needles with local anesthetic. These techniques may be ultrasound-guided and a substance such as corticosteroid or PRP may be injected after disruption of the tendon.[20,115] Peppering can be done with an injectate, such as autologous blood. The needle is inserted into the tendon and a portion of the fluid is injected, then withdrawn without emerging from the skin, redirected and reinserted into the tendon for additional injection.[76,140] The needle may be inserted anywhere from 3 to 50 or more times into the tendon, however the number of insertions necessary for optimal technique is still unknown.[20,123,140] In one study on plantar fasciitis, injections continued until a sensation of crepitation ceased.[123] Despite use as a placebo injection, it has been suggested that the induction of bleeding within the tendon facilitates healing and results in a treatment effect.[8,76,130,142] Adverse events are few, consisting of pain at the treatment site if local anesthetic is not used.[140]

2.3.2. Injections: Corticosteroids

Injectable corticosteroids are commonly used to treat pain and inflammation and improve mobility in individuals with musculoskeletal disorders. Disorders frequently treated with corticosteroids include rheumatic arthritis, synovitis, bursitis, epicondylitis, tendonitis, and fasciitis.[33] Corticosteroids are thought to interfere with the inflammatory and immune response of synovial tissues at several response levels, although the complete mechanism is not yet fully understood.[16,47] Injections may be delivered to the intra- or extra-articular space, although intra-articular injections are more commonly used and more widely studied.[47] Five corticosteroids have been approved by the FDA for intra-articular injections: methylprednisolone acetate, triamcinolone acetate, betamethasone acetate, betamethasone sodium phosphate, triamcinolone hexacetonide and dexamethasone.[16] For the treatment of knee osteoarthritis, the American College of Rheumatology generally recommends the use of intra-articular corticosteroids,[108] although there is little evidence to support their use in the long term.[22]

2.3.3. Injections: Anesthetic

Local anesthetics can be used to treat various musculoskeletal disorder symptoms, but despite widespread use, their efficacy is still unclear.[191] Potential adverse effects associated with local anesthetic therapy for musculoskeletal disorders include flushing, hives, chest or abdominal discomfort, nausea, cardiac arrhythmia and seizure.[37] Additionally, there is also risk for swelling, redness, and tenderness at the injection site.[37] Local anesthetics are frequently used in conjunction with corticosteroids.

2.3.4. Injections: Hyaluronic Acid (HA)

Hyaluronic acid is endogenously in connective tissues, and is a component of extracellular matrix[88]—as such, HA therapies aim to improve depleted HA levels and restore the viscosity of the synovial fluid[194] common in musculoskeletal disorders such as osteoarthritis. Three exogenous hyaluronan products have been approved by the FDA: sodium hyaluronate, Hylan G-F 20, and high-molecular-weight hyaluronan.[16] Commercial preparations of HA differ in respect to source, molecular size and dosing.[194] Preparations tend to be high in molecular weight as a result of greater cross-linking, and can be bioengineered in yeast cultures. Preparations may be designed to be delivered in single or multiple doses.[194] Major possible complications only include infection at the injection site, although safety and effectiveness have not been studied in pregnant or lactating women or in children.[6]

2.3.5. Injections: Dextrose Prolotherapy

Prolotherapy involves injecting a small volume of growth factors or growth factor stimulators into a treatment site, such as a ligament or tendon.[237] Treatment involves two to five injection sessions at 2 to 6 week intervals.[237] Hypersomolar dextrose has been shown to increase expression of growth factors that are active in tendon repair,[66,198,199] and is used in a variety of tendinopathies to decrease pain and improve function.[212,213]

2.3.6. Exercise

Among those with knee osteoarthritis, land-based exercise has been shown to provide short-term but not long-term improvements in pain and physical function, and short-term improvements in quality of life.[86] For patients with hip osteoarthritis, exercise is effective at reducing pain and improving physical function in both the short- and long-term.[87]

Additionally, eccentric exercises, which cause muscle lengthening during excessive loading,[158] are also used in conservative care protocols for musculoskeletal injuries. Eccentric exercise protocols are used in treatment of lateral elbow epicondylitis, patellar tendinopathy, and Achilles tendon injuries, shoulder tendinopathy, and hamstring strains.[89] Although more high-quality RCTs are needed to prove the effectiveness of eccentric exercise for treatment of these conditions, eccentric exercise is a cost-effective and feasible treatment option.[89]

2.3.7. Extracorporeal Shock Wave Therapy (ESWT)

Extracorporeal shock wave therapy (ESWT) is used to treat a variety of musculoskeletal injuries by promoting the wound healing cascade[293] and reducing short-term pain during daily activities.[144] ESWT procedures include introducing shockwaves at increasing levels for approximately ten minutes. Of note, application of ESWT is heterogeneous— energy levels, number of treatment sessions, and number of impulses vary across publications,[169] making evaluation of effectiveness difficult. It has been shown to effectively reduce pain in patients with chronic plantar fasciitis.[13,168]

2.3.8. Low Level Laser Therapy

Also known as photobiomodulation, low level laser therapy exposes tissues to low levels of red or near-infrared light,[45] which is thought to promote cellular proliferation.[285] Data regarding effectiveness is inconclusive-- although it has been shown to successfully reduce pain in lateral tendinopathies,[44] a systematic review showed contradictory for treatment of tennis elbow.[27]

2.3.9. Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous electrical nerve stimulations (TENS) is a pain-management tool that acts by producing low-voltage electrical currents in the skin.[161] These currents are thought to alter pain signals in the nervous system, providing relief. TENS is often used in patients with knee osteoarthritis and chronic musculoskeletal pain, and has been shown to be successful in the short-term for knee osteoarthritis pain relief.[28] TENS is considered safe if used properly; serious adverse events are rare.[122]

2.3.10. Surgery

Common surgical techniques for musculoskeletal disorders include decompression and debridement for tendinopathies; arthroscopy, arthroplasty, and osteotomy in osteoarthritis; and intermaxillary fixation for temporomandibular (TMJ) dislocation. Surgery is usually the last option for tendinopathy treatment, as failure rates for debridement and/or decompression are has high as 20% to 30%.[9] Fixation for TMJ dislocation aids in stabilization of the hypermobile jaw; however, it is usually unsuccessful in patients with chronic TMJ dislocation.[250]

2.4. Clinical Guidelines

The National Guideline Clearinghouse (NGC), PubMed, and Google were searched for guidelines related to the use of platelet-rich plasma (PRP) injections and autologous blood injections (ABI) in patients with musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain. Key word searches were performed: ("platelet rich plasma") OR ("whole blood injection*") OR ("whole blood") OR ("autologous blood injection") OR ("autologous blood"). Of the 13 identified guidelines, seven provide recommendations for the use of ABI and PRP, and the remaining six provide recommendations only for PRP.

Guidelines from the following sources are summarized:

- American Academy of Orthopedic Surgeons
- American College of Occupational and Environmental Medicine
- Colorado Division of Workers Compensation
- Hsu et al. (2013)
- International Cellular Medicine Society
- Work Loss Data Institute

Details of each included recommendation for the injection of platelet-rich plasma or autologous blood for treatment of musculoskeletal soft tissue injuries, tendinopathies, or osteoarthritis, including the class/ grade of recommendation and level of evidence, can be found in Table 2.
A summary of the guidelines from available full-texts from the more prominent organizations in which the level of recommendation was evaluated is provided below.

Tendinopathies

Colorado Division of Workers Compensation, 2010: *Cumulative Trauma Conditions: Medical Treatment Guidelines:* Both platelet-rich plasma injections and autologous blood injections are recommended for patients with lateral or medial epicondylitis symptoms lasting longer than six months.

International Cellular Medicine Society, 2011: *Section VII: Platelet Rich Plasma (PRP) Guidelines:* It is recommended that further research be conducted on the effects of platelet-rich plasma injections in individuals with tendinopathies.

Hsu et al., 2013: *Platelet-rich Plasma in Orthopaedic Applications: Evidence-based Recommendations for Treatment:* Platelet-rich plasma injections are recommended in patients with elbow epicondylitis refractory to conventional nonsurgical treatment. It is recommended that further research be conducted on the use of platelet-rich plasma injections for the treatment of other chronic tendinopathies.

Plantar Fasciitis

No full-texts of guidelines providing recommendations pertaining to the use of platelet-rich plasma or autologous blood injections for the treatment of plantar fasciitis were obtained.

Acute Injuries

International Cellular Medicine Society, 2011: *Section VII: Platelet Rich Plasma (PRP) Guidelines:* It is recommended that further research be conducted on the effects of platelet-rich plasma injection in individuals with ligament sprains and muscle strains.

Hsu et al., 2013: *Platelet-rich Plasma in Orthopaedic Applications: Evidence-based Recommendations for Treatment:* It is recommended that further research be conducted on the use of platelet-rich plasma injections for rotator cuff repair, Achilles tendon repair, and treatment of cartilage injuries.

Osteoarthritis

American Academy of Orthopedic Surgeons, 2013: *Treatment of Osteoarthritis of the Knee:* An inconclusive recommendation is provided for the use of platelet-rich plasma and/or growth factor injections for the treatment of symptomatic knee osteoarthritis.

Table 2. Summary of Clinical Guidelines

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
Colorado Division of Workers Compensation Cumulative Trauma Conditions: Medical Treatment Guidelines (2010)[262]	NR	In patients with lateral or medial epicondylitis and symptoms lasting longer than 6 months: • There is good evidence to support PRP injections (2 injections optimum) • There is some evidence to support ABI (2 injections optimum)	NR
ACOEM Ankle and Foot	NR	ACOEM **recommends** both PRP injections and ABI for the following pathologies: • Chronic lateral epicondylitis	Limited (C)† for both PRP and ABI

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
Disorders (2011)[175]* Knee Disorders (2011)[176]* Elbow Disorders (2012)[177]*		ACOEM **does not recommend** – PRP injections for the following pathologies: • Achilles tendinopathy ABI for the following pathologies: • Plantar fasciitis ACOEM **provides no recommendation** for – PRP injections and ABI for the following pathologies: • Ankle sprain • Knee sprains • Anterior and posterior cruciate ligament tears • Meniscal tears • Patellar tendinosis/tendinopathy • Anterior knee pain • Acute or subacute lateral epicondylitis PRP injections only for the following pathologies: • Plantar fasciitis	Moderate (B)† Limited (C)† Insufficient (I)† for both PRP and ABI Insufficient (I)†
ICMS Section VII: Platelet Rich Plasma (PRP) Guidelines (2011)[112]	Tendinopathies 3 studies (type NR) 1 animal study Ligament Sprains 1 study (type NR) Muscle Sprains 1 study (type NR) Joints 1 study (type NR)	ICMS **suggests the need for further research** on the effects of PRP injections on the following pathologies: • Tendinopathies • Ligament sprains • Muscle strains • Joints • Intervertebral discs	NR
Hsu et al. Platelet-rich Plasma in Orthopaedic Applications: Evidence-based Recommendations for Treatment (2013)[110]	Cartilage Injuries 3 level I studies 1 level II study Chronic Tendinopathies 4 level I studies 1 level III study Rotator Cuff Repair 5 level I and level II studies Achilles Tendon Repair 1 level II study 1 level III study	Hsu et al. **recommends** the use of PRP injections in the following pathologies: • Elbow epicondylitis refractory to standard nonsurgical treatment Hsu et al. **suggests the need for further research** on the effects of PRP on the following pathologies: • Cartilage injuries • Chronic tendinopathies (excluding elbow epicondylitis refractory to standard nonsurgical treatment) • Rotator cuff repair • Achilles tendon repair	NR
Work Loss Data Institute Ankle & Foot (acute	NR	Work Loss Data Institute **recommends** the use of both PRP injection and ABI for the following pathologies:	NR

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
& chronic) (2013)[296]* Elbow (acute & chronic) (2013)[297]* Hip & Pelvis (acute & chronic) (2013)[298]* Low Back – Lumbar & Thoracic (acute & chronic) (2013)[299]* Pain (acute & chronic) (2013)[300]* Shoulder (acute & chronic) (2013)[301]*		• Acute and chronic elbow disorders (not further defined) Work Loss Data Institute **does not recommend**– PRP injection for the following pathologies: • Ankle and foot disorders (not further defined). • Low back pain (lumbar and thoracic) • Chronic pain, unless used in a research setting ABI for the following pathologies: • Ankle and foot disorders (not further defined). Work Loss Data Institute **provides no recommendation** for – PRP injections for the following pathologies: • Hip and pelvis injuries (not further defined) • Shoulder disorders (not further defined) ABI for the following pathologies: • Shoulder disorders (not further defined)	
AAOS Treatment of Osteoarthritis of the Knee (2013)[34]	2 studies of low SOE 1 study of moderate SOE	AAOS **cannot make a recommendation** for or against the use of PRP and/or growth factor injections for patients with symptomatic osteoarthritis of the knee.	Inconclusive‡

AAOS: American Academy of Orthopedic Surgeons; ABI: autologous blood injection; ACOEM: American College of Occupational and Environmental Medicine; ICMS: International Cellular Medicine Society; NR: not reported; PRP: platelet-rich plasma; SOE: strength of evidence

* Guideline information is based off an AHRQ summary.

† ACOEM guidelines for rating the strength of the recommendation's evidence:
Strongly recommend (A): Intervention is strongly recommended for appropriate patients. Intervention improves important health and functional outcomes based on high quality evidence, and the Evidence-Based Practice Panel concludes that benefits substantially outweigh the harms and costs.
Moderately recommend (B): Intervention is recommended for appropriate patients. Intervention improves important health and functional outcomes based on intermediate quality of evidence that benefits substantially outweigh the harms and costs.
Recommend (C): Intervention is recommended for appropriate patients. Limited evidence that the intervention may improve important health and functional outcomes.
Insufficient – recommend (I): Intervention recommended for appropriate patients and has nominal costs and essentially no potential for harm. The Evidence-Based Practice Panel feels that the intervention constitutes best medical practice to acquire or provide information in order to best diagnose and treat a health condition and restore function in an expeditious manner. The Evidence-Based Practice Panel believes based on the body of evidence, first principles, or collective experience that patents are best served by these practices, although the evidence is insufficient for an evidence-based recommendation.
Insufficient – no recommendation (I): Evidence is insufficient to recommend for or against routinely providing the intervention. The Evidence-Based Practice Panel makes no recommendation. Evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits, harms, and costs cannot be determined.
Insufficient – not recommended (I): Evidence is insufficient for an evidence-based recommendation. Intervention is not recommended for appropriate patients because of high costs or high potential for harm to the patient.

Not recommended (C): Recommendation is against routinely providing the intervention. The Evidence-Based Practice Panel found at least intermediate evidence that harms and costs exceed benefits based on limited evidence.
Moderately not recommended (B): Recommendation is against routinely providing the intervention to eligible patients. The Evidence-Based Practice Panel found at least intermediate evidence that the intervention is ineffective, or that harms or costs outweigh benefits.
Strongly not recommended (A): Strong recommendation against providing the intervention to eligible patients. The Evidence-Based Practice Panel found high quality evidence that the intervention is ineffective, or that harms or costs outweigh the benefits.

‡ AAOS guidelines for evidence strength:
Strong: Benefits clearly exceed the potential harm (not true if a negative recommendation), and/or the strength of evidence is high.
Moderate: Benefits exceed the potential harm (or the potential harm exceeds the benefits in the case of a negative recommendation), but the quality/ applicability of the supporting evidence is not as strong.
Limited: Strength of evidence is unconvincing, or the well-conducted studies show little clear advantage to one approach over another.
Inconclusive: Lack of compelling evidence that has resulted in an unclear balance between the benefits and potential harms.
Consensus: Expert opinion supports the guideline recommendation even though there is no empirical evidence that meets the inclusion criteria in the SR.

2.5. Previous Systematic Reviews/Technology Assessments

Health Technology Assessments (HTAs) were found by searching for *"Platelet rich plasma", "Whole blood injection*", "whole blood", "autologous blood injection*",* and *"autologous blood"* in PubMed, the University of York Centre for Reviews and Dissemination database, the NICE Guidance Database, and Google Scholar. A total of seven HTAs were identified: five report on PRP, one reports on ABI, and one reports on both PRP and ABI (Table 3). The following provides a summary of outcomes from HTAs in which the strength of evidence for each conclusion was evaluated. None of the included SRs and HTAs provided levels of recommendations for their evidence base.

Systematic reviews were found by searching PubMed using the search strategies in Appendix B**.** A total of six systematic reviews were summarized (Table 4): one reported on autologous blood injection (ABI) and six reported on platelet rich plasma (PRP) injections.

Table 3. Previous Health Technology Assessments

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
NICE Interventional Procedures Programme (2013)[76] National Institute for Health and Clinical Excellence (NICE) *Autologous blood injection for tendinopathy*	NR to 9/2012	Tendinopathy (elbow, Achilles, patellar)	PRP or ABI†	5 RCTs 3 case series	**Efficacy:** - The evidence on efficacy remains inadequate, with few studies available that use appropriate comparators. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. ○ Significantly more patients achieved success at 24 months with PRP vs. steroid (1 RCT, tennis elbow) ○ No difference in function between PRP and placebo groups 12 months (1 RCT, Achilles tendinopathy) ○ Fewer patients who received PRP initially required further intervention within 2-14 months compared with steroids (1 RCT, tennis elbow) ○ No difference between PRP and placebo in proportion of patients that returned to their previous level of sporting activity by 12 months (1 RCT, Achilles tendinopathy) **Safety:** - The evidence raises no major safety concerns. ○ No serious complications reported by 2 RCTs comparing ABI or PRP with steroid (tennis elbow) and 1 RCT comparing PRP with placebo (Achilles tendinopathy). ○ Post-injection pain was reported by two case series: 7% of patients needed narcotic analgesia for pain after ABI for tennis elbow; moderate pain and stiffness after PRP injection in all patients treated for patellar tendinosis. **Economic: NR** **Future Research**: - Trials comparing ABI (with or without techniques to produce platelet-rich plasma) against established nonsurgical methods for managing tendinopathy are needed. - Trials should clearly describe patient selection (including the site of tendinopathy, duration of symptoms and any	NR

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
					prior treatments) and document whether a 'dry needling' technique is used. - Outcomes should include specific measures of pain, quality of life and function, and whether subsequent surgical intervention is needed	
Tice (2010)[276] California Technology Assessment Forum (CTAF) *Platelet-Rich Plasma Injection for Achilles Tendinopathy*	1966 to 9/2010	Achilles tendinopathy	PRP	1 RCT 1 case series 1 case repot	**Efficacy:** - PRP was not found to improve net health outcomes or to be as beneficial as established alternatives for the treatment of Achilles tendinopathy. - One RCT found no benefit to PRP compared with sham injections. - One case series reported dramatic improvements in pain and function within 3 months and sustained through 18 months. **Safety:** - One case series reported no significant complications of PRP. **Economic:** NR	NR
NICE Interventional Procedures Programme (2013) National Institute for Health and Clinical Excellence (NICE)[3] *Autologous Blood Injection for Plantar Fasciitis*	NR to 9/2012	Plantar fasciitis	ABI	2 RCTs 1 non-randomized comparative	**Efficacy:** - The evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. ○ Mean pain scores were significantly reduced at 6 months after ABI compared with steroid injection (2 RCTs) and peppering alone (1 RCT). ○ No difference in function was seen at 6 months between ABI versus steroid or peppering alone (1 RCT). ○ Significantly fewer ABI patients reported excellent/good outcome compared with those who received corticosteroids with or without peppering (1 non-randomized comparative). ○ A third injection was necessary in significantly more patients receiving ABI and peppering alone versus steroid (1 RCT).	NR

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal

					Safety:
					- The evidence raises no major safety concerns.
					  ○ A greater proportion of patients complained of post-injection pain following PRP versus steroids in one RCT.
					  ○ No adverse events were reported in one non-randomized comparative study.
					Economic: NR
					Future research:
					- In the context of RCTs that define chronicity of tendinopathy and clearly describe any previous or adjunctive treatments (including physiotherapy and 'dry needling') as well as the tendons treated; trials should address the role of ultrasound guidance and include functional and quality of life outcomes with a minimum follow-up of 1 year.	

CADTH Rapid Response Service (2014)[1] Canadian Agency for Drugs and Technologies in Health (CADTH) *Rapid Response Report*: Platelet Rich Plasma Lumbar Disc Injections for Lower Back Pain: Clinical Effectiveness, Safety, and Guidelines**	1/2009 to 2/2014	Low back pain	PRP	1 SR 1 RCT 2 non-randomized studies 1 evidence-based guideline	**Efficacy:** - There is insufficient evidence (from 1 SR, 1 RCT, and 1 non-randomized study) to guide the use of PRP for various orthopedic conditions. - Most literature underlined the uncertainty surrounding the use of PRP. **Safety:** - Two non-randomized studies indicated that PRP appeared to involve very little risk to patients. **Economic:** - One RCT indicated that PRP could not be economically justified due to a lack of statistical significance in outcome measures. - Most literature underlined the uncertainty surrounding economic benefit.	NR
Ghazali and Thye (2013)[93] Health Technology Assessment Section	Database inception (MEDLINE, Embase, EBM reviews)to	Osteoarthritis	PRP	2 SRs 2 RCTs 2 non-RCTs 1 retrospective cohort	**Efficacy:** - There is insufficient evidence to support the effectiveness of PRP for the treatment of OA. - Limited short-term evidence indicates that PRP may be beneficial for young patients (<50 years) with early OA and	Yes, Critical Appraisal Skills Programme (CASP) and

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
(MaHTAS): Medical Development Division, Ministry of Health Malaysia *Platelet Rich Plasma for Treatment of Osteoarthritis*	4/2013				not overweight or obese. **Safety:** - No major complications were reported in patients treated with PRP. **Economic:** - No formal economic studies were identified. - Cost of treatment ranges from $500-$2,000.	the US / Canadian Preventative Services Task Force
HealthPACT, Queensland Department of Health (Australia) (2013)[2] Health Policy Advisory Committee on Technology (HealthPACT) *Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis*	NR	Osteoarthritis of the knee	PRP	3 comparative studies	**Efficacy:** - There is low-quality evidence to support the use of PRP for patients with OA of the knee. - All studies reported short-term improvements in function and pain; however effects were not sustained over time. - There is no evidence that PRP injections alter the natural progression of OA. **Safety:** - PRP appears to be safe; short-term pain following injection was the only reported adverse event. **Economic:** - No cost-effectiveness analyses were identified.	Yes, NHMRC levels of evidence
NICE Interventional Procedures Programme (2014)[4] National Institute for Health and Clinical Excellence (NICE) *Platelet-rich plasma injections for osteoarthritis of the knee*	Database inception (MEDLINE, PREMEDLINE, Embase, Cochrane Library, etc.) to 1/2014	Osteoarthritis of the knee	PRP	4 RCTs 2 non-RCT comparative studies 2 prospective case series	**Efficacy:** - Evidence on efficacy is inadequate in quality; therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. ○ A meta-analysis (n=577; 4 RCTs, 2 nonrandomized comparative studies) reported statistically significant improvement in WOMAC function scores in patients treated with PRP compared to HA. ○ PRP resulted in significantly greater patient satisfaction compared with HA (1 nonrandomized comparative study). **Safety:** - Evidence raises no major safety concerns. ○ Syncope, dizziness, headache, nausea, gastritis, sweating and tachycardia in 33% of patients at the time	NR

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
					of initial PRP injection was reported in one RCT ○ Pain and stiffness of the knee which lasted for up to two days in 14% of patients was reported by one RCT. ○ Mild swelling or pain of the knee which resolved within 2 weeks in 63% of patients was reported by one case series. **Economic:** NR **Future research**: - Further research into platelet-rich plasma injections for treating osteoarthritis of the knee should clearly describe patient selection and should take the form of well-designed, controlled studies that compare the procedure against other methods of management. - Outcomes should include measures of knee function, patient-reported outcome measures and the timing of subsequent interventions. - Studies aimed at assessing possible cartilage repair after platelet-rich plasma injections should include detailed radiographic or MRI imaging before and after the procedure.	

ABI: autologous whole blood injections; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized control trial; SR: systematic review; PRTEE: Patient-Related Tennis Elbow Evaluation; WOMAC: Western Ontario and McMaster OA index

*Rapid Response Report Summary of Abstracts: Summary based on the abstracts of the best available evidence.

†This report considered autologous blood injections to be either autologous whole blood or platelet-rich plasma. Studies comparing the use of whole blood and platelet-rich plasma did not demonstrate any substantial differences in efficacy. Therefore, the Committee considered it reasonable to evaluate the evidence on injection with either whole blood or platelet-rich plasma as equivalent treatments in this guidance.

Table 4. Selected Previous Systematic Reviews

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
Moraes (2014)[188] Database inception to varying dates†† Cochrane Bone, Joint and Muscle Trauma Group Specialized Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS	To assess the effects (benefits and harms) of platelet-rich therapies for treating soft tissues injuries.	Acute or chronic musculoskeletal soft tissue injuries, including: rotator cuff tears (arthroscopic repair, 6 RCTs), shoulder impingement syndrome surgery (1 RCT), elbow epicondylitis (3 RCTs), ACL reconstruction (6 RCTs), patellar tendinopathy (1 RCT), Achilles tendinopathy (1 RCT), and Achilles rupture surgical repair (1 RCT).	Platelet-rich therapies vs. placebo, ABI, or dry needling vs. no platelet-rich therapy	Function Disabilities of the Arm, Shoulder, and Hand Questionnaire, VISA-A, AOFAS foot questionnaire Pain VAS Adverse events	17 RCTs and 2 quasi-RCTs (1088 patients)	Yes	Yes	Function Data from pooled analyses showed no difference between PRP and control therapies up to 3 months (4 trials, 3 conditions), 6 months (5 trials, 5 conditions) or 12 months (10 trials, 5 conditions) follow-up. Pain There is very low quality evidence suggesting a marginally significant reduction in pain with PRP versus control up to 3 months (4 RCT, 3 conditions) Adverse Events There is weak evidence across four RCTs that adverse events occur at comparable, low rates in patients treated with PRP and those who are not (another 7 trials reported an absence of adverse events). Overall: Overall, and for the individual clinical conditions, there is currently insufficient evidence to support the use of PRP for treating musculoskeletal soft tissue injuries.
Kearney (2015)[131] Database inception to	To assess the effects (benefits and harms) of injection therapies for people with Achilles	Achilles tendinopathy	Injection therapies‡ vs. placebo injection vs. no injection	Function VISA-A Pain VAS	18 studies, study type NR (732 patients)	Yes	Yes	Function Low quality evidence from pooled analyses showed no difference in function between injection therapies and placebo and/or no injection at 6 weeks (5 trials), 3 months (5 trials), or 6-

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
April 20, 2015 Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED, CINAHL, and SPORTDiscus	tendinopathy.			Adverse events				12 months (3 trials) Pain Very low quality evidence from a pooled analysis favored injection therapies compared with placebo and/or no injection therapies for pain reduction up to 3 months (7 trials) Adverse Events Very low quality evidence from a pooled analysis of 13 trials showed no significant difference between groups in the risk adverse events, most of which were minor and short-lasting.
Laudy (2014)[149] Database inception to June 2014 MEDLINE, EMBASE, CINAHL, CENTRAL, Web of Science, and PEDro	To assess the effectiveness of PRP injections in treating knee osteoarthritis.	Knee osteoarthritis (monolateral or bilateral)	PRP vs. HA injection PRP vs. saline injection	Function WOMAC Lequesne Algofunctional Index Pain VAS NRS	6 RCTs (5 for PRP vs. HA; 1 for PRP vs. saline) 4 non-RCTs, PRP vs. HA) (1110 patients)	Yes	Yes	Function PRP injections are more effective at improving function compared with HA injections (limited to moderate evidence)§ and saline injections (limited evidence)§ at 6 months. Pain PRP injections are more effective at reducing pain compared with HA injections (moderate evidence)§ and saline injections (limited evidence)§ at 6 months.

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
Meheux (2015)[178] Database inception to February 12, 2015 PubMed, Cochrane Central Register of Controlled Trials, SCOPUS, and SPORTDiscus	To determine whether PRP injections improve outcomes in knee osteoarthritis at 6 and 12 months; to determine differences between outcomes for PRP and corticosteroid injections or visco-supplementation or placebo injections at 6 to 12 months; and to investigate whether outcomes vary based on the PRP formulation used.	Knee osteoarthritis	PRP vs. HA injection PRP vs. normal saline injection	Function WOMAC IKDC Tegner Activity Level Rating Scale Lequesne Algofunctional Index Pain WOMAC VAS Quality of Life SF-36	6 RCTs (5 for PRP vs. HA; 1 for PRP vs. saline) (739 patients)	Yes	No	Function There is moderate evidence suggesting that PRP injections are more efficacious than HA and saline at improving function up to 12 months post-injection (5/6 trials showed significant differences) Pain The evidence suggests that PRP injections are more efficacious than HA and saline at decreasing pain up to 12 months post-injection (5/6 trials showed significant differences) Quality of Life PRP significantly improved both the PCS and MCS subscales of the SF-36 compared to HA (data from 1 RCT). *Strength of Recommendation* for this review – "B"**
Chang (2014)[41] Database inception to September 2013 PubMed and SCOPUS	To assess the effectiveness of PRP in treating cartilage degenerative pathology in knee joints.	Knee chondral degenerative lesions	PRP vs. HA injection or placebo	Function IKDC KOOS WOMAC Adverse Events Various	8 single-arm studies 3 quasi-experimental studies 5 RCTs (1543 patients)	Yes	Yes	Function The evidence suggests that PRP injections are associated with significantly greater functional improvement at 2 and 6 months compared with HA (16 studies; similar results when only the 4 RCTs were pooled) and saline (1 RCT); however, due to the low methodological quality of the included trials, these results should be interpreted with caution. Adverse Events PRP and HA injections resulted in a similar risk of post injection discomfort

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								(8 trials).
Kanachanatwan (2015)[124] Database inception to August 13, 2015 MEDLINE and SCOPUS	To compare the outcomes and adverse events associated with treatment of knee osteoarthritis with platelet-rich plasma, hyaluronic acid, or placebo.	Knee osteoarthritis	Platelet-rich plasma injection vs. hyaluronic acid injection or placebo	Function WOMAC Lequesne Algofunctional Index IKDC EQ-VAS Adverse Events	8 RCTs (6 for PRP vs. HA; 1 for PRP vs. saline*; 1 for PRP vs. placebo) (total number of patients included NR)	Yes	Yes	Function PRP was associated with better short-term (≤1 year) functional outcomes (WOMAC, IKDC, and EQ-VAS) than that of treatment with HA or placebo. Adverse Events No statistically significant differences between adverse events associated with PRP, HA, or placebo treatment were observed. *Quality of Evidence* for this review – "2B"†

ABI: autologous whole blood injections; ACL: Anterior cruciate ligament; AOFAS: American Orthopedic Foot and Ankle Society; HA: hyaluronic acid; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; NRS: Numeric Rating Scale; PRP: platelet-rich plasma; SF-36: Short Form-36; VAS: visual analog scales; VISA-A: Victorian Institute of Sport Assessment-Achilles questionnaire; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

* Kanachanatwan (2015) classified saline as placebo.

† Using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE), a 2B grade indicates an intermediate-strength recommendation which is based on individual cohort studies or low quality randomized controlled trials.

‡ Includes platelet-rich plasma injections, but results not stratified by injection type.

§ Level of evidence is rated as "limited" due to the high risk of bias and "moderate" due to the generally high risk of bias.

** Using the Strength of Recommendation Taxonomy (SORT), a B-level recommendation is based on inconsistent or limited-quality patient-oriented evidence.

†† Cochrane Bone, Joint and Muscle Trauma Group Specialized Register (March 25, 2013), the Cochrane Central Register of Controlled Trials (2013, Issue 2), MEDLINE (March 2013), EMBASE (2013 Week 12) and LILACS (March 2012).

2.6. Medicare and Representative Private Insurer Coverage Policies

Individual payer websites, the Centers for Medicare and Medicaid Services (CMS) website, and Google were searched for coverage decisions on the use of platelet-rich plasma (PRP) injections or autologous blood injections (ABI) for the treatment of musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain. Policy plans were identified from eight payers, three of which are bellwether national payers. Coverage policies are consistent and do not support coverage of PRP or ABI across numerous pathologies, including all those of interest to this report.

Coverage decisions are summarized briefly below and policy details are provided in Table 5.

Centers for Medicare Service (CMS): National Coverage Determination for Blood-Derived Products for Chronic Non-Healing Wounds
The Centers for Medicare and Medicaid Services (CMS) has determined that PRP – an autologous blood-derived product – will be covered only for the treatment of chronic non-healing diabetic, venous and/or pressure wounds and only when (certain) conditions are met.

Aetna Policy: Blood Product Injections for Selected Indications
Aetna considers ABI to be experimental and investigational for the treatment of tendinopathies and all other indications because its effectiveness has not been established.
Aetna considers PRP to be injections experimental and investigational for all indications, including (but not limited to) the following, because its effectiveness has not been established:

- Achilles tendon ruptures
- Ankle sprains
- Gastrocnemius (calf) tears
- Hamstring injury
- Hip and knee osteoarthritis
- Plantar fasciitis
- Temporomandibular joint (TMJ) osteoarthritis
- Tendinopathies

Anthem Medical Policy: Growth Factors, Silver-based Products and Autologous Tissues for Wound Treatment and Soft Tissue Grafting
Anthem does not consider the use of PRP, including autologous conditioned plasma (ACP), to be medically necessary and is considered investigational for all treatment indications including, but not limited to soft tissue injuries.

Cigna Medical Coverage Policy: Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP])
Cigna does not cover the use of autologous platelet-derived growth factors (also known as PRP, platelet gel, platelet-rich concentrate, autogenous platelet gel, or platelet releasate) for ANY condition or indication, including the following, because their use is considered experimental, investigational, or unproven:

- Anterior cruciate ligament (ACL) repair
- Degenerative joint disease
- Epicondylitis

- Muscle injuries and disorders
- Knee osteoarthritis
- Plantar fasciitis
- Soft tissue trauma
- Tendonitis

Group Health Clinical Review Criteria: Platelet Rich Plasma
The use of autologous platelet derived wound healing factors in the treatment of tendinopathy does not meet the Group Health Medical Technology Assessment Criteria.

Harvard Pilgrim Health Care Medical Policy: Dry Needling and Platelet-rich Plasma Injections
Harvard Pilgrim does not cover PRP injections. They are considered experimental/ investigational and unproven for the following:

- Tendinopathies (elbow, knee, shoulder, and heel)
- Other musculoskeletal injuries

Health Net Inc. National Medical Policy: Blood Product Injections for Tendinopathies (e.g., Autologous Blood Injection, Platelet-Rich Plasma Injections)
Health Net Inc. considers ABI, autologous PRP injections, autologous PRP gel, and bone marrow plasma injections investigational for all indications, including but not limited to:

- Various tendinopathies
- Plantar fasciitis

Premera Blue Cross Medical Policy: Orthopedic Applications of Platelet-Rich Plasma
Premera Blue Cross considers the use of PRP to be investigational for all orthopedic indications. This includes, but is not limited to:

- Achilles tendinopathy
- Lateral epicondylitis
- Osteochondral lesions
- Osteoarthritis
- Plantar fasciitis
- ACL reconstruction
- Patellar tendon repair
- Rotator cuff repair

Table 5. Overview of payer technology assessments and policies

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Centers for Medicare Services (CMS) National Coverage Determination (NCD) for Blood-Derived Products for Chronic Non-Healing Wounds (270.3) Last review: NR Next review: NR	NR	NR	The Centers for Medicare and Medicaid Services has determined that PRP – an autologous blood-derived product – will be covered only for the treatment of chronic non-healing diabetic, venous and/or pressure wounds and only when (certain) conditions are met.	NR
Aetna Blood Product Injections for Selected Indications (0784) Last review: 11/24/2015 Next review: 09/23/2016	NR	<u>ABI for TMJ osteoarthritis:</u> 1 review 4 prospective clinical trials 3 case reports <u>ABI for tendinopathies:</u> 1 prospective cohort 2 RCTs 2 type NR <u>PRP for Achilles tendon ruptures:</u> 1 RCT 2 SRs 1 type NR <u>PRP for ankle sprains:</u> 1 type NR <u>PRP for gastrocnemius (calf) tear:</u> NR <u>PRP for hamstring injury:</u> 1 RCT 1 meta-analysis	Aetna considers ABI experimental and investigational for the treatment of tendinopathies and all other indications because its effectiveness has not been established. Aetna considers PRP injections experimental and investigational for all indications including the following because its effectiveness has not been established: • Achilles tendon ruptures • Ankle sprains • Gastrocnemius (calf) tears • Hamstring injury • Hip and knee osteoarthritis • Plantar fasciitis • Temporomandibular joint osteoarthritis • Tendinopathies	CPT Code not covered for indications listed in the CPB: 0232T HCPCS Codes not covered for indications listed in the CPB: P9020 ICD-10 Codes not covered for indications listed in the CPB: M15.0-M19.93, M22.40-M22.42, M70.031-M79.9, S83.401+ - S83.409+, S83.8X1+ - S83.8X9+, S86.111+ - S86.119+, S86.211+ - S86.219+, S86.311+ - S86.319+, S86.811+ - S86.819+

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
		1 type NR PRP for hip osteoarthritis: 1 type NR PRP for knee osteoarthritis: 1 pilot study 3 type NR PRP for plantar fasciitis: 1 type NR PRP for TMJ osteoarthritis: NR PRP for tendinopathies: NR		
Anthem Growth Factors, Silver-based Products and Autologous Tissues for Wound Treatment and Soft Tissue Grafting (MED.00110) Last review: 04/07/2015 Next review: NR	NR	PRP for soft tissue injuries: 16 RCTs 1 SR 2 type NR	Anthem does not consider the use of PRP, including ACP, to be medically necessary and is considered investigational for all treatment indications including: • Soft tissue injuries	CPT code when services are also investigational and not medically necessary: 0232T
Cigna Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP]) (0507) Last review: NR Next review: 09/15/2015	NR	PRP for ACL repair: 2 RCTs PRP for degenerative joint disease: 1 prospective case series PRP for epicondylitis: 1 RCT 1 SR PRP for muscle injuries and disorders: NR PRP for knee osteoarthritis:	Cigna does not cover the use of autologous platelet-derived growth factors* for ANY condition or indication, including the following, because their use is considered experimental, investigational, or unproven: • ACL repair • Degenerative joint disease • Epicondylitis • Muscle injuries and disorders • Knee osteoarthritis	CPT Code 0232T HCPCS Code S9055

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
		1 SR 1 health technology forecast PRP for plantar fasciitis: 1 SR PRP for soft tissue trauma: 1 RCT PRP for tendonitis: NR	• Plantar fasciitis • Soft tissue trauma • Tendonitis	
Group Health Platelet Rich Plasma – Injections for the Treatment of Non-Healing Fractures and Tendinopathy Last review: 04/07/2015 Next review: NR	NR	PRP for tendinopathy: 2 RCTs	The use of Autologous Platelet Derived Wound Healing Factors* in the treatment of Tendinopathy does not meet the *Group Health Medical Technology Assessment Criteria*.	NR
Harvard Pilgrim Health Care Dry Needling and Platelet-rich Plasma Injections Last review: 12/2013 Next review: NR	NR	PRP for tendinopathy and other musculoskeletal injuries: 4 SRs 1 RCT 1 consensus paper 3 type NR PRP for ACL repair: 5 type NR	Harvard Pilgrim does not cover PRP injections. They are considered experimental/ investigational and unproven for the following: • Tendinopathies (elbow, knee, shoulder, and heel) • Other musculoskeletal injuries	CPT Codes: 20552, 20553, 38206, 86999
Health Net Inc. Blood Product Injections for Tendinopathies (e.g. Autologous Blood Injection, Platelet-Rich Plasma Injections) (NMP195) Last review: 08/2015 Next review: NR	NR	PRP for tendinopathy and plantar fasciitis: 3 RCTs	Health Net Inc. considers ABI, autologous PRP injections, autologous PRP gel, and bone marrow plasma injections investigational for all indications, including but not limited to: • Various tendinopathies • Plantar fasciitis	CPT Codes: 0232T ICD-9 Codes: 736.10-726.12, 726.32, 726.64, 726.71, 728.71 ICD-10 Codes: M75.20-M75.22, M75.30-M75.32, M76.50-M76.52, M76.60-M76.62, M77.00-M77.02,

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
				M77.10-M77.12
Premera Blue Cross Orthopedic Applications of Platelet-Rich Plasma (2.01.98) Last review: N/A Next review: NR	Databases NR "Literature review through April 15, 2015"	PRP for Achilles tendinopathies: 1 RCT PRP for lateral epicondylitis: 1 SR PRP for osteochondral lesions: 1 quasi-RCT PRP for osteoarthritis: 5 RCTs 1 SR 3 quasi-RCTs 8 prospective single-arm studies PRP for plantar fasciitis: 3 RCTs 1 SR 8 prospective studies PRP for ACL reconstruction: 1 SR 11 RCTs or prospective cohorts 4 type NR PRP for patellar tendon repair: 1 RCT PRP for rotator cuff repair: 1 SR 8 RCTs 6 type NR	Premera Blue Cross considers the use of PRP to be investigational for all orthopedic indications. This includes, but is not limited to: • Achilles tendinopathy • Lateral epicondylitis • Osteochondral lesions • Osteoarthritis • Plantar fasciitis • ACL reconstruction • Patellar tendon repair • Rotator cuff repair	CPT Codes: 0232T, 86999 HCPCS Code: P9020

ABI: autologous blood injection; ACL: anterior cruciate ligament; ACP: autologous conditioned serum; CPB: Clinical Policy Bulletin; CPT: Current Procedural Terminology; HCPCS: The Healthcare Common Procedure Coding System; ICD: international classification of diseases; NMP: National Medical Policy; PRP: platelet-rich plasma.

*Also known as platelet-rich plasma, platelet gel, platelet-rich concentrate, autogenous platelet gel, or platelet releasate.

3. The Evidence

3.1. Methods of the Systematic Literature Review

3.1.1. Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of PRP in adults for treating musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain. The differential effectiveness and safety of PRP for subpopulations will be evaluated, as will the cost effectiveness.

Key Questions

In patients with musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain (evaluated separately):

1. What is the evidence of the short- and long-term efficacy and effectiveness of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?
2. What is the evidence regarding short- and long-term harms and complications of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?
3. Is there evidence of differential efficacy, effectiveness, or safety of autologous PRP or whole blood injections compared with alternative treatment options no treatment/placebo? Include consideration of age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation?
4. What is the evidence of cost-effectiveness of autologous PRP or whole blood injections compared with alternative treatment options?

3.1.2. Inclusion/exclusion criteria

Inclusion and exclusion criteria are summarized in Table 6. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Patients with musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, or low back pain.
- **Intervention:** Autologous PRP or whole blood injections (injections used in conjunction with other procedures such as surgery will be excluded).
- **Comparators:** Alternative treatment(s), placebo, or no treatment.
- **Outcomes:** Function (primary), pain (primary), time to recovery, return to normal activities (sports, work, or activity level), quality of life, patient satisfaction, recurrence, medication use, secondary procedures (e.g., surgery), adverse events (primary), cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcomes.
- **Study design**: Eligible studies compared autologous PRP or whole blood injections with an included comparator treatment utilizing a randomized or cohort study design. Case series specifically designed to evaluate harms/adverse events that enrolled at least 100 patients and that had follow-up of at least 70% of patients were considered for Key Question 2. Only RCTs

that stratified results by patient characteristics of interest so that statistical interaction (effect modification) could be evaluated were considered for Key Question 3; subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. For Key question 4, formal economic analyses were eligible for inclusion (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies).

Table 6. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Patients with any of the following conditions: • Musculoskeletal soft tissue injuries • Tendinopathies • Osteoarthritis, or • Low back pain:	• Cutaneous wounds • Bone fractures • Neurosurgery • Ophthalmological conditions • Cosmetic conditions • Maxillofacial surgery • Urological conditions • Cardiothoracic conditions • Dental conditions
Intervention	Autologous PRP or whole blood injections* used as the primary intervention or in conjunction with conservative care	• PRP or whole blood injections used in conjunction with another intervention (e.g., open or arthroscopic or minimally invasive surgery) • Other biologics (growth factor injections, etc.) • Whole blood injections for OA*
Comparator	• Alternative treatment(s) • Placebo	
Outcomes	• Function (primary) • Pain (primary) • Time to recovery • Return to normal activities (sports, work, or activity level) • Quality of life • Patient satisfaction • Recurrence • Medication use • Secondary procedures (e.g., surgery) • Adverse events (primary)	• Non-clinical outcomes

Study Component	Inclusion	Exclusion
Study Design	**Focus will be on studies with the least potential for bias.** **Key Questions 1-2:** • High quality systematic reviews will be considered if available. • Randomized controlled trials (RCTs) • High quality non-randomized comparative studies **Key Question 2:** • KQ2: High-quality non-comparative studies (case series) designed specifically to evaluate harms/adverse events. **Key Question 3:** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest. **Key Question 4:** • Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Indirect comparisons • Noncomparative studies (case series) (except as described to evaluate harms) • Incomplete economic evaluations such as costing studies • Studies with fewer than 10 patients per treatment group • Case reports • Studies in which <80% of patients have a condition of interest
Publication	• Studies published in English in peer reviewed journals or publically available FDA reports	• Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

*Whole blood injections will not be considered for osteoarthritis based on clinical expert input

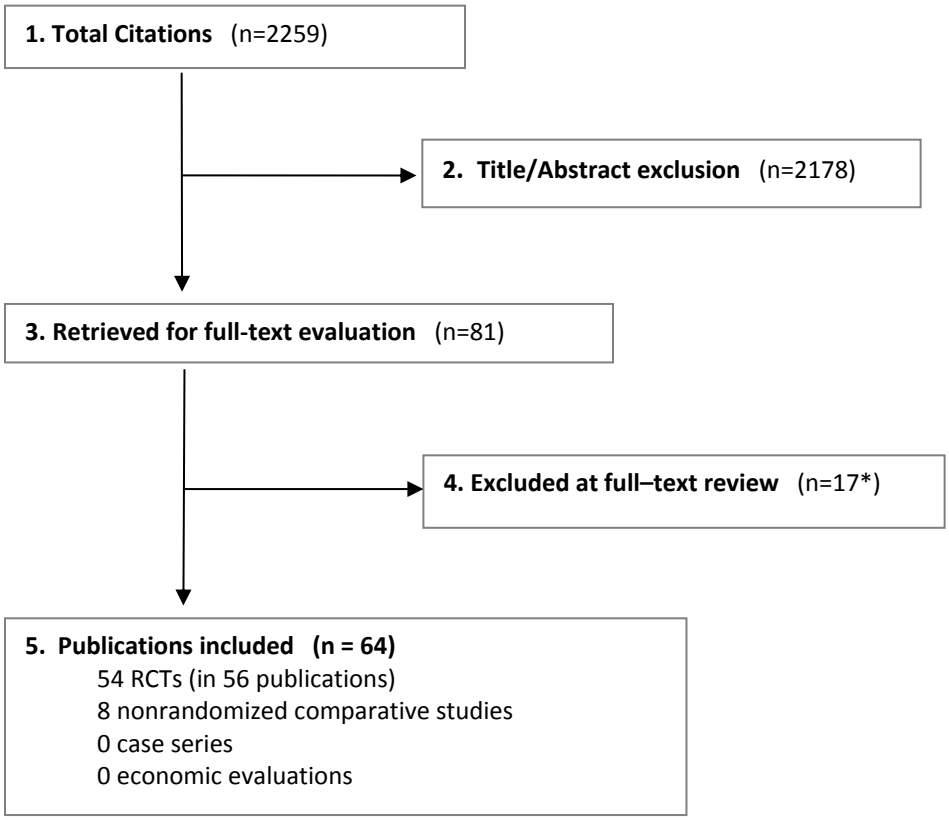
3.1.3. Data sources and search strategy

Electronic databases were searched from their inception through November 23, 2015. Electronic databases searched included PubMed, EMBASE, and AHRQ for eligible studies, including health technology assessments (HTAs), systematic reviews, and primary studies. The search strategies used for PubMed are shown in Appendix B; hand-searching was also conducted. Figure 2 shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed with reason for exclusion in Appendix C.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. All possible relevant articles were screened using titles and abstracts in stage two. This was done by one to two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final

stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Figure 2. Flow chart of literature search results



*Studies listed with reason for exclusion in Appendix C.

3.1.4. Data extraction

Reviewers extracted the following data from the studies included to address Key Questions 1-3: study design, country, setting, number of patients enrolled, inclusion and exclusion criteria, intervention details, use of dry needling and imaging guidance, co-interventions, patient characteristics (age, sex, duration of symptoms, baseline pain and function scores), length of follow-up, follow-up rate, study funding, clinical efficacy outcomes (function, pain, time to recovery, return to normal activities, quality of life, patient satisfaction, recurrence, medication use, secondary procedures), safety outcomes (adverse events, harms, complications), and differential efficacy or safety outcomes for any subgroup. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. Detailed study and patient characteristics is available in Appendix G, all results are available in the results section of this document.

3.1.5. Quality assessment: Overall Strength of evidence (SoE), Risk of Bias, and QHES evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine,[208] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,[15] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[294] Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[197] Details of the risk of bias and QHES methodology are available in Appendix D. Based on these quality criteria, each study chosen for inclusion for a Key Question was given a risk of bias (or QHES) rating; details of each study's rating with reasons for not given credit when applicable are available in Appendix E. Standardized abstraction guidelines were used to determine the risk of bias (or QHES) rating for each study included in this assessment. Observational studies were considered to have been conducted retrospectively unless clearly stated otherwise.

The strength of evidence for the overall body of evidence for all critical health outcomes was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ).[24] The strength of evidence was based on the highest quality evidence available for a given outcome. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results that are similar in terms of range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes.
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing.

Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was

observed, and large magnitude of effect (strength of association). Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

3.1.6. Analysis

Outcomes were stratified by duration of follow-up as short term (≤3 months), intermediate term (>3 months to <1 year), and long term (≥1 year). When more than one follow-up time was reported within a category, data from the longest duration available within that category was used.

Evidence for different conditions was analyzed separately. Based on clinical expert input, data for the various tendinopathies were analyzed separately rather than combined. PRP and ABI were assessed separately. Based on clinical expert input, conservative control treatments for tendinopathies and plantar fasciitis were combined in order to facilitate understanding the comparative impact of PRP (or ABI) compared with conservative control treatments. However, across all outcomes, subgroup analysis was performed to assess for potential heterogeneity due to differences in control treatment, outcomes measures, disease severity, duration of symptoms (mean symptom duration <6 vs. >6 months was used as a cut-off based on clinical expert input), use of leukocyte-rich or leukocyte-poor PRP (LR-PRP or LR-PRP) when that information was provided, number of injections, platelet concentration, risk of bias, or blinding of patients. If results varied by any subgroup assessed, results were stratified by that subgroup (e.g., use of steroid vs. anesthetic injection in the control group).

For Key Question 1, an attempt was made to pool results when there were two or more RCTs of similar quality and which employed similar interventions and outcome timing/interpretation. However, because of differences in study quality, RCTs were not pooled with nonrandomized studies. For all dichotomous outcomes, risk ratios (RR) and their respective 95% confidence intervals (CI) were calculated to compare the rate of occurrence between treatments. For those dichotomous outcomes that could be pooled, risk ratios and figures were produced using Review Manager v5.2.6 and the difference within each study was weighted and pooled using the Mantel-Haenszel method. For those dichotomous outcomes that could

not be pooled, risk ratios were calculated using the Rothman Episheet (www.krothman.org/episheet.xls).

For all continuous outcomes, mean differences (MD) and their respective 95% confidence intervals were calculated. For outcomes that could be pooled, mean differences were weighted according to the inverse of their variance; results and figures were produced using Review Manager v5.2.6. The more conservative random effects model was assumed to account for inter-study variability. In some instances, when a study did not report effect sizes for individual treatments, the standard deviation was imputed by taking the average from other studies within respective subgroups. If outcome measures with different scales were reported, the standard deviation (SD) was first scaled before being averaged, and standardized mean differences (SMD) were calculated by dividing the MD by the SD. In some studies, standard errors (SE) or 95% confidence intervals were reported in lieu of standard deviations; these values were converted to standard deviations: SD = SE*√n), and SE = (95% CI upper bound – 95% CI lower bound) ÷ 3.92. In some studies, the follow-up SD had to be calculated from the baseline (B) and change (C) SD: follow-up SD = $\left[-1.6B \pm \sqrt{[(-1.6B)^2 - 4(B^2-C^2)]}\right] \div 2$. If the standard deviation of the change score needed to be calculated the correlation between baseline and follow-up scores was assumed to be 0.8. Baseline scores were assessed for imbalances by determining whether the difference between groups was had the potential to be clinically meaningful as recommended by AHRQ.[91] For outcomes in which there was a potential baseline imbalance between treatment groups, both follow-up and change scores were considered, and the focus of the results was placed on the estimate which provided the more conservative estimate (i.e., the estimate that shows the least difference between groups).

For Key Question 1, the focus was placed on validated outcome measures, which are described in Table 1. The primary outcome measures were those which measured function and pain; these were designated primary outcomes a priori based on clinical expert input. Information on the minimal clinically important difference (MCID) was obtained for the population being evaluated whenever statistical differences were found between groups (Table 1). Based on recommendations from both AHRQ[90] and Cochrane[274] methods guides, continuous outcomes were not placed in context of MCID, as the relationship between outcome scores and the percentage of patients who achieved a defined measure of success (e.g., responders) requires further research. Data on the percentage of "responders," or patients who achieved a defined measure of success (such as ≥50% pain reduction on VAS) was evaluated separately. In the SoE tables, such data was referred to as pain or function success.

4. Results

4.1. Key Question 1: Efficacy and effectiveness

4.1.1. Number of studies retained

Overall, 54 randomized trials (in 56 publications) and 8 cohort studies were included. The selection of the studies are summarized in Figure 2. The comparisons evaluated and their respective studies are listed in Table 7; comparisons of interest not listed in the table below had no comparative evidence available that met the inclusion criteria. Diagnoses for which comparative evidence was identified include tendinopathies (elbow epicondylitis, Achilles tendinopathy, patellar tendinopathy, rotator cuff tendinosis and/or partial tears), plantar fasciitis, acute injuries (acute muscle injuries, Achilles tendon rupture, ankle sprain), osteochondral lesions of the talus, temporomandibular joint (TMJ) dislocation, and osteoarthritis (OA) (knee OA, hip OA, and TMJ OA). No comparative studies were identified that met the inclusion criteria for any other diagnosis of interest.

Table 7. Number of studies for each comparison of efficacy for included conditions of the lumbar and cervical spine.

Comparisons	Studies
TENDINOPATHIES	
Elbow Epicondylitis	
PRP vs. ABI	4 RCTs[55,215,216,273]
PRP vs. Conservative Control	8 RCTs (9 publications)[18,92,96,143,150,184,205,263,302], 2 cohort studies[272,278]
PRP vs. Surgery	1 cohort study[83]
ABI vs. Conservative Control	6 RCTs[14,68,120,129,202,253]
Achilles Tendinopathy	
PRP vs. Conservative Control	2 RCTs (in three publications)[61,64,130]
ABI vs. Conservative Control	2 RCTs[20,204]
Patellar Tendinopathy	
PRP vs. Conservative Control	2 RCTs[70,284]
Rotator Cuff Tendinosis and/or partial tears	
PRP vs. Conservative Control	2 RCTs[134,221], 1 cohort study[287]
PLANTAR FASCIITIS	
PRP vs. Conservative Control	5 RCTs[43,114,135,186,277], 3 cohort studies[7,245,248]
ABI vs. Conservative Control	3 RCTs[123,140,153]
ACUTE INJURIES	
Acute Muscle Injuries	
PRP vs. Conservative Control	4 RCTs[35,100,192,219]
Achilles Tendon Rupture	
PRP vs. Conservative Control	1 cohort study[125]

Comparisons	Studies
Ankle Sprain	
PRP vs. Conservative Control	1 RCT[235]
OSTEOCHONDRAL LESIONS OF THE TALUS	
PRP vs. Hyaluronic Acid (HA)	1 RCT[180]
TEMPOROMANDIBULAR JOINT (TMJ) DISLOCATION	
ABI vs. Surgery	1 RCT[104]
OSTEOARTHRITIS (OA)	
Knee OA	
PRP vs. HA	6 RCTs[39,80,95,214,242,281], 4 cohort studies[141,241,246,260]
PRP vs. Corticosteroid	1 RCT[84]
PRP vs. Saline	2 RCTs[95,203]
PRP vs. Exercise ± TENS	2 RCTs[10,218]
Hip OA	
PRP vs. HA	1 RCT[17]
TMJ OA	
PRP vs. HA	1 RCT[105]

ABI: autologous blood injection; HA: hyaluronic acid; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized control trial; TENS: transcutaneous electrical nerve stimulation; TMJ: temporomandibular joint

4.1.2. Elbow Epicondylitis

Summary of results

PRP vs. ABI: Four RCTs[55,215,216,273] (and no cohort studies) were included which enrolled between 28 and 150 patients; the trials were found to be at moderately low (3 RCTs) or moderately high (1 RCT) risk of bias. With respect to primary outcomes, the report concluded that in the short-term, there was greater improvement with PRP versus ABI in function (4 RCTs) and pain (3 RCTs) scores based on low quality evidence. In the intermediate-term, while there was greater improvement with PRP versus ABI in function (3 RCT), there was no difference between groups in pain (2 RCTs) based on low quality evidence. There was insufficient quality evidence for the following primary outcomes: no difference between groups in long-term function and pain (1 RCT for each), and no difference between groups in the percentage of patients who achieved pain success at any time point (1 RCT). There was no evidence on function success. With respect to secondary outcomes, there was no difference between groups in the intermediate-term risk of surgery or the composite outcome of function success and no surgery (1 RCT).

PRP vs. Control: Eight RCTs (in nine publications)[92,96,205,143,302,150,18,184,263] and two prospective cohort studies[272,278] were included. The trials enrolled between 25 and 240 patients and were found to be at moderately high (6 RCTs) or moderately low (2 RCTs) risk of bias. The RCTs compared PRP to steroid injections (5 RCTs) or anesthetic injections (2 RCTs); one RCT compared PRP plus dry needling (DN) to DN alone. With respect to primary outcomes, in the short-term, there were no differences between PRP and control groups in any primary outcomes, including pain scores (7 RCTs, moderate quality

evidence), pain or function success (1 RCT for each, low quality evidence), or in function scores (7 RCTs, insufficient quality evidence). In the intermediate term, low quality evidence suggested that PRP (versus control) resulted in significantly better function scores (5 RCTs), pain scores (3 RCTs), and pain success (1 RCT- for PRP vs. steroid or anesthetic only), while there was low quality evidence of no difference between groups in function success (1 RCT). In the long-term, there was low quality evidence of better function scores (3 RCTs), pain scores (2 RCTs), and pain success (1 RCT) with PRP versus control; there was insufficient quality evidence for long-term function success with inconsistent results between the 2 RCTs reporting. With respect to secondary outcomes, results were mixed, with one RCT reporting that fewer additional procedures with PRP versus steroid through the long-term, while another RCT found that PRP patients were less likely than steroid patients to achieve full recovery/no symptoms in the short-, intermediate-, and long-term. The cohort studies were at moderately high risk of bias and enrolled 52 and 81 patients; both compared PRP to low level laser radiation therapy. While one study reported no difference between groups in short-, intermediate-, and long-term pain and function, the other found better pain scores in the PRP group at these same time points.

PRP vs. Surgery: One moderately high risk of bias retrospective cohort study[83] (N=78) (and no RCTs) was included and found no differences between groups in function, pain, symptoms, and secondary outcomes through the intermediate-term (mean 10-12 months follow-up).

ABI vs. Control: Six moderately high risk of bias RCTs[14,68,120,129,202,253] (three of which were quasi-randomized) and no cohort studies were included that compared ABI to a conservative control treatment (steroid in all 6 trials, one of which also compared ABI to extracorporeal shock wave therapy (ESWT)). Trial size ranged from 50 to 80 patients. With respect to primary outcomes, in the short-term, there was low quality evidence of better function and pain scores (3 RCTs + 1 quasiRCT each) with ABI. In the intermediate-term, while pain scores were better with ABI versus steroid (2 RCTs, low quality evidence), there was insufficient evidence regarding any difference between groups in function scores (1 quasiRCT). In addition, there was insufficient quality evidence and unclear results for the following: long-term function (1 quasiRCT), short-term pain success (1 RCT + 1 quasiRCT), and intermediate-term pain success (better with ABI, 1 RCT). There was no evidence on function success for any time point or for long-term pain or pain success. No secondary outcomes were reported.

4.1.2.1. PRP vs. ABI for elbow epicondylitis

Studies included

Four RCTs compared PRP to ABI (Creaney 2011[55], Raeissadat 2014a[215], Raeissadat 2014b[216], Thanasas 2011[273]); no cohort studies were identified. Detailed information on patient and study characteristics is available in Appendix Table F1. Trials enrolled between 28 and 150 patients, with 14 to 80 patients allocated to PRP and 14 to 70 patients allocated to ABI. For inclusion, all patients were required to have chronic elbow epicondylitis, with a minimum duration of symptoms of 3 to 6 months. Mean duration of symptoms in two trials was 15 months (both Raeissadat trials) and a third trial reported median duration of symptoms to be 5 months; Creaney et al. only reported a 6-month minimum duration of symptoms and also required that patients have failed conservative therapy such as physical therapy. Imaging guidance was used in two trials (Creaney, Thanasas); three trials employed a peppering technique in both groups (both Raeissadat RCTs, Thanasas). Three trials performed one injection only, while a fourth trial employed a total of two injections over a one-month period (in both groups) (Creaney). Other than a potential baseline imbalance in PRTEE score between PRP and ABI groups in one trial (45.8 vs. 52.5) (Creaney), baseline characteristics were similar between groups. Methodological limitations included

unclear allocation concealment (Creaney), unclear random sequence generation (Creaney), failure to report intention-to-treat analyses (both Raeissadat RCTs), and failure to control for potentially confounding differences in baseline characteristics (Creaney). Patients were blinded in one trial (Creaney), but blinding was unclear (both Raeissadat RCTs) or not done (Thanasas) in the remaining trials. Overall, three trials were considered to be at moderately low risk of bias (both Raeissadat RCTs, Thanasas), and one was considered to be at moderately high risk of bias (Creaney).

Efficacy Results

Function

All four trials reported function outcomes using continuous outcome measures, including the clinician-reported PRTEE and MMCPIE and the patient- and clinician-reported Liverpool elbow score (Figure 3).[55,215,216,273] The PRP group had significantly better functional outcomes than the ABI group in both the short-term (SMD 0.31 (95% CI 0.06, 0.56), 4 RCTs[55,215,216,273]) and intermediate-term (SMD 0.48 (95% CI 0.21, 0.75), 3 RCTs[55,215,273]). One trial[215] found no significant differences between groups in long-term MMCPIE scores (SMD 0.27 (95% CI -0.23, 0.78)) (Raeissadat 2014a). Symptom duration had no apparent impact on the results: only one trial[273] (Thanasas) reported a mean symptom duration of less than six months, and results were similar to those of the other studies (Figure 3).

Pain

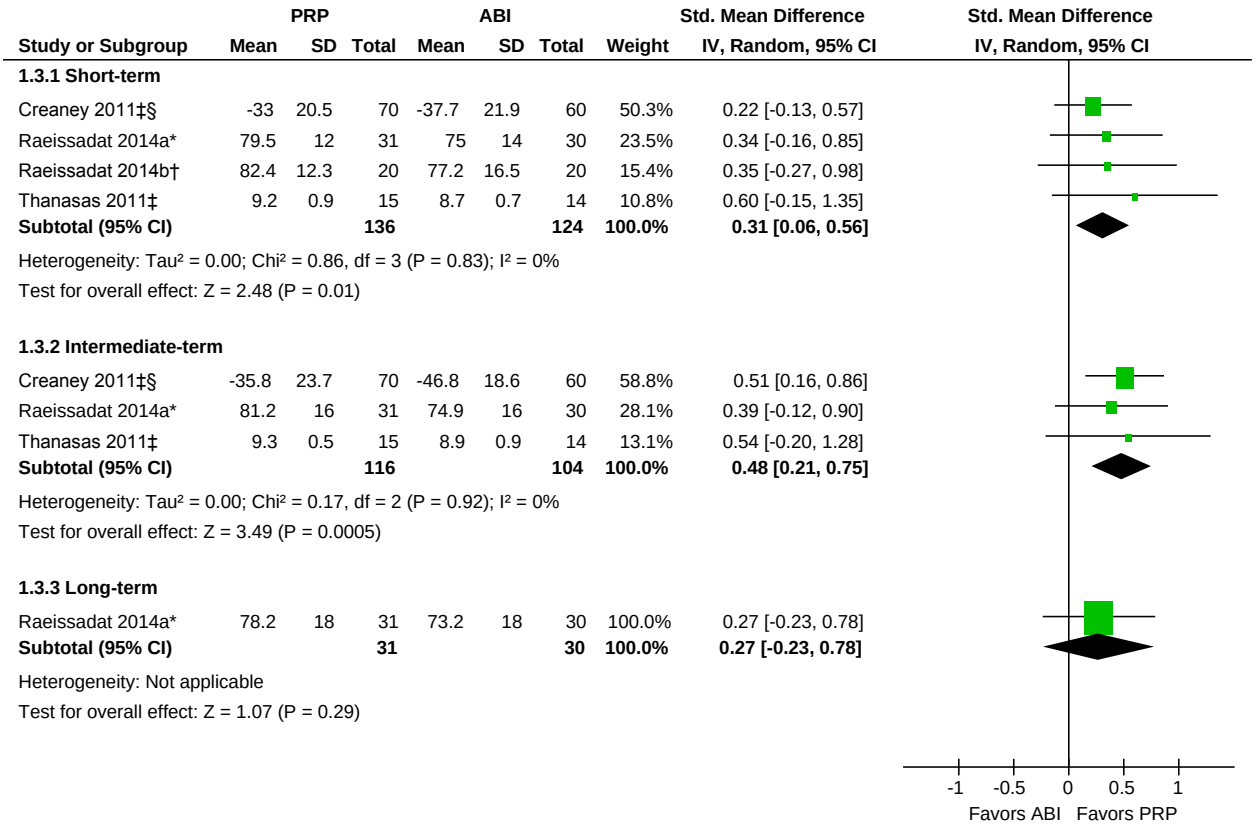
Three trials[215,216,273] evaluated pain outcomes (both Raeissadat RCTs, Thanasas). One trial[215] (Raeissadat 2014a) reported no significant differences in the percentage of patients who achieved 25% improvement in VAS scores at any time point (75% vs. 73% in the short-term, 81% vs. 77% in the intermediate-term, 75% vs. 60% in the long-term (RR 1.2 (95% CI 0.9, 1.8)) (Table 8). No MCID information was found for VAS pain in patients with elbow epicondylitis. Three trials[215,216,273] (both Raeissadat RCTs, Thanasas) reported patient-evaluated VAS pain (0-10 (worst)) (Figure 4). Pooled results suggest that short-term pain was significantly better in the PRP group (WMD -0.8 (95% CI, -1.3, -0.2), 3 RCTs[215,216,273]). However, there were no differences between groups in intermediate-term (WMD -0.6 (95% CI -1.4, 0.1), 2 RCTs[215,273]) or long-term pain outcomes (3.3 vs. 3.9, MD -0.6 (-1.8, 0.6), 1 RCT[215]). Symptom duration had no apparent impact on the results: only one trial[273] (Thanasas) reported a mean symptom duration of less than six months, and results were similar to those of the other studies (Figure 4).

Other outcomes

<u>*Surgery:*</u> One trial[55] (Creaney) found no difference between PRP and ABI groups in the intermediate-term risk of surgery (10% vs. 20%, RR 0.5 (95% CI 0.2, 1.2)) (Table 9).

<u>*Composite of function and surgery*</u>: One trial[55] (Creaney) reported a composite outcome of "success", which was defined as an improvement in PRTEE (function) by at least 25 points from baseline plus no surgery. A similar proportion of PRP and ABI groups achieved "success" in the intermediate-term (66% vs. 72%, RR 0.9 (95% CI 0.7, 1.2)) (Table 9).

Figure 3. Elbow Epicondylitis RCTs comparing PRP to ABI: SMD Function



*Raeissadat 2014a "Is platelet…"
†Raeissadat 2014b "Effect…"
‡SD calculated from study-reported 95% CI
§Study-reported change from baseline

Outcome measures reported:
-Creaney: inverse of ΔPRTEE (thus PRTEE (0-100 (best))
-Raeissadat 2014a, 2014b: MMCPIE (0-100 (best))
-Thanasas: Liverpool elbow score (0-10 (best))

Table 8. Elbow epicondylitis RCTs for PRP vs. ABI: 25% improvement in VAS

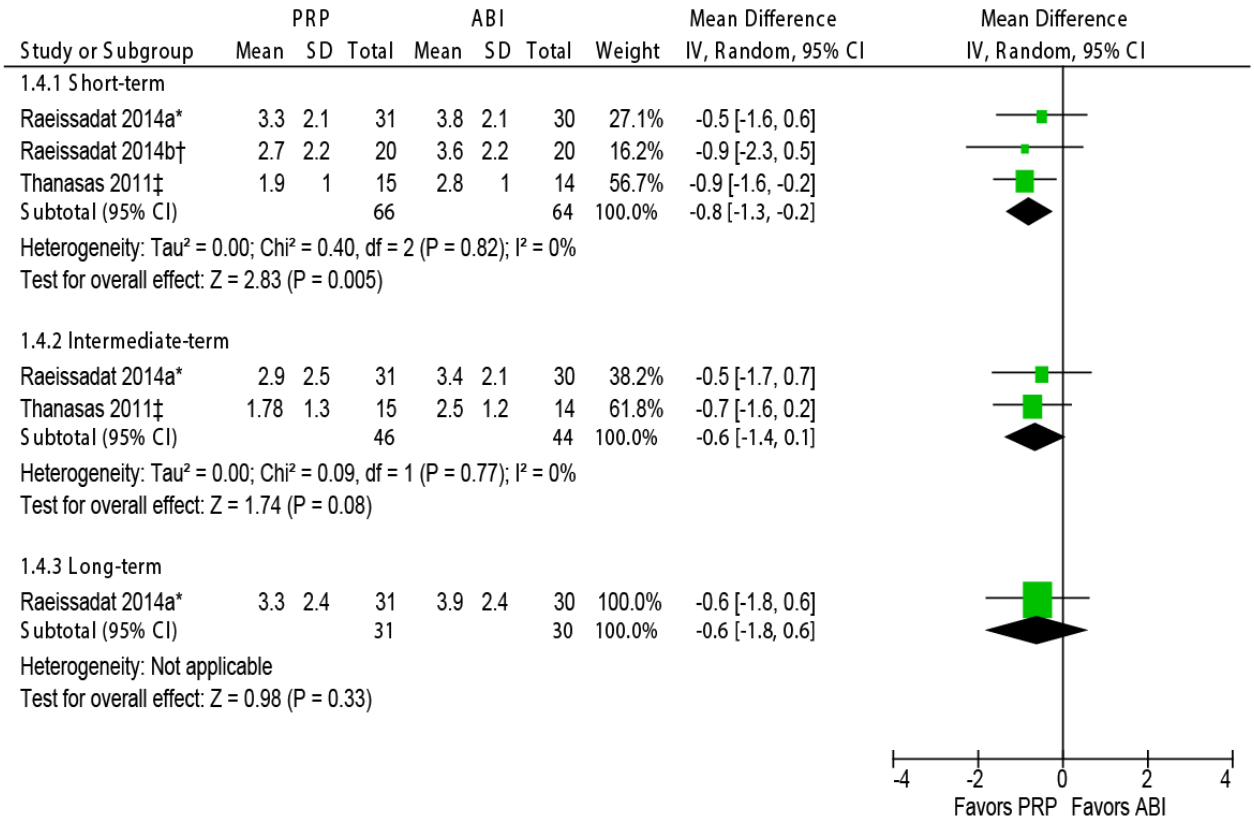
Study	F/U (months)	PRP % (n/N)	ABI % (n/N)	RR (95% CI)†	p-value†
Raeissadat 2014(a)*	2 mos.	75% (23/31)	73% (22/30)	1.0 (0.7, 1.4)	NS
	6 mos.	81% (25/31)	77% (23/30)	1.1 (0.8, 1.4)	NS
	12 mos.	75% (23/31)	60% (18/30)	1.2 (0.9, 1.8)	NS

ABI: autologous blood injection; CI: confidence interval; F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio; VAS: Visual Analog Scale

*Raeissadat 2014 "Is platelet…"

†Calculated unless otherwise indicated

Figure 4. Elbow Epicondylitis RCTs comparing PRP to ABI: WMD VAS Pain



*Raeissadat 2014 "Is platelet…"
†Raeissadat 2014 "Effect…"
‡SD calculated from study-reported 95% CI

Table 9. Elbow epicondylitis RCTs for PRP vs. ABI: Other outcomes

Study	F/U	Outcome Measure	PRP % (n/N)	ABI % (n/N)	RR (95% CI)*	p-value*
Creaney 2011	6 mos.	Surgery	10% (7/70)	20% (12/60)	0.5 (0.2, 1.2)	NS
		Success (ΔPRTEE ≥25 points + no surgery)	66% (46/70)	72% (43/60)	0.9 (0.7, 1.2)	NS

ABI: autologous blood injection; CI: confidence interval; F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; PRTEE: Patient-Rated Tennis Elbow Evaluation; RCT: randomized controlled trial; RR: risk ratio

*Calculated unless otherwise indicated

4.1.2.2. PRP vs. Conservative Control for elbow epicondylitis

Studies included

In sum, eight trials (in nine publications) and two cohort studies compared PRP to a conservative control intervention.

RCTs: Eight trials (in nine articles) compared PRP to an injection or dry needling control. Of these, five RCTs compared PRP (n=15-53) to steroid injections (n=15-49) (Gautam 2015[92], Gosens 2011[96]/Peerbooms 2010[205], Krogh 2013[143], Yadav 2015[302], Lebiedzinski 2015[150]) – one of which also compared PRP (n=20) to saline injections (n=20) (Krogh 2013[143]). While two RCTs compared PRP (n=15-116) to local anesthetic injection (n=10-114), one used a leukocyte-rich preparation (LR-PRP, Mishra 2014[184]) and the other used a leukocyte-poor PRP (LP-PRP, Behera 2015[18]). One trial compared PRP plus dry needling (n=15) to dry needling alone (n=13) (Stenhouse 2012[263]). Detailed information on patient and study characteristics is available in Appendix Tables F2 and F3. Total trial size ranged from 25 to 240 patients. Minimum duration of symptoms ranged from 1.5 to 6 months in seven trials reporting this variable. Mean duration of symptoms was relatively short (1.9-2.2 months) in one trial (Yadav) and was more chronic (10-36 months) in three trials (Krogh, Behera, Stenhouse); the remaining four trials did not report mean duration of symptoms (Gautam, Gosens, Lebiedzinski, Mishra). Five trials required failure of previous conservative therapy (Gautam, Gosens, Mishra, Behera, Stenhouse). PRP injectate volume ranged from 1 to 3 ml in the six trials reporting this information; local anesthetic was injected with PRP in four trials (Gosens, Lebiedzinski, Mishra, Stenhouse), and epinephrine was also injected with PRP in two trials (Gosens, Mishra). Of the steroid injection trials, two used methylprednisolone (Gautam, Yadav), two used triamcinolone (Gosens, Krogh) (one of which also injected epinephrine (Gosens)), and one used a proprietary steroid (Diprophos, Schering-Plough) (Lebiedzinski). One trial (comparing PRP to local anesthetic) may have used an activating agent, although this was not clear and no details were reported (Behera); this trial used leukocyte-poor PRP. Both injection groups underwent peppering in five trials (Gautam, Gosens, Mishra, Behera, Stenhouse); one trial used a peppering technique in the PRP and saline groups but not in the steroid group (Krogh). Only three trials reported using imaging guidance (Krogh, Behera, Stenhouse). Six of the trials had baseline imbalances between groups, including the percentage of males (Krogh, Yadav, Lebiedzinski, Behera, Stenhouse), mean age (Lebiedzinski), baseline VAS pain (Stenhouse; worse in PRP group), baseline DASH score (Gosens; worse in the control group), and Nirschl score (Stenhouse; worse in the PRP group). Methodological limitations included unclear random sequence generation (Behera, Gautam, Yadav), unclear allocation concealment (Behera, Gautam, Mishra, Stenhouse, Yadav), data not analyzed (or not clearly analyzed) according to the intention to treat principle (Gautam, Lebiedzinski, Mishra), lack of blinding (Gautam, Lebiedzinski, Stenhouse, Yadav), unclear follow-up rate (Gautam), and failure to control for confounding (all trials). Overall, two trials were considered to be at moderately low risk of bias (Gosens, Krogh); the remaining six trials were considered to be at moderately high risk of bias (Gautam, Yadav, Lebiedzinski, Mishra, Behera, Stenhouse).

Cohort studies: Two prospective cohort studies compared PRP (n=26-39) to low level laser radiation therapy (n=26-42) (Tetschke 2015[272], Tonk 2014[278]). Detailed information on patient and study characteristics is available in Appendix Table F4. One study (Tetschke) required that patients have symptoms of at least 3 months' duration (mean duration not reported); the other study only required that patients have symptoms for at least one week, and more than half were considered to be subacute (Tonk). Both required that patients have failed conservative therapy. While one study treated PRP with a total of 3 injections over a 3-week period (Tetschke), the other study used one injection only (Tonk). Both employed low level radiation therapy in the control group. There were baseline imbalances in both studies, with both enrolling more males in the PRP group, and one enrolling more subacute patients in the PRP group (Tonk). Both studies were considered to be at moderately high risk of bias due to methodological limitations surrounding lack of blinding (both), high and differential loss to follow-up (Tonk), and failure to control for potential confounding (both).

Efficacy Results

Function

Function outcomes were reported by seven trials that compared PRP to either steroid (Gautam[92], Krogh[143], Gosens[96], Lebiedzinski[150], Yadav[302]), local anesthetic injection (Behera[18], Mishra[184]), or saline (Krogh[143]); outcome measures reported included the patient report outcome measures (quick) DASH (0-100 (worst)), PRTEE disability (0-100 (best)), PRTEE total (0-100 (best)), and the Oxford Elbow Score (0-48 (best)), and the clinician-reported MMCPIE (0-100 (worst)). Two trials evaluated the percentage of function responders; that is, the percentage of patients who achieved some measure of functional success (Lebiedzinski[150], Gosens[96]).

Short-term: Overall results suggest no difference between groups in short-term functional outcomes, although there was considerable inconsistency across studies. The percentage of functional responders was similar between PRP and steroid groups (60% vs. 59%) as evaluated by one trial (Lebiedzinski[150]) (Table 10); in this case responders were patients with "very good" DASH scores (i.e., scores of 0-25). Data from seven studies contributed to pooled analysis and included DASH, MMCPIE, and change in PRTEE scores. The pooled estimate suggested no difference between PRP and steroid or LA groups (WMD -2.35 (95% CI -6.27, 1.58), 7 RCTs) (Figure 5a); across these seven trials, three showed no effect (Gautam[92], Krogh[143], Mishra[184]), three showed results were significantly better following PRP (Gosens[96], Behera[18], Yadav[302])- one of which (Yadav[302]) was the only trial with mean duration of symptoms less than 6 months, and one found results were significantly better following steroid injections (Lebiedzinski[150]). One of these trials reported two additional functional outcomes for PRP versus steroid (Gautam[92]): while there was no difference between groups in MMCPIE scores, there were significantly worse results in the PRP group in mean Oxford Elbow Score (Table 11).

Intermediate-term: Overall results suggest better intermediate-term functional results following PRP versus steroid or local anesthetic injections. In contrast, one trial reported no difference in the percentage of functional responders; in this case, that was defined as those with "very good" DASH scores (i.e., scores of 0-25) between PRP and steroid groups (72% vs. 70%) (Lebiedzinski[150]) (Table 10). Pooled analysis across five trials using DASH, MMCPIE, and PRTEE scores suggested significantly better results in the PRP group (WMD 7.67 (95% CI -11.67, -3.66), 5 RCTs) (Figure 5b); across these five studies, four suggested results were significantly better following PRP (Gautam[92], Gosens[96], Behera[18], Mishra[184]), and one found no difference between PRP and steroid groups (Lebiedzinski[150]). One of these trials reported two additional functional outcomes for PRP versus steroid (Gautam[92]), both of which suggested statistically better results in the PRP group as evaluated by the Oxford Elbow Score (MD 4.9 (95% CI 1.5, 8.4)) and the MMCPIE (MD 9.2 (95% CI 5.2, 12.7)) (Table 11).

Long-term: Long-term functional results were better following PRP versus steroid or local anesthetic injections based on pooled analysis across three trials reporting DASH or MMCPIE scores (WMD -14.04 (95% CI -22.75, -5.33), 3 RCTs) (Gosens[96], Lebiedzinski[150], Behera[18]) (Figure 5c). Across these studies, two suggested results were significantly better following PRP (Gosens[96], Behera[18]), and one found no difference between PRP and steroid groups (Lebiedzinski[150]). Although the latter trial also reported no difference in the percentage of patients with "very good" DASH scores (i.e., scores of 0-25) between PRP and steroid groups (81% vs. 78%) (Lebiedzinski[150]), another trial (Gosens[96]) found that significantly more PRP versus steroid patients achieved at least a 25% reduction in DASH scores without re-intervention (73% vs. 39%, RR 1.9 (95% CI 1.3, 2.8) (Table 10).

Pain

Pain outcomes were reported by seven trials that compared PRP to either steroid (Gautam[92], Krogh[143], Gosens[96], Yadav[302]), local anesthetic injection (Behera[18], Mishra[184]), or saline (Krogh[143]); and PRP plus dry needling to dry needling alone (Stenhouse[263]). Pain outcomes were evaluated using the patient-reported outcome measures VAS pain (0-10 or 100 (worst)) and PRTEE pain (0-50 (worst)), as well as using the patient- and clinician-reported Nirschl scores (scale and interpretation varied). Two trials reported on the percentage of patients who achieved meaningful pain improvement (Mishra[184], Gosens[96]) (Table 12). Meta-analysis was performed across studies reporting mean VAS or PRTEE pain scores (Gautam[92], Gosens[96], Krogh[143], Behera[18], Stenhouse[263]) (Figure 6); subgroup analysis was performed according to the control intervention used (i.e., steroid, local anesthetic, or dry needling). Two studies reported continuous outcomes that were not included in the pooled analysis due to missing data (Yadav[302] (VAS), Mishra[184] (PRTEE pain)) (Table 13). Finally, mean Nirschl scores, which evaluates pain during activity, were pooled across the two studies reporting (Behera[18], Stenhouse[263]) (Figure 7). Subgroup analysis was not performed on chronicity of pain because all included trials either had greater than six months mean duration of pain or did not report mean pain duration.

Short-term: Overall results suggest no difference between LR-PRP and LA groups in short-term pain outcomes. One trial (Mishra[184]) reported no difference in the percentage of patients who achieved at least a 25% reduction in VAS pain levels (75% vs. 66%) (Table 12). Pooled VAS and PRTEE pain scores suggested no difference between PRP and control groups (SMD 0.02 (95% CI -0.22, 0.25), 6 RCTs) (Gautam[92], Gosens[96], Krogh[143], Yadav[302], Behera[18], Stenhouse[263]) regardless of control group (Figure 6a). Similarly, one trial (Mishra[184]) reported no difference between LR-PRP and LA groups in mean percent VAS improvement (55% vs. 47%) (Table 13). As was found when comparing PRP to steroid injections (included in the meta-analysis), Krogh et al.[143] also found no difference between PRP and saline injections in PRTEE pain scores (Table 13). There was no difference between PRP and steroid or dry needling groups in mean Nirschl scores (SMD -0.29 (95% CI -0.86, 0.29), 2 RCTs) (Behera[18], Stenhouse[263]) (Figure 7).

Intermediate-term: Overall, intermediate-term results suggest that pain outcomes were better following PRP compared with either steroid or local anesthetic injections. However, there was no difference between PRP plus dry needling and dry needling alone in the one study evaluating this comparison (Stenhouse[263]). For LR-PRP versus LA, one trial reported that significantly more PRP versus steroid patients achieved at least 50% reduction in VAS scores (82% vs. 60%, RR 1.3 (95% CI 1.1, 1.7)) (Mishra[184]) (Table 12). The same trial reported significantly greater percent improvement in the PRP group at six months (72% vs. 56%) (Mishra[184]) (Table 13). Pooled VAS results for PRP versus steroid or local anesthetic injection showed significantly better pain results in the PRP group (SMD -1.17 (95% CI -1.71, -0.62), 3 RCTs) (Gautam[92], Gosens[96], Behera[18]) (Figure 6b). For PRP versus local anesthetic injections, one trial reported significantly better scores in the LP-PRP group as measured by the Nirschl staging system (1.5 vs. 3.7, SMD -2.06 (95% CI -3.1, -1.02)) (Behera[18]) (Figure 7). The trial comparing PRP plus dry needling to dry needling alone (Stenhouse[263]) found no differences between groups in VAS scores (4.2 vs. 4.5) (Figure 6c) or Nirschl scores (-51.1 vs. -45.4, SMD -0.22 (95% CI -1.01, 0.57)) (Figure 7).

Long-term: One trial found that significantly more PRP than steroid patients had achieved at least 25% reduction in VAS scores with no repeat interventions at 24 months (77% vs. 43%, RR 1.8 (95% CI 1.2, 2.6)) (Gosens[96]) (Table 13). Two trials reported better long-term VAS scores following PRP versus steroid injections (21.3 vs. 42.4, SMD -0.76 (95% CI -1.17, -0.36)) (Gosens[96]) or versus local anesthetic injections (12.7 vs. 41.7, SMD -2.09 (95% CI -3.14, -1.04)) (Behera[18]) (Figure 6d); the latter trial also reported better

long-term Nirschl staging system scores in the PRP versus local anesthetic group (1.2 vs. 2.3, SMD -1.66 (95% CI -2.64, -0.69)) (Behera[18]) (Figure 7).

Other Outcomes

Symptoms/recurrence: One trial (Lebiedzinski[150]) reported that a significantly lower percentage of the PRP versus steroid groups achieved no symptoms (patient-reported)/ full recovery in the short-, intermediate-, and long-term (Table 14).

Secondary procedures: One trial (Gosens[96]) reported that overall, the PRP group required fewer additional procedures than the steroid group over the two-year follow-up period (12% vs. 29%, RR 0.4 (95% CI 0.2, 0.985), including surgery (details not reported) (6% vs. 12%), re-injection of the original treatment (0% vs. 2%), and injection of the other treatment (6% vs. 14%) (Table 15).

Table 10. Elbow epicondylitis RCTs for PRP vs. Conservative Control (Steroid): Function responders

Outcome	Study	F/U	PRP % (n/N)	Steroid % (n/N)	RR (95% CI)*	p-value*
"Very good" DASH scores (0-25)	Lebiedzinski 2015	1.5 mos.	60% (32/53)‡	59% (27/46)	1.0 (0.7, 1.4)	NS
		6 mos.	72% (38/53)	70% (32/46)	1.0 (0.8, 1.3)	NS
		12 mos.	81% (43/53)	78% (36/46)	1.0 (0.8, 1.3)	NS
Composite: ≥25% DASH reduction without reintervention	Gosens 2011	24 mos.	73% (37/51)	39% (19/49)	1.9 (1.3, 2.8)	<0.01
Deteriorated DASH scores†	Gosens 2011	24 mos.	14% (7/51)	47% (23/49)	0.3 (0.1, 0.6)	<0.01

CI: confidence interval; DASH: Disabilities of the Arm, Shoulder, and Hand, 0-100 (worst); F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio

DASH: 0-100 (worst)

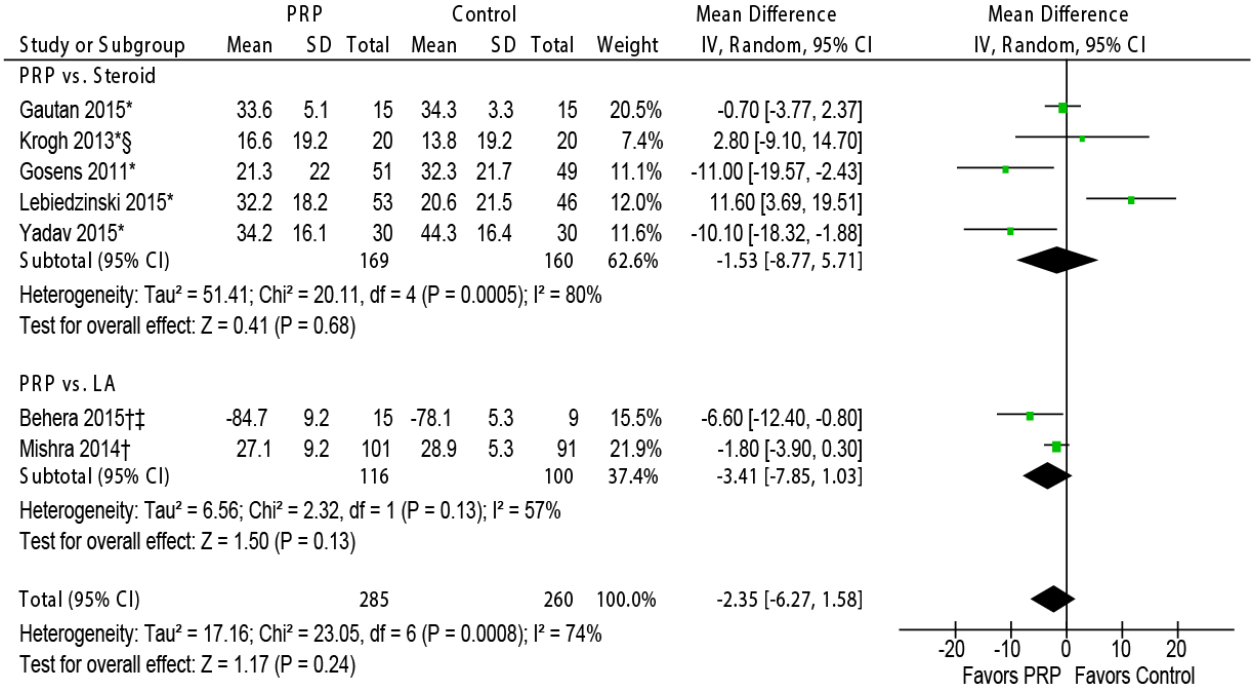
*Calculated unless otherwise indicated

†Compared to baseline, not otherwise defined

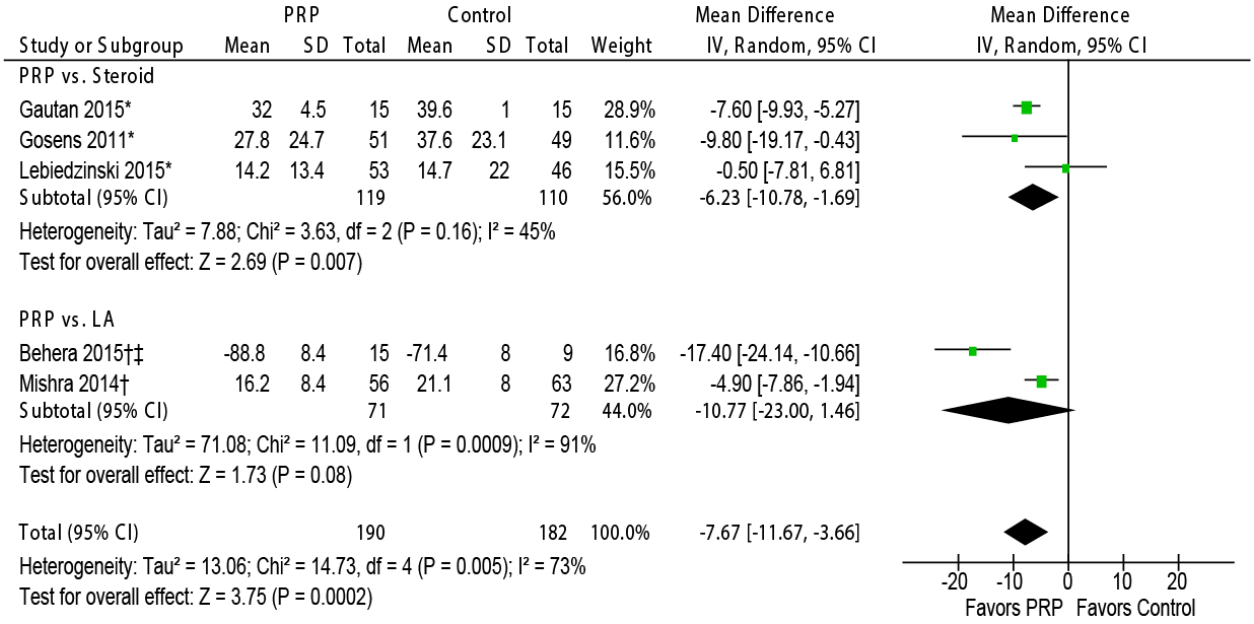
‡The study reported conflicting data (i.e., 32 patients (43%) PRP patients achieved this outcome, but 32/53=60%); we accepted the result that produced no difference between groups because the study concluded there were no differences between groups.

Figure 5. Elbow Epicondylitis RCTs comparing PRP to Conservative Control (Steroid or LA): WMD Function

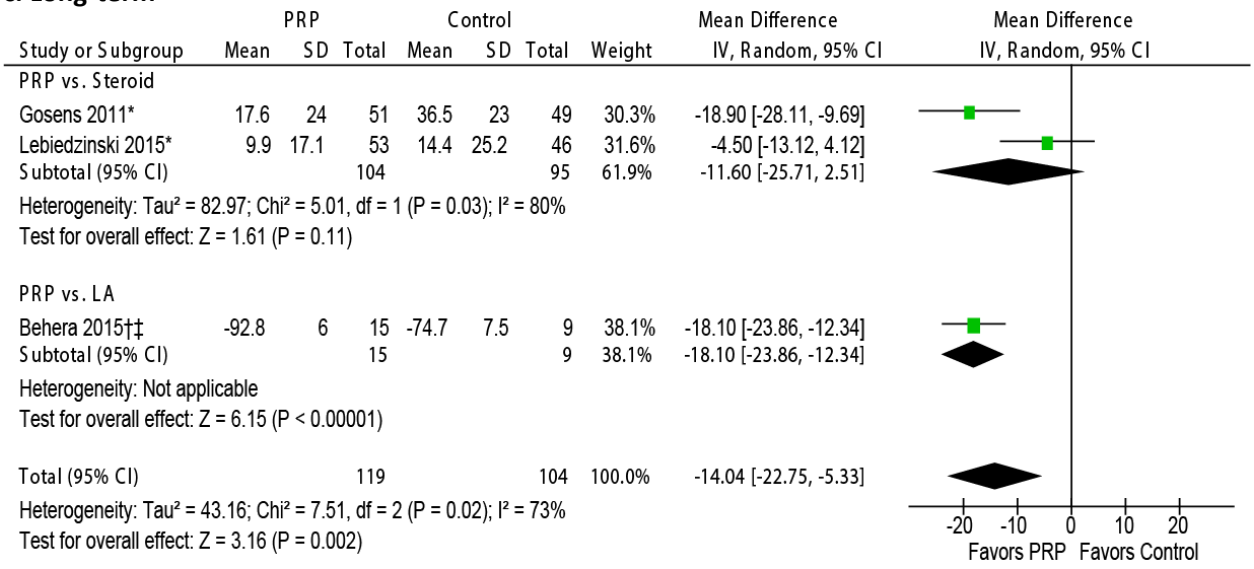
a. Short-term



b. Intermediate-term



c. Long-term



*PRP vs. steroid; Gosens had baseline imbalances in DASH scores, follow-up scores were used here as they provided a more conservative estimate than change scores
†PRP vs. local anesthetic
‡Study reported MMCPIE (0-100 (best)), so took inverse of scores to transform into (0-100 (worst)) to be consistent with other outcomes.
§study-reported Δscores; SD calculated from study-reported SE

Outcome measures reported:
-Mishra: PRTEE (0-100 (worst))
-Krogh: ΔPRTEE disability (0-100 (worst))
-Gautam, Lebiedzinski: DASH (0-100 (worst))
-Yadav: qDASH (0-100 (worst))
-Gosens: ΔDASH (0-100 (worst))
-Behera: inverse of MMCPIE (thus 0-100 (worst))

Table 11. Elbow epicondylitis RCTs for PRP vs. Conservative Control (Steroid): Additional Function Outcomes

Study	F/U	Outcome	PRP Mean ± SD	Steroid Mean ± SD	MD (95% CI)*	p-value*
Gautam 2015	3 mos.	Oxford Elbow Score (0-48 (best))	39.3 ± 3.3 (n = 15)	41.7 ± 2.4 (n = 15)	-2.4 (-4.6, -0.2)	0.03
		Modified MMCPIE (0-100 (best))	70.2 ± 2.2 (n = 15)	69.6 ± 3.5 (n = 15)	0.6 (-1.6, 2.8)	NS
	6 mos.	Oxford Elbow Score (0-48 (best))	41.2 ± 2.7 (n = 15)	36.3 ± 5.9 (n = 15)	4.9 (1.5, 8.4)	<0.01
		Modified MMCPIE (0-100 (best))	70.7 ± 3.0 (n = 15)	61.5 ± 5.8 (n = 15)	9.2 (5.7, 12.7)	<0.01

CI: confidence interval; MCPIE: Mayo Clinic Performance Index of the Elbow; F/U: follow-up; MD: mean difference; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; SD standard deviation

*Calculated unless otherwise indicated

Table 12. Elbow epicondylitis RCTs for PRP vs. Conservative Control (Steroid or LA): Pain responders

Outcome	Study	F/U	PRP % (n/N)	Control % (n/N)	RR (95% CI)§	p-value§
≥25% VAS reduction	Mishra 2014*‡	3 mos.	75% (76/101)	66% (60/91)	1.1 (0.9, 1.4)	NS
		6 mos.	84% (47/56)	68% (43/63)	1.2 (1.0, 1.5)	0.048††
≥50% VAS reduction	Mishra 2014*‡	6 mos.	82% (46/56)	60% (38/63)	1.3 (1.1, 1.7)	0.02
Composite: ≥25% VAS reduction without reintervention	Gosens 2011	24 mos.	77% (39/51)	43% (21/49)	1.8 (1.2, 2.6)	<0.01
Deteriorated VAS scores**	Gosens 2011†	24 mos.	4% (2/51)	18% (9/49)	0.2 (0.05, 0.9)	0.02

CI: confidence interval; LA: local anesthetic; F/U: follow-up; LA: local anesthetic; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio; VAS: Visual Analog Scale

*PRP vs. local anesthetic

†PRP vs. steroid

‡Note that only a subset (N=136) of the originally randomized patients (N=231 (116 vs. 114)) enrolled in the 6-month protocol, as the study was originally designed to have only a 3-month follow-up period. Six-month data were available for 56 PRP patients and 63 PRP patients (i.e., 119/136 enrolled in 6-month protocol).

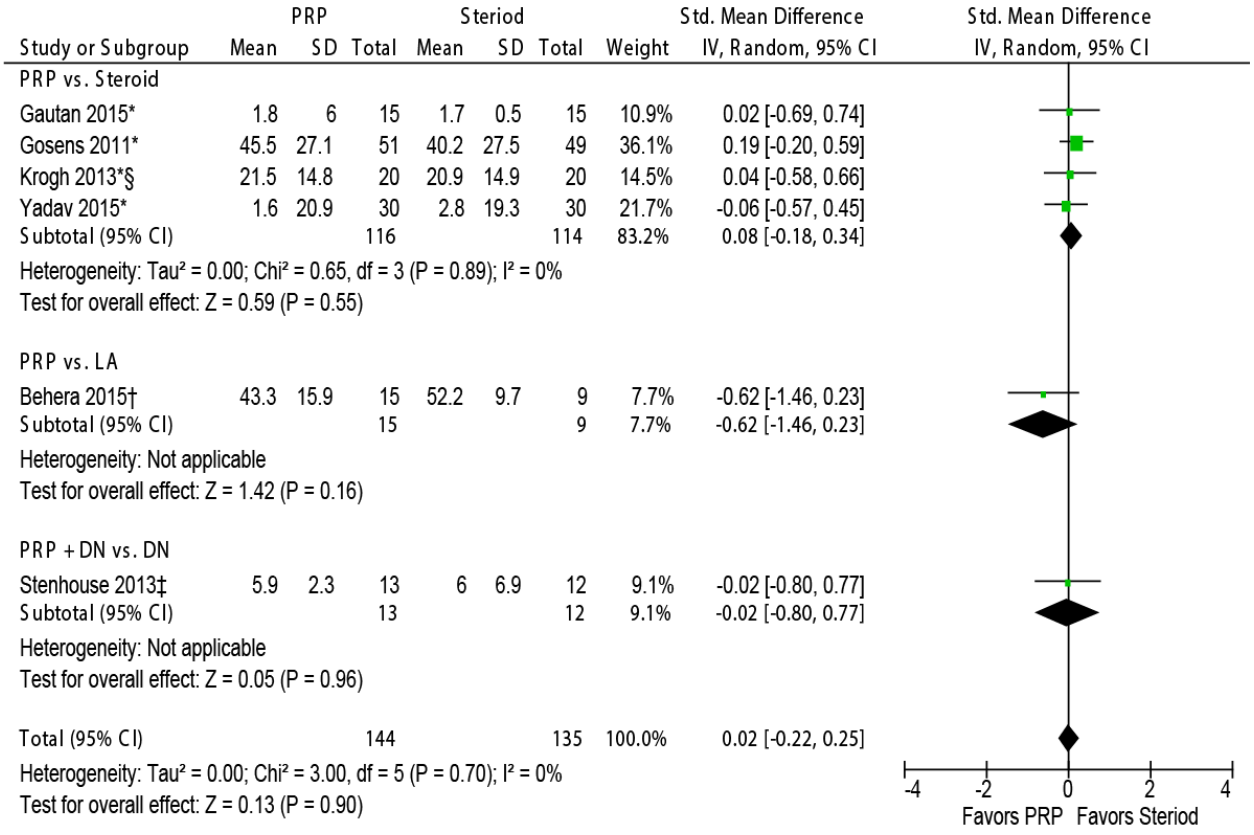
§Calculated unless otherwise indicated

**Compared to baseline, not otherwise defined

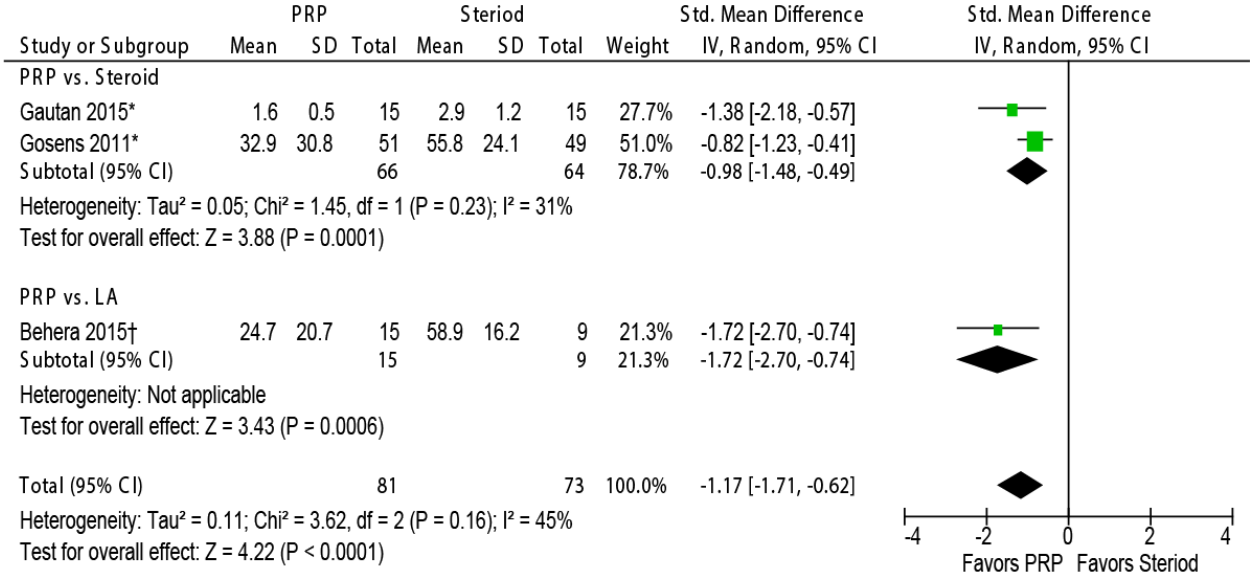
††Authors reported a p-value of 0.037.

Figure 6. Elbow Epicondylitis RCTs comparing PRP to Conservative Control (Steroid, LA, or DN): SMD Pain

a. Short-term

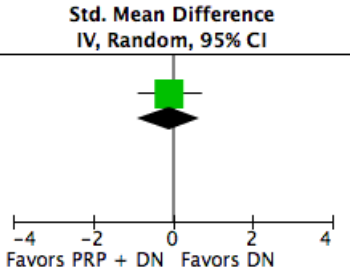


b. Intermediate-term: PRP vs. injection control



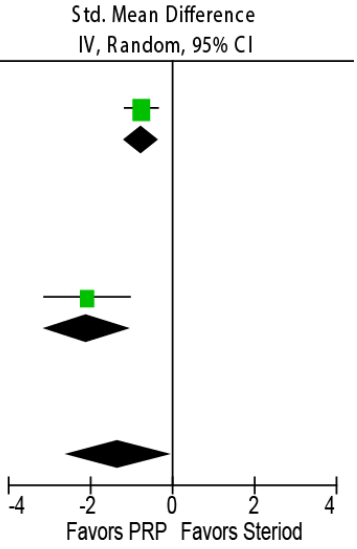
c. Intermediate-term: PRP + DN vs. DN

Study or Subgroup	PRP + DN Mean	SD	Total	DN Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.22.3 PRP + DN vs. DN								
Stenhouse 2013‡	4.2	3.1	13	4.5	3.2	12	100.0%	-0.09 [-0.88, 0.69]
Subtotal (95% CI)			**13**			**12**	**100.0%**	**-0.09 [-0.88, 0.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.23 (P = 0.82)								



d. Long-term

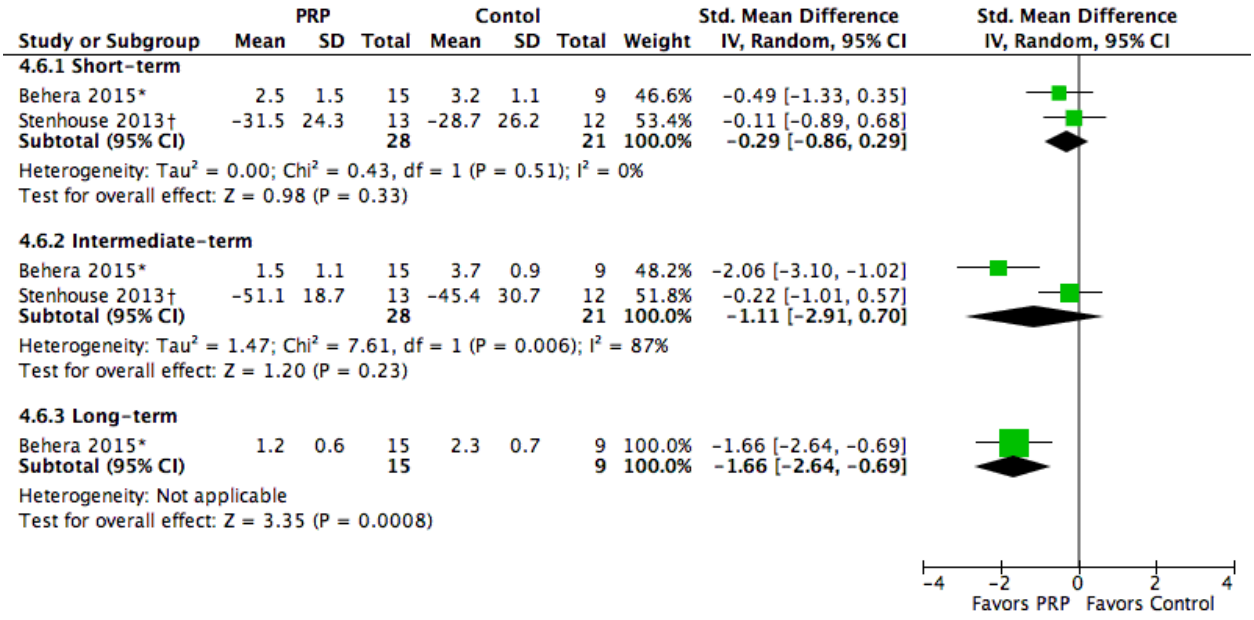
Study or Subgroup	PRP Mean	SD	Total	Steriod Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.19.1 PRP vs. Steroid								
Gosens 2011*	21.3	28.1	51	42.4	26.8	49	56.9%	-0.76 [-1.17, -0.36]
Subtotal (95% CI)			51			49	56.9%	-0.76 [-1.17, -0.36]
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.67 (P = 0.0002)								
1.19.2 PRP vs. LA								
Behera 2015†	12.7	13.9	15	41.1	11.7	9	43.1%	-2.09 [-3.14, -1.04]
Subtotal (95% CI)			15			9	43.1%	-2.09 [-3.14, -1.04]
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.90 (P < 0.0001)								
Total (95% CI)			66			58	100.0%	-1.33 [-2.62, -0.05]
Heterogeneity: Tau² = 0.71; Chi² = 5.32, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 2.03 (P = 0.04)								



*PRP vs. steroid
†PRP vs. local anesthetic
‡PRP + dry needling vs. dry needling;
§SD calculated from study-reported SE; SD calculated from study-reported SE; f/u SD calculated from study-reported ΔSD; follow-up scores were used as they provided a more conservative (i.e., smaller) effect estimate

Outcome measures reported:
-Gautam, Stenhouse: VAS 0-10 (worst)
-Gosens, Behera: VAS 0-100 (worst)
-Krogh: PRTEE pain 0-50 (worst):

Figure 7. Elbow Epicondylitis RCTs comparing PRP to Conservative Control (Steroid or DN): Nirschl scores



*PRP vs. local anesthetic; Nirschl score (1-7 (worst))

†PRP + dry needling vs. dry needling; SD calculated from study-reported SE; study reported Nirschl score on 0-80 (best) scale and inverse was used for these calculations; there were baseline imbalances between groups in Nirschl scores that weren't controlled for (mean 11.1 vs. 22.9); the follow-up scores were used as they provided a more conservative (i.e., smaller) effect estimate

Table 13. Elbow epicondylitis RCTs for PRP vs. Conservative Control (Steroid, LA, or Saline): Additional Pain Outcomes

Outcome	Study	F/U	PRP Mean ± SD	Control Mean ± SD	MD (95% CI)**	p-value††
Δ PRTEE pain‡‡ (0-50 worst))	Krogh 2013‡	3 mos.	-6.0 ± 9.8 (n = 20)	-3.3 ± 9.8 (n = 20)	-2.7 (-9.0, 3.6)	NS
Mean % VAS improvement	Mishra 2014†	3 mos.	55% (n = 101)	47% (n = 91)	8% (NC)	NS
		6 mos.§	72% (n = 56)	56% (n = 63)	16% (NC)	0.02

CI: confidence interval; LA: local anesthetic; F/U: follow-up; MD: mean difference; NC: not calculable; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; PRTEE: Patient Reported Tennis Elbow Evaluation; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale

†PRP vs. anesthetic

‡PRP vs. saline

§Note that only a subset (N=136) of the originally randomized patients (N=231 (116 vs. 114)) enrolled in the 6-month protocol, as the study was originally designed to have only a 3-month follow-up period. Six-month data were available for 56 PRP patients and 63 PRP patients (i.e., 119/136 enrolled in 6-month protocol).

**Calculated

††As reported by the study

‡‡SD calculated from study-reported SE

Table 14. Elbow epicondylitis RCTs for PRP vs. Conservative Control (Steroid): Symptoms

Study	Outcome	F/U	PRP % (n/N)	Steroid % (n/N)	RR (95% CI)*	p-value*
Lebiedzinski 2015	No symptoms†/ full recovery	1.5 mos.	0% (0/53)	17% (8/46)	0.0 (NC)	<0.01
		6 mos.	15% (8/53)	61% (28/46)	0.2 (0.1, 0.5)	<0.01
		12 mos.	36% (19/53)	65% (30/46)	0.5 (0.4, 0.8)	<0.01

CI: confidence interval; F/U: follow-up; NC: not calculable; PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio; VAS: Visual Analog Scale

*Calculated unless otherwise indicated

†As reported by the patient

Table 15. Elbow epicondylitis RCTs for PRP vs. Conservative Control (Steroid): Secondary procedures

Study	F/U	Procedure	PRP % (n/N)	Steroid % (n/N)	RR (95% CI)*	p-value*
Gosens 2011	≤24 mos.	Re-intervention† (any)	12% (6/51)	29% (14/49)	0.4 (0.2, 0.985)	0.04
	≤12 mos.	Re-intervention: Surgery (details NR)	6% (3/51)	12% (6/49)	0.5 (0.1, 1.8)	NS
	≤24 mos.	Re-intervention: Re-injection of original treatment	0% (0/51)	2% (1/49)‡	0.0 (NC)	NS
	≤24 mos.	Re-intervention: Re-injection of other treatment (i.e., cross-over)	6% (3/51)	14% (7/49)	0.4 (0.1, 1.5)	NS

CI: Confidence interval; F/U: follow-up; NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio

*Calculated unless otherwise indicated

†All but two re-interventions (both of which were re-injections) occurred within 12 months of baseline.

‡Patient received a re-injection every 3 months; did not want to undergo surgery.

Effectiveness Results

Function

One cohort study (Tetschke[272]) found no difference between PRP and low level laser therapy groups in mean DASH scores in the short-, intermediate-, and long-term (Table 16).

Pain

While one cohort study (Tetschke[272]) reported no difference between PRP and low level laser therapy groups in mean VAS scores in the short-, intermediate-, and long-term (Table 16). The other cohort study (Tonk[278]) reported that the PRP group had significantly better Nirschl stage scores than the laser group as evaluated in the short-, intermediate-, and long-term (Table 16).

Composite: Function and Pain

One cohort study (Tetschke[272]) found that a statistically similar percentage of PRP and laser therapy patients achieved a composite outcome of success (VAS ≤30%, DASH ≤10.2 points (both from baseline), and no re-intervention) through the study period of 12 months: 72% (19/26) vs. 54% (14/26), p=0.15.

Table 16. Elbow epicondylitis cohort studies for PRP vs. Conservative Control (Low Level Laser Therapy): Pain and function outcomes

Study	Outcome	F/U	PRP Mean ± SD	Laser Mean ± SD	p-value*
Function					
Tetschke 2015	DASH (0-100 (worst))	2 mos.	29.8 ± 21.1 (n = 26)	38.9 ± 20.7 (n = 26)	NS
		6 mos.	26.5 ± 21.2 (n = 26)	29.0 ± 19.6 (n = 26)	NS
		12 mos.	18.2 ± 19.5 (n = 26)	26.7 ± 21.8 (n = 26)	NS
Pain					
Tetschke 2015	VAS (0-10 (worst))	2 mos.	3.7 ± 2.0 (n = 26)	4.7 ± 2.3 (n = 26)	NS
		6 mos.	2.7 ± 1.6 (n = 26)	3.6 ± 2.2 (n = 26)	NS
		12 mos.	1.8 ± 2.0 (n = 26)	2.7 ± 2.3 (n = 26)	NS
Pain with activity					
Tonk 2014	Nirschl stage (0-7 (worst))	3 mos.	2.13 (n = 39)	3.24 (n = 42)	<0.05
		6 mos.	1.36 (n = 39)	2.26 (n = 42)	<0.05
		12 mos.	1.23 (n = 39)	1.76 (n = 42)	<0.05

DASH: Disabilities of the Arm, Shoulder, and Hand; F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; SD: standard deviation; VAS: Visual Analog Scale

*As reported by the study

4.1.2.3. PRP vs. Surgery for elbow epicondylitis

Studies included

Cohort study: One retrospective cohort study compared PRP (n=28) to surgery (n=50) (Ford 2015[83]). Detailed information on patient and study characteristics is available in Appendix Table F5. The study required that patients have symptoms of at least 3 months' duration; the mean duration was 6.8 months. For eligibility, patients were required to have failed at least one form of conservative therapy. The study protocol utilized a single PRP treatment with peppering; use of imaging guidance was not reported. Surgery consisted of open lateral extensor release. Baseline imbalances included fewer males and fewer patients who had previously undergone a steroid injection for epicondylitis symptoms in the PRP group. The study was considered to be at moderately high risk of bias due to methodological limitations surrounding lack of blinding, unclear loss to follow-up, and failure to control for potential confounding.

Effectiveness Results

Function

The study[83] reported no difference between groups in the percentage of patients who returned to full activity (82% vs. 82%) (Ford) (Table 17).

Pain

Ford et al.[83] reported no difference between the PRP and surgery groups in the percentage of patients who reported pain improvement (89% vs. 84%) or in the overall percent pain reduction (61% vs. 55%) (Table 17).

Other outcomes

Symptoms: There were no differences between the PRP and surgery groups in the percentage of patients who reported symptoms besides pain, or in those who reported residual associated symptoms besides pain (Ford[83]) (Table 17).

Secondary procedures: A similar percentage of patients in both PRP and surgery groups underwent additional procedures (7% vs. 6%): two in both groups underwent surgery, and one in the surgery group received steroid injections (Ford) (Table 17).[83]

Table 17. Elbow epicondylitis cohort studies for PRP vs. Surgery: All outcomes

Study	F/U	Outcome	PRP % (n/N)	Surgery % (n/N)	p-value*
Ford 2015	Mean 10-12 months	Return to full activity	82% (23/28)	82% (41/50)	NS
		Patient-reported pain improvement	89% (25/28)	84% (42/50)	NS
		Patient-reported symptom improvement (besides pain)†	86% (24/28)	88% (44/50)	NS
		Residual associated symptoms (besides pain)†	14% (4/28)	10% (5/50)	NS
		Secondary intervention	7% (2/28)‡	6% (3/50)‡	NS
Study	**F/U**	**Outcome**	**PRP Mean ± SD**	**Surgery Mean ± SD**	**p-value***
Ford 2015	Mean 10-12 months	Percent pain reduction	61% (n = 28)	55% (n = 50)	NS

F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; SD: Standard deviation

*As reported by the study

†Symptoms include paresthesia, numbness, grip weakness

‡PRP: both patients underwent surgery; Surgery: two patients had additional surgery (additional debridement and extensor release) and one received steroid injections

4.1.2.4. ABI vs. Conservative Control for elbow epicondylitis

Studies included

Six trials (and no cohort studies) compared ABI to a conservative control (Arik 2014[14], Dojode 2012[68], Jindal 2013[120], Kazemi 2010[129], Ozturan 2010[202], Singh 2013[253]). Detailed information on patient and study characteristics is available in Appendix Tables F6 and F7. All six trials compared ABI to steroid injection, one of which (Ozturan[202]) also compared ABI to ESWT. Total trial size ranged from 50 to 80 patients, with 20 to 40 patients allocated to each treatment group. Minimum duration of symptoms was specified in the inclusion criteria in only one of the trials (Ozturan, >6 months). The mean duration of symptoms ranged from 1.0 to 10 months across five trials reporting; mean symptom duration was less than 6 months in three (Arik, Dojode, Jindal) and more than 6 months in two trials (Ozturan, Singh). Most required that patients were previously untreated or at least had not received steroid injections in the previous three months (Dojode, Jindal, Kazemi, Ozturan, Singh). All six trials reported an ABI injectate volume of 2 ml and injection of local anesthetic; all six trials used methylprednisolone as the steroid injectate. None of the trials reported use of imaging guidance; only one used a peppering technique during the PRP and steroid injections (Ozturan). There were baseline imbalances in the

percentage of males between treatment groups in five trials: four trials had a higher percentage of males in the steroid group (Dojode, Jindal, Ozturan, Singh), while a fifth had a higher percentage of males in the ABI group (Kazemi). Otherwise, there were no apparent differences in baseline characteristics between groups. All trials were considered to be at moderately high risk of bias. Three trials (Jindal, Kazemi, Ozturan) were quasi-randomized, with patients randomized by alternate allocation. Other methodological limitations included unclear random sequence generation (Arik, Ozturan), unclear allocation concealment (all trials), data not analyzed (or not clearly analyzed) according to the intention to treat principle (Dojode, Ozturan, Singh), lack of blinding (all trials), unclear percent follow-up (Dojode, Jindal, Singh), and differential loss to follow-up (Ozturan for ABI vs. steroid only).

Efficacy Results

Function

Functional outcomes were evaluated by four trials (Arik[14], Singh[253], Kazemi[129], Ozturan[202]) using three different outcome measures: the clinician-reported PRTEE, DASH, and Upper Extremity Functional Scale. No studies reported on functional responders. Based on pooled analysis across all four trials, ABI had significantly better scores than the steroid group in the short-term (SMD -0.87 (95% CI -1.41, -0.33), 4 RCTs). However, results were somewhat inconsistent, with a high I^2 (74%) and one trial (Ozturan[202]) finding no difference between groups (Figure 8). Chronicity of symptoms (<6 months versus >6 months) had no apparent impact on results, with results from the one included study evaluating patients with mean symptom duration less than six months (Arik[14]) reporting an effect estimate close to that of the pooled estimate (Figure 8). One trial (Ozturan[202]) reported significantly better Upper Extremity Functional Scale scores in the ABI versus steroid group in both the intermediate-term (20.7 vs. 27.1, MD -6.4 (95% CI -11.9, -0.9)) and long-term (18.6 vs. 27.5, MD -8.9 (95% CI -15.1, -2.7)) (Table 18). In contrast, the same trial found no difference between ABI and ESWT groups in the short-term (19.5 vs. 18.1, MD 1.4 (95% CI -6.1, 8.9)), intermediate-term (20.7 vs. 19.2, MD 1.5 (-4.4, 7.4)), or long-term (18.6 vs. 19.5, MD -0.9 (95% CI -6.1, 4.3)) (Table 18).

Pain

Two trials reported on pain responders (Dojode[68], Jindal[120]) (Table 19). In addition, pain was evaluated by the VAS scale by four trials (Dojode[68], Jindal[120], Arik[14], Kazemi[129]) (Figure 9) and pain during activity was assessed by the Nirschl Staging System in three trials (Jindal[120], Kazemi[129], Dojode[68]) (Figure 10). Subgroup analysis was not performed on chronicity of pain because all trials reporting had mean duration of pain less than six months except for one (Kazemi[129]) which did not report mean pain duration.

Short-term: In terms of pain responders, one trial (Jindal[120]) reported no difference between ABI and steroid groups in VAS improvement by 7 points or more in the short-term (1.5 months) (12% vs. 4%, RR 3.0 (95% CI 0.3, 27), while another trial (Dojode[68]) found that significantly fewer ABI patients had achieved “complete pain relief” (not defined) than those in the steroid group (17% vs. 63%, RR 0.3 (95% CI 0.1, 0.6)) (Table 19). No MCID was identified for VAS pain in patients with elbow epicondylitis. With respect to pain as evaluated by continuous outcome, short-term pooled VAS results suggested that the ABI group had better pain outcomes than the steroid group (SMD -0.83 (95% CI -1.17, -0.50), 4 RCTs) (Dojode[68], Jindal[120], Arik[14], Kazemi[129]) (Figure 9). Similarly, short-term pooled Nirschl scores were significantly better in the ABI versus steroid group (SMD -0.80 (95% CI -1.23, -0.37), 3 RCTs) (Jindal[120], Kazemi[129], Dojode[68]) (Figure 10).

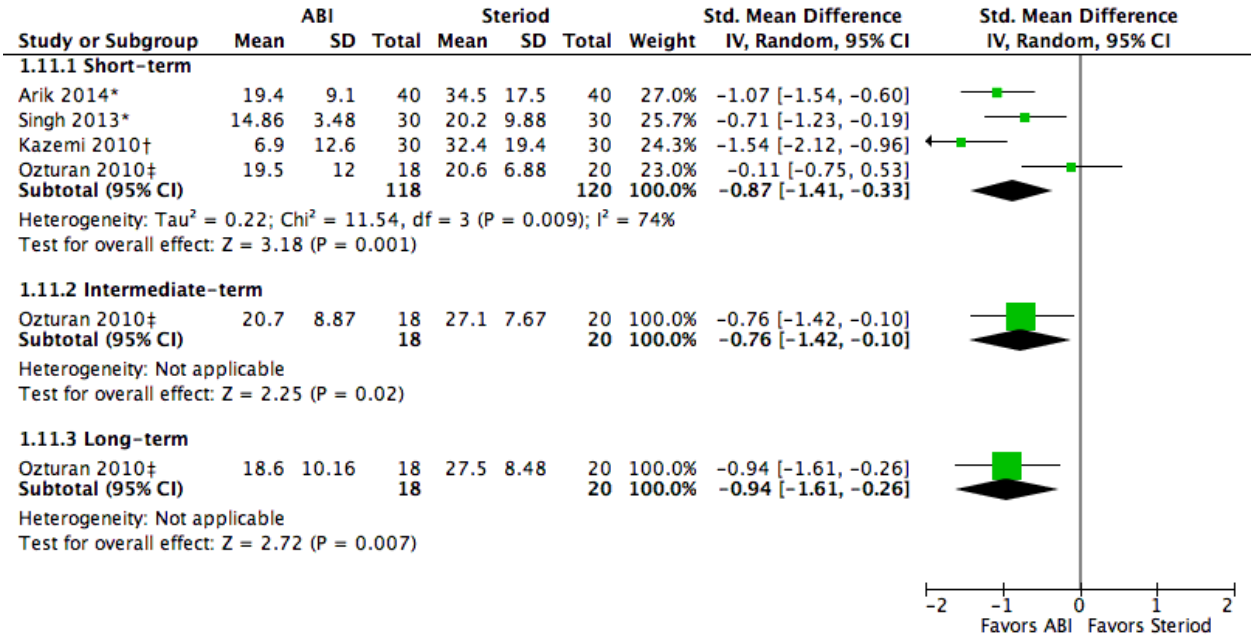
Intermediate-term: One trial (Dojode[68]) found that significantly more patients in the ABI group had achieved "complete pain relief" (not defined) than those in the steroid group (90% vs. 47%, RR 1.9 (95% CI 1.3, 2.9)) (Table 19). Intermediate-term pooled VAS results from two trials showed significantly better pain results in the ABI versus steroid group (SMD -0.8 (95% CI -1.2, -0.5), 2 RCTs) (Arik[14], Dojode[68]) (Figure 9). Nirschl results were also significantly better in the ABI versus steroid group in the intermediate-term (SMD -0.61 (95% CI -1.13, -0.10), 1 RCT) (Dojode[68]) (Figure 10).

One trial (Ozturan[202]) only reported pain in terms of that with provocation (Thomsen provocation test) and found no statistical differences between ABI and steroid groups in the short-term but less pain in the ABI group in both the intermediate- and long-term (data not shown); there were no differences between the ABI and ESWT groups at any time point (data not shown).

Other Outcomes

No data reported.

Figure 8. Elbow Epicondylitis RCTs comparing ABI to Conservative Control (Steroid): SMD Function



*PRTEE (0-100 (worst))

†Quick DASH (0-100 (worst))

‡Upper Extremity Functional Scale (8-80 (worst))

Table 18. Elbow epicondylitis RCTs for ABI vs. Conservative Control (Steroid or ESWT): Additional functional outcomes

Study	Outcome	F/U	ABI mean ± SD	ESWT mean ± SD	MD (95% CI)*	p-value*
Ozturan 2010	Upper Extremity Functional Scale (8-80 (worst))	3 mos.	19.5 ± 12.0 (n = 18)	18.1 ± 10.3 (n = 19)	1.4 (-6.1, 8.9)	NS
		6 mos.	20.7 ± 8.9 (n = 18)	19.2 ± 8.7 (n = 19)	1.5 (-4.4, 7.4)	NS
		12 mos.	18.6 ± 10.2 (n = 18)	19.5 ± 4.3 (n = 19)	-0.9 (-6.1, 4.3)	NS
Study	**Outcome**	**F/U**	**ABI mean ± SD**	**Steroid mean ± SD**	**MD (95% CI)***	**p-value***
Ozturan 2010	Upper Extremity Functional Scale (8-80 (worst))	3 mos.	19.5 ± 12.0 (n = 18)	20.6 ± 6.9 (n = 20)	-1.1 (-7.5, 5.3)	NS
		6 mos.	20.7 ± 8.9 (n = 18)	27.1 ± 7.7 (n = 20)	-6.4 (-11.9, -0.9)	0.02
		12 mos.	18.6 ± 10.2 (n = 18)	27.5 ± 8.5 (n = 20)	-8.9 (-15.1, -2.7)	0.01

ABI: autologous blood injection; CI: confidence interval; ESWT: extracorporeal shock wave therapy; F/U: follow-up; MD: mean difference; NS: not statistically significant RCT: randomized controlled trial; SD: standard deviation

*Calculated unless otherwise indicated

Table 19. Elbow epicondylitis RCTs for ABI vs. Conservative Control (Steroid): Pain responders

Study	Outcome	F/U	ABI % (n/N)	Steroid % (n/N)	RR (95% CI)*	p-value*
Dojode 2012	Complete pain relief†	1 mos.	17% (5/30)	63% (19/30)‡	0.3 (0.1, 0.6)	<0.01
	Complete pain relief†	6 mos.	90% (27/30)	47% (14/30)	1.9 (1.3, 2.9)	<0.01
Jindal 2013	VAS improvement ≥7 points ("excellent" pain relief)§	1.5 mos.	12% (3/25)	4% (1/25)	3.0 (0.3, 26.9)	NS

ABI: autologous blood injection; CI: confidence interval; F/U: follow-up; NS: not significant; RCT: randomized controlled trial; RR: risk ratio; VAS: Visual Analog Scale

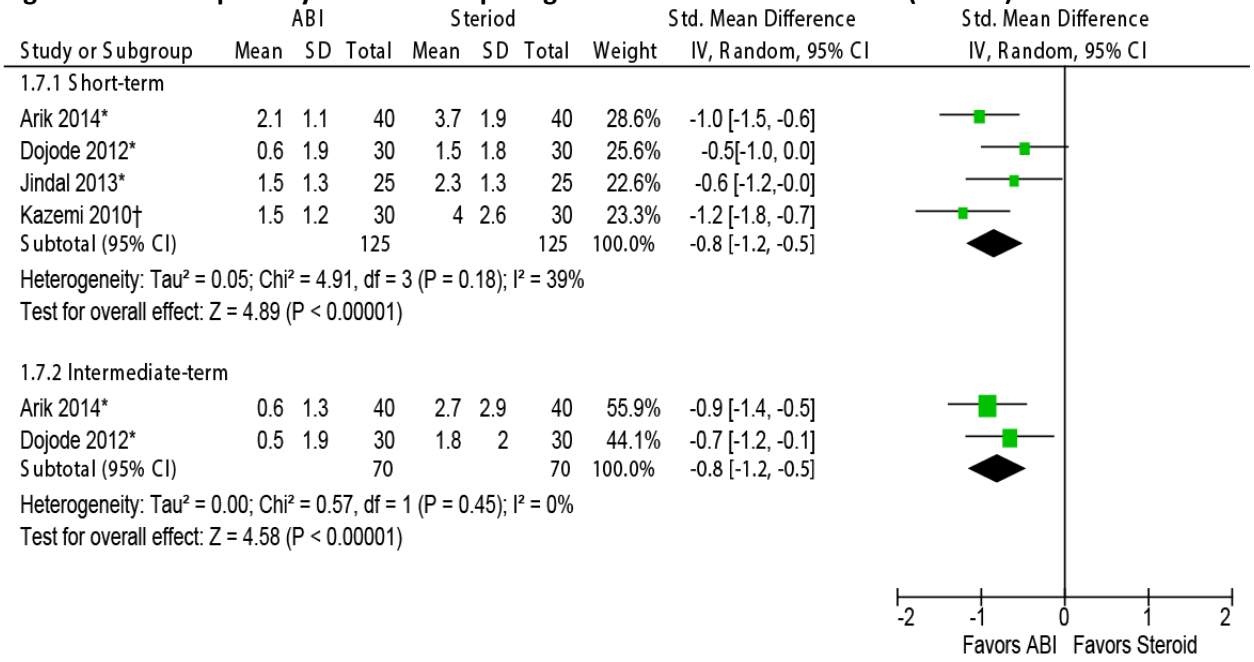
*Calculated unless otherwise indicated

†Not defined

‡The study reported that recurrence of pain occurred in "many of these patients" at 3 (data NR) and 6 months.

§Both "good" (VAS improvement 4-6 points) and "fair" (VAS improvement 0-3 points) pain relief occurred similarly between ABI and steroid groups: "good" (56% vs. 48%, RR 1.2 (95% CI 0.7, 2.0)), "fair" (32% vs. 48%, RR 0.7 (95% CI 0.3, 1.3)

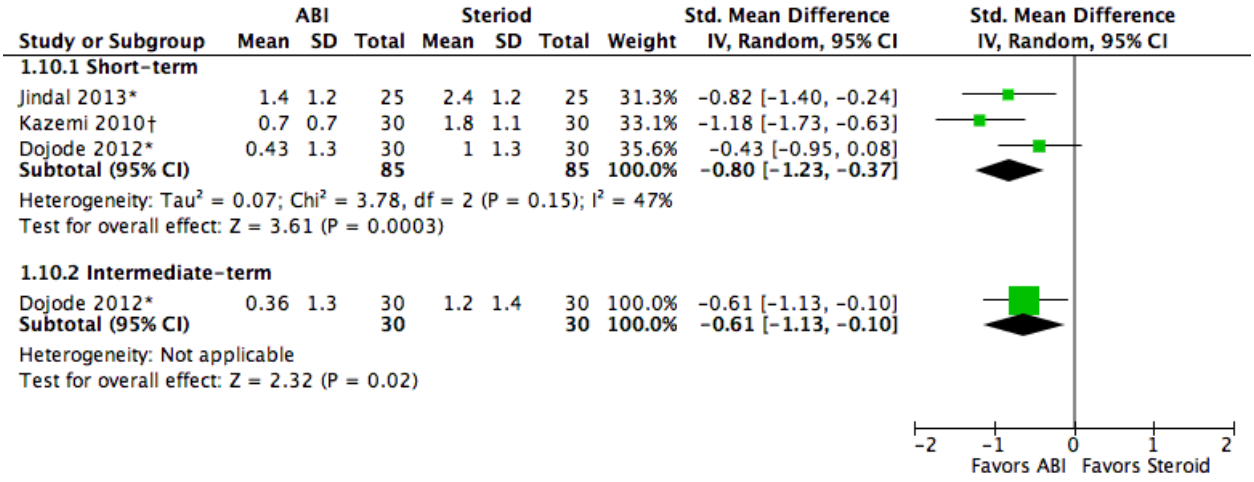
Figure 9. Elbow Epicondylitis RCTs comparing ABI to Conservative Control (Steroid): VAS Pain



*VAS 0-10

†VAS 0-9

Figure 10. Elbow Epicondylitis RCTs comparing ABI to Conservative Control (Steroid): Nirschl Staging System



*Nirschl stage (1-7 (worst))

†Modified Nirschl stage (0-4 (worst))

4.1.3. Achilles Tendinopathy

Summary of results

PRP vs. Control: Two RCTs (in three publications)[61,64,130] (and no cohort studies) were included that compared PRP to a conservative control (saline injection or exercise); the trials were found to be at moderately low (1 RCT) or moderately high (1 RCT) risk of bias. Trial size was 20 and 54 patients. With respect to primary outcomes, there were no differences between groups in function scores as measured in the short-term (2 RCTs, moderate quality evidence), intermediate-term (2 RCTs, low quality evidence), or long-term (1 RCT, low quality evidence). No other primary outcomes were reported. With respect to secondary outcomes, there were no differences between the PRP and exercise groups in short- or intermediate-term health-related quality of life or overall health state in one RCT; the other trial reported no differences between the PRP and saline groups in short-, intermediate-, or long-term patient satisfaction or return to sport as well as a similar risk of secondary procedures through the intermediate-term.

ABI vs. Control: Two RCTs[20,204] (and no cohort studies) were included that compared ABI to a conservative control: one trial compared ABI to DN (N=53) and the other trial compared ABI plus exercise to exercise alone (40 tendons). The trials were found to be at moderately low (1 RCT) or moderately high (1 RCT) risk of bias. With respect to primary outcomes, there was insufficient quality evidence regarding function scores in the short- (2 RCTs) and intermediate-term (1 RCT). No other primary outcomes were reported. With respect to secondary outcomes, one trial reported no differences between ABI and DN groups in intermediate-term patient-reported recovery or return to sport.

4.1.3.1. PRP vs. Conservative Control for Achilles tendinopathy

Studies included

Two RCTs (in three publications) and no cohort studies were identified (de Jonge 2011[61]/de Vos 2010[64], Kearney 2013[130]). Detailed information on patient and study characteristics is available in Appendix Table F8. Both trials were small and enrolled patients with Achilles tendinopathy of at least 2 to 3 months' duration. The mean duration of symptoms was considerably longer in one trial (Kearney, mean 28-31 months) compared to the other (de Jonge, mean 7-9 months). One trial required failure of conservative therapy (Kearney) while the other prohibited previous injection with PRP and completion of an eccentric exercise program (de Jonge). One trial (de Jonge) compared PRP (n=27) to saline injections (n=27), with all patients undergoing a standard rehabilitation program. The other trial (Kearney) compared PRP (n=10) injected with a peppering technique (and gradual return to daily activities and sports) to a 12-week eccentric exercise program (n=10). No repeat injections were reported. The volume of PRP injected was similar between trials (3.5 and 4 ml); one trial (de Jonge) also injected a local anesthetic. Neither trial used an activating agent. Ultrasound guidance was used in one trial (de Jonge). Patients were blinded to treatment received in one trial (de Jonge) but blinding was not possible in the trial that compared PRP injections to exercise (Kearney). With two exceptions, baseline characteristics were similar between groups. Baseline VISA-A scores were slightly worse in the PRP group in one trial (de Jonge), however adjusted analyses were performed to control for these differences. The other trial (Kearney) had baseline imbalances in EQ-5D scores such that the PRP had worse scores than the exercise group; these differences were not controlled for and are likely attributable to the very small sample size (n=10 per group). Overall, one trial (de Jonge) was found to be at low risk of bias while the other trial (Kearney) was considered to be at moderately high risk of bias.

Methodological limitations in the latter trial included lack of blinded outcome assessment, differential follow-up between groups, and failure to control for confounding (Kearney).

Efficacy Results

Function

No differences in the patient-reported VISA-A outcome measure (0-100 (best)) were found in either trial[61,64,130] or in pooled analysis as evaluated in the short-term (WMD -1.5 (95% CI -11.3, 8.4), 2 RCTs), intermediate-term (WMD -6.5 (95% CI -25.7, 12.7), 2 RCTs), or long-term (MD 6.6 (95% CI -5.1, 18.3), 1 RCT (de Jonge[61])) (Figure 11). De Jonge et al.[61] reported similar conclusions (i.e., no significant difference between groups) when adjusting for baseline differences between groups in VISA-A change scores and duration of symptoms (data not shown).

Pain

No data reported.

Other Outcomes

Quality of life: One trial (Kearney[130]) found no differences between the PRP and exercise groups in EQ-5D quality of life follow-up scores in the short- or intermediate-term (Table 20). This study had imbalances in baseline scores, with worse scores in the PRP group, thus change scores were calculated and also suggested no differences between groups.

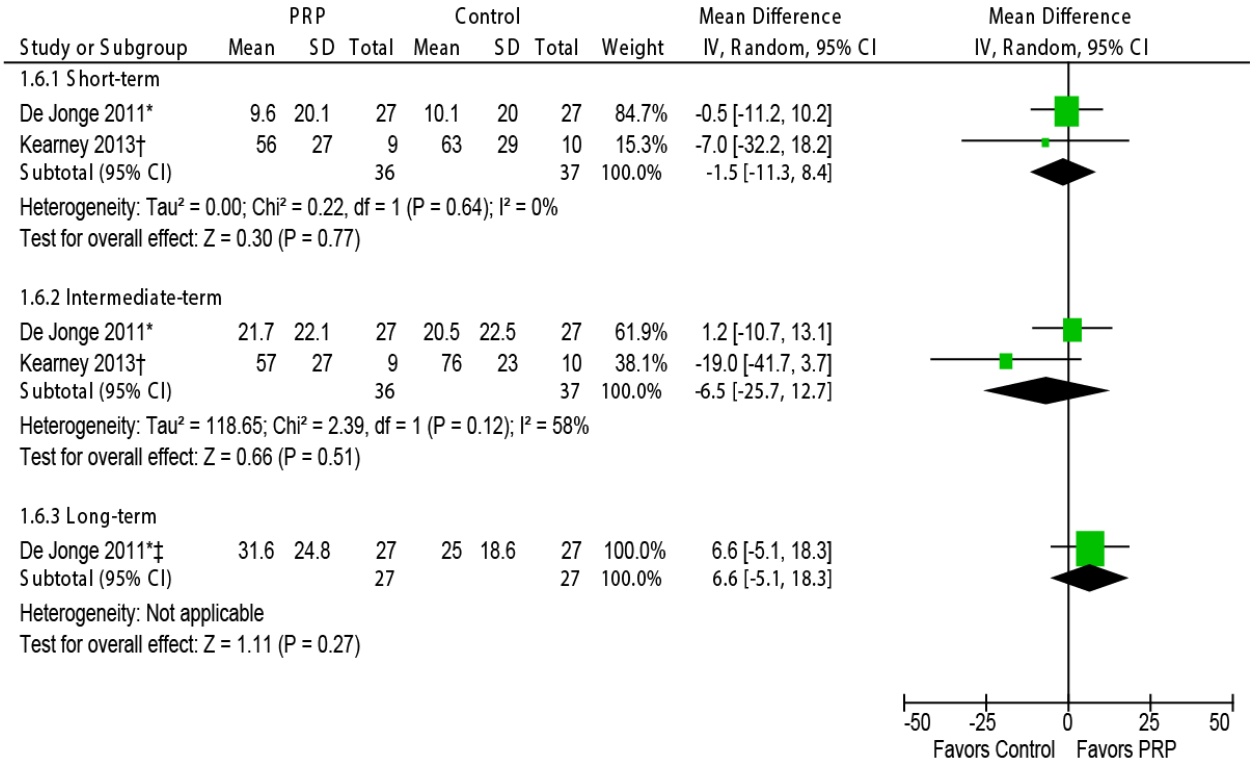
Overall health state: One trial (Kearney[130]) found no differences between PRP and exercise groups in EQ-5D VAS health state scores in either the short- or intermediate-term (Table 20).

Patient satisfaction: One trial (de Jonge[61]) reported similar proportions of patients in the PRP and saline groups considered their satisfaction to be excellent or good in the short-, intermediate-, and long-term, even after controlling for baseline differences between groups in VISA-A scores and symptom duration (Table 21).

Return to sport: One trial (de Jonge[61]) found no statistical differences between PRP and saline groups in return to desired sport (at any level) in the short- or intermediate-term; similarly, there were no statistical differences between groups in long-term return to desired sport at the pre-injury level (Table 21), even after controlling for baseline differences between groups in VISA-A scores and symptom duration.

Secondary procedures: One trial (de Jonge[61]) reported that 15% (4/27) of PRP patients underwent additional procedures for failure to improve at 6 months, including ESWT, orthotics, and topical glyceryl nitrate; in the saline group, 4% (1/27) of patients were treated with topical glyceryl nitrate. The difference between groups did not achieve statistical significance (RR 4.0 (95% CI 0.5, 33.5). After the 12-week exercise program, over half of patients in both groups continued eccentric exercises, with no difference between groups (Table 21). The other trial (Kearney[130]) reported at the end of the study (6 months), 20% (2/10) of patients in both the PRP and exercise groups crossed over to receive the other treatment; by 12 months, half of these patients (i.e., 2 of the 4) proceeded to surgery (initial percutaneous tenotomy and subsequent tendon debridement) (Table 21).

Figure 11. Achilles Tendinopathy RCTs comparing PRP to Conservative Control (Saline or Exercise): WMD VISA-A Function



*de Jonge 2011: PRP vs. saline; study reported Δscore

†Kearney 2013: PRP vs. exercise

‡SD calculated from study-reported 95% CI

Table 20. Achilles tendinopathy RCTs for PRP versus Conservative Control (Saline or Exercise): Quality of Life and Health State

Study	Outcome Measure	F/U	PRP mean ± SD	Control mean ± SD	MD (95% CI)*	p-value*
QoL						
Kearney 2013**	EQ-5D QoL (0-1 (best))	0 mos.	0.56 ± 0.32 (n = 10)	0.75 ± 0.14 (n = 10)	-	-
		3 mos.	0.66 ± 0.41 (n = 9)	0.74 ± 0.28 (n = 10)	-0.08 (-0.42, 0.26)	NS
		6 mos.	0.74 ± 0.36 (n = 9)	0.82 ± 0.35 (n = 10)	-0.08 (-0.42, 0.26)	NS
	ΔEQ-5D	3 mos.	0.10 ± 0.25†	-0.01 ± 0.19†	0.11 (-0.10, 0.32)	NS
		6 mos.	0.18 ± 0.22†	0.07 ± 0.25†	0.08 (-0.15, 0.31)	NS
Health State						
Kearney 2013**	EQ-5D VAS health state (0-100 (best))	3 mos.	68 ± 29 (n = 9)	69 ± 32 (n = 10)	-1.0 (-30.7, 28.7)	NS
		6 mos.	76 ± 20	68 ± 30	8.0 (-16.0, 33.0)	NS

Study	Outcome Measure	F/U	PRP mean ± SD	Control mean ± SD	MD (95% CI)*	p-value*
			(n = 9)	(n = 10)		
Other						
De Jonge 2011§	Adherence to eccentric exercises‡	6 mos.	70.9% ± 27.0% (n = 27)	74.6% ± 17.3% (n = 27)	-3.7% (-16.1%, 8.7%)	NS

CI: confidence interval; EQ-5D: EuroQoL 5-Dimension Questionnaire; F/U: follow-up; MD: mean difference; NS: not significant; PRP: platelet-rich plasma; QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale

*Calculated unless otherwise indicated

†SD calculated from study-reported 95% CI

‡Patient-reported percentage of prescribed repetitions performed

§De Jonge: PRP versus saline injection

**Kearney: PRP versus exercise

Table 21. Achilles tendinopathy RCTs for PRP versus Conservative Control (Saline or Exercise): Patient Satisfaction, Return to Sport, and Surgery

Study	Outcome	F/U	PRP % (n/N)	Control % (n/N)	Difference in proportions (95% CI) RR (95% CI)*	p-value*
De Jonge 2011††	Patient-rated satisfaction of excellent/good‡	3 mos.	26% (7/27)	30% (8/27)	-3% (-21%, 14%) (adj.†) 0.9 (0.4, 2.1)	NS†
		6 mos.	56% (15/27)	63% (17/27)	-4% (-26%, 18%) (adj.†) 0.9 (0.6, 1.4)	NS†
		12 mos.	54% (16/27)	54% (16/27)	-3% (-24%, 18%) (adj.†) 1.0 (0.6, 1.6)	NS†
De Jonge 2011††	Return to desired sport (any level)	3 mos.	57% (13/23)	58% (14/24)	2% (-21%, 25%) (adj.†) 0.9 (0.5, 1.6)	NS†
		6 mos.	78% (18/23)	67% (16/24)	1% (-17%, 20%) (adj.†) 1.1 (0.7, 1.7)	NS†
De Jonge 2011††	Return to desired sport at previous level	12 mos.	57% (13/23)	42% (10/24)	2% (-25%, 28%) (adj.†) 1.3 (0.7, 2.4)	NS†
De Jonge 2011††	Eccentric exercises continued at lower frequency after 12 week program	6 mos.	56% (15/27)	63% (17/27)	-7% (-34%, 19%) 0.9 (0.6, 1.4)	NS†
Kearney 2013**	Cross-over (at end of study)	6 mos.	20% (2/10)	20% (2/10)	NA 1.0 (0.2, 5.8)	NS
De Jonge 2011††	Alternative treatment (for failure to improve)	6 mos.	15% (4/27)	4% (1/27)	11% (-4%, 26%) 4.0 (0.5, 33.5)	NS
Kearney 2013**	Surgery	12 mos.	10% (2/20)§		-	-

CI: confidence interval; F/U: follow-up; NS: not significant; PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation

*Calculated unless otherwise indicated

†Adjusted for baseline VISA-A Score and duration of symptoms.

‡Versus fair/poor, no other details reported
§After cross-over and an additional 6 months non-operative treatment. 2 patients underwent surgery (initial percutaneous tenotomy and later tendon debridement)
**Kearney: PRP versus exercise
††De Jonge: PRP versus saline injection

4.1.3.2. ABI vs. Conservative Control for Achilles tendinopathy

Studies included

Two RCTs (and no cohort studies) were included (Bell 2013[20], Pearson 2012[204]). Detailed information on patient and study characteristics is available in Appendix Table F9. Both required a minimum duration of symptoms of 3 months. Although the average duration of pain was longer in one trial (Bell, mean 23-39 months), the authors noted that when those with symptoms of 100 months or less were excluded from this calculation that the mean dropped to 15 to 18 months (N not reported). The other trial (Pearson) enrolled patients with a mean duration of symptoms of 9 to 13 months. Both trials placed limits on previous treatment for eligibility. One trial (Bell) randomized patients to ABI (n=26) or DN (n=27), with both injections performed using the same dry needling technique, while the other (Pearson) compared ABI plus eccentric exercise (n=20 tendons) to eccentric exercise alone (n=20 tendons). One trial treated all patients with 2 injections over a one-month period (Bell), while the other performed repeat injections at 1.5 months only in those patients with continued symptoms (50% tendons, Pearson). Local anesthetic was injected with ABI in one trial (Pearson); neither trial used imaging guidance. One trial (Bell) blinded patients to treatments received, while blinding was not possible in the other trial (Pearson). One trial (Bell) had baseline imbalances between ABI and DN groups in both mean duration of symptoms and the percentage of males which were not controlled for; otherwise, groups were similar. One trial (Bell) was considered to be at moderately low risk of bias due to lack of controlling for confounding. The other trial (Pearson) was also found to be at moderately low risk of bias, with methodological limitations surrounding blind assessment and high loss to follow-up.

Efficacy Results

Function

The patient-reported VISA-A outcome measure (0-100 (best)) was used by both trials[20,204], however pooled analysis was not reported as one trial (Pearson[204]) reported mean score per tendon (instead of per patient). Both trials reported change scores from baseline (Table 22). Short-term results were inconsistent, with one trial (Pearson[204]) reporting significantly greater improvement following ABI plus exercise versus exercise alone in mean score per tendon (18.9 vs. 9.6, MD 9.3 (95% CI 2.1, 16.5)) and the other trial (Bell[20]) reporting no difference between ABI and DN groups in mean score per patient (15.2 vs. 14.9, MD 0.3 (95% CI -8.1, 8.7)); the latter trial (Bell[20]) found no difference between ABI and DN groups in the intermediate-term (18.7 vs. 19.9, MD -1.2 (95% CI -10.2, 7.8)).

Pain

No data reported.

Other Outcomes

Patient-reported recovery: One trial (Bell[20]) reported no difference between ABI and DN groups in "complete recovery" as reported by the patients (40% vs. 36%) (Table 23).

Return to sport: The ability to return to the desired sport at pre-injury levels was achieved in 62% (13/21) of ABI patients and 38% (9/24) of DN patients; this difference did not reach statistical significance due to small sample sizes (RR 1.7 (95% CI 0.9, 3.1)) (Table 23).

Table 22. Achilles tendinopathy RCTs for ABI versus Conservative Control: VISA-A Function Results

Outcome Measure	F/U	Study	ABI mean ± SD (n)	Control mean ± SD (n)	MD (95% CI)*	p-value*
ΔVISA-A	3 mos.	Bell 2013†	15.2 ± 16.2§ (n = 25)	14.9 ± 14.2§ (n = 25)	0.3 (-8.1, 8.7)	NS
		Pearson 2012‡	18.9 ± 7.4 (14 tendons)	9.6 ± 11.5 (14 tendons)	9.3 (2.1, 16.5)	0.02
	6 mos.	Bell 2013†	18.7 ± 16.4§ (n = 25)	19.9 ± 16.1§ (n=25)	-1.2 (-10.2, 7.8)	NS

ABI: autologous blood injection; CI: confidence interval; F/U: follow-up; MD: mean difference; NS: not statistically significant (p≥0.05); RCT: randomized controlled trial; SD: standard deviation; VISA-A: Victorian Institute of Sports Assessment-Achilles

*Calculated unless otherwise indicated

†Bell 2013: ABI vs. DN; study reported Δscore

‡Kearney 2013: ABI + exercise vs. exercise; study reported Δscore

Table 23. Achilles tendinopathy RCTs for ABI versus DN: Patient Recovery and Return to Sport

Study	Outcome	F/U	ABI % (n/N)	DN % (n/N)	RR (95% CI)*	p-value*
Bell 2013	Patient-reported complete recovery†	6 mos.	40% (10/25)	36% (9/25)	1.1 (0.5, 2.3)	NS
	Returned to pre-injury level in desired sport‡ (in those normally active in sport)	6 mos.	62% (13/21)	38% (9/24)	1.7 (0.9, 3.1)	NS

ABI: autologous blood injection; CI: confidence interval; DN: dry needling; F/U: follow-up; NS: not statistically significant (p≥0.05); RCT: randomized controlled trial; RR: risk ratio

*Calculated unless otherwise indicated

†Of those not completely recovered, 52% of patients in both groups were "much better", and 8% vs. 12% were "a little better". No patients considered themselves "unchanged" to "much worse".

‡Of those normally active in sport, 14% vs. 42% returned to desired sport but not at a pre-injury level, 5% vs. 16% returned to sport but not in desired sport, and 5% vs. 4% did not return to sport.

4.1.4. Patellar Tendinopathy

Summary of results

PRP vs. Control: Two RCTs[15,75] (and no cohort studies) were included that compared PRP to a conservative control: one trial compared PRP plus DN to DN alone (N=20) and the other trial compared PRP to ESWT (N=46). The trials were found to be at moderately low (1 RCT) and moderately high (1 RCT) risk of bias. With respect to primary outcomes, in the short-term, there was no difference between groups in function (2 RCTs) or pain scores (2 RCTs) based on low quality evidence. In the intermediate- and long-term, the quality of evidence was insufficient for both pain and function scores. No other primary outcomes were reported. With respect to secondary outcomes, results were mixed, with one trial reporting no differences between PRP and ESWT in short- or intermediate-term health-related

quality of life, and the other trial reporting better long-term outcomes for pain during sports with PRP plus DN (although there were no differences between groups in the short- or intermediate-term).

4.1.4.1. PRP vs. Conservative Control for patellar tendinopathy

Studies included

Two small RCTs (and no cohort studies) met the inclusion criteria. Detailed information on patient and study characteristics is available in Appendix Table F10. One trial (Dragoo[70]) compared leukocyte-rich PRP (LR-PRP) plus dry needling (n=10) to dry needing alone (n=13) in patients with subacute patellar tendinopathy (>1.5 months); the other trial (Vetrano[284]) compared PRP (n=23) to three sessions of extracorporeal shock wave therapy (ESWT) (n=23) in patients with chronic patellar tendinopathy (≥6 months). Mean duration of symptoms was 18 to 19 months in one trial (Vetrano) and not reported in the other trial (Dragoo). The trials were small, with 23 to 46 patients enrolled. PRP injectate ranged from 2 ml to 6 ml; one trial (Dragoo) also injected epinephrine and bupivacaine. Neither trial reported use of an activating agent; one trial used a peppering technique in both groups (Dragoo). Imaging guidance was used for all injections. One trial (Vetrano) performed a total of two injections in the PRP group; the other trial (Dragoo) reported used of a single injection. One trial (Dragoo) reported that 23% of control group patients crossed over after 3 months; these patients were excluded from 6-month analysis. Dragoo et al. had some imbalances at baseline between the PRP + DN and DN groups that were not controlled for (age, VAS, Lysholm, VISA-P scores); both trials had imbalances in the percentage of males that comprised each group. These imbalances, particularly those in the Dragoo trial, are likely attributed to small sample size. Methodological shortcomings included unclear allocation concealment (Vetrano), failure to report intention-to-treat analyses (Dragoo), lack of blinded outcomes assessment (Vetrano), low and differential follow-up (Dragoo for intermediate follow-up), and failure to control for potentially confounding differences in baseline characteristics (Dragoo). Overall, the Dragoo trial was considered to be at moderately low risk of bias with respect to short-term outcomes and moderately high with respect to intermediate-term outcomes; the quality of the trial was downgraded for intermediate-term outcomes due to low follow-up (74% overall) and differential follow-up between PRP and DN groups (80% vs. 69%)) (Dragoo). The other trial was found to be at moderately low risk of bias (Vetrano).

Efficacy Results

Function

The patient-reported VISA-P outcome measure (0-100 (best)) was used by both trials[70,284], and meta-analysis was performed (Figure 12). One trial (Dragoo[70]) also reported two additional patient-reported functional outcome measures: Lysholm Knee Function (0-100 (best)) and Tegner Activity Level (0-10 (best)) (Table 24). At baseline, the PRP + DN group had better Lysholm scores than the DN group (58.3 vs. 48.5); this imbalance was not controlled for. Both follow-up and change scores were evaluated, and the more conservative estimate is presented here.

Short-term: There was no difference between groups in short-term VISA-P scores (WMD 7.4 (95% CI -1.5, 16.2), 2 RCTs) (Vetrano[284], Dragoo[70]) (Figure 12). For Lysholm scores, there was no difference between LR-PRP + DN and DN groups in change scores (23.8 vs. 26.5), with a MD between groups of 2.7 (95% CI -25.4, 20.0) (Dragoo[70]) (Table 24). The same trial found similar results between groups in Tegner activity scores (4.9 vs. 4.0, MD 0.9 (95% CI -0.7, 2.5)) (Dragoo[70]) (Table 24).

Intermediate-term: Results differed by control group. For PRP versus ESWT, VISA-P scores were better with PRP (MD 13.0 (95% CI 3.0, 23.0)) based on results from one trial (Vetrano[284]) (Figure 12). For PRP + DN versus DN, there was no difference between groups in VISA-P scores (MD -4.3 (95% CI -24.0, 15.4)) based on results from one trial (Dragoo[70]) (Figure 12). Results for the Lysholm scores were unclear: while

follow-up scores (which provided the more conservative estimate) (76.3 vs. 91.8) suggested no difference between LR-PRP + DN versus DN groups (MD -15.5 (95% CI -33.3, 2.3)), the change scores (14.7 vs. 45.4) suggested that there was statistically less improvement in the LR-PRP group (MD -30.7 (95% CI -50.3, -11.1)) (Dragoo[70]). There was no difference between these groups in Tegner activity scores (5.8 vs. 6.4, MD -0.6 (95% CI -2.6, 1.4)) (Dragoo[70]) (Table 24).

Long-term: One trial found that long-term VISA-P scores were significantly better in the PRP versus ESWT group (MD 13.7 (95% CI 4.6, 22.8)) (Vetrano[284]) (Figure 12).

Pain

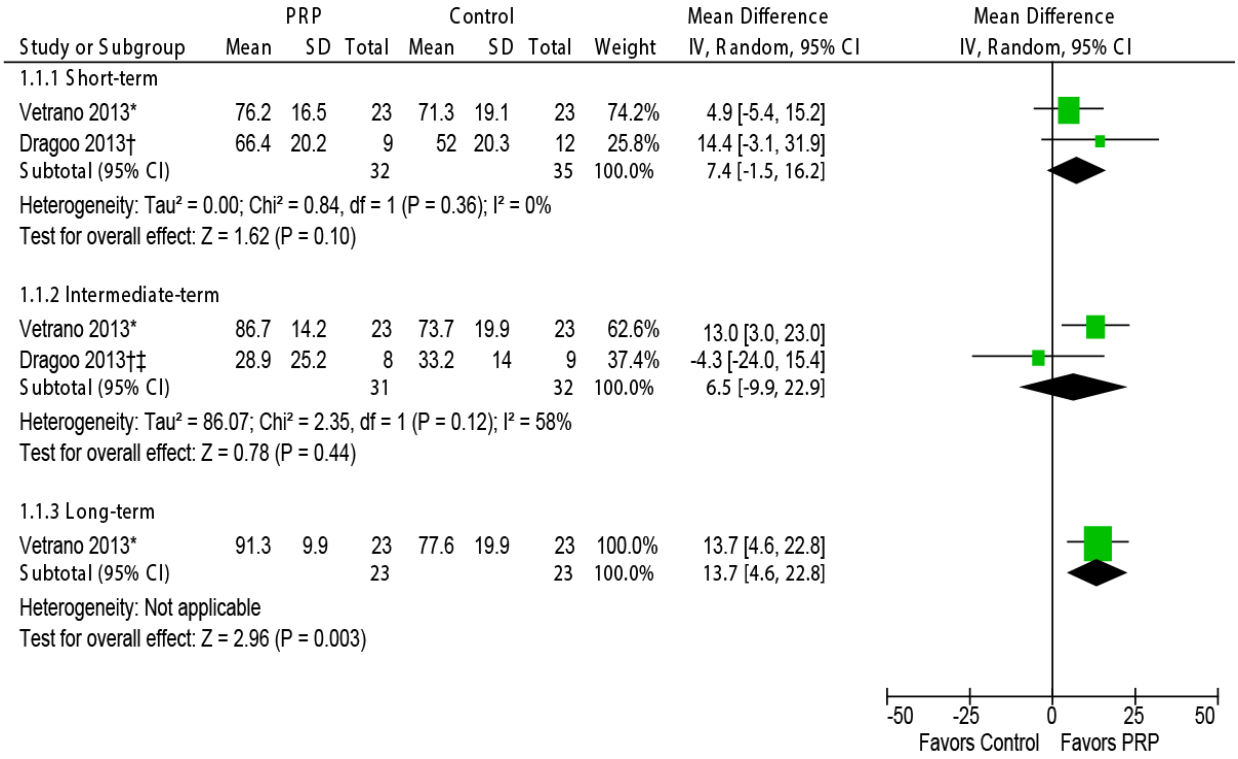
Both trials reported patient-evaluated VAS pain (0-10 (worst)) (Figure 13). Pooled analysis suggests no statistical difference between groups in the short-term (WMD -0.7 (95% CI -1.5, 0.2), 2 RCTs) or intermediate-term (WMD -1.1 (95% CI -2.3, 0.2), 2 RCTs). For intermediate-term results, one trial favored PRP over ESWT (Vetrano[284]) while the other found no difference between LR-PRP + DN and DN alone groups (Dragoo[70]). In the long-term, one trial (Vetrano[284]) reported significantly better function in the PRP versus ESWT group (MD -1.7 (95% CI -2.9, -0.5)).

Other outcomes

Symptoms/recurrence: Pain during sports was assessed with the patient-reported Blazina scale in one trial (Vetrano[284]) (Table 25). A Blazina scale stage of 0 or 1 indicates that there is no pain (0) or pain only after intense sports activity without functional impairment (1). The proportion of patients with a Blazina scale stage of 0 or 1 in the short-term was identical between groups (52% vs. 52%, RR 1.0 (95% CI 0.6, 1.7)), slightly but not statistically higher in the PRP group in the intermediate-term (83% vs. 57%, RR 1.5 (95% CI 1.0, 2.2)), and statistically higher in the PRP group in the long-term (91% vs. 65%, RR 1.4 (95% CI 1.0, 1.9)) (Table 25). A similar trend was seen when results were presented in terms of "satisfactory results" (Blazina scale stage 0 or stage 1 with improvement by ≥2 stages from baseline), with better long-term outcomes in the PRP group (91% vs. 61%, RR 1.5 (95% CI 1.1, 2.1)) (Table 25).

Quality of life: There were no differences in SF-12 quality of life scores between LR-PRP + DN and DN groups in the short- or intermediate-term as reported by one trial (Dragoo[70]) (Table 26).

Figure 12. Patellar Tendinopathy RCTs comparing PRP to Conservative Control (ESWT or DN): WMD VISA-P Function



*Vetrano: PRP vs. ESWT

†Dragoo: LR-PRP + DN vs. DN

‡Change score used (there are possible baseline imbalances favoring the control group, in this case the change score provides a more conservative estimate (smaller effect size) than the f/u score)

Table 24. Patellar tendinopathy RCTs comparing LR-PRP + DN to DN: Lysholm function and Tegner activity scores

Study	Outcome Measure	F/U	LR-PRP + DN mean ± SD (n)†	DN mean ± SD (n)†	MD (95% CI)*	p-value*
Dragoo 2013	Lysholm knee function (0-100 (best))	0 mos.	58.3 ± 14.5 (n=9)	48.5 ± 16.5 (n=12)	-	-
		3 mos.	82.1 ± 22.1 (n=9)	74.8 ± 19.4 (n=12)	7.3 (-11.7, 26.2)	NS
		6 mos.	76.3 ± 20.7 (n=8)	91.8 ± 13.4 (n=9)	-15.5 (-33.3, 2.3)	NS
	Δ Lysholm‡	3 mos.	23.8 ± 27.0 (n=9)	26.5 ± 22.7 (n=12)	-2.7 (-25.4, 20.0)	NS
		6 mos.	14.7 ± 19.1 (n=8)	45.4 ± 18.8 (n=9)	-30.7 (-50.3, -11.1)	0.01
	Tegner activity (0-10 (best))	0 mos.	3.7 ± 2.5 (n=9)	4.0 ± 2.1 (n=12)	-	-
		3 mos.	4.9 ± 2 (n=9)	4.0 ± 1.6 (n=12)	0.9 (-0.7, 2.5)	NS
		6 mos.	5.8 ± 2.4 (n=8)	6.4 ± 1.4 (n=9)	-0.6 (-2.6, 1.4)	NS

CI: confidence interval; DN: dry needling; F/U: follow-up; LR-PRP: leukocyte-rich platelet-rich plasma; MD: mean difference; NS: not statistically significant (p≥0.05); RCT: randomized controlled trial; SD: standard deviation

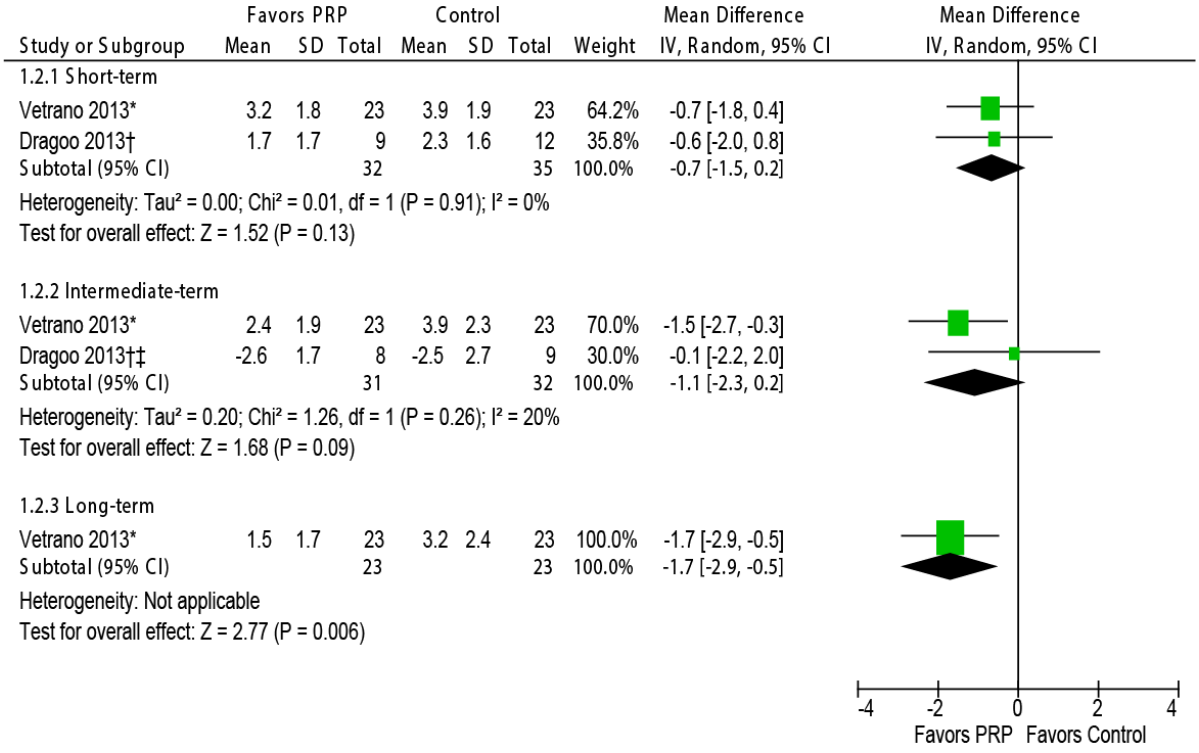
DN: dry needling; LR: leukocyte-rich; NS: p≥0.05

*Calculated unless otherwise indicated

†Excludes patients that crossed over from Dry Needling group to PRP group, this data is per protocol. Was reported that ITT analysis yielded nearly identical results.

‡Change score assessed because there are possible baseline imbalances in Lysholm scores.

Figure 13. Patellar Tendinopathy RCTs comparing PRP to Conservative Control (ESWT or DN): WMD VAS Pain



*Vetrano: PRP vs. ESWT

†Dragoo: LR-PRP + DN vs. DN

‡Change score used (there are possible baseline imbalances favoring the control group, in this case the change score provides a more conservative estimate (smaller effect size) than the f/u score)

Table 25. Patellar tendinopathy RCTs for PRP vs. ESWT: Symptoms

Study	Outcome Measure	F/U	PRP % (n/N)	ESWT % (n/N)	RR (95% CI)*	p-value*
Vetrano 2013	Blazina Scale Stage 0-1†	2 mos.	52% (12/23)	52% (12/23)	1.0 (0.6, 1.7)	NS
		6 mos.	83% (19/23)	57% (13/23)	1.5 (1.0, 2.2)	0.06
		12 mos.	91% (21/23)	65% (15/23)	1.4 (1.0, 1.9)	0.03
	Satisfactory results‡	2 mos.	47.8% (11/23)	43.4% (10/23)	1.1 (0.6, 2.1)	NS
		6 mos.	82.6% (19/23)	65.2% (15/23)	1.3 (0.9, 1.8)	NS
		12 mos.	91.3% (21/23)	60.8% (14/23)	1.5 (1.1, 2.1)	0.02

CI: confidence interval; ESWT: extracorporeal shock wave therapy; F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio

*Calculated unless otherwise indicated

†Blazina score ranges from 0-5; 0-1 is no pain (0) to pain only after intense sports activity without functional impairment; 2-5 is pain that does not interfere with sports activity performance (2), pain that prevents satisfactory performance or participation in sports (3) to pain that interferes with activities of daily living and prevents participation in sports (5).

‡Satisfactory results defined as those which were excellent (Blazina scale stage 0 at follow-up) or good (Blazina scale stage 1 and improvement by ≥2 stages from baseline).

Table 26. Patellar tendinopathy RCTs for LR-PRP + DN vs. DN: Quality of life

Study	Outcome Measure	F/U	LR-PRP + DN mean ± SD (n)†	DN mean ± SD (n)†	MD (95% CI)*	p-value*
Dragoo 2013	SF-12 QoL (0-100 (best))	3 mos.	50.7 ± 2.7 (n=9)	50.0 ± 8.5 (n=12)	0.7 (-5.5, 6.9)	NS
		6 mos.	49.0 ± 4.2 (n=8)	50.6 ± 5.0 (n=9)	-1.6 (-6.4, 3.2)	NS

CI: confidence interval; DN: dry needling; F/U: follow-up; LR-PRP: leukocyte-rich platelet-rich plasma; MD: mean difference; NS: not statistically significant (p≥0.05); QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation

*Calculated unless otherwise indicated

†Excludes patients that crossed over from Dry Needling group to PRP group, this data is per protocol. Was reported that ITT analysis yielded nearly identical results.

4.1.5. Rotator Cuff Tendinosis or Partial Tears

Summary of results

PRP vs. Control: Two RCTs[134,221] and one retrospective cohort study[287] were included that compared PRP to a conservative control; the trials compared PRP to DN (both groups used same technique, N=39) or to saline injections (N=40). The trials were found to be at low (1 RCT) and moderately low (1 RCT) risk of bias. With respect to primary outcomes in the short- and intermediate term, function scores were better with PRP versus control based on moderate quality evidence (2 RCTs); pain scores were also better with PRP but the quality of evidence was insufficient for both time points (1 RCT). In the long-term, there were no differences between groups in function scores based on low quality evidence (1 RCT). No other primary outcomes were reported. With respect to secondary outcomes, one trial found no differences between PRP and saline groups in short-, intermediate-, or long-term health-related quality of life. The cohort study (N=50) was found to be at moderately high risk of bias and reported better short-term function with PRP but no difference between groups by the intermediate term. Both groups had a similar risk of surgery through six months.

4.1.5.1. PRP vs. Conservative Control for rotator cuff tendinosis or partial tears

Studies included

Two RCTs and one retrospective cohort study were included, all of which enrolled patients with tendinosis and/or partial tears and chronic symptoms (minimum duration ranged from 3 to 6 months). Detailed information on patient and study characteristics is available in Appendix Table F11.

RCTs: One RCT (Kesikburun[134]) compared PRP (n=20) to saline injections (n=20). The other RCT (Rha[221]) compared PRP (n=20) to dry needling (DN) (n=19); both injections were performed using the same peppering technique. The volume of PRP injected ranged from 3 to 5 ml; both studies also injected lidocaine in all patients and used ultrasound guidance. One trial (Rha) performed two sessions of injections (or dry needling) on all patients; the other trial (Kesikburun) did not report whether more than one injection was performed. All patients underwent a rehabilitation or exercise program. All patients were blinded to treatment received. Duration of symptoms was similar between the trials, with a mean (or median) ranging from 8.5 to 10 months; the minimum duration of symptoms was three (Kesikburun) and six months (Rha). In general, baseline characteristics were similar between groups, with the

exception of slightly better median VAS scores in the PRP versus saline group at baseline in one trial (Kesikburun). Methodological shortcomings in one trial (Rha) included unclear allocation concealment as well as low follow-up rate (for intermediate-term follow-up only). Overall, the Kesikburun trial was considered to be at low risk of bias and the Rha trial was found to be at moderately low risk of bias.

Cohort study: The retrospective cohort study (von Wehren[287]) compared PRP (n=25) to steroid injections (n=25) in patients with symptoms of at least 3 months' duration (mean duration was not reported); patients had not received prior steroid injections or ESWT for inclusion. All patients received a total of 3 injections over a 3-week period. Aside from the PRP group being slightly younger than the steroid group, baseline characteristics were similar between groups, although relatively few were reported. The study was found to be at moderately high risk of bias due to methodological limitations surrounding lack of blinding, high and differential loss to follow-up, and failure to control for potential confounding.

Efficacy Results

Function

Both trials used the patient-reported SPADI (shoulder pain and disability index) (0-100 (worst)) to evaluate function (Table 27); because one trial (Kesikburun[134]) reported outcomes in terms of median and range, results could not be pooled. In the short-term, both trials reported better SPADI scores in the PRP group than the control group; while Rha et al.[221] reported this difference to be statistically significant (21.1 vs. 34.6, MD -13.5 (95% CI -24.8, -2.2)), Kesikburun et al.[134] reported that there was not a statistically significant difference between groups (median 27.6 vs. 45.3). Similar intermediate-term results were found (Rha: 17.7 vs. 29.5, MD -11.8 (95% CI, -22.5, -1.1); Kesikburun: median 21.7 vs. 40.9, study reported no significant difference between groups). One study (Kesikburun[134]) reported no difference in long-term median scores between PRP and saline groups (14.6 vs. 15.4).

Pain

One RCT (Rha[221]) reported significantly less pain with PRP versus dry needling as measured by the VAS (0-100 (worst)) in both the short-term (7.6 vs. 12.8, MD -5.2 (95% CI -9.5, -0.9)) and intermediate-term (6.2 vs. 10.9, MD -4.7 (95% CI -8.9, -0.5)) (Table 28).

Other outcomes

Quality of life: One trial (Kesikburun[134]) found no differences in Western Ontario Rotator Cuff index (WORC) quality of life scores PRP and saline groups in the short-, intermediate-, or long-term as reported (Table 29).

Table 27. Rotator Cuff Tendinopathy RCTs for PRP vs. Conservative Control (DN or Saline): Function

Outcome Measure	Study	F/U	PRP Mean ± SD†	Dry Needling Mean ± SD†	MD (95% CI)*	p-value*
SPADI pain and Disability (0-100 (worst))	Rha 2013	3 mos.	21.1 ± 17.4 (n = 16)	34.6 ± 17.4 (n = 16)	-13.5 (-24.8, -2.2)	0.02
		6 mos.	17.7 ± 16.5 (n = 16)	29.5 ± 16.6 (n = 14)	-11.8 (-22.5, -1.1)	0.03
Outcome Measure	**Study**	**F/U**	**PRP Median (range)**	**Saline Median (range)**	**MD (95% CI)‡**	**p-value‡**
SPADI pain and disability (0-100 (worst))	Kesikburun 2013	3 mos.	27.6 (1.2 to 84.0) (n = 20)	45.3 (2.9 to 95.5) (n = 20)	NR/NC	NS
		6 mos.	21.7 (0.0 to 96.1) (n = 20)	40.9 (0.0 to 95.5) (n = 20)	NR/NC	NS
		12 mos.	14.6 (0.0 to 86.3) (n = 20)	15.4 (0.0 to 96.0) (n = 20)	NR/NC	NS

CI: confidence interval; DN: dry needling; F/U: follow-up; MD: mean difference; NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; SPADI: Shoulder Pain and Disability Index

*Calculated unless otherwise indicated

†SD calculated from study-reported SE

‡As reported by the study

Table 28. Rotator Cuff Tendinopathy RCTs for PRP vs. DN: Pain

Study	Outcome measure	F/U	PRP Mean ± SD†	Dry Needling Mean ± SD†	MD (95% CI)*	p-value*
Rha 2013	VAS pain (0-100 (worst))	3 mos.	7.6 ± 6.7 (n = 16)	12.8 ± 6.5 (n = 16)	-5.2 (-9.5, -0.9)	0.02
		6 mos.	6.2 ± 6.3 (n = 16)	10.9 ± 6.5 (n = 14)	-4.7 (-8.9, -0.5)	0.03

CI: confidence interval; DN: dry needling; F/U: follow-up; MD: mean difference; PRP: platelet-rich plasma; RCT: randomized, controlled trial; SD: standard deviation; VAS: Visual Analog Scale

*Calculated unless otherwise indicated

†SD calculated from study-reported SE

Table 29. Rotator Cuff Tendinopathy RCTs for PRP vs. Saline: Quality of Life

Study	Outcome Measure	F/U	PRP Median (range)	Saline Median (range)	Effect size*	p-value*
Kesikburun 2013	WORC QoL (0-100% (best))	3 mos.	79.1 (19.8 to 96.6) (n = 20)	58.5 (0.0 to 97.1) (n = 20)	NR/NC	NS
		6 mos.	82.5 (16.9 to 100.0) (n = 20)	69.9 (0.0 to 99.2) (n = 20)	NR/NC	NS
		12 mos.	84.6 (26.7 to 100.0) (n = 20)	79.7 (0.0 to 99.3) (n = 20)	NR/NC	NS

F/U: follow-up; NC: not calculable; NR: not reported; NS: not significant; PRP: platelet-rich plasma; QoL: Quality of Life; RCT: randomized, controlled trial; WORC: Western Ontario Rotator Cuff Index

*As reported by the study

Effectiveness Results

Function

The retrospective cohort study (von Wehren[287]) reported statistically greater short-term functional improvement following PRP versus steroid injections using three different outcome measures (Table 30): the patient-reported Simple Shoulder Test, the clinician-reported Constant-Murley functional assessment of the shoulder, and the patient- and clinician-reported American Shoulder and Elbow Surgeons Standardized Shoulder Assessment. For the intermediate-term, the study reported no significant difference between groups in any of these outcome measures.

Pain

No data reported.

Other outcomes

The retrospective cohort study (von Wehren[287]) reported no statistical difference between PRP and steroid groups in the percentage of patients who underwent shoulder surgery through 6 months (16% vs. 28%) (Table 30).

Table 30. Rotator Cuff Tendinopathy Cohort Study for PRP vs. Steroid: All outcomes

Study	Outcome Measure	F/U	PRP Mean ± SD†	Steroid Mean ± SD†	p-value*
Function					
von Wehren 2015	Simple Shoulder Test†	3 mos.	10.3 ± 1.7 (n = 21)	8.3 ± 2.8 (n = 18)	<0.05
		6 mos.	10.3 ± 2.1 (n = 21)	9.3 ± 2.6 (n = 18)	NS
	CMS (0-100 (best))	3 mos.	91.1 ± 10.2 (n = 21)	77.6 ± 15.4 (n = 18)	<0.05
		6 mos.	90.7 ± 9.4 (n = 21)	87.5 ± 12.3 (n = 18)	NS
	ΔASES (0-100 (best))	3 mos.	34 ± 21.3 (n = 21)	16.2 ± 21.4 (n = 18)	<0.05
		6 mos.	31.8 ± 25.4 (n = 21)	26.5 ± 19.3 (n = 18)	NS
Study	**Outcome**	**F/U**	**PRP % (n/N)**	**Steroid % (n/N)**	**p-value***
von Wehren 2015	Surgery‡	≤6 mos.	16% (4/25)	28% (7/25)	NS

ASES: American Shoulder and Elbow Surgeons Standardized Shoulder Assessment; CMS: Constant-Murley functional assessment of the shoulder; F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; SD: standard deviation

*As reported by the study

†Although the Simple Shoulder Test is typically reported on a scale of 0-100% (higher scores are better), it appears that this study may have used a different scale based on the reported scores (the scale used was NR). The measure asks 12 yes or no questions thus it is possible that the study reported outcomes on a 0-12 (best) scale.

‡Patients withdrew from study

4.1.6. Plantar Fasciitis

Summary of results

PRP vs. Control: Five moderately high risk of bias RCTs[114,186,277,43,135] and three prospective cohort studies[7,245,248] were included. The trials compared PRP to steroid injection (3 RCTs), prolotherapy (1 RCT), ESWT or conservative care (1 trial with both control groups) and enrolled between 21 and 60 patients each. With respect to primary outcomes in both the short- and intermediate-term, there was no difference between groups in function or pain scores based on low quality evidence (4 RCTs

for each). In the long-term, low quality evidence suggested better function scores with PRP versus steroid (2 RCTs), while there was insufficient quality evidence of more PRP patients achieving function success (1 RCT) and better pain scores with PRP versus steroid (1 RCT). No other primary outcomes were reported. With respect to secondary outcomes, results were mixed, with one trial reporting no differences between PRP and prolotherapy in short- or intermediate-term disability, and the other trial reporting better long-term symptoms with PRP versus steroid (although there were no differences between groups in the short- or intermediate-term). The cohort studies were all at moderately high risk of bias and compared PRP to steroid injections, with 50 to 60 patients per study. Function was better in PRP patients in the short- (2 studies) and intermediate-term (1 study), while results for pain were mixed (some studies showed no difference and some favored PRP) in both the short- (3 studies) and intermediate-term (2 studies). One study reported no difference between groups in short- and intermediate-term symptoms.

ABI vs. Control: Three small moderately high risk of bias RCTs[123,140,153] (and no cohort studies) were included and compared PRP to steroid injections; two of the trials also compared ABI to anesthetic plus DN. With respect to primary outcomes in the short-term, the ABI group had worse pain scores than the steroid group (2 RCTs, low quality evidence), while there was no difference between the ABI and anesthetic plus DN group (1 RCT, insufficient quality evidence). In the intermediate-term, there was no difference between ABI and either control group in pain scores (3 RCTs, low quality evidence) or in function scores (1 RCT, insufficient quality evidence). No other primary outcomes were reported. With respect to secondary outcomes, one trial found no differences between ABI and both comparator groups in intermediate-term symptoms. Results were mixed regarding repeat injections, with one trial showing no difference between ABI and steroid groups in the short-term and another finding that more ABI patients required additional injections than steroid patients through the intermediate-term; the latter trial found no difference between ABI and anesthetic plus DN in the need for additional injections through the intermediate-term.

4.1.6.1. PRP vs. Conservative Control for plantar fasciitis

Studies included

RCTs: Five small RCTs were identified that met the inclusion criteria. Detailed information on patient and study characteristics is available in Appendix Tables F12 and F13. Three trials (Jain 2015[114], Monto 2014[186], Tiwari 2013[277]) compared PRP to steroid injections in patients with plantar fasciitis. One trial randomized 46 patients by heal, with 30 heels each in the PRP and steroid groups (Jain). The other two trials randomized 20 to 30 patients to both treatment groups. PRP was compared to prolotherapy in another small trial (Kim 2014[135]), with 10 to 11 patients per treatment group (Table 43). Another trial (Chew 2014[43]) compared PRP plus conservative care (CC) to extracorporeal shockwave therapy (ESWT) plus CC or to CC alone, with 16 to 19 patients per group (Table 43). Minimum duration of symptoms ranged from 4 to 12 months across four trials (Jain, Monto, Kim, Chew). Mean or median duration of symptoms suggest that most patients had chronic plantar fasciitis, and ranged from 5 to 35 months across the trials. Failure of prior conservative therapy varied across studies; three trials required that no steroid injections had been given in the months prior to enrollment (Tiwari, Kim, Chew). PRP injectate volume ranged from 2.5 to 5 ml; most studies also injected sodium citrate and/or sodium bicarbonate, and one (Kim) also injected glucose. Co-injection with local anesthetic varied, as did use of ultrasound imaging guidance. Type of steroid injected in the control group varied, and all three of these trials also injected local anesthetic (Jain, Monto, Tiwari). The prolotherapy group received dextrose and lidocaine injections (Kim). The ESWT group underwent two sessions over one week of ESWT (Chew). Three trials employed eccentric exercise and/or physical therapy for all patients (Jain, Monto, Chew). Three trials had some imbalances at baseline between PRP and control groups that were not adjusted for, including

percentage of males, as well as baseline function, pain, and/or disability scores (Monto, Kim, Chew); a fourth trial did not report a robust set of baseline characteristics between groups (Tiwari). All trials were found to be at moderately high risk of bias, with methodological shortcomings including unclear randomization protocol (Kim, Monto, Tiwari), unclear allocation concealment (all trials), unclear as to whether data were assessed using intention-to-treat analyses (Chew, Jain, Monto, Tiwari), lack of blinded outcomes assessment (Chew, Jain, Tiwari), unclear follow-up rate (Jain, Monto, Tiwari), differential follow-up between groups (Chew for PRP vs. ESWT), and failure to control for potentially confounding differences in baseline characteristics (all trials).

Cohort studies: Three prospective cohort studies compared PRP (n=25-30) to steroid injection (n=25-30) (Aksahin 2012[7], Say 2014[245], Shetty 2014[248]). Detailed information on patient and study characteristics is available in Appendix Table F14. All three studies required that patients have symptoms for at least 3 months; mean duration of pain was 8.6 months in one study (Aksahin). All required that patients have failed conservative therapy, and all prohibited prior steroid injection and surgery. While two studies injected 2.5 to 3 ml of PRP and used calcium chloride as an activating agent (Aksahin, Say), the third study injected 8 ml of PRP and did not use an activating agent (Shetty). Steroid used was methylprednisolone or triamcinolone; local anesthetic was also injected in both groups in two studies (Aksahin, Shetty) but only in the steroid group in the third study (Say). Only one study used the peppering technique (in both groups) (Say). Imaging guidance was not used in two studies (Aksahin, Say) and not reported by a third (Shetty). Use of repeat injections was not reported. One study had baseline imbalances in VAS pain scores (worse in PRP group). All three studies were considered to be at moderately high risk of bias due to methodological limitations surrounding lack of blinding (Say, Shetty), lack of information as to whether co-interventions were applied equally (Say), unclear follow-up rate (all), and failure to control for potential confounding (all).

Efficacy Results

Function

Four trials reported functional outcomes as measured on a continuous scale (Jain[114], Kim[135], Chew[43], Monto[186]); meta-analysis could not be performed due to limitations and differences in data reporting. One trial reported the percentage of heels that achieved a measure of functional success in the long-term (Monto).

Short- and intermediate-term: Four trials reported short-and intermediate-term functional outcomes as measured on a continuous scale. While three trials found no differences between groups in short- or intermediate-term mean (or median) scores (Jain[114], Kim[135], Chew[43]) as measured by the AOFAS Ankle-Hindfoot scale or Foot Function Index (FFI), one trial reported significantly better AOFAS Ankle-Hindfoot scale scores in the PRP group compared with the steroid group (short-term: median 95 vs. 81, study-reported $p<0.01$; intermediate-term: median 94 vs. 74, study-reported $p<0.01$) (Monto[186]) (Tables 31-32).

Long-term: The percentage of patients who achieved some measure of improvement was reported by one trial (Jain[114]). At 12 months, significantly more heels in the PRP group had achieved 90% or more improvement on the AOFAS Ankle and Hindfoot scale compared with those in the steroid group (60% (18/30) vs. 33% (10/30) heels; RR 1.8 (95% CI 1.0, 3.2), $p=0.04$). Two trials reported that PRP patients significantly better AOFAS Ankle-Hindfoot scale scores compared with the steroid group (Jain: 88.5 vs. 75.1, MD 13.4 (95% CI 4.6, 22.3); Monto: median 92 vs. 56, study-reported $p<0.01$) (Table 31).

Pain

Pain outcomes were reported by four trials scale ((Jain[114], Kim[135], Chew[43], Tiwari[277]); meta-analysis could not be performed due to limitations and differences in data reporting. No trials reported the percentage of patients that achieved any measure of pain success.

Short- and intermediate-term: Four trials reported short-and intermediate-term pain outcomes as measured by one of the following patient-reported outcome measures: VAS pain, FFI pain subscale. Three trials reported no differences between groups in short- or intermediate-term mean (or median) scores (Jain[114], Kim[135], Chew[43]) (Tables 33-34), one trial reported significantly better VAS pain scores in the PRP group compared with the steroid group in both the short- and intermediate-term (scores same for both time points: 2.0 vs. 2.8, MD -0.8 (95% CI -1.1, -0.5)) (Tiwari[277]) (Table 33).

Long-term: One trial found significantly better pain scores in the PRP group compared with the steroid group as measured by VAS pain (3.3 vs. 5.3, MD -2.0 (95% CI -3.9, -0.1)) (Jain[114]) (Table 46).

Other outcomes

Disability: One trial (Kim[135]) found no differences in FFI disability subscale scores between PRP and prolotherapy groups in the short- or intermediate-term (Table 35).

Symptoms: Symptoms were assessed by one trial (Jain[114]) using the patient-reported Roles-Maudlsey outcome measure. In the short- and intermediate-term, there was no difference in mean scores between groups, but in the long-term mean scores were significantly better in the PRP group compared with the steroid group (1.9 vs. 2.7, MD -0.8 (95% CI -1.4, -0.2)) (Table 35).

Table 31. Plantar Fasciitis RCTs for PRP vs. Steroid: Function

Study	Outcome	F/U	PRP Mean ± SD	Steroid Mean ± SD	MD (95% CI)*	p-value*
Jain 2015	AOFAS Ankle and Hindfoot score (0-100 (best))	3 mos.	83.7 ± 15.3 (n=30 heels)	86.4 ± 17.2 (n=30 heels)	-2.7 (-11.1, 5.7)	NS
		6 mos.	88.5 ± 11.8 (n=30 heels)	83.8 ± 18.3 (n=30 heels)	4.7 (-3.3, 12.7)	NS
		12 mos.	88.5 ± 13.4 (n=30 heels)	75.1 ± 20.1 (n=30 heels)	13.4 (4.6, 22.3)	<0.01
Study	**Outcome**	**F/U**	**PRP Mean (range)**	**Steroid Mean (range)**	**MD (95% CI)**	**p-value†**
Monto 2014	AOFAS Ankle and Hindfoot score (0-100 (best))	3 mos.	95 (88-100) (n=20)	81 (56-90) (n=20)	NR/NC	<0.01
		6 mos.	94 (87-100) (n=20)	74 (54-87) (n=20)	NR/NC	<0.01
		24 mos.	92 (77-100) (n=20)	56 (30-75) (n=20)	NR/NC	<0.01

AOFAS: American Orthopaedic Foot and Ankle Society; CI: confidence interval; MD: mean difference; NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation

*Calculated

†As reported by the study

Table 32. Plantar Fasciitis RCTs for PRP vs. Prolotherapy, ESWT, or CC: Function

Study	Outcome	F/U	PRP Mean ± SD	Prolotherapy Mean ± SD	MD (95% CI)	p-value*
Kim 2014	FFI total score (0-230 (worse))	2.5 mos.	123.8 ± 45.4† (n=9)	123.7 ± 47.4† (n=11)	0.1 (-44, 44)	NS
		6.5 mos.	81.6 ± 55.3† (n=9)	97.7 ± 52.5† (n=11)	-16.1 (-67, 35)	NS
	FFI activity limitation subscale score (0-100 (worse))	2.5 mos.	22.7 ± 11.2† (n=9)	20.4 ± 10.4† (n=11)	2.3 (-7.8, 12)	NS
		6.5 mos.	17.3 ± 11.6† (n=9)	16.4 ± 12.9† (n=11)	0.9 (-10.8, 12.6)	NS
Study	**Outcome**	**F/U**	**PRP + CC Median (range)**	**CC Alone Median (range)**	**MD (95% CI)**	**p-value‡**
Chew 2013	AOFAS ankle-hindfoot scale score (0-100 (best))	3 mos.	86 (67–100)† (n = 15)	80 (53–90)† (n = 13)	NR/NC	NR
		6 mos.	90 (77–100)† (n = 15)	87 (73–100)† (n = 13)	NR/NC	NR
Study	**Outcome**	**F/U**	**PRP + CC Median (range)**	**ESWT Median (range)**	**MD (95% CI)**	**p-value‡**
Chew 2013	AOFAS ankle-hindfoot scale score (0-100 (best))	3 mos.	86 (67–100) (n = 15)	85 (72–100) (n = 17)†	NR/NC	NR
		6 mos.	90 (77–100) (n = 15)	90 (72–100) (n = 17)	NR/NC	NR

AOFAS: American Orthopaedic Foot and Ankle Society; CC: conservative care; CI: confidence interval; ESWT: extracorporeal shock wave therapy; FFI: Foot Function Index; F/U: follow-up; MD: mean difference; NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation

*Calculated

†Because there were baseline imbalances in baseline scores between groups, both follow-up and change scores were considered; follow-up scores provided the more conservative effect estimate and thus were used for the analysis.

‡As reported by the study

Table 33. Plantar Fasciitis RCTs for PRP vs. Steroid: Pain

Outcome	F/U	Study	PRP Mean ± SD	Steroid Mean ± SD	MD (95% CI)*	p-value*
VAS pain (0-10 (worst))	3 mos.	Jain 2015	3.5 ± 3.3 (n=30 heels)	2.8 ± 3.4 (n=30 heels)	0.7 (-1.0, 2.4)	NS
		Tiwari 2013	2.0 ± 0.5 (n=30)	2.8 ± 0.8 (n=30)	-0.8 (-1.1, -0.5)	<0.01
	6 mos.	Jain 2015	3.7 ± 3.6 (n=30 heels)	3.3 ± 3.6 (n=30 heels)	0.4 (-1.5, 2.3)	NS
		Tiwari 2013	2.0 ± 0.5 (n=30)	2.8 ± 0.8 (n=30)	-0.8 (-1.1, -0.5)	<0.01
	12 mos.	Jain 2015	3.3 ± 3.7 (n=30 heels)	5.3 ± 3.5 (n=30 heels)	-2.0 (-3.9, -0.1)	0.04

CI: confidence interval; F/U: follow-up; MD: mean difference; NS: not significant; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale

*Calculated

Table 34. Plantar Fasciitis RCTs for PRP vs. Prolotherapy, ESWT, or CC: Pain

Study	Outcome	F/U	PRP Mean ± SD	Prolotherapy Mean ± SD	MD (95% CI)	p-value*
Kim 2014	FFI pain subscale (0-100 (worse))	2.5 mos.	51.9 ± 17.6 (n=9)	52.5 ± 18.0 (n=11)	-0.6 (-17, 16)	NS
		6.5 mos.	33.7 ± 23.4 (n=9)	41.1 ± 21.4 (n=11)	-7.7 (-29, 14)	NS
Study	**Outcome**	**F/U**	**PRP + CC Median (range)**	**CC Alone Median (range)**	**MD (95% CI)**	**p-value‡**
Chew 2013	VAS (0-10 (worst))	3 mos.	4 (0–8)† (n=15)	4 (1–9)† (n = 13)	NR/NC	NR
		6 mos.	2 (0–6)† (n = 15)	3 (0–7)† (n = 13)	NR/NC	NR
Study	**Outcome**	**F/U**	**PRP + CC Median (range)**	**ESWT Median (range)**	**MD (95% CI)**	**p-value‡**
Chew 2013	VAS (0-10 (worst))	3 mos.	4 (0–8) (n=15)	4 (0–7) (n = 17)	NR/NC	NR
		6 mos.	2 (0–6) (n = 15)	3 (0–8) (n = 17)	NR/NC	NR

CC: conservative care; CI: confidence interval; ESWT: extracorporeal shock wave therapy; FFI: Foot Function Index; F/U: follow-up; MD: mean difference; NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale

*Calculated

†Because there were baseline imbalances in baseline scores between groups, both follow-up and change scores were considered; follow-up scores provided the more conservative effect estimate and thus were used for the analysis.

‡As reported by the study

Table 35. Plantar Fasciitis RCTs for PRP vs. Prolotherapy, ESWT, or CC: Disability

Study	Outcome	F/U	PRP Mean ± SD	Prolotherapy Mean ± SD	MD (95% CI)	p-value*
Disability						
Kim 2014	FFI disability subscale score (0-100 (worse))	2.5 mos.	49.2 ± 19.4 (n=9)	50.9 ± 22.4 (n=11)	-1.7 (-22, 18)	NS
		6.5 mos.	31.9 ± 22.4 (n=9)	40.3 ± 21.8 (n=11)	-8.4 (-29, 12)	NS
Symptoms						
Jain 2015	Roles–Maudsley Score (1-4 (worst))	3 mos.	2.0 ± 1.3 (n=30 heels)	1.9 ± 1.2 (n=30 heels)	0.1 (-0.5, 0.7)	NS
		6 mos.	2.1 ± 1.3 (n=30 heels)	2.2 ± 1.2 (n=30 heels)	-0.1 (-0.7, 0.5)	NS
		12 mos.	1.9 ± 1.2 (n=30 heels)	2.7 ± 1.2 (n=30 heels)	-0.8 (-1.4, -0.2)	0.01

CC: conservative care; CI: confidence interval; ESWT: extracorporeal shock wave therapy; FFI: Foot Function Index; F/U: follow-up; MD: mean difference; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation

*Calculated

Effectiveness Results

Function

Function outcomes were reported for PRP versus steroid by two cohort studies (Say[245], Shetty[248]) (Table 36). In the short-term, both studies reported significantly better scores in the PRP group as evaluated by the clinician-reported AOFAS outcome measure, and one study (Shetty[248]) also found significantly better scores with PRP as evaluated by the patient-reported Foot and Ankle Disability Index (FADI). In the intermediate-term, one study (Say[245]) reported significantly better AOFAS scores in the PRP group versus the steroid group (Table 36).

Pain

Pain outcomes were evaluated following treatment with PRP versus steroid by all three cohort studies using the VAS pain scale (Aksahin[7], Say[245], Shetty[248]) (Table 37); results were mixed. In the short-term, two studies reported significantly better pain scores in the PRP group (Say[245], Shetty[248]), while one study reported no difference between groups (Aksahin[7]). In the intermediate-term, one study reported better results in the PRP group (Say[245]) while the other study found similar scores between groups (Aksahin[7]). Of these three studies, Aksahin et al.[7] was the only one in which patients were blinded to treatment received, and patients had a mean duration of symptoms of approximately nine months; mean duration of symptoms was not reported in the other two studies.

Other outcomes

Symptoms: One study reported no difference between groups in the short- and intermediate-term in the percentage of patients who achieved "excellent or good" modified Roles-Maudlsey scores (Aksahin[7]) (Table 38).

Table 36. Plantar Fasciitis cohort studies for PRP vs. Steroid: Function

Outcome	F/U	Study	PRP Mean ± SD	Steroid Mean ± SD	p-value*
AOFAS score (0-100 (best))	1.5 mos.	Say 2014	85.5 ± 4.2 (n=25)	75.3 ± 4.8 (n=25)	<0.01
	3 mos.	Shetty 2014	83.1 ± 10.1 (n=30)	70.5 ± 9.2 (n=30)	<0.01
	6 mos.	Say 2014	90.6 ± 2.6 (n=25)	80.3 ±4 .7 (n=25)	<0.01
FADI score (0-100 (best))	3 mos.	Shetty 2014	90.5 ± 7.4 (n=30)	63.3 ± 9.0 (n=30)	<0.01

AOFAS: American Orthopaedic Foot and Ankle Society; CI: confidence interval; FADI: Foot and Ankle Disability Index; NR: not reported; F/U: follow-up; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; SD: standard deviation.

*As reported by the study.

Table 37. Plantar Fasciitis cohort studies for PRP vs. Steroid: Pain

Outcome	F/U	Study	PRP Mean ± SD	Steroid Mean ± SD	p-value*
VAS pain (0-10 (worst)); mean ± SD	0.75 mos.	Aksahin 2012	5.6 ± 1.6 (n=30)	4.4 ± 2.1 (n=30)	NS
	1.5 mos.	Say 2014	2.4 ± 0.8 (n=25)	4.0 ± 1.1 (n=25)	<0.01
	3 mos.	Shetty 2014	1.8 ± 1.1 (n=30)	4.3 ± 1.4 (n=30)	<0.01
	6 mos.	Aksahin 2012	3.9 ± 2.0 (n=30)	3.4 ± 2.3 (n=30)	NS
		Say 2014	1.0 ± 0.8 (n=25)	2.6 ± 0.9 (n=25)	<0.01

F/U: follow-up; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; SD: standard deviation; VAS: Visual Analog Scale.

*As reported by the study.

†A subjective pain score where 1 = excellent, no pain, full movement, full activity; 2 = good, occasional discomfort, full movement, and full activity; 3 = fair, some discomfort after prolonged activity; and 4 = poor, pain limiting activities.

Table 38. Plantar Fasciitis cohort studies for PRP vs. Steroid: Symptoms

Study	Outcome	F/U	PRP % (n/N)	Steroid % (n/N)	p-value*
Aksahin 2012	Modified Roles–Maudsley score†, Excellent/Good	0.75 mos.	37% (11/30)	33% (10/30)	NS
		6 mos.	33% (10/30)	47% (14/30)	NS

F/U: follow-up; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma.

*As reported by the study.

†1 = excellent, no pain, full movement, full activity; 2 = good, occasional discomfort, full movement, and full activity; 3 = fair, some discomfort after prolonged activity; and 4 = poor, pain limiting activities.

4.1.6.2. ABI vs. Conservative Control for plantar fasciitis

Studies included

Three small RCTs (and no cohort studies) met the inclusion criteria (Kalaci 2009[123], Kiter 2006[140], Lee 2007[153]). Detailed information on patient and study characteristics is available in Appendix Table F15. All three trials compared injection of ABI (n=15-30) to steroid (n=14-31); in addition, two trials had an additional anesthetic plus dry needling comparison group (n=15-25) (Kalaci, Kiter). Minimum symptom duration was 1.5 months in one trial (Lee), with a mean duration of pain of 7 to 8 months. Another trial (Kalaci) did not require a minimum symptom duration, but reported mean duration of pain ranged from 8 to 12 months between groups. Another trial (Kiter) required at least six months' of symptoms, with a mean duration of 19 months. Failure of prior conservative therapy varied across studies, with two trials limiting prior injections (Kalaci, Kiter), two limiting prior surgery (Kalaci, Lee), and one trial prohibiting use of any prior treatment except NSAIDs or heel pads (or steroid injections within the past year) (Kiter). ABI injectate volume ranged from 1.5 to 2 ml; two studies also injected anesthetic (Kiter, Lee). Type of steroid injected in the control group varied, and two these trials co-injected local anesthetic (Kiter, Lee). Imaging guidance was not reported in any of the trials. One trial allowed up to three injections (Kiter), the other two did not report any repeat injections. While two trials did not employ any specific co-interventions (Kalaci, Kiter), one trial prescribed a stretching program (Lee). All three trials had some imbalances at baseline between PRP and control groups that were not adjusted for, including mean duration of pain (Kalaci, ABI vs. LA + DN only), baseline pain scores (Kiter, ABI vs. LA + DN only), and the percentage of patients with calcaneal spurs (Lee). All were found to be at moderately high risk of bias, with methodological shortcomings including unclear randomization protocol (Kalaci), unclear allocation concealment (all trials), failure to perform intention-to-treat analysis (Kalaci), lack of blinded outcomes assessment (Kiter, Lee), unclear follow-up rate (Kalaci), and failure to control for potentially confounding differences in baseline characteristics (all trials).

Efficacy Results

Function

Functional outcomes were reported by only one trial[140] using the clinician-reported AOFAS Ankle-Hindfoot scale (Table 39). There were no intermediate-term differences between ABI and steroid groups (MD 0.8 (95% CI -11.2, 12.8)) or between ABI and LA + DN groups (MD 2.7 (95% CI -7.2, 12.6)) (Kiter[140]).

Pain

Pain outcomes were reported by all three trials[123,140,153] using the patient-reported VAS pain scale (0-10 (worst)) (Figure 14). In the short-term, pooled analysis from two trials comparing ABI to steroid injections suggested worse results following ABI (WMD 1.68 (95% CI 0.70, 2.66), 2 RCTs (Kalaci[123], Lee[153])), while one trial found no difference between ABI and LA + DN groups (MD -0.30 (95% CI -1.80, 2.36)) (Kalaci[123]). In the intermediate-term, pooled VAS scores were worse in the ABI group than the steroid group, though the difference did not reach statistical significance (WMD 1.09 (95% CI -0.09, 2.27), 3 RCTs (Kalaci[123], Kiter[140], Lee[153])), while two trials reported no difference between ABI and LA+ DN groups (WMD 0.27 (95% CI -0.82, 1.36), 2 RCTs (Kalaci[123], Kiter[140])).

Other outcomes

Symptoms: One trial (Kalaci[123]) assessed symptoms using the patient-reported Roles-Maudlsey outcome measure. In the intermediate-term, the percentage of patients who achieved "excellent or good" modified Roles-Maudlsey scores were similar between ABI and steroid groups (60% vs. 80%, RR 0.8 (95% CI 0.5, 1.1)) as well as between ABI and LA + DN groups (60% vs. 52%, RR 1.2 (95% CI 0.7, 1.9)) (Table 40).

Repeat injections: Two trials reported the need for repeat injections (Kiter[140], Lee[153]) (Table 41). For ABI versus steroid injections, one trial reported no difference between groups in the short-term (10% vs. 7%) (Lee[153]), while another trial (Kiter[140]) reported that patients in the ABI group underwent significantly more repeat injections than those in the steroid group through six months (intermediate-term) (87% vs. 50%, RR 1.7 (95% CI 1.0, 3.0)). For ABI versus LA + DN, one trial reported no difference in the need for additional injections through six months (87% vs. 73%) (Kiter[140]).

Table 39. Plantar Fasciitis RCTs for ABI vs. Conservative Control (Steroid or LA + DN): Function

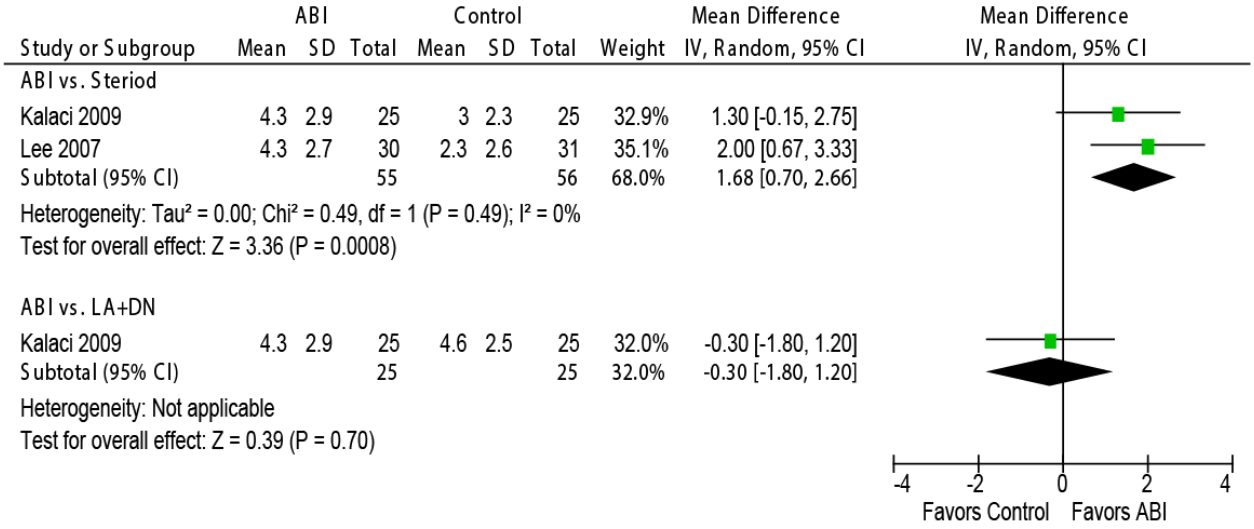
Study	Outcome	F/U	ABI Mean ± SD	Steroid Mean ± SD	MD (95% CI)*	p-value*
Kiter 2006	AOFAS Ankle and Hindfoot score (0-100 (best))	6 mos.	80.9 ± 13.9 (n=15)	80.1 ± 17.5 (n=14)	0.8 (-11.2, 12.8)	NS
Study	**Outcome**	**F/U**	**ABI Mean ± SD**	**LA + DN Mean ± SD**	**MD (95% CI)***	**p-value***
Kiter 2006	AOFAS Ankle and Hindfoot score (0-100 (best))	6 mos.	80.9 ± 13.9 (n=15)	78.2 ± 12.4 (n=15)	2.7 (-7.2, 12.6)	NS

ABI: autologous blood injection; AOFAS: American Orthopaedic Foot and Ankle Society; CI: confidence interval; DN: dry needling; F/U: follow-up; LA: local anesthetic; MD: mean difference; NS: not statistically significant (p≥0.05); PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation

*Calculated

Figure 14. Plantar Fasciitis RCTs comparing ABI to Conservative Control (Steroid or LA + DN): WMD VAS Pain

a. Short-term



b. Intermediate-term

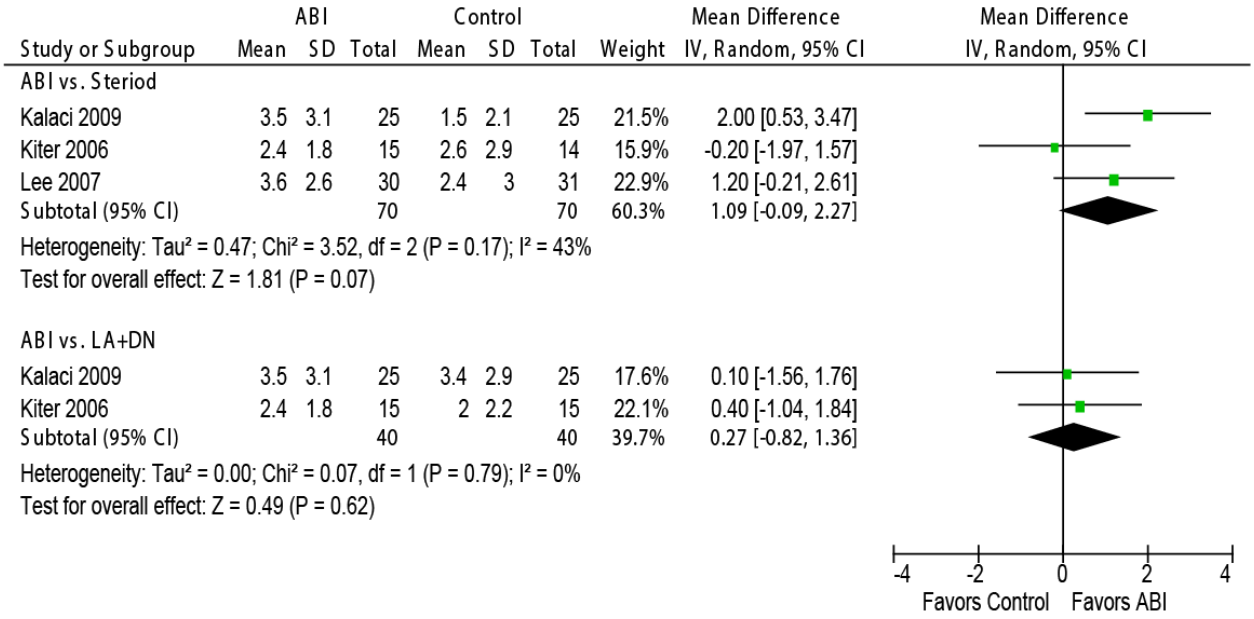


Table 40. Plantar Fasciitis RCTs for ABI vs. Conservative Control (Steroid or LA + DN): Symptoms

Study	Outcome	F/U	ABI % (n/N)	LA + DN % (n/N)	RR (95% CI)*	p-value*
Kalaci 2009	Modified Roles–Maudsley score†, Excellent/Good	6 mos.	60% (15/25)	80% (20/25)	0.8 (0.5, 1.1)	NS‡
Study	**Outcome**	**F/U**	**ABI % (n/N)**	**LA + DN % (n/N)**	**RR (95% CI)***	**p-value***
Kiter 2006	AOFAS Ankle and Hindfoot score (0-100 (best))	6 mos.	60% (15/25)	52% (13/25)	1.2 (0.7, 1.9)	NS

ABI: autologous blood injection; AOFAS: American Orthopaedic Foot and Ankle Society; CI: confidence interval; DN: dry needling; F/U: follow-up; LA: local anesthetic; NS: not statistically significant (p≥0.05); RCT: randomized controlled trial; RR: risk ratio

*Calculated

†1 = excellent, no pain, full movement, full activity; 2 = good, occasional discomfort, full movement, and full activity; 3 = fair, some discomfort after prolonged activity; and 4 = poor, pain limiting activities

‡The trial reported significantly more patients with an excellent or good score in the steroid group than the ABI group, however our calculations did not show this effect.

Table 41. Plantar Fasciitis RCTs for ABI vs. Conservative Control (Steroid or LA + DN): Repeat injections

Outcome	Study	F/U	ABI % (n/N)	Steroid % (n/N)	RR (95% CI)*	p-value*
Repeat injection(s)	Lee 2007	3 mos.	10% (3/30)	7% (2/31)	1.5 (0.3, 8.3)	NS
	Kiter 2006	≤6 mos.	87% (13/15)†	50% (7/14)†	1.7 (1.0, 3.0)	0.04
Outcome	**Study**	**F/U**	**ABI % (n/N)**	**LA + DN % (n/N)**	**RR (95% CI)***	**p-value***
Repeat injection(s)	Kiter 2006	≤6 mos.	87% (13/15)‡	73% (11/15)‡	1.2 (0.8, 1.7)	NS

ABI: autologous blood injection; CI: confidence interval; DN: dry needling; F/U: follow-up; LA: local anesthetic; NS: not statistically significant (p≥0.05); RCT: randomized controlled trial; RR: risk ratio

*Calculated

†Includes one and two repeat injection(s) for ABI vs. steroid:

- One repeat injection: 20% (3/15) vs. 50% (7/14)
- Two repeat injections: 67% (10/15) vs. 0% (0/14)

‡Includes one and two repeat injection(s) for ABI vs. LA + DN:

- One repeat injection: 20% (3/15) vs. 27% (4/15)
- Two repeat injections: 67% (10/15) vs. 47% (7/15)

4.1.7. Acute Muscle Injuries

Summary of results

PRP + Conservative Care (CC) vs. Control: Four RCTs[35,98,100,220] were included; trial size ranged from 28 to 80 patients each. One trial was found to be at low risk of bias, two at moderately low risk of bias, and one at moderately high risk of bias. The trials compared PRP plus CC to either CC alone (2 RCTs) or plus saline injection (1 RCT). With respect to primary outcomes, there was low quality evidence of no difference in pain scores between groups (3 RCTs); short-term function was better with PRP plus CC compared with CC alone (1 RCT), however the quality of evidence was insufficient. In the intermediate-term, there was low quality evidence of no difference between PRP plus CC versus

saline plus CC in function and pain scores (1 RCT each). No other primary outcomes were reported. With respect to secondary outcomes, short-term return to sport results were mixed, with two studies finding better results with PRP plus CC and one finding no difference between groups. One trial reported no difference between groups in short-term recovery and patient satisfaction as well as in intermediate-term symptoms, health-related quality of life, and return to sport. There were no differences between groups in re-injury rates in the short- (2 RCTs), intermediate- (1 RCT), or long-term (1 RCT).

4.1.7.1. PRP vs. Conservative Control for acute muscle injuries

Studies included

Four RCTs and no cohort studies were identified evaluated PRP for the treatment of acute muscle injuries (Bubnov 2013[35], Hamid 2014[98], Hamilton 2015[100], Reurink 2015[220]). Detailed information on patient and study characteristics is available in Appendix Table F16. Three trials compared PRP plus conservative care (CC) (n=14-30) to CC alone (n=14-30) (Bubnov, Hamid, Hamilton) while a fourth trial compared PRP plus CC (n=41) to saline injections plus CC (n=39) (Reurink). All patients presented within days of their injury, which was to the hamstring muscle in three trials (Hamid, Hamilton, Reurink) and to the thigh (59% vs. 47% for PRP+CC vs. CC), foot-ankle (29% in both groups), or shoulder muscle (12% vs. 24%) in the fourth trial (Bubnov). Two trials exclusively enrolled male professional athletes (Bubnov, Hamilton) and the other two trials enrolled primarily males (Hamid, Reurink). One trial was comprised primarily of competitive athletes playing at the national level (54%) (Hamid). A high proportion (39%-63%) of injuries were recurrent in three of the trials reporting (Hamid, Hamilton, Reurink), and patients were relatively young across all four trials, with a mean age ranging from 20 to 30 years. The volume of PRP injected ranged from 3 to 5 ml; none of the trials reported co-injection with an anesthetic or activating agent. Ultrasound guidance was used in three trials (Bubnov, Hamid, Reurink) while the fourth did not use imaging guidance during needle placement (Hamilton). Two trials employed a single injection of PRP (Hamid, Hamilton), one used a two-injection procedure with injections spaced 5 to 7 days apart (Reurink), and one did not report on repeat injections (Bubnov). In all trials, patients in both groups received conservative care, which consisted of standardized, supervised physiotherapy or rehabilitation programs geared toward strengthening, core stability, and agility. Two trials reported the use of anti-inflammatory therapy, specifically acetaminophen as needed in one trial (Bubnov, Hamid). There were baseline imbalances in the percentage of patients with recurrent injury in two trials such that more of these patients were allocated to PRP (Hamid, Hamilton), and one trial had more males in the PRP group (Hamid). Otherwise, groups were well-balanced in terms of baseline characteristics. One trial was considered to be at low risk of bias (Reurink), two were found to be at moderately low risk of bias (Hamid, Hamilton), and one was found to be at moderately high risk of bias (Bubnov). Methodological limitations included unclear random sequence generation (Bubnov), unclear method of concealed allocation (Bubnov, Hamilton), lack of information as to whether data were analyzed with intention to treat analyses (Bubnov), lack of blinding (Bubnov, Hamid), unclear follow-up rate (Bubnov), differential attrition between groups (Hamilton- 6 months outcomes only), and failure to provide baseline characteristics for both treatment groups (Bubnov).

Efficacy Results

Function

Two trials[35,220] reported functional outcomes (Table 42). While the trial of patients with thigh, foot/ankle, or shoulder injuries (Bubnov[35]) reported significantly better subjective global function scores (0-100 (best)) in the PRP + CC versus CC group at one month (92 vs. 74, study-reported p-value <0.05), one trial of acute hamstring injury (Reurink[220]) reported no difference between PRP + CC and CC + saline

injection groups at 6.5 months in the patient-reported Hamstring Outcome Score (HOS) measure (0-100 (best)) (86 vs. 88, MD -3 (95% CI -12, 7)).

Pain

Continuous pain outcomes were reported by three trials (Table 43).[35,192,220] In the short-term, two trials reported no significant difference between PRP + CC and CC (alone or with saline injection) groups in VAS or NRS pain scores (Bubnov[35], Reurink[220]), while another trial (Hamid[98]) reported mixed results: there was greater improvement in with PRP + CC versus CC alone as measured by the patient-reported Brief Pain Inventory–Short Form (BPI-SF) pain severity scale (β ± SE: -0.390 ± 0.142 (95% CI -0.67, -0.11)) but not the BPI-SF pain interference scores (β ± SE: -0.185 ± 0.130 (95% CI -0.44, -0.07)) (Table 43). In both cases, between-group differences were evaluated over time using a linear mixed-model analysis. Of note, the PRP group was only evaluated up to 7 weeks (2 months) while the control group was evaluated up to 10 weeks (2.5 months) in this trial. In the intermediate-term, one trial reported no difference between groups in the patient-reported HOS pain or soreness scales (Reurink[220]) (Table 43).

Other outcomes

Symptoms and recovery: One trial found no difference between PRP + CC versus CC + saline injections in the HOS-Symptoms or the HOS-Function in Sports subscale scores at 6.5 months (Reurink[220]) (Table 44). The same trial also reported no difference in the percentage of patients with perceived full recovery between groups at 2.5 months (Table 45).

Quality of life: The HOS-Quality of Life subscale score was similar between PRP + CC and CC + saline groups at 6.5 months in one trial (Reurink[220]) (Table 44).

Patient satisfaction: At 2.5 months, one trial reported a similar percentage of patients had good or excellent patient satisfaction (Reurink[220]) (Table 45).

Return to sport: All four trials reported time to return to sport (Table 44). Three trials reported short-term data, two of which compared PRP plus CC with CC alone and found that the addition of PRP significantly reduced recovery time over 1 month follow-up in one trial (10 vs. 22 days, MD -12.0 (95% CI -13.0, -11.0)) (Bubnov[35]) and over 2 months in the other trial (27 vs. 43 days, adjusted HR 4.8 (95% CI 1.3, 19.3)) (Hamid[192]). Conversely, the third trial that found no differences between PRP plus CC and saline plus CC groups over 2 months of follow-up (Reurink[220]). Intermediate-term data was provided by a fourth trial which found no differences between patients who received PRP plus CC and CC alone (Hamilton[100]). This data should be interpreted with caution given the variability in return-to-play criteria (or lack thereof) across the trials.

Re-injury: There were no significant differences in re-injury rates between groups over the short- (Hamilton[100], Reurink[220]), intermediate- (Hamilton[100]), or long-term (Reurink[220]) (Table 45).

Table 42. Acute Muscle Injury RCTs for PRP + CC vs. Conservative Control (alone or with saline injection): Function

Study	F/U	Outcome	PRP + CC Mean ± SD	Control Mean ± SD	MD (95% CI)*	p-value*
Bubnov 2013†	1 mos.	Subjective global function score (0-100 (best))	92 (n=15)	74 (n=15)	18 (NC)	<0.05
Reurink 2015‡	6.5 mos.	HOS–Overall (0-100 (best))	86 ± 19 (n=41)	88 ± 21 (n=39)	-3 (-12, 7)	NS

CC: conservative care; F/U: follow-up; HOS: Hamstring Outcome Score; NC: not calculable; NS: not statistically significant; PRP: platelet rich plasma; SD: standard deviation.

*As reported by the study unless otherwise indicated.

†PRP + CC versus CC alone.

‡PRP + CC versus saline + CC.

Table 43. Acute Muscle Injury RCTs for PRP + CC vs. Conservative Control (alone or with saline injection): Pain

F/U	Outcome	Study	PRP + CC Mean ± SD	Control Mean ± SD	MD (95% CI)*	p-value*
1 mos.	VAS/NRS pain (0-10 (worst))	Bubnov 2013†	0.4 (n=15)	1.0 (n=15)	0.6 (NC)	NS
2.5 mos.		Reurink 2015‡	0.1 ± 0.4 (n=40)	0.2 ± 0.7 (n=38)	-0.1 (-0.5, 0.3)	NS
2 mos.	BPI-SF pain severity (scale NR (higher is worse))	Hamid 2014†	0§ (n=12)	0.6§ (n=12)	β= -0.390 ± 0.142 (-0.67, -0.11)**	<0.01
	BPI-SF pain interference (scale NR (higher is worse))	Hamid 2014†	0§ (n=12)	0.7§ (n=12)	β= -0.185 ± 0.130 (-0.44, -0.07)**††	NS
6.5 mos.	HOS–Soreness (0-100 (best))	Reurink 2015‡	89 ± 18 (n=41)	91 ± 19 (n=39)	-2 (-11, 7)	NS
	HOS–Pain (0-100 (best))	Reurink 2015‡	91 ± 18 (n=41)	90 ± 20 (n=39)	1 (-9, 10)	NS

CC: conservative care; F/U: follow-up; HOS: Hamstring Outcome Score; NC: not calculable; NRS: numerical rating scale; NS: not statistically significant; PRP: platelet rich plasma; SD: standard deviation; VAS: Visual Analog Scale.

*As reported by the study unless otherwise indicated.

†PRP + CC versus CC alone.

‡PRP + CC versus saline + CC.

§Estimated from figures 3 and 4 provided in the article.

**Between group differences over time assessed using a linear mixed-model analysis. The scores listed are regression coefficients (β) ± standard error (95% CI). Authors state that lower (better) scores were seen in the PRP group at all time points, but the difference was not statistically significant for pain interference. Of note, the PRP group was only evaluated up to 7 weeks (2 months) while the control group was evaluated up to 10 weeks (2.5 months).

††The confidence interval contains a typographical error. The authors state that even though patients in the PRP group had lower pain interference scores at all time points, the difference between the groups was not statistically significantly.

Table 44. Acute Muscle Injury RCTs for PRP + CC vs. Conservative Control (alone or with saline injection): Other outcomes

Outcome	Study	F/U	PRP + CC Mean ± SD	Control Mean ± SD	MD (95% CI)*	p-value*
HOS–Symptoms (0-100 (best))	Reurink 2015‡	6.5 mos.	79 ± 28 (n=41)	86 ± 26 (n=39)	-7 (-20, 6)	NS
HOS–Function in sports (0-100 best))			95 ± 14 (n=41)	92 ± 22 (n=39)	4 (-6, 13)	NS
HOS–QoL (0-100 (best))			77 ± 27 (n=41)	82 ± 26 (n=39)	6 (-18, 7)	NS
Time to return to sport (days)	Bubnov 2013†	1 mo.	10 ± 1.2 (n=15)	22 ± 1.5 (n=15)	-12.0 (-13.0, -11.0)	0.001
	Hamid 2014†	2 mos.	26.7 ± 7.0 (n=12)	42.5 ± 20.6 (n=12)	HR 4.8 (1.3, 19.3) (adj.)§**	0.02§ **
	Reurink 2015‡	2 mos.‡‡	42 (30, 58)§§ (n=41)	42 (37, 56)§§ (n=39)	HR 0.96 (0.61, 1.51)§	NS§
	Hamilton 2015†	6 mos.	21 ± 8.4*** (n=28)	25 ± 9.3*** (n=27)	MD-2.9 (-7.2, 1.4) (adj.)§†† HR 1.48 (0.87, 2.52) (adj.)§††	NS§

CC: conservative care; F/U: follow-up; HR: hazards ratio; MD: mean difference; NR: not reported; PRP: platelet rich plasma; RR: relative risk.

*Calculated unless otherwise indicated.

†PRP + CC versus CC alone.

‡PRP + CC versus saline + CC.

§Effect estimate reported by study

**adjusted for age, length of injured area, duration of injury before enrollment, active knee extension differences between injured and uninjured, and previous injuries.

††Adjustments were made for baseline variables that influenced the primary outcome with p<0.10 (variables not reported).

‡‡Reurink 2015 reported this outcome in figure-form only and stated there were no significant differences between groups; the trial referenced a 2014 letter published in the NEJM which contained the original data on this outcome.

§§Median (interquartile range).

***SDs calculated from study-reported 95% CI (17.9-24.1 vs. 21.5-28.5).

Table 45. Acute Muscle Injury RCTs for PRP + CC vs. Conservative Control (alone or with saline injection): Additional outcomes

Outcome	Study	F/U	PRP + CC % (n/N)	Control % (n/N)	RR (95% CI)*	p-value*
Perceived full recovery	Reurink 2015‡	2.5 mos.	80% (32/40)	76% (29/38)	RR 1.0 (0.8, 1.3)	NS
Patient satisfaction (good/excellent)	Reurink 2015‡	2.5 mos.	93% (37/40)	100% (38/38)	RR 0.9 (0.9, 1.0)	NS
Re-injury (cumulative)	Hamilton 2015†	2 mos.	8.0% (2/25)	7.7% (2/26)	RR 1.0 (0.2, 6.8)	NS
	Reurink 2015‡	2 mos.††	16% (7/41)	14% (6/39)	RR 1.1 (0.4, 3.0)	NS
	Hamilton 2015†	6 mos.	7.7% (2/26)	10.3% (3/29)	RR 0.7 (0.1, 4.1)	NS
	Reurink 2015‡	12 mos.	27% (10/37)	30% (11/37)	HR 0.89 (0.38, 2.13) (adj.)§	NS

*Calculated unless otherwise indicated.

†PRP + CC versus CC alone.

‡PRP + CC versus saline + CC.

§As reported by the study; adjusted for ipsilateral hamstring injuries in the preceding 12 months, as a history of hamstring injury is previously reported as a predictor for re-injury.

4.1.8. Acute Achilles Tendon Rupture

Summary of results

PRP + CC vs. CC: One moderately high risk of bias retrospective cohort study[125] was included (N=145). The only outcome reported was long-term function, for which there was insufficient quality evidence of no difference in function scores between PRP plus CC compared with CC alone.

4.1.8.1. PRP vs. Conservative Control for Achilles tendon rupture

Studies included

One retrospective cohort study was identified (Kaniki 2014[125]); no RCTs were identified for this condition. Detailed information on patient and study characteristics is available in Appendix Table F17. The 73 patients who received PRP were prospectively enrolled in the study while the control group was comprised of 72 patients from the non-operative arm of a previous RCT. Per protocol, all patients presented within 14 days of injury. Mean time from injury to first injection in the PRP group was 8.3 days; a second injection was administered 2 weeks later. PRP volume injected was 3 to 4 ml; lidocaine was co-injected. Both groups received a removable below the knee arthrosis with instructions for progression to weight-bearing over six weeks. All patients underwent an identical standardized functional rehabilitation program under a therapist's supervision and discretion. The two groups were similar, respectively, with regard to sex (81% vs. 82% male), mean age (42 vs. 41 years) and mechanism of injury (85% vs. 79% due to sports). Baseline outcome scores were not reported. Methodological shortcomings included lack of patient blinding (and unclear blinding of outcome assessor), low follow-up rate (69%), differential attrition between groups (81% vs. 57%), and lack of controlling for potential confounding. This study was considered to be at moderately high risk of bias.

Results

Function

The study assessed long-term function using the clinician-reported disease-specific Leppilahti score (0-100 (best)). At 24 months, no significant difference was seen between patients who received PRP in plus CC versus CC alone (84.2 vs. 82.2) (Kaniki[125]) (Table 46).

Pain

No data reported.

Other outcomes

No data reported.

Table 46. Acute Achilles tendon rupture cohort study for PRP + CC vs. CC: Function

Study	Outcome	F/U	PRP + CC Mean ± SD	CC Mean ± SD	p-value*
Kaniki 2014	Leppilahti Score	12 mos.	81.4 ± 11.6 (n=53)	79.2 ± 13.1 (n=40)	NS
	(0-100 (best))	24 mos.	84.2 ± 10.8 (n=59)	82.2 ± 12.3 (n=41)	NS

CC: conservative care; CI: confidence interval; F/U: follow-up; PRP: platelet rich plasma; NR: not reported; SD: standard deviation.

*As reported by the study

4.1.9. Ankle Sprain

Summary of results

PRP vs. Placebo: One moderately high risk of bias RCT[235] was included that compared PRP injection with saline injection (N=33). Only short-term pain and function were reported, for which there was insufficient quality evidence of no difference between groups.

4.1.9.1. PRP vs. Conservative Control for ankle sprain

Studies included

One small RCT was identified that compared injection with PRP (n=18) to that with sterile normal saline (n=15) (Rowden 2015[235]); no cohort studies were identified that compared these two treatments. Detailed information on patient and study characteristics is available in Appendix Table F18. The trial was conducted in an urban Level I emergency department and included patients with severe, traumatic ankle sprains and no fracture on X-ray. All injections were performed under ultrasound guidance after application of local anesthetics. The total volume of injectate was similar between groups (3-4 ml for PRP and 4 ml for saline). The use of repeat injections was not reported. Patients were blinded to the treatment received. Both groups received conservative care, which consisted of a posterior splint, crutches and training, and pain medication per the treating physician; NSAID use was prohibited. The PRP group included fewer males (22% vs. 40%) and somewhat younger patients (30 vs. 35 years) compared with the control group. Baseline outcome scores were also different between the groups with PRP patients showing worse function on the Lower Extremity Function Scale (LEFS) (12.9 vs. 18.6) and greater pain on VAS (8.8 vs. 7.7) compared with the saline group, respectively. Methodological shortcomings included lack of information regarding random sequence generation and allocation concealment, failure to account for four patients who withdrew prior to receiving treatment, unclear follow-up rate, and lack of controlling for differences in baseline characteristics. The trial was considered to be at moderately high risk of bias.

Results

Function

Function was evaluated at one month using the patient-reported LEFS scores (0-80 (best)) (Rowden[235]). Because there was an imbalance in baseline scores (12.9 vs. 18.6) favoring the control group, both follow-up and change scores were evaluated (Table 47). While follow-up scores (which provided the more conservative estimate) suggested no difference between groups (68.0 vs. 64.1, MD 3.9 (95% CI -4.4, 12.2), change scores suggested a greater improvement in the PRP group in the short-term (55.1 vs. 45.5, MD 9.6 (95% CI 4.5, 14.7)).

Pain

The trial assessed pain at one month using the patient-reported VAS (range, 0-10) (Rowden[235]). There were baseline imbalances in the VAS score favoring the PRP group (8.8 vs. 7.7), thus both follow-up and change scores were evaluated (Table 47). There was no between-group difference in follow-up scores (which provided the more conservative estimate) (1.1 vs. 1.6, respectively; MD -0.5 (95% CI -2.0, 1.0)), however, the change score (-7.7 vs. -6.1) suggested that a statistically greater improvement in pain in the PRP group compared with the saline group (-7.7 vs. -6.1, MD -1.6 (95% CI -2.6 to -0.6)).

Other outcomes

No data reported.

Table 47. Ankle sprain RCTs for PRP vs. Saline: Pain and function

Outcome	F/U	PRP Mean ± SD	Saline Mean ± SD	MD (95% CI)*	p-value*
Function					
LEFS (0-80 (best))	0 mos.	12.9 ± 9.5 (n=18)	18.6 ± 12.2 (n=15)	–	-
	1 mos.	68.0 ± 9.1 (n=18)	64.1 ± 14.0 (n=15)	3.9 (-4.4 to 12.2)	NS
Δ LEFS‡	1 mos.	55.1 ± 5.9 (n=18)	45.5 ± 8.5 (n=15)	9.6 (4.5 to 14.7)	<0.01
Pain					
VAS pain (0-10 (worst))	0 mos.	8.8 ± 1.8 (n=18)	7.7 ± 2.2 (n=15)	–	-
	1 mos.	1.1 ± 1.6 (n=18)	1.6 ± 2.6 (n=15)	-0.5 (-2.0 to 1.0)	NS
Δ VAS‡	1 mos.	-7.7 ± 1.1 (n=18)	-6.1± 1.6 (n=15)	-1.6 (-2.6 to -0.6)	<0.01

CI: confidence interval; F/U: follow-up period; LEFS: Lower Extremity Function Scale; PRP: platelet rich plasma; SD: standard deviation; VAS: Visual Analog Scale.

*Calculated unless otherwise indicated.

†As reported by the study.

‡Change scores calculated because there are possible baseline imbalances in LEFS and VAS pain scores.

4.1.10. Osteochondral lesions of the talus

Summary of results

PRP vs. Hyaluronic Acid (HA): One moderately high risk of bias quasi-RCT[180] was included (N=29). With respect to primary outcomes in both the short- and intermediate-term, PRP resulted in significantly better function and pain scores compared with HA, though the quality of evidence was insufficient. No other primary outcomes were reported. With respect to secondary outcomes, the PRP group had marginally better stiffness scores in the short-term, and the difference reached significance for the intermediate-term.

4.1.10.1. PRP vs. Hyaluronic acid (HA) for osteochondral lesions of the talus

Studies included

One small quasi-RCT was identified that evaluated patients with osteochondral lesion of the talus patients (Mei-Dan 2012[180]); no cohort studies were identified. Detailed information on patient and study characteristics is available in Appendix Table F19. The trial compared PRP (n=14) to hyaluronic acid (HA) (n=15) in symptomatic patients who had failed previous non-operative intervention consisting of

temporary immobilization, the use of analgesics and anti-inflammatories, partial weight bearing, and orthotic provision. The majority of patients in both groups were male (PRP 80% vs. HA 73%). Patients were not blinded to the treatment received. PRP was activated using calcium chloride. Local anesthetic was given to patients in the HA group only upon request. The injectate volume was identical in both groups (2 ml), and use of imaging guidance was not reported. All patients received a total of 3 injections; PRP patients received an injection every two weeks while HTA patients received an injection every week. Baseline imbalances were present between the groups; PRP patients were older on average (43 vs. 37 years), had a shorter mean duration of pain (7.2 vs. 9.2 years) as well as better VAS pain (4.1 vs. 5.6) and function (4.7 vs. 5.8) scores. Methodological shortcomings included lack of a randomized sequence generation (treatment was randomized according to presentation in blocks of 5), unclear concealed allocation, unclear loss-to-follow-up (short-term only), and lack of both blinded assessment and controlling for confounding. This study was considered to be at moderately high risk of bias.

Results

Function

The study[180] evaluated function using three different measures: the clinician-reported AOFAS Ankle Hindfoot Scale (0-100 (best)), as well as the patient-reported VAS function (0-10 (worst) and subjective global function and disability scale (0-100 (best)) (Table 48) (Mei-Dan[180]). Function results were better in the PRP group compared with the HA group in both the short and intermediate term on nearly all outcomes assessed. While short-term AOFAS modified Ankle and Hindfoot Scale scores were statistically similar between groups (89.7 vs. 81.2, MD 8.5 (95% CI -0.3, 17.0)), by 7 months the scores were significantly better in the PRP group (92.5 vs. 78.3, MD 14.2 (95% CI 5.4, 23.0)). Because there was an imbalance in baseline VAS function scores (4.7 vs. 5.8) favoring the PRP group, both follow-up and change scores were evaluated (Table 48), and both suggested better outcomes in the PRP group. The change scores, which provided the more conservative estimate, favored PRP in both the short-term (-3.6 vs. -2.3, MD -1.3 (95% CI -2.4, -0.2)) and the intermediate-term (-3.9 vs. -2.3, MD -1.6 (95% CI -2.7, -0.5)). Subjective global function and disability scores were better in the PRP group in both the short-term (90 vs. 71, MD 19.0 (95% CI 6.5, 31.5)) and intermediate-term (91 vs. 73, MD 18.0 (95% CI 5.8, 30.2)).

Pain

The study[180] evaluated pain using the patient-reported VAS (0-10 (worst)). There were baseline imbalances that favored the PRP group (4.1 vs. 5.6), thus both follow-up and change scores were evaluated (Table 48). Change scores provided the more conservative estimate and suggested no difference between groups in the short-term (-3.2 vs. -2.6, MD -0.6 (95% CI -1.6, 0.4)) and intermediate-term (-3.2 vs. -2.5, MD -0.7 (95% CI -1.7, 0.3)). In contrast, follow-up scores suggested significantly better pain scores at both time points (Table 48).

Other

The patient-reported VAS stiffness scores were marginally better in the PRP group in the short-term; between-group differences reached statistical significance by the intermediate-term and favored PRP (Table 48) (Mei-Dan).

Table 48. Osteochondral lesions of the talus RCTs for PRP vs. HA injection: Pain, function, and stiffness

Outcome	F/U	PRP Mean ± SD	HA Mean ± SD	MD (95% CI)*	p-value*
Function					
AOFAS modified Ankle and	3 mos.	89.7 ± 7 (n=14)	81.2 ± 14 (n=15)	8.5 (-0.3 to 17.0)	0.05
Hindfoot Scale (0-100 (best))	7 mos.	92.5 ± 8 (n=14)	78.3 ± 14 (n=15)	14.2 (5.4 to 23.0)	<0.01
VAS function (0-10 (worst))	0 mos.	4.7 ± 2.1 (n=14)	5.8 ± 1.9 (n=15)	–	–
	3 mos.	1.1 ± 1.1 (n=14)	3.5 ± 2.5 (n=15)	-2.4 (-3.9 to -0.9)	<0.01
	7 mos.	0.8 ± 1.2 (n=14)	3.5 ± 2.6 (n=15)	-2.7 (-4.3 to -1.1)	<0.01
Δ VAS function†	3 mos.	-3.6 ± 1.4 (n=14)	-2.3 ± 1.5 (n=15)	-1.3 (-2.4 to -0.2)	0.02
	7 mos.	-3.9 ± 1.4 (n=14)	-2.3 ± 1.6 (n=15)	-1.6 (-2.7 to -0.5)	<0.01
Subjective global function	3 mos.	90 ± 9 (n=14)	71 ± 21 (n=15)	19.0 (6.5 to 31.5)	<0.01
and disability‡ (0-100 (best))	7 mos.	91 ± 10 (n=14)	73 ± 20 (n=15)	18.0 (5.8 to 30.2)	<0.01
Pain					
VAS pain (0-10 (worst))	0 mos.	4.1 ± 2.1 (n=14)	5.6 ± 1.7 (n=15)	–	–
	3 mos.	0.9 ± 1.0 (n=14)	3.0 ± 2.1 (n=15)	-2.1 (-3.4 to -0.8)	<0.01
	7 mos.	0.9 ± 1.4 (n=14)	3.1 ± 2.1 (n=15)	-2.2 (-3.6 to -0.8)	<0.01
Δ VAS pain†	3 mos.	-3.2 ± 1.4 (n=14)	-2.6 ± 1.3 (n=15)	-0.6 (-1.6 to 0.4)	NS
	7 mos.	-3.2 ± 1.3 (n=14)	-2.5 ± 1.3 (n=15)	-0.7 (-1.7 to 0.3)	NS
Other					
VAS stiffness (0-10 (worst))	3 mos.	1.4 ± 1.8 (n=14)	3.0 ± 2.4 (n=15)	-1.6 (-3.2 to 0.03)	0.05
	7 mos.	0.8 ± 1.2 (n=14)	2.9 ± 2.3 (n=15)	-2.1 (-3.5 to -0.7)	<0.01

AOFAS: American Orthopaedic Foot and Ankle Society; F/U: follow-up; HA: hyaluronic acid; PRP: platelet rich plasma; NR: not reported; SD: standard deviation; VAS: Visual Analog Scale.

*Calculated unless otherwise indicated.

†Change scores calculated because there are possible baseline imbalances in VAS function and pain scores.

‡Each patient was asked to assess their function during activities of daily living and subjective well-being compared to prior function; comparisons were determined as a percentage of the patient's previous functional capability and ''well-being'' before developing ankle symptoms.

4.1.11. Temporomandibular Joint Dislocation

Summary of results

ABI vs. Intermaxillary Fixation (IMF)

One moderately high risk of bias RCT[104] was included (N=32). The only outcome reported was long-term recurrent dislocation, for which there was insufficient quality evidence for a greater risk of recurrence of dislocation following PRP compared with IMF.

4.1.11.1. ABI vs. Intermaxillary Fixation (IMF) for temporomandibular joint (TMJ) dislocation

Studies included

One small RCT was identified that randomized patients to receive ABI (n=16) or intermaxillary fixation (IMF) (n=16) for the treatment of chronic, bilateral dislocation of the temporomandibular joint (TMJ) (Hegab 2013[104]); no cohort studies were identified for this condition. Detailed information on patient and study characteristics is available in Appendix Table F20. This trial included a third arm that was

treated with a combination of ABI and IMF; this group was excluded from our analysis because it did not meet the inclusion criteria. ABI patients were injected bilaterally with a total of 5 ml of blood drawn from the cubital fossa. Imaging guidance was not used and it was unclear what type(s) of anesthetic were employed. Patients could receive up to three injections total (37.5% received 2 injections; 12.5% received 3 injections). IMF was achieved with eyelet wiring or wires applied into orthodontic brackets for a duration of 4 weeks. Co-interventions were equal between groups. Demographics were reported for the study population as a whole only; mean age was 33 (range, 23-53) years and 23% of patients were male. Methodological shortcomings included follow-up rate, and controlling for confounding. This study was considered to be at moderately high risk of bias.

Results

Function, pain

No data reported.

Other

Recurrent dislocation: Over the long-term, dislocation recurred almost three times as often following ABI compared with IMF (50% (8/16) vs. 19% (3/16) at 12 months) however, the difference did not reach statistical significance (RR 2.7 (95% CI 0.9, 8.3)), which was likely due to small sample size (Hegab[104]).

4.1.12. Osteoarthritis (OA) of the Knee

Summary of results

PRP vs. HA: Six RCTs[39,80,281,242,95,214] and four cohort studies (3 prospective[141,246,260] and 1 retrospective[241]) were included. The RCTs enrolled between 96 and 192 patients; trials were found to be at low (2 RCTs), moderately low (2 RCTs), or moderately high (2 RCTs) risk of bias. With respect to primary outcomes, in the short-term, there was no difference between groups in function (4 RCTs, moderate quality evidence) or pain (1 RCT, low quality evidence) scores. In the intermediate-term, function scores were better with PRP (5 RCTs, moderate quality evidence), however it was unclear whether functional success was more common following PRP versus HA (2 RCTs, low quality evidence); intermediate-term pain scores were similar between groups (3 RCTs, moderate quality evidence) while pain success was more common following PRP (2 RCTs, moderate quality evidence). In the long-term, function success was more common following PRP (1 RCT, low quality evidence), and function scores were slightly better with PRP (3 RCTs, low quality evidence); long-term pain success was more common following PRP (1 RCT, low quality evidence), although long-term pain scores were similar between groups (3 RCTs, low quality evidence). No other primary outcomes were reported. With respect to secondary outcomes, health-related quality of life was similar between groups in the short-term (1 RCT), the same or better (varying by outcome measure) with PRP across in the intermediate-term (2 RCTs), and better with PRP in the long-term (2 RCTs). Patient satisfaction was similar between groups in the intermediate- and long-term (1 RCT each), and medication use was similar between groups through six months (1 RCT). The cohort studies enrolled between 60 and 150 patients each; all were considered to be at moderately high risk of bias. Function scores were better in the PRP group in in the short-term (in 3 of the 4 studies and similar between groups in the 4th) and intermediate-term (3 studies). Pain was better in both the short- (3 studies) and intermediate-term (2 studies). One study also reported better intermediate-term health-related quality of life and patient satisfaction with PRP.

LR-PRP vs. Steroid: One moderately low risk of bias RCT[84] was included (N=48) that found better short- and intermediate-term pain and function scores with LR-PRP versus corticosteroid injection,

although the quality of evidence was insufficient. No other primary outcomes were reported. With respect to secondary outcomes, there was no difference between groups in health-related quality of life in the short-term, but by the intermediate-term, this outcome was better in the PRP group. There was no difference between groups in medication use through six months.

PRP vs. Saline: Two moderately low risk of bias RCTs[203,95] (and no cohort studies) were included; trial size was 78 and 136 patients. With respect to primary outcomes, in the short-term, function and pain scores were better in the PRP versus saline groups (1 RCT each, low quality evidence). Similarly, in the intermediate-term, function (2 RCTs) and pain (1 RCT) scores were better in the PRP versus saline groups based on low quality evidence. No other primary outcomes were reported. With respect to secondary outcomes, in the intermediate-term, both trials reported that patient satisfaction was more common in the PRP group, and one trial found better health-related quality of life with PRP.

PRP vs. Exercise ± TENS: Two moderately low risk of bias RCTs[218,10] (and no cohort studies) were included; one compared LR-PRP plus exercise to exercise alone (N=65), the other compared PRP to exercise plus transcutaneous electrical nerve stimulation (TENS) (N=54). With respect to primary outcomes, in the short- and intermediate term, there were no clear differences between groups in function or pain scores (1 RCT for each) based on insufficient quality evidence. No other primary outcomes were reported. With respect to secondary outcomes, there was no difference between groups in short- or intermediate-term quality of life (1 RCT each); in addition, acetaminophen use was higher in the PRP plus exercise group than the exercise alone group through six months.

4.1.12.1. PRP vs. HA for knee OA

Studies included

RCTs: Six RCTs compared PRP to HA (Cerza 2012[39], Filardo 2015[80], Vaquerizo 2013[281], Sanchez 2012[242], Gormeli 2015[95], Raeissadat 2015[214]). Detailed information on patient and study characteristics is available in Appendix Tables F21 and F22. Trials enrolled between 96 and 192 patients with 48 to 96 patients allocated to receive PRP and 46 to 86 patients allocated to receive HA. Minimum duration of symptoms for inclusion ranged from 3 to 6 months; mean symptom duration was reported in only two trials (Filardo, Cerza) and ranged from 65 to 68 months. All patients in one trial (Cerza) and approximately a third of patients in another trial (Filardo) received prior nonoperative treatment, otherwise, history of nonoperative treatment was not reported. Two trials reported no history of operative treatment (Gormelli, Cerza) and one trial reported that 55% of patients had undergone previous operative treatment (Filardo); otherwise previous operative treatment was not reported. Based on radiographic classification (Kellgren-Lawrence or Albäck classifications), OA severity appeared to be mild to moderate in most study populations, however, radiographic findings may not correlate with clinical presentation or baseline pain and function scores. Comparison across studies on baseline function scores such as WOMAC, IKDC and KOOS may provide insight regarding clinical differences between study populations but is challenging given different scales of measurement and variety of measures used. IKDC (0-100 (best)) was reported by two trials, with baseline scores in one trial (Filardo) 9-12 points higher than those in the other trial (Gormeli) suggesting that on average, participants in the Filardo trial may have presented with less disability clinically. In both these trials, treatment groups were otherwise similar at baseline. Two studies reported the Lequesne (Algofunctional) Index (0-24 (worst)) (Sanchez 2012, Vaquerizo), with 3 to 4 point differences in baseline values between the trials. It is unclear whether this difference may indicate clinically meaningful differences in OA presentation between these two populations. Four trials reported total WOMAC scores, but the use of different scales across trials precluded meaningful comparisons: two trials appear to use a 0-96 point scale (Cerza, Vaquerizo), one trial used what appeared to be a 0-300 scale for total scores (and a scale of 0-100 for

the WOMAC subscales) (Sanchez), the remaining trial used a five-point Likert scale for each item for an assumed scale of 0-120 across the 24 items (Raeissadat). For the two trials reporting the 0-96 scale, the mean total WOMAC score was 76 in one trial (Cerza) compared with 46 in the other (Vaquerizo), suggesting less severe disability in the population enrolled in the later trial. Baseline difference in total WOMAC score and WOMAC subscores between PRP and HA groups were noted in one trial (Raeissadat). One trial reported using imaging guidance for the HA (but not PRP) injection (Raeissadat), otherwise, use of imaging guidance was not reported. The number of injections varied across trials and treatment groups. Three PRP injections were given in three trials (Filardo, Sanchez 2012, Vaquerizo); in two of these trials HA injections were given once in one trial (Vaquerizo) and three times in the other two trials (Filardo, Sanchez 2012). One trial (Gormeli) had two PRP groups that varied by number of injections (3 PRP injections in one group, 1 PRP + 2 two saline injections in another group) which were combined for this analysis; the HA group received three injections. In the remaining trials, four injections were given in each group in one trial (Cerza) while two PRP injections were compared with three HA injections in the other trial (Raeissadat). Leukocyte-poor PRP (LP-PRP) was used in three trials (Cerza, Vaquerizo, Sanchez 2012) and leukocyte-rich PRP (LR-PRP) was used in two trials (Raeissadat, Filardo); one trial did not specify leukocyte characteristics (Gormeli). PRP injectate volume ranged from 4 to 8 ml across all six trials, and HA injectate volume was 2 ml in four trials reporting this variable (Fildardo, Gormeli, Cerza, Raeissadat). Mean ages of enrolled participants ranged from 53 to 66 years old and were similar across groups in all studies. One trial enrolled predominately female participants and the proportion differed between treatments (90% for PRP, 76% for HA) (Raeissadat); across the other trials, the proportion of male participants ranged from 33% to 58% with differences between treatments noted in one study (33% versus 46%) (Vaquerizo). None of the trials were conducted in the United States. Methodological limitations included unclear random sequence generation in one trial (Cerza), unclear or no statement of allocation concealment in three trials (Cerza, Raeissadat, Gormeli), and failure to control for potentially confounding differences in baseline characteristics in one trial (Raeissadat). Credit for intention to treat analysis was not given in three trials as it appears that patients were excluded following randomization (Raeissadat, Gormeli, Sanchez 2012). Patients were blinded to treatment received in four trials (Filardo, Gormeli, Sanchez 2012, Vaquerizo), but not in the remaining trials (Cerza, Raeissadat). All trials had adequate follow-up. Overall, two trials were considered to be at low risk of bias (Vaquerizo, Filardo), two trials at moderately low risk of bias (Gormeli, Sanchez 2012) and two at moderately high risk of bias (Cerza, Raeissadat).

Cohort studies: Three prospective comparative cohort studies (Kon 2011[141], Say 2013[246], Spakova 2012[260]) and one retrospective cohort study (Sanchez 2008[241]) met the inclusion criteria. Detailed information on patient and study characteristics is available in Appendix Tables F23 and F24. Studies enrolled between 60 and 150 patients with 30 to 60 patients allocated to receive PRP and 30 to 100 patients allocated to receive HA. Minimum duration of symptoms was reported to be 4 months in one study (Kon) and 12 months in another (Spakova); none reported mean duration of symptoms. Populations across studies were predominately female (89% to 40%) with mean ages ranging from 53 to 64 years. As with the trials, radiographically based OA severity assessment may suggest mild to moderate severity with one study (Kon) indicating 40% of patients had cartilage degeneration but not OA. Classifications may not correlate to clinical presentation; it is not clear how populations may have differed clinically by baseline functional measures. Three PRP injections were given in all studies and compared with one HA injection (2 studies) (Kon, Say) and with three HA injections (2 studies) (Say, Spakova). LP-PRP was used in two studies (Sanchez 2012, Say) and LR-PRP in two (Kon, Spakova). All controlled for confounding. All observational studies were considered at moderately high risk of bias as blinded assessment, patient blinding and completeness of follow-up were not clear. One study included participants from the United States (Kon).

Efficacy Results

Function

All six trials evaluated function. Reported outcomes measures included WOMAC (total and subscales), IKDC, KOOS, Lequesne Index, and the Tegner Score, all of which are patient reported measures. Two trials reported the proportion of OMERACT-OARSI Responders (Sanchez 2012[242], Vaquerizo[281]). Across time frames and measures, there was substantial heterogeneity in pooled estimates, particularly during the intermediate term. Potential sources of heterogeneity were examined in all instances, including whether patients were blinded (patients were blinded in all but two trials- Cerza[39] and Raeissadat 2015[214]), risk of bias, use of LP-PRP versus LR-PRP, difference in OA severity either radiographically or clinically (which was generally unclear based on reported data), number of injections, or platelet concentration; no clear source of heterogeneity was determined.

Short-term: None of the studies reported the percentage of patients with short-term functional success. Function was evaluated using the Lequesne Index in two trials (Sanchez 2012[242], Vaquerizo[281]) (Figure 15) as well as with the WOMAC total and IKDC measures in two additional trials (Cerza[39], Filardo[80]) (Figure 16). One of these trials also reported KOOS subscale and Tegner scores (Table 49). Overall, three of the four trials identified no difference between PRP and HA across multiple measures; the trial (Cerza) that found significantly better results with PRP was also the lowest quality of the four, as patients were not blinded, and the overall risk of bias was found to be moderately high.

There was no difference between PRP and HA groups in mean short-term Lequesne Index scores as reported by two trials (Sanchez 2012[242], Vaquerizo[281]) (WMD -0.20 (95% CI -1.0, 0.60)) (Figure 15). Short-term WOMAC total scores and IKDC scores were pooled across two studies (Cerza[39], Filardo[80]) and suggest no statistical difference between groups (SMD 0.57 (95% CI -0.60, 1.75)) (Figure 16), however the pooled estimate had substantial statistical heterogeneity (I^2=96%). This heterogeneity likely stems from the fact that one (moderately high risk of bias and unblinded, LP-PRP) trial found significantly better results with PRP (Cerza[39]) while the other (low risk of bias and blinded, LR-PRP) trial found no difference between groups (Filardo[80]); the confidence intervals of these estimates did not overlap. The latter trial[80] similarly reported no difference between groups on all short-term KOOS subscale scores and Tegner scores (Table 49).

Intermediate-term: Two trials, both of which used LP-PRP, reported the proportion of OMERACT-OSARSI responders in the intermediate-term (Sanchez 2012[242], Vaquerizo[281]). While the pooled estimate suggests no statistical difference between groups (pooled RR 1.78 (95% CI 0.62, 5.09)) (Figure 17), there was again considerable heterogeneity in this estimate (I^2=93%), with one trial reporting significantly more responders following PRP (Vaquerizo[281], low risk of bias, blinded) while the other found no difference between groups (Sanchez 2012[242], moderately low risk of bias, blinded). The trial that reported significantly more responders (Vaquerizo[242]) also reported that significantly more PRP patients achieved a 50% or more decrease in WOMAC physical function scores (40% vs. 11%, RR 3.8 (95% CI 1.5, 9.3)), and while there was no difference between groups in the percentage of patients who achieved a 50% or more decrease in WOMAC stiffness scores, significantly more PRP patients achieved at least a 30% decrease in these scores than HA patients (52% vs. 27%, RR 2.2 (95% CI 1.2, 3.9)). Similarly, the PRP group was more likely to achieve a 50% decrease in Lequesne Index scores (29% vs. 4%, RR 7.0 (95% CI 1.7, 29.2)) (Table 50).

Five trials (Cerza[39], Vaquerizo[281], Sanchez 2012[242], Filardo[80], Gormeli[95]) reported continuous outcomes data using the WOMAC total or IKDC scores, and results were pooled across studies (Figure 16). The

pooled effect estimate suggests better intermediate-term functional results in the PRP group (SMD 0.84 (95% CI 0.19, 1.48)). This result had high statistical heterogeneity (I^2=94%), which may in part be due to differences in the magnitude of effect estimates and failure of two trials (Sanchez 2012[242], Vaquerizo[281]) to reach statistical significance, as well as in limitations of the meta-analysis method used. Heterogeneity persisted when WOMAC and IKDS measures were analyzed separately (data not shown). Patients were blinded in all but one trial (Cerza[39]). Difference in OA severity between the studies is not clear and the extent to which this may explain heterogeneity is unknown. Similarly it is not clear that differences in procedures (e.g. number of injections, platelet concentration) may have created heterogeneity. Three trials used LP-PRP (Cerza[39], Sanchez 2012[242], Vaquerizo[281]), one used LR-PRP (Filardo[80]) and one did not report which type was used (Gormeli[95]). Trials using LP-PRP did not consistently show a significant effect. Pooled estimates across two of these trials (Vaquerizo[281], Raeissadat[214]) for WOMAC stiffness (SMD 0.36 (95% CI -0.34, 1.06) and WOMAC physical function (SMD 0.57 (95% CI -0.54, 1.68)) subscales (Figure 18) similarly show inconsistent results with one trial (Vaquerizo[281], low risk of bias, blinded) finding better outcomes with PRP and the other trial (Sanchez 2012, moderately low risk of bias, blinded) finding no difference between groups. Two trials included in the pooled analysis also reported no difference in other functional measures in the intermediate term, including on all KOOS subscale scores and the Tegner score (Filardo[80]) (Table 49) as well as on the percentage of patients with no change in WOMAC scores (Cerza[39]) (Table 50).

Long-term: One trial (Vaquerizo[281]) found that significantly more PRP patients achieved a 50% or more decrease in both WOMAC physical function scores (31% vs. 0%, RR NC, p<0.01) and WOMAC stiffness scores (33% vs. 5%, RR 8.0 (95% CI 1.9, 32.9)), and while there was no difference between groups in the percentage of patients who achieved a 50% or more decrease in Lequesne Index scores, significantly more PRP patients achieved at least a 30% decrease in these scores than HA patients (48% vs. 2%, RR 23.0 (95% CI 3.2, 164)) (Table 50).

The same trial (Vaquerizo[281]) reported significantly better long-term Lequesne Index scores in the PRP group (Figure 15). Three trials provided long-term WOMAC total or IKDC follow-up scores (Vaquerizo[281], Raeissadat[214], Filardo[80]); the pooled estimate suggests function may be better following PRP although the result just reached statistical significance (SMD 0.66 (95% CI 0.01, 1.31)) (Figure 16). Substantial statistical heterogeneity was present in the pooled estimate (I^2=90%) which may be partly due to differences in the magnitudes of individual effect estimates. As is the case with the intermediate term results, the impact of OA severity or procedural differences is not known. Pooled estimates across two of these trials (Vaquerizo[281], Raeissadat[214]) for WOMAC stiffness (SMD 0.90 (95% CI 0.32, 1.49) and WOMAC physical function (SMD 0.93 (95% CI 0.19, 1.67)) subscales support the conclusion of better functional results with PRP versus HA (Figure 18). In contrast, another of the pooled trials (Filardo[80]) reported no difference between treatments for any KOOS subscale score or the Tegner Score (Table 49).

Pain

Four RCTs reported pain subscale scores from the patient-reported WOMAC (Vaquerizo[281], Sanchez 2012[242], Raeissadat[214]) and KOOS (Filardo[80]) instruments.

Short-term: One trial (Filardo[80]) reported no difference between groups in KOOS pain subscale scores (MD -0.1 (95% CI -5.63, 5.43), SMD -0.05 (95% CI -0.34, 0.24)) (Figure 19).

Intermediate-term: Significantly more patients in the PRP versus HA group experienced a 50% decrease in WOMAC pain scores in each of two trials, with a RR of 5.2 (95% CI 2.18, 12.41) in one trial

(Vaquerizo[281]) and a RR of 1.58 (95% CI 1.0, 2.5) in the other (Sanchez 2012[242]) (Figure 20). However, the pooled estimate was within the limits of chance given no true difference between treatments (RR 2.71 (95% CI 0.83, 8.87)); this result is likely due to the wide confidence intervals in one trial and difference in point estimates in combination with limitations of the meta-analysis method used. Both trials used LP-PRP. One of the trials (Sanchez 2012[242]) additionally reported no difference between treatments for a 20% decrease in normalized WOMAC Pain Score (RR 1.08 (95% CI 0.8, 1.4)) (Table 51); it is not clear why the 50% threshold (used in the pooled analysis) approached significance when the lower (20%) threshold did not. Patients were blinded in both trials and both were considered at low risk of bias. Differences in OA severity are difficult to ascertain across studies and its impact on findings is not clear; there was a 3 to 4 point difference in Lequesne index between these studies, but it is not clear if this difference in clinically meaningful.

Three trials reported intermediate-term WOMAC and KOOS pain subscale scores (Vaquerizo[281], Sanchez 2012[242], Filardo[80]) (Figure 19). The pooled results suggested slightly better pain results in the PRP group, however the estimate was within the limits of chance given no true difference between treatments (SMD -0.45 (95% CI -1.14, 0.24)). There was high statistical heterogeneity in this estimate (I^2=92%), which likely stems at least in part from the fact that the smallest trial showed significantly better results in the PRP group (Vaquerizo[281]) while the other two trials showed no effect. Patients in all three trials were blinded and two were at low risk of bias (Vaquerizo[281], Filardo[80]). Two used LP-PRP (Vaquerizo[281], Sanchez 2012[242]).

Long-term: One trial (Vaquerizo[281]) reported that significantly more PRP patients achieved a 30% decrease in WOMAC pain scores (RR 4.9 (95% CI 2.1, 11.5)) (Table 51) as well as a 50% decrease (RR 13.1 (95% CI 1.81, 95)) (Figure 20) compared with HA, however confidence intervals are very wide calling the stability of the estimates into question.

Three trials reported long-term WOMAC and KOOS pain subscale scores (Vaquerizo[281], Sanchez 2012[242], Filardo[80]) (Figure 19). Overall, improvement in pain with PRP compared with HA was within the limits of chance given no true difference between treatments (SMD -0.49 (95% CI -1.16, 0.18)); high statistical heterogeneity (I^2=91%) and observed confidence interval width again may be due at least in part to a significant difference favoring PRP reported in the smallest trial (Vaquerizo[281]). Differences in OA severity are difficult to ascertain across studies. Patients were blinded in two of the trials (Vaquerizo[281], Filardo[80]).

Other outcomes

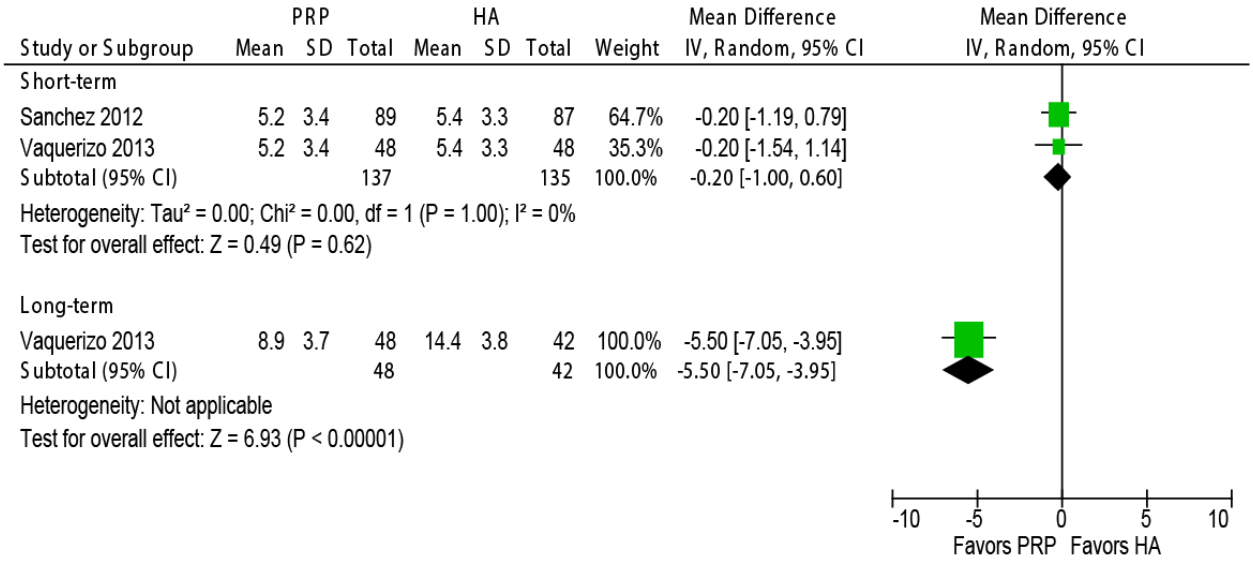
Health-Related Quality of Life (HRQoL): Health-related quality of life (QoL) was evaluated using three different patient-reported outcome measures: EQ-VAS (0-100 (best)), the KOOS QOL subscale (0-100 (best)) and the SF-36 (range varies, higher scores are better). Results across measures and time frames were inconsistent and no firm conclusions can be drawn. In the short-term, one trial (Filardo[80]) reported no differences between PRP and HA groups in quality of life as measured by the KOOS QoL subscale scores (MD 0.7 (95% CI -5.9, 7.3)) (Table 52) and the EQ-VAS scores (MD 2.4 (95% CI -1.43, 6.23) (Figure 21). In the intermediate-term, across two trials (Filardo[80], Gormeli[95]), the pooled mean difference in EQ-VAS score suggested significantly better intermediate-term results with PRP (WMD 4.7 (95% CI 0.59, 7.96)) (Figure 21). One of these trials (Filardo[80]) reported no difference between groups in EQ-VAS scores (as included in the pooled analysis) or in KOOS QoL subscale scores (MD -0.7 (95% CI-7.5, 6.1) (Table 52). In the long-term, one trial (Filardo[80]) reported slightly better EQ-VAS scores in the PRP group (MD 4.20 (95% CI 0.33, 8.07)) (Figure 21). Another trial reported significant differences favoring PRP in all SF-36 domains at 13 months except for the role-emotional domain (Raeissadat[214]) (Table 52).

Patient Satisfaction: Across two trials, there were no difference in the proportions of patients who were satisfied with their treatment in the intermediate term (Gormeli[95]) or in the long term (Filardo[80]) (Table 52). Neither study provided detail regarding how this was assessed.

Medication use: One trial (Sanchez 2012[242]) reported no difference between PRP and HA groups in median dose of acetaminophen used through six months' post-intervention (0.1 mg/day in both groups).

Other treatments/failure to improve: One trial (Sanchez 2012[242]) reported use of corticosteroid injections in 1.1% of PRP and 5.7% of HA recipients, presumably due to treatment failure; these patients were excluded from analysis. Further, 2.3% of PRP and 4.6% of HA recipients withdrew based on subjectively assessed lack of improvement during the study period and are not reflected in the analyses.

Figure 15. Knee OA RCT Results for PRP vs. HA: Function Lequesne Index WMD

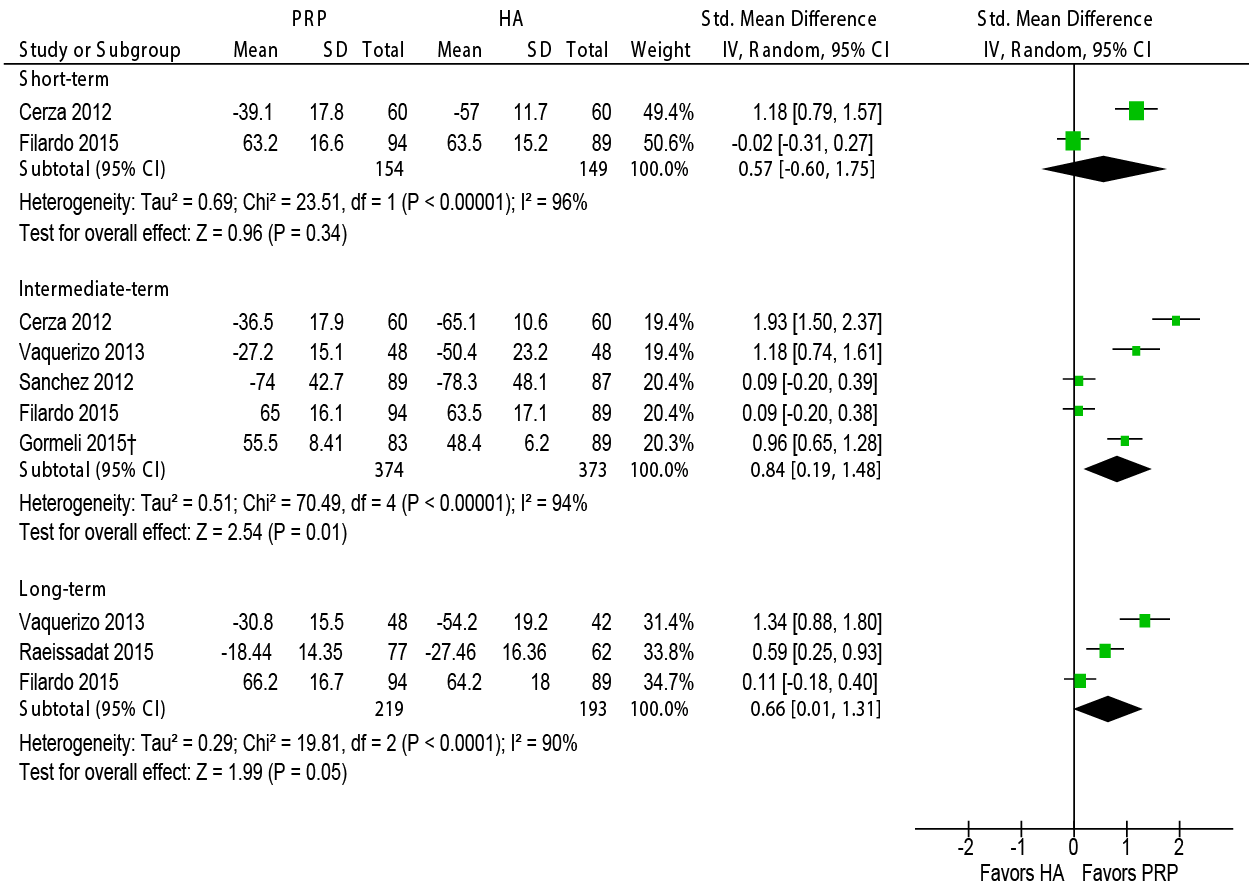


*Vaquerizo 2013: It is unclear if these are final raw scores or change scores; we have interpreted them as final scores.

Outcomes measures reported:

- Vaquerizo 2013, Raeissadat 2015: Lequesne Index (0-24 (worst))

Figure 16. Knee OA RCT Results for PRP vs. HA: SMD WOMAC Total and IKDC Scores



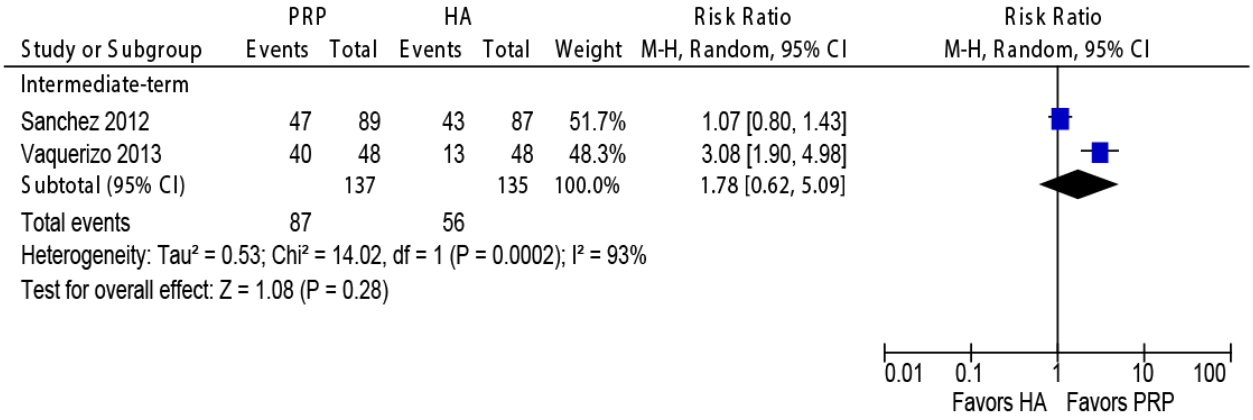
*Vaquerizo 2013: It is unclear if these are final raw scores or change scores; we have interpreted them as final scores.

†Gormeli 2015: PRP group is comprised of patients receiving either 3 PRP injections (n=46) or a single PRP injection (n=45).

Outcomes measures reported:

- Cerza 2012, Vaquerizo 2013, Raeissadat 2015: final mean WOMAC total score (0-96 (worst); multiplied by -1 to coincide with IKDC direction (higher score, better function)
- Sanchez 2012: Normalized‡ WOMAC total score (0-300 (worst); multiplied by -1 to coincide with IKDC direction (higher score, better function)
- Filardo 2015, Gormeli 2015: IKDC subjective score (0-100 (best)

Figure 17. Knee OA RCT Results for PRP vs. HA: OMERACT-OSARSI Responder Index*



* OMERACT-OSARSI responders are those who experienced a high improvement in pain or function ≥50% and absolute change ≥20; OR had improvement in 2 of the following: 1) Pain ≥20% and absolute change in ≥10; 2) Function ≥20% and absolute change in ≥10; 3) Patient's global assessment ≥20% and absolute change in ≥10.

Table 49. Knee OA RCT Results for PRP vs. HA: Additional function results

Study	Outcome	F/U	PRP Mean ± SD	HA Mean ± SD	MD (95% CI)*	p-value*
Filardo 2015	KOOS Symptoms score (0-100 (best))	2 mos.	72.9 ± 17.0 (n=94)	70.9 ± 16.6 (n=89)	2.0 (-2.9, 6.9)	NS
		6 mos.	74.7 ± 16.9 (n=94)	72.7 ± 17.4 (n=89)	2.0 (-3.0, 7.0)	NS
		12 mos.	73.9 ± 17.2 (n=94)	73.9 ± 18.4 (n=89)	0.0 (-5.1, 5.2)	NS
	KOOS ADL score (0-100 (best))	2 mos.	79.0 ± 19.8 (n=94)	78.0 ± 17.9 (n=89)	1.0 (-4.5, 6.5)	NS
		6 mos.	79.1 ± 19.6 (n=94)	78.4 ± 18.6 (n=89)	0.7 (-4.9, 6.3)	NS
		12 mos.	78.4 ± 20.7 (n=94)	78.4 ± 19.3 (n=89)	0.0 (-5.8, 5.8)	NS
	KOOS Sports score (0-100 (best))	2 mos.	48.0 ± 26.1 (n=94)	44.0 ± 25.5 (n=89)	4.0 (-13.7, 21.7)	NS
		6 mos.	49.6 ± 28.6 (n=94)	45.1 ± 27.0 (n=89)	4.5 (-3.6. 12.6)	NS
		12 mos.	49.3 ± 28.6 (n=94)	46.3 ± 28.1 (n=89)	3.0 (-5.3, 11.3)	NS
	Tegner Score (0-10 (worst))	2 mos.	3.6 ± 1.4 (n=94)	3.3 ± 1.5 (n=89)	0.3 (-0.12, 0.72)	NS
		6 mos.	3.7 ± 1.5 (n=94)	3.5 ± 1.5 (n=89)	0.2 (-0.24, 0.63)	NS
		12 mos.	3.4 ± 1.3 (n=94)	3.4 ± 1.5 (n=89)	0.0 (-0.40, 0.40)	NS

ADL: activities of daily living; CI: confidence interval; F/U: follow-up; HA: Hyaluronic Acid; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: mean difference; NS: not statistically significant; OA: osteoarthritis; PRP: platelet-rich protein; RCT: randomized controlled trial; SD: standard deviation.

*Effect sizes calculated by Spectrum Research.
†Difference in proportions and p-values as reported by the study, unless otherwise indicated.
‡Calculated by Spectrum Research.

Table 50. Knee OA RCT Results for PRP vs. HA: Percentage of patients with functional improvement

Study	Outcome Measure	F/U	PRP % (n/N)	HA % (n/N)	RR (95% CI)*	p-value*
Vaquerizo 2013	≥50% decrease WOMAC	6 mos.	40% (19/48)	11% (5/48)	RR 3.8 (1.5, 9.3)	<0.01
	physical function	12 mos.	31% (15/48)	0% (0/42)	NC	<0.01
	≥50% decrease	6 mos.	35% (16/48)	16% (7/48)	RR 2.3 (1.0, 5.1)	NS
	WOMAC stiffness	12 mos.	33% (16/48)	5% (2/42)	RR 8.0 (1.9, 32.9)	<0.01
	≥30% decrease WOMAC	6 mos.	60% (29/48)	17% (7/48)	RR 4.1 (2.0, 7.6)	<0.01
	physical function	12 mos.	54% (26/48)	17% (7/42)	RR 3.7 (1.8, 7.7)	<0.01
	≥30% decrease	6 mos.	52% (24/48)	27% (11/48)	RR 2.2 (1.2, 3.9)	0.02
	WOMAC stiffness	12 mos.	52% (24/48)	12% (5/42)	RR 4.8 (2.0, 11.5)	<0.01
	≥50% decrease in	6 mos.	29% (14/48)	4% (2/48)	RR 7.0 (1.7, 29.2)	<0.01
	Lequesne Index	12 mos.	19% (9/48)	2% (1/42)	RR 9.0 (1.2, 68.3)	0.2
	≥30% decrease in	6 mos.	73% (35/48)	17% (7/48)	RR 5.0 (2.5, 10.1)	<0.01
	Lequesne Index	12 mos.	48% (23/48)	2% (1/42)	RR 23.0 (3.2, 163.6)	<0.01
Cerza 2012	No improvement in symptoms and unchanged WOMAC score (all follow-up times)	6 mos.	2% (1/60)	2% (1/60)	RR 1.0 (0.06, 16.5)	NS
	Slight response and overall improvement in symptoms with score reduction of 5 WOMAC points	6 mos.	3% (2/60)	NR	NC	NC

CI: confidence interval; F/U: follow-up; HA: Hyaluronic Acid; NC: Not calculable; NS: not statistically significant; OA: osteoarthritis; PRP: platelet-rich protein; RCT: randomized controlled trial; RR: relative risk; WOMAC: Western Ontario and McMaster score

*calculated

Figure 18. Knee OA RCT Results for PRP vs. HA: WOMAC Stiffness and Physical Function SMD

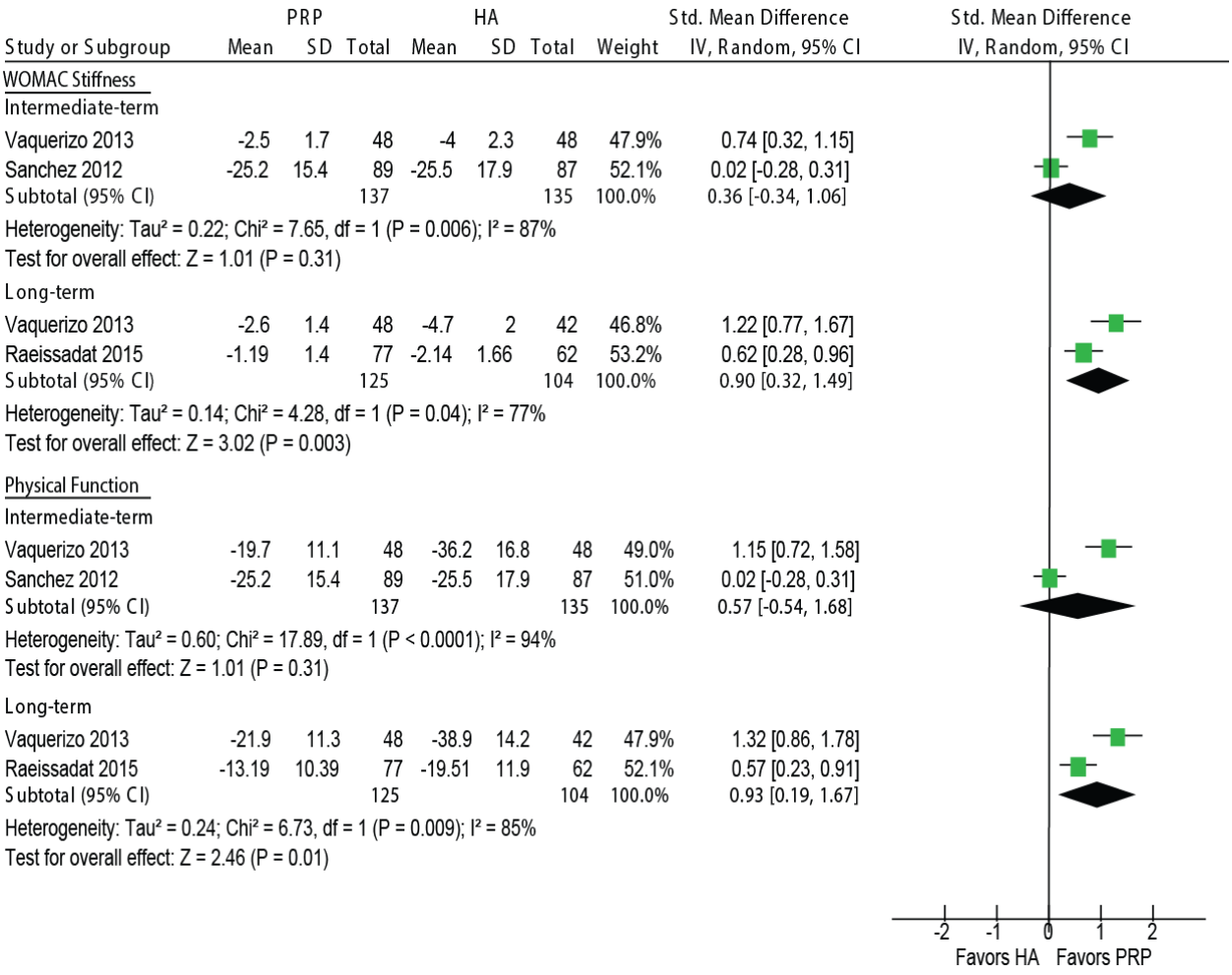
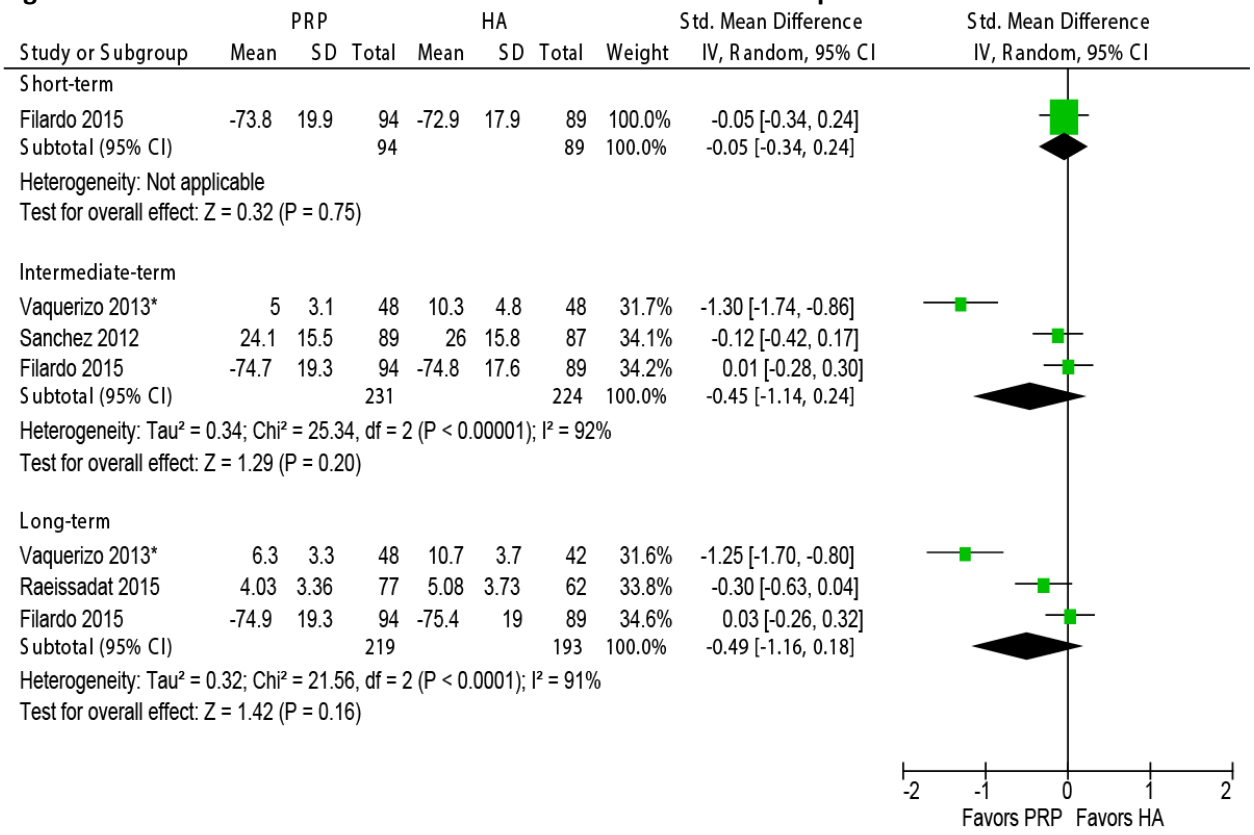


Figure 19. Knee OA RCT Results for PRP vs. HA: WOMAC and KOOS pain SMD

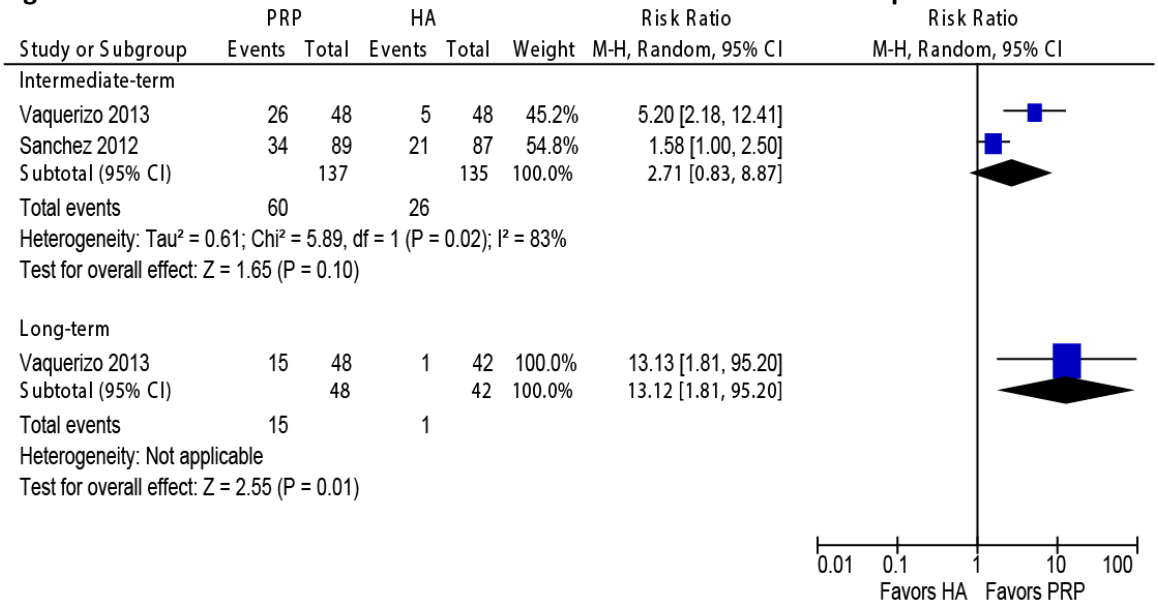


*Vaquerizo 2013: It is unclear if author reported final scores or change scores. We interpreted them as final scores

Outcomes measures reported:

- Vaquerizo 2013, Raeissadat 2015: final mean WOMAC Pain Score (0-20, worst);
- Sanchez 2012: Normalized WOMAC Pain (0-100 (worst));
- Filardo: KOOS Score Pain (0-100 (best)); multiplied by -1 change direction (higher score, worse pain) to be consistent with WOMAC

Figure 20. Knee OA RCT Results for PRP vs. HA: 50% decrease in WOMAC pain



Outcomes measures reported:

- Vaquerizo 2013: 50% decrease in WOMAC pain score from baseline
- Sanchez 2012: 50% decrease in normalized WOMAC pain score from baseline

Table 51. Knee OA RCT Results for PRP vs. HA: Percentage of patients with pain improvement

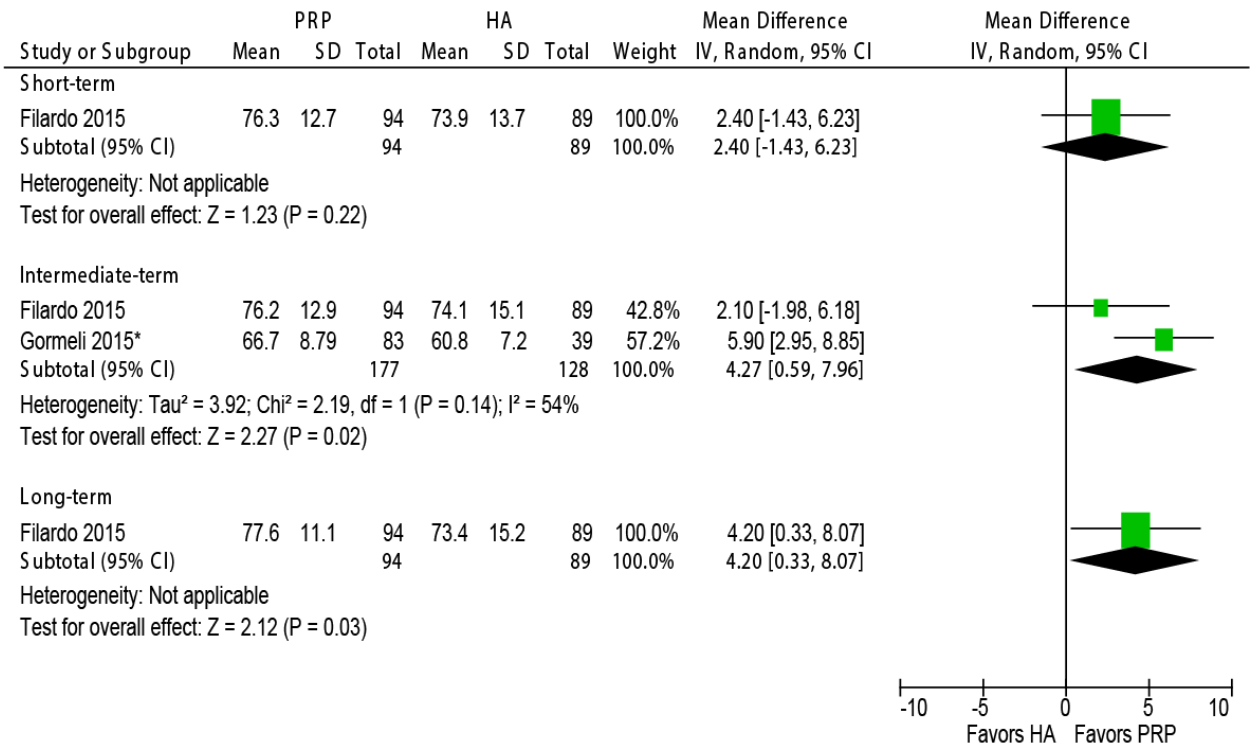
Study	Outcome	F/U	PRP % (n/N)	HA % (n/N)	RR (95% CI)*	p-value†
Sanchez 2012	20% decrease in normalized WOMAC pain	6 mos.	57% (51/89)	53% (46/87)	RR 1.08 (0.8, 1.4)	0.555
Vaquerizo 2013	30% decrease in WOMAC pain	6 mos.	83% (40/48)	17% (7/48)	RR 5.7 (2.8, 11.5)	<0.001
		12 mos.	58% (28/48)	12% (5/42)	RR 4.9 (2.1, 11.5)	<0.001

CI: confidence interval; F/U: follow-up; HA: hyaluronic acid; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: relative risk; WOMAC: Western Ontario and McMaster score

*Relative risks calculated by Spectrum Research, Inc.

†Difference in proportions and p-values as reported by study, unless otherwise indicated.

Figure 21. Knee OA RCT Results for PRP vs. HA: Quality of Life (EQ VAS): PRP vs. HA



* Gormeli 2015: PRP group is comprised of patients receiving either 3 PRP injections (n=46) or a single PRP injection (n=45).

Outcomes measures reported:

- EQ-VAS Score (0-100 (best)) EuroQol visual analog scale

Table 52. Knee OA RCT Results for PRP vs. HA: Quality of Life and Patient Satisfaction

Study	Outcome Measure	F/U	PRP Mean ± SD	HA Mean ± SD	MD (95% CI)*	p-value*
Filardo 2015	KOOS Score: QoL (0-100 (best))	2 mos.	48.4 ± 23.1 (n=94)	47.7 ± 22.1 (n=89)	0.7 (-5.9, 7.3)	NS
		6 mos.	49.2 ± 23.4 (n=94)	49.9 ± 23.1 (n=89)	-0.7 (-7.5, 6.1)	NS
		12 mos.	50.8 ± 24.0 (n=94)	50.9 ± 24.4 (n=89)	-0.1 (-7.2, 6.9)	NS
Raeissadat 2015	SF-36: Sum of physical health components (0-400 (best))†	13 mos.	256.0 ± 78.6 (n=77)	189.4 ± 103.7 (n=62)	66.5 (36.1, 99.9)	<0.01
	SF-36: Sum of mental health components (0-400 (best))†	13 mos.	269.9 ± 91.5 (n=77)	216.9 ± 100.9 (n=62)	53.0 (20.7, 85.3)	<0.01
	SF-36: Physical functioning (0-100 (best))	13 mos.	56.82 ± 25.68 (n=77)	44.3 ± 28.1 (n=62)	11.5 (2.5, 20.6)	<0.01
	SF-36: Role-physical (0-100 (best))	13 mos.	54.0 ± 38.8 (n=77)	33.5 ± 42.0 (n=62)	20.5 (6.9, 34.1)	<0.01
	SF-36: Bodily pain (0-100 (best))	13 mos.	77.1 ± 19.6 (n=77)	53.6 ± 27.9 (n=62)	23.6 (15.6, 31.5)	<0.01
	SF-36: General health (0-100 (best))	13 mos.	68.6 ± 18.8 (n=77)	60.7 ± 26.7 (n=62)	7.9 (0.2, 15.5)	<0.01
	SF-36: Vitality (0-100 (best))	13 mos.	63.1 ± 26.7 (n=77)	54.6 ± 26.1 (n=62)	8.5 (-0.4, 17.4)	<0.01
	SF-36: Social functioning (0-100 (best))	13 mos.	79.4 ± 21.6 (n=77)	63.3 ± 32.6 (n=62)	16.1 (6.9, 25.2)	<0.01
	SF-36: Role-emotional (0-100 (best))	13 mos.	45.2 ± 39.0 (n=77)	45.2 ± 39.0 (n=62)	0.0 (-13.2, 13.2)	NS
	SF-36: Mental health (0-100 (best))	13 mos.	70.3 ± 25.2 (n=77)	56.5 ± 24.5 (n=62)	13.8 (5.4, 22.2)	<0.01
Study	**Outcome**	**F/U**	**PRP % (n/N)**	**HA % (n/N)**	**RR (95% CI)***	**p-value***
Gormeli 2015§	Patients satisfied‡	6 mos.	75% (62/83)	64% (25/39)	1.2 (0.8, 1.5)	NS
	Patients partially satisfied‡	6 mos.	16% (13/83)	23% (9/39)	0.6 (0.3, 1.5)	NS
	Patients not satisfied‡	6 mos.	10% (8/83)	13% (5/39)	0.7 (0.3, 2.1)	NS
Filardo 2015	Satisfaction rate‡	12 mos.	89% (84/94)	90% (80/89)	0.9 (0.9, 1.1)	NS

CI: confidence interval; F/U: follow-up; HA: hyaluronic acid; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: mean difference; NC: not calculable; NS: not statistically significant; OA: osteoarthritis; PRP: platelet-rich plasma; RCT:

randomized controlled trial; QoL: quality of life; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SF-36: short form 36.

* Effect sizes and p-values calculated by Spectrum Research, Inc.

† Raeissadat 2015: "Sum of physical health components" outcome is called PCS-36 by authors; mean appears to be the sum of SF-36 subscales physical functioning, role-physical, bodily pain, and general health. "Sum of mental health components" outcome is called MCS-36 by authors; mean appears to be the sum of SF-36 subscales vitality, social functioning, role-emotional, and mental health. Authors have not reported the MCS/PCS-36 in the standard method, as described by Ware et al. 1994.

‡ Details for measuring patient satisfaction not given.

§ Gormeli 2015: Groups receiving either 3 PRP injections or a single PRP injection were statistically combined to form a single PRP group.

Effectiveness Results

Note that all four included cohort studies[141,241,246,260] were found to be at moderately high risk of bias; it is not clear that patients were blinded and the extent to which this may have influenced results is unknown.

Function

Short-term: In contrast to the efficacy results which overall suggest no difference between groups, all but one cohort study reported better short-term function with PRP versus HA (Table 53). Two cohort studies reported statistically better short-term WOMAC total scores with PRP (Sanchez 2008[241], Spakova[260]) and a third study reported a significant improvement in KOOS scores, although the subscale was not specified (Say[246]); the fourth study found no significant difference between groups in IKDC scores at 2 months (Kon[141]).

Intermediate-term: Three cohort studies reported significantly improved function favoring PRP in the intermediate term as measured by WOMAC total scores (Spakova[260]), IKDC (Kon 2011[141]) and KOOS (subscale not specified) (Say 2013[246]) (Table 53).

Long-term: No data reported

Pain

Short-term: Three cohort studies reported short-term pain outcomes. Outcome measures used included WOMAC pain scores (Sanchez 2008[241]), VAS (Say[246]), and NRS (Spakova[260]). All three studies reported significantly better pain scores following PRP compared with HA (Table 54). In addition, one small cohort study (Sanchez 2008[241]) reported that significantly more PRP than HA patients achieved at least 40% reduction in WOMAC pain scores in the short term (Table 54).

Intermediate-term:

Two cohort studies reported significantly better mean VAS (Say) and NRS (Spakova[260]) pain scores with PRP versus HA as evaluated in the intermediate-term (Table 54).

Long-term: No data reported

Other outcomes

Health-Related Quality of Life: One cohort study reported significantly better ES-VAS scores following PRP versus HA injection in both the short- and intermediate-term (Kon[141]) (Table 55).

Patient satisfaction: One cohort study reported that at 6 months, significantly more PRP patients were satisfied than HA patients, however, no details of how this was measured were provided (Kon[141]) (Table 55).

Table 53. Knee OA Cohort Study Results for PRP vs. HA: Function

Outcome	Study	F/U	PRP Mean ± SD	HA Mean ± SD	p-value*
Total WOMAC (0-96 (worst))	Spakova 2012	3 mos.	14.4 ± 14.2 (n=60)	26.2 ± 17.5 (n=60)	<0.01
		6 mos.	18.9 ± 14.1 (n=60)	30.9 ± 16.6 (n=60)	<0.01
IKDC (0-100 (best))	Kon 2011	0 mos.	41.2 ± 10.9 (n=50)	46.0 ± 10.8 (n=50)	-
		2 mos.	62.7 ± 14.0 (n=50)	58.3 ± 14.4 (n=50)	NS
		6 mos.	64.0 ± 18.7 (n=50)	53.9 ± 14.8 (n=50)	<0.01
KOOS (0-100 (best))	Say 2013	3 mos.	76.9 ± 7.5 (n=45)	68.6 ± 3.7 (n=45)	0.02
		6 mos.	84.4 ± 6.2 (n=45)	73.2 ± 4.6 (n=45)	<0.01
Outcome	**Study**	**F/U**	**PRP median (IQR)**	**HA median (IQR)**	**p-value***
% reduction total WOMAC†	Sanchez 2008	1.25 mos.	-10% (-40%, 10%) (n=30)	0% (-20%, 30%) (n=30)	0.01
% reduction WOMAC: Joint stiffness†	Sanchez 2008	1.25 mos.	-20% (-50%, 0%) (n=30)	0% (-25%, 0%) (n=30)	NS
% reduction WOMAC: Physical Function†	Sanchez 2008	1.25 mos.	-10% (-40%, 20%) (n=30)	0% (-15%, 40%) (n=30)	0.04

F/U: follow-up; HA: hyaluronic acid; IKDC: International Knee Documentation Committee; IQR: interquartile range; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: mean difference; NS: not statistically significant; PRP: platelet-rich plasma; WOMAC: Western Ontario and McMaster score

*calculated

†Sanchez 2008: All "% reduction WOMAC" outcomes were estimated from Figure 1 in paper. Negative values indicate there was a reduction in WOMAC subscale score; positive values indicate there was an increase.

Table 54. Knee OA Cohort Study Results for PRP vs. HA: Pain

Outcome	Study	F/U	PRP % (n/N)	HA % (n/N)	p-value*
≥40% decrease in WOMAC Pain	Sanchez 2008	1.25 mos.	33% (10/30)	10% (3/30)	0.02
Outcome	**Study**	**F/U**	**PRP Mean ± SD**	**HA Mean ± SD**	**p-value***
VAS score (0-10 (worst))	Say 2013	3 mos.	2.3 ± 1.6 (n=45)	4.1 ± 1.3 (n=45)	<0.01
		6 mos.	1.7 ± 1.4 (n=45)	3.0 ± 1.0 (n=45)	<0.01
NRS (0-11(worst))	Spakova 2012	3 mos.	2.1 ± 2.0 (n=60)	4.0 ± 2.3 (n=60)	<0.01
		6 mos.	2.7 ± 1.9 (n=60)	4.3 ± 2.1 (n=60)	<0.01
Outcome	**Study**	**F/U**	**PRP Median (IQR)**	**HA Median (IQR)**	**p-value***
% change WOMAC: Pain‡	Sanchez 2008	1.25 mos.	-25% (-50%, -5%) (n=30)	0% (-15%, 30%) (n=30)	<0.01

F/U: follow-up; HA: hyaluronic acid; IQR: interquartile range; MD: mean difference; NC: Not calculable; NRS: numeric rating scale; OA: osteoarthritis; PRP: platelet-rich plasma; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster score

*calculated

†reported by the study

‡Sanchez 2008: All "% reduction WOMAC" outcomes were estimated from Figure 1 in paper. Negative values indicate there was a reduction in WOMAC subscale score; positive values indicate there was an increase.

Table 55. Knee OA Cohort Study Results for PRP vs. HA: Quality of life and patient satisfaction

Outcome	Study	F/U	PRP Mean ± SD	HA Mean ± SD	p-value*
EQ-VAS (0-100 (best))	Kon 2011	2 mos.	73.0 ± 13.9 (n=50)	60.5 ± 13.1 (n=50)	<0.01
		6 mos.	72.3 ± 17.3 (n=50)	62.1 ± 14.9 (n=50)	<0.01
Outcome	**Study**	**F/U**	**PRP % (n/N)**	**HA % (n/N)**	**p-value***
Patients satisfied†	Kon 2011	6 mos.	82% (41/50)	65% (65/100)	0.03

EQ-VAS: EuroQol visual analog scale; F/U: follow-up; HA: hyaluronic acid; OA: osteoarthritis; PRP: platelet-rich plasma.

*calculated

†Kon 2011: No details regarding determination of patient satisfaction were provided.

4.1.12.2. PRP vs. Corticosteroid for knee OA

Studies included

One small RCT (and no cohort studies) comparing LR-PRP to corticosteroid injection was identified (Forogh 2015[84]); detailed information on patient and study characteristics is available in Appendix Table F25. The trial enrolled a total of 41 knee OA patients and randomized 24 knees to each group. Minimum symptom duration required was 3 months (mean duration not reported). Approximately two-thirds of knees were rated as Kellgren-Lawrence Grade III, while the remaining knees were Kellgren-Lawrence Grade II. The majority of patients were women (67%) with a mean age of 61 years. Both groups received a single injection. A total of 5 ml activated PRP was injected; use of LP- or LR-PRP was not reported. The steroid group received a 1 ml injection of depro-medrol. It is assumed that in patients with two treated

knees that each knee received the same type of injection. Baseline characteristics and measures were comparable between groups. Subjects and clinicians were blinded to treatment. There appeared to be differential loss to follow-up between groups (95.8% vs. 66.7%) and exclusion of participants following randomization which appears to compromise intention to treat analysis; overall the study was considered to be at moderately low risk of bias.

Efficacy Results

All analyses were done based on number of knees, not patients.

Function

The trial (Forogh[84]) evaluated function using KOOS subscales for symptom relief, activities of daily living, and sporting ability (Table 56). In both the short- and intermediate-term, the PRP group had significantly better follow-up scores than the corticosteroid group in the symptom relief and activities of daily living subscales, however, the sporting abilities subscale scores were similar between groups at both time points.

Pain

Forogh et al.[84] reported significantly better short- and intermediate-term pain scores in the PRP group compared with the corticosteroid group based on both KOOS Pain relief subscale and VAS pain intensity (Table 57).

Other outcomes

Quality of Life: No difference between treatments in KOOS QoL subscore was seen in the short-term; by the intermediate-term, results were significantly better in the PRP group (Table 58) (Forogh[84]).

Medication usage: The number of analgesic tablets taken daily did not differ between treatments as measured at intermediate-term follow-up (Table 58) (Forogh[84]).

Table 56. Knee OA RCT Results for PRP vs. Steroid: Function

Study	Outcome	F/U	PRP Mean ± SD	Steroid Mean ± SD	MD (95% CI)*	p-value*
Forogh 2015	KOOS: Symptom relief (0-100 (best))	2 mos.	74.1 ± 18.6 (n=23)	59.4 ± 14.7 (n=16)	14.7 (3.4, 25.9)	0.01
		6 mos.	78.1 ± 8.0 (n=23)	58.3 ± 16.4 (n=16)	19.8 (11.8, 27.8)	<0.01
	KOOS: ADL (0-100 (best))	2 mos.	75.4 ± 13.1 (n=23)	55.1 ± 20.3 (n=16)	20.3 (9.5, 31.1)	<0.01
		6 mos.	74.9 ± 15.0 (n=23)	62.9 ± 19.1 (n=16)	12.0 (0.93, 23.1)	<0.01
	KOOS: Sporting ability (0-100 (best))	2 mos.	13.3 ± 9.9 (n=23)	10.6 ± 6.8 (n=16)	2.7 (-3.1, 8.5)	NS
		6 mos.	11.3 ± 8.0 (n=23)	11.6 ± 10.4 (n=16)	-0.3 (-3.6, 5.7)	NS

ADL: activities of daily living; CI: confidence interval; F/U: follow-up; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: mean difference; NS: not statistically significant; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation

*calculated

Table 57. Knee OA RCT Results for PRP vs. Steroid: Pain

Study	Outcome	F/U	PRP Mean ± SD	Steroid Mean ± SD	MD (95% CI)*	p-value*
Forogh 2015	KOOS: Pain relief (0-100 (best))	2 mos.	73.5 ± 15.0 (n=23)	60.0 ± 16.3 (n=16)	13.5 (3.2, 23.8)	0.01
		6 mos.	78.0 ± 10.5 (n=23)	54.4 ± 20.4 (n=16)	23.6 (13.5, 33.7)	<0.01
	VAS pain (0-100 (worst))	2 mos.	45.1 ± 23.4 (n=23)	65.3 ± 19.3† (n=16)	-20.2 (-34.5, -5.8)	<0.01
		6 mos.	44.6 ± 15.6 (n=23)	72.5 ± 16.2† (n=16)	-27.9 (-38.4, -17.4)	0.01

CI: confidence interval; F/U: follow-up; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: mean difference; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analog scale.

*calculated

† Values in author's Table 3 differ from those given in text for the following outcomes:

VAS-based pain intensity at 2 months (CS only): 63.2 ± 19.7

VAS-based pain intensity at 6 months (CS only): 75.5 ± 16.2

Table 58. Knee OA RCT Results for PRP vs. Steroid: Other outcomes

Study	Outcome	F/U	PRP Mean ± SD	Steroid Mean ± SD	MD (95% CI)*	p-value*
Forogh 2015	KOOS: QoL (0-100 (best))	2 mos.	25.4 ± 19.2 (n=23)	17.6 ± 12.6 (n=16)	7.8 (-3.3, 18.9)	NS
		6 mos.	30.5 ± 15.3 (n=23)	17.4 ± 11.0 (n=16)	13.1 (4.1, 22.1)	0.02
	Number of analgesic tablets taken	6 mos.	14.1 ± 6.6 (n=23)	17.7 ± 10.5 (n=16)	-3.6 (-9.1, 1.9)	NS

CI: confidence interval; F/U: follow-up; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: mean difference; NS: not statistically significant; OA: osteoarthritis; PRP: platelet-rich plasma; QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation.

*calculated

4.1.12.3. PRP vs. Saline for knee OA

Studies included

Two trials (and no cohort studies) of knee OA patients were identified that compared PRP with saline injections (Patel 2013[203], Gormeli 2015[95]); see Appendix Table F26 for detailed study and patient characteristics. Both trials were multi-armed: Patel et al. compared two PRP groups (of 1 vs. 2 PRP injections) to a single saline injection; Gormeli et al. also compared two PRP groups (of 1 vs. 3 PRP injections) to a control group that received three saline injections. For the purposes of this analysis, the PRP arms were combined such that the PRP groups contained 52 and 91 patients and the saline groups consisted of 23 and 45 patients (for Patel and Gormeli, respectively). LP-PRP was used by Patel; Gormeli did not report on type of PRP. PRP injectate volume was 5 to 8 ml, and both trials used an activating agent in the PRP group. The Patel trial enrolled patients with bilateral knee OA, and although it was not clearly stated as such it is assumed for this analysis that both knees in the same individual received the same treatment. One trial required a minimum symptom duration of 4 months (Gormeli); no other information on symptom duration was reported. Different radiographic classification systems of OA were used in each trial, making comparison across them difficult. One trial (Gormeli) classified 67% of participants as having early OA (Kellgren-Lawrence grade 0 with cartilage degeneration or grades I-III);

the other trial (Patel) classified the majority of knees as Ahlbäck Grade I (70% vs. 44% for PRP vs. saline). Females comprised the majority of participants in both trials; and Patel enrolled more females than Gormeli (71% versus 55%). Other baseline characteristics were similar between treatment groups in both trials. Patients were blinded in both trials however neither trial contained a clear statement of allocation concealment and it appears that both may have excluded patients after randomization so no credit was given for intention to treat analysis. Both trials were considered to be at moderately low risk of bias.

Efficacy Results

Function

Each trial reported on different functional outcomes; Patel[203] used the patient-reported WOMAC total, stiffness and physical function scores, while Gormeli[95] reported patient-reported IKDC scores. Studies could not be combined as one trial (Patel[203]) reported analysis per knee while the other trial reported analysis per patient (Gormeli[95]).

Short-term: Limited data from one trial (Patel[203]) suggests that LP-PRP resulted in significantly improved function compared with saline based on comparison of percent change from baseline between treatments for WOMAC total score (-57% vs. 12%), stiffness score (-47% vs. 10%) and physical function score (-56% vs. 11%) (Table 59). Authors provide mean differences and p-values but no confidence intervals or other indicators of estimate variability.

Intermediate-term: Overall, both trials[95,203] reported that PRP resulted in improved function in the intermediate-term. Patel et al. reported greater percent change from baseline for LP-PRP on WOMAC total score (-47% vs. 20%), stiffness score (-41% vs. 2.0%) and physical function score (-46% vs. 20%), while Gormeli et al. reported higher IKDC scores with PRP (MD 19.0 (95% CI 16.2, 21.8)).

Long-term: No data reported.

Pain

Pain was assessed by one trial (Patel[203]) using the patient-reported WOMAC pain score (0-20 (worst)) and VAS (0-10 (worst)) outcome measures. Analyses were reported based on number of knees treated (Table 60). In the short-term, limited data suggest that treatment with LP-PRP resulted in significantly better pain scores compared with saline alone based on percent change from baseline in WOMAC pain scores (-64% vs. 18%, MD -82% (95% CI not reported), p<0.01). In the intermediate term, limited data suggest that LP-PRP resulted in significantly improved pain based on percent change in WOMAC pain scores (-50% vs. 25%, MD -75% (95% CI not reported), p<0.01) and in VAS pain scores (2.4 vs. 4.6, MD -2.3 (95% CI -2.7, -1.8)). No long-term data were reported.

Other outcomes

Health-Related Quality of Life: One trial (Gormeli[95]) reported significantly greater improvement with PRP in quality of life as measured by the patient-reported EQ-VAS outcome measure (0-100 (best)) in the intermediate-term (Table 61).

Patient satisfaction: Both trials reported that significantly more patients receiving PRP were satisfied with treatment in the intermediate-term (Table 62) (Patel[203], Gormeli[95]); however wide confidence intervals call the stability of the estimate into question. No methodological details were reported regarding how this outcome was assessed.

Table 59. Knee OA RCT Results for PRP vs. Saline: Function

Study	Outcome	F/U	PRP Mean ± SD	Saline Mean ± SD	MD (95% CI)*	p-value*
Patel 2013†	WOMAC total score (0-96 (worst))	0 mos.	51.4 ± 16.9 (n=102 knees)	45.5 ± 17.3 (n=46 knees)	-	-
		3 mos.	24.1 (n=102 knees)	50.7 (n=46 knees)	-26.6 (NR/NC)	NC
		6 mos.	28.8 (n=102 knees)	53.1 (n=46 knees)	-24.3 (NR/NC)	NC
	% Δ WOMAC total score	3 mos.	–57% (n=102 knees)§	12% (n=46 knees)	-69% (NR/NC)	<0.01‡
		6 mos.	–47% (n=102 knees)§	20% (n=46 knees)	-67% (NR/NC)	<0.01‡
	WOMAC: stiffness score (0-8 (worst))	0 mos.	3.3 ± 2.1 (n=102 knees)	2.7 ± 2.0 (n=46 knees)	-	-
		3 mos.	2.0 (n=102 knees)	2.9 (n=46 knees)	-0.9 (NR/NC)	NC
		6 mos.	2.0 (n=102 knees)	2.8 (n=46 knees)	-0.8 (NR/NC)	NC
	% Δ WOMAC: stiffness score	3 mos.	–47% (n=102 knees)§	10% (n=46 knees)	-57% (NR/NC)	<0.01‡
		6 mos.	–41.2% (n=102 knees)§	2.0% (n=46 knees)	-43.2% (NR/NC)	<0.01‡
	WOMAC: physical function score (0-68 (worst))	0 mos.	37.6 ± 12.17 (n=102 knees)	38.8 ± 12.4 (n=46 knees)	-	-
		3 mos.	17.9 (n=102 knees)	37.4 (n=46 knees)	NC	NC
		6 mos.	21.6 (n=102 knees)	39.5 (n=46 knees)	NC	NC
	% Δ WOMAC: physical function score	3 mos.	–56% (n=102 knees)§	11% (n=46 knees)	NC	<0.01‡
		6 mos.	–46% (n=102 knees)§	20% (n=46 knees)	NC	<0.01‡
Gormeli 2015**	IKDC subjective score (0-100 (best))	0 mos.	40.8 ± 5.5 (n=91)	40.4 ± 4.3 (n=45)	-	-
		6 mos.	55.5 ± 8.4 (n=83)	36.5 ± 4.8 (n=40)	19.0 (16.2, 21.8)	<0.01

CI: confidence interval; EQ-VAS: EuroQol visual analog scale; F/U: follow-up; IKDC: International Knee Documentation Committee Subjective Knee Form; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; WOMAC: Western Ontario and McMaster score

*calculated unless otherwise indicated.

†Patel 2013: PRP results reflect number of knees receiving either a single PRP injection or two PRP injections. Results from these injection groups were statistically combined to create a single PRP group.

‡As reported by the study.

§Patel 2013: Negative values indicate improvement from baseline.

**Gormeli 2015: Groups receiving 3 PRP injections or a single PRP injection were statistically combined to create a single PRP group.

Table 60. Knee OA RCT Results for PRP vs. Saline: Pain

Study	Outcome	F/U	PRP* Mean ± SD	Saline Mean ± SD	MD (95% CI)†	p-value†
Patel 2013	WOMAC pain score 0-20 (worst))	0 mos.	10.4 ± 3.7 (n=102 knees)	9.0 ± 3.7 (n=46 knees)	-	-
		3 mos.	4.3 (n=102 knees)	10.4 (n=46 knees)	-6.1 (NR/NC)	NC
		6 mos.	5.6 (n=102 knees)	10.9 (n=46 knees)	-5.3 (NR/NC)	NC
	% ΔWOMAC	3 mos.	–63.6% (n=102 knees)	18% (n=46 knees)	-81.6% (NR/NC)	<0.01‡
		6 mos.	–50.1% (n=102 knees)	25% (n=46 knees)	-75.1% (NR/NC)	<0.01‡
	VAS pain (0-10 (worst))	6 mos.	2.4 ± 1.6 (n=102 knees)	4.6 ± 0.7 (n=46 knees)	-2.3 (-2.7, -1.8)	<0.01
	ΔVAS pain	6 mos.	2.2 ± 1.6 (n=102 knees)	–0.04 ± 0.6 (n=46 knees)	2.3 (1.8, 2.8)	<0.01

CI: confidence interval; F/U: follow-up; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster score.

*PRP results reflect number of knees receiving either a single PRP injection or two PRP injections. Results from these injection groups were statistically combined to create a single PRP group.

†calculated unless otherwise indicated.

‡As reported by the study.

Table 61. Knee OA RCT Results for PRP vs. Saline: Quality of life

Outcome	Study	F/U	PRP Mean ± SD	Saline Mean ± SD	MD (95% CI)*	p-value*
EQ-VAS Score (0-100 (best))	Gormeli 2015†	0 mos.	50.3 ± 5.47 (n=91)	50.2 ± 4.5 (n=45)	-	-
		6 mos.	66.7 ± 8.79 (n=83)	48.0 ± 5.1 (n=40)	18.7 (15.7, 21.7)	<0.01

CI: confidence interval; EQ-VAS: EuroQol visual analog scale; F/U: follow-up; MD: mean difference; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation.

*calculated

†Gormeli: Groups receiving 3 PRP injections or a single PRP injection were statistically combined to create a single PRP group.

Table 62. Knee OA RCT Results for PRP vs. Saline: Patient satisfaction

F/U	Outcome	Study	PRP % (n/N)	Saline % (n/N)	RR (95% CI)*	p-value*
6 mos.	Patients satisfied‡	Gormeli 2015†	75% (62/83)	5% (2/40)	14.9 (3.8, 58.1)	<0.01
		Patel 2013§	65% (34/52 knees)	4% (1/23 knees)	15.0 (2.2, 103.3)	<0.01
	Patients partially satisfied‡	Gormeli 2015†	16% (13/83)	15% (6/40)	1.0 (0.4, 2.5)	NS
		Patel 2013§	6% (3/52 knees)	7% (2/23 knees)	0.6 (0.1, 3.7)	NS
	Patients not satisfied‡	Gormeli 2015†	10% (8/83)	80% (32/40)	0.1 (0.1, 0.2)	<0.01
		Patel 2013§	25% (13/52 knees)	89% (20/23 knees)	0.3 (0.2, 0.5)	<0.01

CI: confidence interval; F/U: follow-up; NS: not statistically significant; OA: osteoarthritis; PRP; platelet-rich plasma; RCT: randomized controlled trial; RR: relative risk.

*calculated

†Gormeli: Groups receiving 3 PRP injections or a single PRP injection were statistically combined to create a single PRP group.

‡No further methodological details provided for these outcome measures.

§Patel: PRP results reflect number of knees receiving either a single PRP injection or two PRP injections. Results from these injection groups were statistically combined to create a single PRP group.

4.1.12.4. PRP vs. Exercise ± TENS for knee OA

Studies included

Two trials (and no cohort studies) were identified which compared PRP with exercise (Rayegani 2014[218], Angoorani 2014[10]). Detailed information on patient and study characteristics can be found in Appendix Table F27. One trial compared LR-PRP plus exercise (n=32) to exercise alone (n=33) (Rayegani) and another trial compared PRP (80% LP-PRP, 20% LR-PRP (correspondence with author), n=27) to exercise plus 10 sessions of transcutaneous electrical nerve stimulation (TENS) (n=27) (Angoorani). Minimum symptom duration for both trials was 3 months; neither reported mean duration, however 79% of participants in the Rayegani trial had symptoms for longer than 1 year. In one trial (Rayegani), the majority of patients had grade 2 or 3 tibio- or patellofemoral OA; the other trial did not report OA severity (Angoorani). Two PRP injections ranging from 4 to 6 ml were used in both trials; one trial employed activated PRP (Angoorani). One trial employed exercise in all patients (Rayegani) while the other trial employed exercise (plus 10 biweekly TENS sessions) in the control group only. The majority of patients were female in both trials. Although there was no statistical difference in radiographic OA classification in Rayegani the proportion of patients with grades 2 or 3 (either anatomic site) in the PRP group was smaller. There were statistical differences in baseline KOOS subscale scores between treatment groups in one trial (Angoorani) and in WOMAC total and pain scores in the other trial (Rayegani), although it is not clear whether these differences are clinically meaningful or indicative of differences in OA severity between groups. Methodological limitations included no clear statement of allocation concealment (both trials), lack of blinding of patients and assessors (both trials). Overall, both trials were considered to be at moderately low risk of bias.

Efficacy Results

Function

There were no differences between PRP and exercise plus TENS groups in short-term function as measured by the patient-reported KOOS Symptoms, ADL or Sports subscales in one trial (Angoorani[10]) (Table 63). In the intermediate-term, the other trial (Rayegani[218]) reported WOMAC total score as significantly better with LR-PRP plus exercise compared with exercise alone, but no data were provided to support this other than a figure. Visual inspection of author's figure, and data estimation from that figure do not support the author's finding and suggest no difference between groups. The same trial reported no difference between groups in WOMAC stiffness or functional capacity subscales (Rayegani[218]) (Table 63). No long-term data were reported.

Pain

In the short-term, one trial (Angoorani[10]) reported no difference between PRP and exercise plus TENS groups in the KOOS pain or in VAS pain scores (Table 64). In the intermediate-term, one trial (Rayegani[218]) reported that the WOMAC pain score was significantly better with LR-PRP plus exercise versus exercise alone, however data estimation from that trial does not support the author's finding and suggest no difference between groups (Table 64). No long-term data were reported.

Other Outcomes

Quality of life: No difference was found between groups in short-term (Angoorani[10]) or intermediate-term (Rayegani[218]) quality of life (Table 65). Although the latter trial reported significantly better scores with PRP, visual inspection of author's figure, and data estimation from that figure do not support the author's finding and suggest no difference between groups. No long-term data were reported.

Medication usage: One trial (Rayegani[218]) reported that the LR-PRP plus exercise group used nearly twice as many doses of acetaminophen (presumably over the entire 6-month follow-up period, though this was not explicitly stated) than the exercise alone group (Table 65).

Table 63. Knee OA RCT Results for PRP vs. Exercise: Function

Study	Outcome	F/U	PRP Mean ± SD	Exercise Mean ± SD	MD (95% CI)*	p-value*
Angoorani 2015	KOOS: Symptoms (0-100 (best))	0 mos.	51.5 ± 4.5 (n=27)	50.3 ± 3.9 (n=27)	-	-
		2 mos.	61.5 ± 3.9 (n=27)	52.0 ± 4.0 (n=27)	8.3 (-0.4, 17.9) (adj.)§	NS
	KOOS: ADL (0-100 (best))	0 mos.	48.3 ± 3.8 (n=27)	42.4 ± 4.1 (n=27)	-	-
		2 mos.	54.4 ± 3.4 (n=27)	44.2 ± 4.4 (n=27)	4.3 (-6.9, 15.5) (adj.)§	NS
	KOOS: Sport/Rec (0-100 (best))	0 mos.	23.8 ± 4.9 (n=27)	28.4 ± 6.2 (n=27)	-	-
		2 mos.	21.3 ± 4.3 (n=27)	25.4 ± 5.3 (n=27)	0.5 (-12.7, 13.7) (adj.)§	NS
Rayegani 2014	WOMAC total (0-96 (worst))†	0 mos.	43.0 ± 13.6 (n=31)	35.0 ± 9.5 (n=31)	-	-
		6 mos.	20.0 ± 13.6 (n=31)†	20.5 ± 21.8 (n=31)†	-0.5 (-9.7, 8.7)	NS†

Study	Outcome	F/U	PRP Mean ± SD	Exercise Mean ± SD	MD (95% CI)*	p-value*
	WOMAC: Stiffness (0-8 (worst))	0 mos.	2.3 ± 1.76 (n=31)	1.7 ± 1.6 (n=31)	-	-
	Δ WOMAC: Stiffness‡	6 mos.	0.8 ± 1.3 (n=31)	0.8 ± 1.3 (n=31)	0.0 (-0.7, 0.7)	NS
	WOMAC: Physical function (0-68 (worst))	0 mos.	31.9 ± 9.8 (n=31)	25.0 ± 17.3 (n=31)	-	-
	ΔWOMAC: Functional capacity‡	6 mos.	14.1 ± 9.1 (n=31)	13.9 ± 13.4 (n=31)	0.2 (-5.7, 5.9)	NS

ADL: Activity of daily life; CI: confidence interval; f/u: follow-up; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: Mean difference; NS: not statistically significant; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: Standard deviation; WOMAC: Western Ontario and McMaster score

*Calculated unless otherwise indicated

† Rayegani 2014: WOMAC scores estimated from Figure 2A. Spectrum calculated mean difference was nonsignificant although authors reported significance (p = 0.03);

‡ Rayegani 2014: It is not clear if these values are raw scores or change scores; we have interpreted as change scores.

§ Angoorani 2015: Effect sizes (95% CI) from authors' for repeated measures analysis correcting correlated data.

Table 64. Knee OA RCT Results for PRP vs. Exercise: Pain

Study	Outcome	F/U	PRP Mean ± SD	Exercise Mean ± SD	MD (95% CI)*	p-value*
Angoorani 2015	KOOS: Pain (0-100 (best))	0 mos.	44.9 ± 3.6 (n=27)	41.3 ± 3.4 (n=27)	-	-
		2 mos.	50.7 ± 3.2 (n=27)	44.2 ± 3.9 (n=27)	2.9 (-7.7, 13.50)§	NS
	VAS: Pain (0-100 (worst))††	0 mos.	58 (n=27)	66 (n=27)	-	-
		2 mos.	47 (n=27)	53 (n=27)	-6 (NC/NR)	NS
Rayegani 2014	WOMAC: Pain (0-20 (worst))	0 mos.	9.1 ± 3.7 (n=31)	7.1 ± 3.7 (n=31)	-	-
	Δ WOMAC: Pain†	6 mos.	4.2 ± 3.1 (n=31)	5.2 ± 4.5 (n=31)	-0.9 (-2.9, 0.9)	NS‡

CI: confidence interval; f/u: follow-up; KOOS: Knee injury and Osteoarthritis Outcome Score; MD: mean difference; NC: not calculable; NR: not reported; NS: not statistically significant; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster score

*calculated unless otherwise indicated

†Rayegani: Report is not clear if these values or raw scores or change scores; we interpreted as change scores.

‡Rayegani 2014: Authors reported as significant (p=0.006); Spectrum calculated difference was not significant.

§Angoorani: Effect sizes (95% CI) from authors for repeated measures analysis correcting correlated data.

** Angoorani: VAS: Pain outcomes are estimated from Figure 2.

Table 65. Knee OA RCT Results for PRP vs. Exercise: Other outcomes

Study	Outcome	F/U	PRP Mean ± SD	Exercise Mean ± SD	MD (95% CI)*	p-value*
Angoorani 2015	KOOS: QoL (0-100 (best))	0 mos.	17.1 ± 2.62 (n=27)	20.6 ± 3.65 (n=27)	-	-
		2 mos.	22.6 ± 2.49 (n=27)	17.6 ± 2.58 (n=27)	8.5 (-0.5, 17.4)†	NS
Rayegani 2014	SF-36: PCS-36 (0-100 (best))‡	0 mos.	42 ± 38.2 (n=31)	55 ± 23.2 (n=31)	-	-
		6 mos.	62 ± 16.4 (n=31)	63 ± 23.2 (n=31)	-1.0 (-11.2 to 9.2)	NS‡
	SF-36: MCS-36 (0-100 (best))‡	0 mos.	52 ± 19.1 (n=31)	64 ± 20.5 (n=31)	-	-
		6 mos.	59 ± 21.8 (n=31)	60 ± 23.2 (n=31)	-1.0 (-12.43, 10.43)	NS‡
	Acetaminophen doses§	6 mos.	64.0 ± 11.8 (n=31)	31.5 ± 36.5 (n=31)	32.5 (18.8, 46.3)	<0.01

CI: confidence interval; f/u: follow-up; KOOS: Knee injury and Osteoarthritis Outcome Score; MCS: Mental Component Score; MD: mean difference; NS: not statistically significant; OA: osteoarthritis; PCS: Physical Component Score; PRP: platelet-rich plasma; QoL: Quality of Life; RCT: randomized controlled trial; SD: standard deviation; SF-36: short form 36.

*Calculated

†Angoorani 2015: Effect sizes (95% CI) from authors for repeated measures analysis correcting correlated data.

‡Rayegani 2014: SF-36: PCS-36 and MCS-36 outcomes estimated from Figure 2B and 2C, respectively; additionally, authors report statistical significance for both SF-36: PCS-36 and SF-36: MCS-36 outcomes, but calculations from figure inspection and our estimates are non-significant.

§Rayegani 2014: Doses of 500 mg acetaminophen; details regarding timing not provided by authors and thus it was assumed to be over the full follow-up period.

4.1.13. Hip Osteoarthritis

Summary of results

PRP vs. HA: One moderately low risk of bias RCT[17] was included (N=104). With respect to primary outcomes, there were no differences between PRP and HA groups in short-, intermediate-, or long-term function or pain scores based on low quality evidence. No other primary outcomes were reported. The only primary outcome reported was medication use, which was similar between groups at all three time points.

4.1.13.1. PRP vs. HA for hip OA

Studies included

One trial (and no cohort study) was identified that met the inclusion criteria with regards to hip osteoarthritis; this trial compared LR-PRP with HA injections (Battaglia 2013[17]); detailed study characteristics and patient demographics are available in Appendix Table F28. Patients had unilateral hip osteoarthritis with symptoms of 6 to 24 months' duration; Kellgren Lawrence Grade ranged from II to IV. The trial randomized 52 patients to each group, each of which received three injections under ultrasound guidance; sodium citrate was added to the activated LR-PRP preparation. Injectate volume was 5 ml in the PRP group and 2 ml in the HA group; patients were blinded to treatment received. There were baseline imbalances in the percentage of patients considered to be Kellgren-Lawrence Grade II (32% vs. 46%) and Grade IV (26% vs. 8%). In addition, more LR-PRP recipients reported NSAID use at

baseline (92% versus 74%). Authors controlled for baseline OA grade, age and NSAID use and used repeated measures analysis. There was no statement of concealed allocation and patients were not blinded after randomization. Overall, the trial was found to be at moderately low risk of bias.

Efficacy Results

Function

Function was evaluated using the clinician-reported Harris Hip Score (HHS) (0-100 (best)). No differences were seen between groups in the short-, intermediate-, or long-term (Battaglia[17]) (Table 66).

Pain

Pain was assessed using the patient-reported VAS (0-10 (worst)). Mean follow-up scores were statistically similar between groups in the short-, intermediate-, or long-term (Battaglia[17]) (Table 67).

Other Outcomes

Medication usage: Despite baseline imbalances in NSAID usage, there were no differences between groups in the percentage of patients using NSAIDs in the short-, intermediate-, or long-term (Battaglia[17]) (Table 68).

Table 66. Hip OA RCT Results for PRP vs. HA: Function

Study	Outcome	F/U	PRP Mean ± SD	HA Mean ± SD	MD (95% CI)*	p-value*
Battaglia 2013	HHS (0-100 (best))	3 mos.	72.9 ± 15.8 (n=50)	77.2 ± 16.1 (n=50)	-4.3 (-10.6 to 2.0)	NS
		6 mos.	70.2 ± 16.3 (n=50)	75.8 ± 16.3 (n=50)	-5.5 (-12.0 to 0.9)	NS
		12 mos.	65.7 ± 18.5 (n=50)	72.6 ± 18.5 (n=50)	-6.8 (-14.1 to 0.5)	NS

f/u: follow-up; HA: hyaluronic acid; HHS: Harris Hip Score; MD: mean difference; NS: not statistically significant; NSAIDs: Nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation

*calculated

Table 67. Hip OA RCT Results for PRP vs. HA: Pain

Study	Outcome	F/U	PRP Mean ± SD	HA Mean ± SD	MD (95% CI)*	p-value*
Battaglia 2013	VAS (0-10 worst))	3 mos.	3.8 ± 2.1 (n=50)	3.8 ± 2.1 (n=50)	0.0 (-0.84 to 0.84)	NS
		6 mos.	4.3 ± 2.1 (n=50)	4.0 ± 2.2 (n=50)	0.25 (-0.59 to 1.09)	NS
		12 mos.	4.8 ± 2.4 (n=50)	4.6 ± 2.4 (n=50)	0.16 (-0.78 to 1.1)	NS

CI: confidence interval; f/u: follow-up; HA: hyaluronic acid; MD: mean difference; NS: not statistically significant; NSAIDs: Nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; VAS: Visual Analog Scale

*calculated

Table 68. Hip OA RCT Results for PRP vs. HA: Medication usage

Study	Outcome	F/U	PRP % (n/N)	HA % (n/N)	RR (95% CI)*	p-value*
Battaglia 2013	NSAID use	0 mos.	92% (46/50)	74% (36/50)	-	-
		3 mos.	38% (19/50)	32% (16/50)	1.2 (0.69 to 2.03)	NS
		6 mos.	44% (22/50)	30% (15/50)	1.46 (0.86 to 2.48)	NS
		12 mos.	52% (26/50)	40% (20/50)	1.30 (0.84 to 2.00)	NS

CI: confidence interval; f/u: follow-up; HA: hyaluronic acid; MD: mean difference; NS: not statistically significant; NSAIDs: Nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: relative risk.

*calculated

4.1.14. Temporomandibular Joint (TMJ) Osteoarthritis

Summary of results

PRP vs. HA: One moderately high risk of bias RCT[105] was included (N=50). There were no clear differences between PRP and HA groups in short-, intermediate-, or long-term function or pain scores based on insufficient quality evidence. No other outcomes were reported.

4.1.14.1. PRP vs. HA for TMJ OA

Studies included

One trial (and no cohort study) was identified that met the inclusion criteria (Hegab 2015[105]); detailed patient and study characteristics are available in Appendix Table F29. The trial compared PRP (n=25) with HA (n=25) injections for treatment of TMJ osteoarthritis; all patients had joint sounds. Symptom duration and classification of OA were not reported. Three injections were given in each group; anesthetic was injected into the joint cavity prior to treatment-related injection and arthrocentesis was done to remove catabolites from the synovial fluid. Patients were blinded to treatment received. Mean age was 38 years old; more women were enrolled in the PRP group (74% versus 56%). There was no difference in baseline pain between groups. The trial was published ahead of print as an unedited accepted manuscript and may not represent the final published manuscript. Methodological limitations included unclear random sequence generation, unclear as to whether data were analyzed in accordance with the intention to treat principle, lack of blinding of the clinician assessing outcomes, lack of information regarding whether co-interventions were applied equally, and no information on the percentage of patients who completed follow-up. The trial was considered to be at moderately high risk of bias.

Results

Function

The primary functional outcome reported was maximum voluntary mouth opening and was measured in millimeters; no further description of this clinician-based measurement was provided. Prevalence of joint sounds was a secondary outcome. In the short-term, data was reported only for the PRP group, thus no conclusion can be drawn regarding the comparative treatment effect. In the intermediate-term, the measurement appears to be similar for PRP and HA groups (39 vs. 40 mm); no ranges or test of significance were reported. In the long-term, the maximum voluntary mouth opening measurement was greater in the PRP group compared with the HA group (41.6 vs. 39.3 mm; MD 2.8 (95% CI 0.82, 3.7)) (Table 69). The authors also reported no difference between groups in joint sound prevalence at any time point but provide no data or statistical testing (Hegab[105]).

Pain

Pain was evaluated using the patient-reported VAS (0-10 (worst)) (Table 69). In the short-term, the median score was slightly worse with PRP versus HA (4.0 vs. 3.0). In the intermediate-term, the reported median VAS pain score was considerably higher in the PRP group compared with the HA group (4.0 vs. 0.0). In the long term, lower median VAS pain scores were reported for the PRP group (0.0 vs. 2.0). No ranges, effect sizes, or tests of significance were provided for any time frame. The trial also reported statistically greater pain improvement from one month (as measured at 12 months) (0.4 vs. 1.6, MD -1.2 (95% CI -1.8, -0.6), although this difference is not likely to be clinically meaningful (Hegab[105]) (Table 69).

Table 69. TMJ OA RCT Results for PRP vs. HA: Function and Pain

Study	Outcome	F/U	PRP Mean ± SD or median (range)	HA Mean ± SD or median (range)	MD (95% CI)*	p-value
Function						
Hegab 2015	Maximum non-assisted (voluntary) mouth opening (mm)†	0 mos.	33.8 ± 3.1 (n=25)	32.4 ± 2.7 (n=25)	-	-
		3 mos.	37 (range NR) (n=25)	NR (n=25)	NC	NC
		6 mos.	39 (range NR) (n=25)	40 (range NR) (n=25)	NC	NC
		12 mos.	41.6 ± 2.3 (n=25)	39.3 ± 2.8 (n=25)	2.8 (0.8, 3.7)	<0.01
Pain						
Hegab 2015	VAS Pain (0-10 (worst))	0 mos.	7.4 ± 4.9 (n=25)	7.0 ± 4.9 (n=25)	-	-
		3 mos.	4.0 (range NR) (n=25)	3.0 (range 2.0, 5.0) (n=25)	NC	NC
		6 mos.	4.0 (range NR) (n=25)	0.0 (range NR) (n=25)	NC	NC
		12 mos.	0.0 (0.0 to 3.0) (n=25)	2.0 (range NR) (n=25)	NC	NC
	ΔVAS Pain from 1 month f/u	12 mos.	0.4 ± 0.7 (n=25)	1.6 ± 1.3 (n=25)	-1.2 (-1.8, -0.6)	<0.01

CI: confidence interval; HA: hyaluronic acid; MD: mean difference; NC: Not calculable; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; SD: standard deviation; TMJ: temporomandibular; VAS: Visual Analog Scale

*calculated

†No further measurement description provided.

4.2. Key Question 2: Harms and Complications

4.2.1. Number of studies retained

All included comparative studies were evaluated for harms and complications. In addition, case series specifically designed to evaluate harms were considered for inclusion, however none were identified that met the inclusion criteria.

Summary of results: Across all included studies, there was no evidence of any serious adverse events with any intervention or control treatment. The most common no-serious adverse events was injection-site pain (both during and after the injection), which may be more common following PRP or ABI injection than other injections.

4.2.2. Tendinopathies

PRP vs. ABI: Of the four trials that evaluated the comparative efficacy of PRP versus ABI in patients with elbow epicondylitis, adverse events were reported by only one trial (Thanasas[273]). The study reported that more PRP patients experience injection-site pain through the 6-month follow-up period (64% (9/14) vs. 29% (4/14)), although the difference did not reach statistical significance due to small sample size (RR 2.25 (95% CI 0.90, 5.6)).

PRP vs. Conservative Control: Adverse events were reported by 13 RCTs (Behera[18], de Jonge[61]/de Vos[64], Dragoo[70], Gosens[96]/Peerbooms[205], Kearney[131], Kesikburun[134], Krogh[143], Mishra[184], Rha[221], Stenhouse[263], Vetrano[284], von Wehren[287], Yadav[302]) and 3 cohort studies (Ford[83], Tetschke[272], Tonk[278]) that compared PRP injection to a conservative control for treatment of tendinopathy. Control groups included steroid, anesthetic, and/or saline injection; dry needling; and extracorporeal shock wave therapy (ESWT). All adverse events reported are summarized in Table 70. In general, very few adverse events were reported to occur, with seven trials (Rha[221], Dragoo[70], Kearney[131], de Jonge[61]/de Vos[64], Yadav[302], Behera[18], Stenhouse[263]) and all three cohort studies (Ford[83], Tetschke[272], Tonk[278]) reporting no complications or adverse events (no details specified). One trial reported that adverse events (not specified) occurred similarly between PRP and anesthetic injection groups (19% vs. 18%) (Mishra). Transient local post-injection pain was reported in four trials (Gosens[96]/Peerbooms[205], Kesikburun[134], Mishra, Vetrano); in the PRP group the incidence ranged from 2% to 13% of patients across three of these trials (Gosens/Peerbooms, Mishra[184], Vetrano[284], it occurred in no patients as reported by one trial (Mishra[184]), and one trial (Kesikburun[134]) indicated that it had occurred in both groups. One trial reported significantly worse post-injection pain with PRP versus steroid when rated on a NRS pain scale (0-10 (worst)) (9.0 vs. 6.0, MD 3.0 (95% CI 1.5, 4.5)) (Krogh[143]). Persisting pain occurred similarly between PRP, steroid, and saline injection groups in one trial (20% vs. 5% vs. 15%, p≥0.05 for PRP vs. either control) (Krogh[143]); the same trial reported insignificantly more cases of reduced elbow movement in the PRP group compared with either control group (15% vs. 5% vs. 0%, p≥0.05 for PRP vs. either control), as well as fewer cases of skin atrophy with PRP versus steroid injection (0% vs. 15%, p≥0.05). Transient skin reddening or minor rash was reported in some control (ESWT and steroid) patients and no PRP patients in two trials (Krogh[143], Vetrano[284]), and one trial reported one case of loss of pigmentation following steroid injection (5%) (Krogh[143]). There were no cases of infection or device-related complications.

ABI vs. Conservative Control: Adverse events were reported by six RCTs (Arik[14], Bell[20], Dojode[68], Kazemi[129], Ozturan[202], Pearson[204]) that compared ABI to a conservative control for treatment of tendinopathy. Control groups included dry needling, steroid injection, extracorporeal shock wave therapy (ESWT), as well as exercise. All adverse events reported are summarized in Table 71. Two trials (Bell[20], Kazemi[129]) indicated that no complications or adverse events occurred (no details specified). Transient local post-injection pain was reported in four trials (Arik[14], Dojode[68], Ozturan[202], Pearson[204]): one trial reported such pain occurred in all patients in the ABI and both control groups (steroid and ESWT) (Ozturan[202]), while two trials (Arik[14], Dojode[68]) reported that significantly more ABI patients experienced post-injection pain compared with steroid groups (25-60% vs. 0-26%). Another trial reported that 21% of patients experienced severe worsening of pain within 48 hours of ABI injection, while no patients in the exercise control group experienced this event (Pearson[204]). One trial reported

slightly fewer cases of local erythema, swelling, or nausea with PRP versus ESWT (0% vs. 16-21%) (Ozturan[202]), although the difference did not reach statistical significance due to small sample size; the same trial also reported arm tremor in one (5%) ESWT patient. One trial reported two cases (7%) of skin atrophy following ABI (but not steroid injection) (Dojode[68]) while a second trial reported no cases in either ABI or steroid injection group (Arik[14]). Otherwise, there were no adverse events in either group, including facial flushing, elbow stiffness, infection, neurovascular damage, tendon rupture, reflex sympathetic dystrophy, or post-injection flare.

Table 70. Tendinopathies: Harms and complications for PRP vs. conservative control

Adverse Event	RCT	Tendinopathy	Comparison	F/U*	PRP % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
Adverse events or complications (details not specified)	Mishra 2014	Elbow	PRP vs. LA	≤6 mos.	19% (22/116)	18% (20/114)	1.1 (0.6, 1.9)	NS
	Rha 2013	Rotator cuff	PRP vs. DN	≤6 mos.	0% (0/20)	0% (0/19)	NC	NS
	Dragoo 2014	Patellar	PRP+DN vs. DN	≤6 mos.	0% (0/10)	0% (0/13)	NC	NS
	Kearney 2013	Achilles	PRP vs. Exercise	≤6 mos.	0% (0/9)	0% (0/10)	NC	NS
	De Jonge 2011/De Vos 2010	Achilles	PRP vs. Saline	≤12 mos.	0% (0/27)	0% (0/27)	NC	NS
	Yadav 2015	Elbow	PRP vs. Steroid	≤3 mos.	0% (0/30)	0% (0/30)	NC	NS
	Behera 2015	Elbow	PRP vs. LA	≤12 mos.	0% (0/15)	0% (0/10)	NC	NS
	Stenhouse 2013	Elbow	PRP+DN vs. DN	≤6 mos.	0% (0/13)	0% (0/12)	NC	NS
Transient local (often inflammatory) pain	Kesikburun 2013	Rotator cuff	PRP vs. Saline	≤12 mos.	"occurred"	"occurred"	NC	NC
and/or discomfort (lasting a few days)	Vetrano 2013	Patellar	PRP vs. ESWT	≤12 mos.	13.0% (3/23)	NR	NC	NC
Worsening of pain because of the activation of the inflammation cycle (lasted 1-2 weeks)	Gosens 2011, Peerbooms 2010	Elbow	PRP vs. Steroid	≤0.5 mos.	2% (1/51)	NR	NC	NC
Persisting pain	Krogh 2013	Elbow	PRP vs. Steroid	≤12 mos.	20% (4/20)	5% (1/20)	4.0 (0.5, 32.7)	NS
Persisting pain	Krogh 2013	Elbow	PRP vs. Saline	≤12 mos.	20% (4/20)	15% (3/20)	1.3 (0.3, 5.2)	NS
Severe pain	Mishra 2014	Elbow	PRP vs. LA	4 days	1.7% (2/116)	0.0% (0/114)	NC	NS
Transient reddening of skin (without bruising) or	Vetrano 2013	Patellar	PRP vs. ESWT	≤12 mos.	NR	"occurred"	NC	NC
minor rash (resolved spontaneously)	Krogh 2013	Elbow	PRP vs. Steroid	≤12 mos.	0% (0/20)	5% (1/20)	0.0	NS
	Krogh 2013	Elbow	PRP vs. Saline	≤12 mos.	0% (0/20)	0% (0/20)	NC	NS

Adverse Event	RCT	Tendinopathy	Comparison	F/U*	PRP % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
Loss of pigmentation	Krogh 2013	Elbow	PRP vs. Steroid	≤12 mos.	0% (0/20)	5% (1/20)	0.0	NS
	Krogh 2013	Elbow	PRP vs. Saline	≤12 mos.	0% (0/20)	0% (0/20)	NC	NS
Reduced movement of the elbow	Krogh 2013	Elbow	PRP vs. Steroid	≤12 mos.	15% (3/20)	5% (1/20)	3.0 (0.3, 26.5)	NS
	Krogh 2013	Elbow	PRP vs. Saline	≤12 mos.	15% (3/20)	0% (0/20)	NC	NS
Infection	**Von Wehren 2015**	Rotator cuff	PRP vs. steroid	≤12 mos.	0% (0/25)	0% (0/25)	NC	NS
Skin atrophy	**Krogh 2013**	Elbow	PRP vs. Steroid	≤12 mos.	0% (0/20)	15% (3/20)	0.0	NS
	Krogh 2013	Elbow	PRP vs. Saline	≤12 mos.	0% (0/20)	0% (0/20)	NC	NS
Clinically relevant side effects	Vetrano 2013	Patellar	PRP vs. ESWT	≤12 mos.	0% (0/23)	0% (0/23)	NC	NS
"Device-related complications"	Vetrano 2013	Patellar	PRP vs. ESWT	≤12 mos.	0% (0/23)	0% (0/23)	NC	NS
Vague giddiness	Behera 2015	Elbow	PRP vs. LA	Peri-procedural	4% (1/25)		NC	NC
Adverse Event	**RCT**	**Tendinopathy**	**Comparator**	**F/U**	**PRP Mean ± SE**	**Control Mean ± SE**	**MD (95% CI)***	**p-value**
Pain associated with injection (NRS (0-10 (worst))	Krogh 2013	Elbow	PRP vs. Steroid	≤1 mos.	9.0 ± 0.2 (n = 20)	6.0 ± 0.7 (n = 20)	3.0 (1.5 to 4.5)	<0.05
Postinjection pain (VAS (0-5 (worst)), weeks	Krogh 2013	Elbow	PRP vs. Steroid	≤1 mos.	3.0 ± 0.4 (2-3 weeks) (n = 20)	1.0 ± 0.3 (<1 week) (n = 20)	-2.0 (-3.1 to -0.9)	<0.05
Adverse Event	**Cohort study**	**Tendinopathy**	**Comparison**	**F/U***	**PRP % (n/N)**	**Control % (n/N)**	**RR (95% CI)†**	**p-value†**
"Complications"	Ford 2015	Elbow	PRP vs. Steroid	Post-procedural	0% (0/28)	0% (0/50)	NC	NS
	Tetschke 2015	Elbow	PRP vs. Steroid	≤12 mos.	0% (0/26)	0% (0/26)	NC	NS
	Tonk 2014	Elbow	PRP vs. Steroid	≤12 mos.	0% (0/39)	0% (0/42)	NC	NS

CC: conservative care; CI: confidence interval; DN: dry needling; ESWT: extracorporeal shock wave therapy; f/u: follow up; LA: local anesthetic; MD: mean difference; NC: not calculable; NR: not reported; NRS: Numerical Rating Scale; NS: not statistically significant (p≥0.05); PRP: platelet rich plasma; RR: relative risk; VAS: Visual Analogue Scale

*If the timing of events was not specified, the full follow-up period of the study was assumed

†Calculated

Table 71. Tendinopathies: Harms and complications for ABI vs. conservative control

Adverse Event	RCT	Tendinopathy	Comparison	F/U*	ABI % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
Adverse events or complications (details not specified)	Bell 2013	Achilles	ABI vs. DN	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
	Kazemi 2010	Elbow	ABI vs. Steroid	≤2 mos.	0% (0/30)	0% (0/30)	NC	NC
Transient local (often inflammatory) pain and/or discomfort (lasting a few days)	Ozturan 2010	Elbow	ABI vs. ESWT	≤0.25 mos.	100% (18/18)	100% (19/19)	NC	NC
	Arik 2014	Elbow	ABI vs. Steroid	≤6 mos.	25% (10/40)	0% (0/40)	NC*	<0.01*
	Dojode 2012	Elbow	ABI vs. Steroid	<1 mo.	60% (18/30)	26% (8/30)	2.3 (1.2 to 4.4)*	<0.01*
	Ozturan 2010	Elbow	ABI vs. Steroid	≤0.25 mos.	100% (18/18)	100% (20/20)	NC	NC
Pain after second injection > 2 days	Ozturan 2010	Elbow	ABI vs. ESWT	≤12 mos.	6% (1/18)	NA	NC	NC
	Ozturan 2010	Elbow	ABI vs. Steroid	≤12 mos.	6% (1/18)	0% (0/20)	NC	NS
Severe worsening of pain	Pearson 2012	Achilles	ABI vs. Exercise	≤48 hours	21% (6/39)	NA	NC	NC
Facial flushing	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NC
Elbow stiffness	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NC
Erythema at the elbow	Ozturan 2010	Elbow	ABI vs. ESWT	≤12 mos.	0% (0/18)	21% (4/19)	0.0	0.0*
	Ozturan 2010	Elbow	ABI vs. Steroid	≤12 mos.	0% (0/18)	0% (0/20)	NC	NC
Swelling at the elbow	Ozturan 2010	Elbow	ABI vs. ESWT	≤12 mos.	0% (0/18)	16% (2/19)	0.0*	NS*
	Ozturan 2010	Elbow	ABI vs. Steroid	≤12 mos.	0% (0/18)	0% (0/20)	NC	NC
Infection	Arik 2014	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/40)	0% (0/40)	NC	NC
	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NC
Skin atrophy	Arik 2014	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/40)	0% (0/40)	NC	NC
	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	7% (2/30)	0% (0/30)	NC*	NS*
Tendon rupture	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NC
	Arik 2014	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/40)	0% (0/40)	NC	NC
Nausea	Ozturan 2010	Elbow	ABI vs. ESWT	≤12 mos.	0% (0/18)	21% (4/19)	0.0*	0.04*
	Ozturan 2010	Elbow	ABI vs. Steroid	≤12 mos.	0% (0/18)	0% (0/20)	NC	NC

Adverse Event	RCT	Tendinopathy	Comparison	F/U*	ABI % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
Neurovascular damage	Arik 2014	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/40)	0% (0/40)	NC	NC
	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NC
Tremor in the arm	Ozturan 2010	Elbow	ABI vs. ESWT	≤12 mos.	0% (0/18)	5% (1/19)	0.0*	NS*
	Ozturan 2010	Elbow	ABI vs. Steroid	≤12 mos.	0% (0/18)	0% (0/20)	NC	NC
Reflex sympathetic dystrophy	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NC
Post-injection flare	Dojode 2012	Elbow	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NC

ABI: autologous blood injection; CC: conservative care; CI: confidence interval; DN: dry needling; ESWT: extracorporeal shock wave therapy; f/u: follow up; NA: not applicable; NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05); RR: relative risk

*If the timing of events was not specified, the full follow-up period of the study was assumed

†Calculated

4.2.3. Plantar Fasciitis

PRP vs. Conservative Control: Adverse events were reported by four RCTs (Chew[43], Jain[114], Kim[135], Tiwari[277]) and two cohort studies (Aksahin[7], Say[245]) that compared PRP to a conservative control for treatment of plantar fasciitis. Control groups included steroid injection as well as extracorporeal shock wave therapy (ESWT). All adverse events reported are summarized in Table 72. Three trials (Chew[43], Jain[114], Kim[135]) indicated that no complications or adverse events occurred (no details specified), and one trial (Tiwari[277]) reported no cases of soft tissue injection, osteomyelitis, loss of function, or stiffness in either injection group. The two cohort studies reported no cases of adverse events (Aksahin[7], Say[245]).

PRP vs. Conservative Control: Adverse events were reported by two RCTs (Kalaci[123], Lee[153]) that compared ABI to a conservative control for treatment of plantar fasciitis. Control groups included steroid injection as well as anesthetic injection plus dry needling. All adverse events reported are summarized in Table 72. One trial (Lee[153]) reported that significantly more PRP versus steroid injection patients experienced post-injection pain that required analgesia and/or ice (53% vs. 13%, RR 4.1 (95% CI 1.5, 10.9)). Otherwise, there were no adverse events in either group, including infection, plantar fascia rupture, fat pad atrophy, skin hypopigmentation, or hematoma.

Table 72. Plantar Fasciitis: Harms and complications for PRP or ABI vs. conservative control

Adverse Event	RCT	Comparison	F/U*	PRP % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
Adverse events or complications (details not specified)	Chew 2013	PRP+CC vs. CC alone	≤6 mos.	0% (0/19)	0% (0/16)	NC	NS
	Jain 2015	PRP vs. Steroid	≤12 mos.	0% (0/30 heels)	0% (0/30 heels)	NC	NS
	Kim 2014	PRP vs. Prolotherapy	≤6.5 mos.	0% (0/9)	0% (0/11)	NC	NS
	Chew 2013	PRP+CC vs. ESWT+CC	≤6 mos.	0% (0/19)	0% (0/16)	NC	NS
Soft tissue infection	Tiwari 2013	PRP vs. Steroid	≤12 mos.	0% (0/30)	0% (0/30)	NC	NS
Osteomyelitis	Tiwari 2013	PRP vs. Steroid	≤12 mos.	0% (0/30)	0% (0/30)	NC	NS
Loss of function	Tiwari 2013	PRP vs. Steroid	≤12 mos.	0% (0/30)	0% (0/30)	NC	NS
Stiffness	Tiwari 2013	PRP vs. Steroid	≤12 mos.	0% (0/30)	0% (0/30)	NC	NS
Adverse Event	**Cohort study**	**Comparison**	**F/U***	**PRP % (n/N)**	**Control % (n/N)**	**RR (95% CI)†**	**p-value†**
Procedure-related adverse events‡	Aksahin 2012	PRP vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NS
Local or systemic complications‡	Say 2014	PRP vs. Steroid	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
Adverse Event	**RCT**	**Comparison**	**F/U***	**ABI % (n/N)**	**Control % (n/N)**	**RR (95% CI)†**	**p-value†**
Infection	Kalaci 2009	ABI vs. Steroid	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
	Lee 2007	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NS

Adverse Event	RCT	Comparison	F/U*	PRP % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
	Kalaci 2009	ABI vs. Anesthetic+DN	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
Rupture of the plantar fascia	Kalaci 2009	ABI vs. Steroid	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
	Lee 2007	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NS
	Kalaci 2009	ABI vs. Anesthetic+DN	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
Post-injection pain§ requiring analgesia, ice, or both	Lee 2007	ABI vs. Steroid	Peri-procedural	53% (16/30)§	13% (4/31)§	4.1 (1.5, 10.9)	<0.01
Fat pad atrophy	Lee 2007	ABI vs. Steroid	≤6 mos.	0% (0/30)	0% (0/30)	NC	NS
Hypopigmentation of the skin	Kalaci 2009	ABI vs. Steroid	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
	Kalaci 2009	ABI vs. Anesthetic+DN	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
Hematoma	Kalaci 2009	ABI vs. Steroid	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS
	Kalaci 2009	ABI vs. Anesthetic+DN	≤6 mos.	0% (0/25)	0% (0/25)	NC	NS

ABI: autologous blood injection; CC: conservative care; CI: confidence interval; DN: dry needling; ESWT: extracorporeal shock wave therapy; f/u: follow up; NC: not calculable; NS: not statistically significant (p≥0.05); PRP: platelet rich plasma; RR: relative risk

*If the timing of events was not specified, the full follow-up period of the study was assumed

†Calculated

‡Authors stated that no complications occurred in either group.

§Mean duration of pain was 7 (range 2 to 10) days in the autologous blood group and 5 (range 2 to 7) days in the steroid group.

4.2.4. Acute Injuries

Acute muscle injuries, PRP vs. conservative control: Three RCTs (Hamid[98], Hamilton[100], Reurink[220]) reported adverse events following PRP plus CC versus CC alone or with a saline injection for the treatment of acute injuries to the thigh (primarily hamstring), foot/ankle, and shoulder muscles (Table 73). All three trials reported that "no serious adverse events" (not further specified) occurred in either group. Painful dermal hyperaesthesia was reported in one PRP patient (3% vs. 0%, p=NS) (Reurink[220]) and another trial mentioned that "most patients" complained of pain during blood draw and PRP injection (Hamid[98]).

Acute Achilles tendon rupture, PRP vs. conservative control: One cohort study (Kaniki[125]) reported similar incidence of repeat tendon rupture within three months of treatment with PRP or CC (3% vs. 4%, OR 0.65 (95% CI 0.1, 4.0)); of these patients, one in the PRP group and two in the CC group underwent surgical repair while the remaining two patients (one in each group) continued with nonoperative protocol. No other major complications such as superficial and deep infection, venous thrombosis, pulmonary embolus, and numbness, were reported (Table 73).

Table 73. Acute Injury: Harms and complications for PRP vs. conservative control

Adverse Event	Diagnosis	Study	Comparison	F/U **	PRP % (n/N)	Control % (n/N)	RR (95% CI)*	p-value*
Any major adverse event (not usually specified)	Achilles tendon rupture	Kaniki 2014	PRP vs. CC	≤24 mos.	0% (0/73)†	0% (0/72)†	NC	NS
	Muscle injury	Hamid 2014	PRP+CC vs. CC	≤2.5 mos.	0% (0/14)	0% (0/14)	NC	NS
		Hamilton 2015	PRP+CC vs. CC	≤6 mos.	0% (0/26)	0% (0/29)	NC	NS
		Reurink 2015	PRP+CC vs. Saline+CC	≤12 mos.	0% (0/37)	0% (0/37)	NC	NS
Repeated tendon rupture	Achilles tendon rupture	Kaniki 2014	PRP vs. CC	≤3 mos.	2.7% (2/73)‡	4.2% (3/72)‡	OR 0.65 (0.11 to 4.00)§	NS§
Pain during blood draw and PRP injection	Muscle injury	Hamid 2014	PRP vs. CC	≤2.5 mos.	"most patients"	NA	NC	NC
Painful dermal hyper-aesthesia	Muscle injury	Reurink 2015	PRP+CC vs. Saline+CC	≤12 mos.	2.7% (1/37)	0% (0/37)	NC	NS

CC: conservative care; CI: confidence interval; f/u: follow up; NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05); PRP: platelet rich plasma; RR: relative risk

*Calculated unless otherwise indicated.

†Authors state in the discussion that "no major complications occurred in either group"; in the methods authors state *a priori* that they were assessing patients for the following complications at all follow-up visits: superficial and deep infection, venous thrombosis, pulmonary embolus, and numbness

‡PRP group: 1 patient underwent surgical repair and 1 patient continued with nonoperative protocol; CC group: 2 patients underwent surgical repair and 1 patient continued with nonoperative protocol.

§As reported by the study.

**If the timing of events was not specified, the full follow-up period of the study was assumed

4.2.5. Osteochondral Lesions of the Talus

PRP vs. HA: One quasi-randomized trial (Mei-Dan 2010[180]) in which PRP was compared to hyaluronic acid (HA) injections for the treatment of osteochondral lesions of the talus reported adverse events (Table 74). No infections occurred in either group. One patient in the PRP group (7%) complained of acute mild pain following injection compared with no patients in the HA group (p=0.30). Significantly more PRP patients had new symptoms of mild plantar fasciitis compared with HA patients (29% vs. 0%, p=0.03), though the time frame was not clear. In addition, one PRP patient developed new Achilles tendinopathy by seven-month follow-up compared with no patients in the HA group (7% vs. 0%, p=NS).

Table 74. Osteochondral Lesions of the Talus: Harms and complications for PRP vs. HA

Study	Adverse Event	F/U*	PRP % (n/N)	HA % (n/N)	RR (95% CI)†	p-value†
Mei-Dan 2012	Acute mild pain following injection	Peri-procedural	7% (1/14)	0% (0/15)	NC	NS
	New symptoms—mild plantar fasciitis	NR ("after treatment")	29% (4/14)	0% (0/15)	NC	0.03
	New symptoms—Achilles tendinopathy	7 mos.	7% (1/14)	0% (0/15)	NC	NS
	Infection	NR	0% (0/14)	0% (0/15)	NC	NC

CI: confidence interval; f/u: follow up; HA: hyaluronic acid; NC: not calculable; NR: not reported; NS: not statistically significant; PRP: platelet rich plasma; RR: relative risk

*If the timing of events was not specified, the full follow-up period of the study was assumed

†Calculated

4.2.6. TMJ Dislocation

ABI vs. intermaxillary fixation (IMF): One trial compared ABI with IMF for the treatment of TMJ dislocation (Hegab 2013[104]). The trial reported no major complications (not further specified) following ABI but reported no information for the IMF group. Over 12 months of follow-up, patients who received IMF complained of weight loss due to their restricted diet and those who had IMF with eyelet wiring versus with orthodontic braces developed marginal gingivitis; the percentage of patients with these complications was not reported.

4.2.7. Osteoarthritis

Harms, complications and adverse events related to PRP use were poorly reported across included studies of patients with osteoarthritis. No serious procedure-related adverse events were identified in studies reporting on harms and complications. Study sample sizes were small.

Knee OA, PRP vs. HA: Three trials (Filardo[80], Sanchez 2012[242], Vaquerizo[281]) and two cohort studies (Say[246], Spakova[260]) comparing PRP with HA in knee osteoarthritis patients provided data on harms or complications (Table 75). All five studies reported that all treatment-related complications were mild and resolved; no serious treatment-related adverse events were identified. Injection-related pain and swelling were most commonly described. Across trials, no differences between treatments were seen for injection pain and/or swelling which were reported in 0% to 17% of PRP and 0% to 14% of HA recipients. The cohort studies (reported pain and/or swelling in the PRP group only, ranging from 10% to 18% (Say[246], Spakova[260]). One trial (Filardo[80]) reported higher median pain intensity (VAS pain (0-10 scale) x days duration) with PRP (median 9, IQR 0-20) versus HA (median 1, IQR 0-7) and higher median swelling intensity (VAS (0-10 scale) x days duration) with PRP (median 6, IQR 0, 16) versus HA (median 1, IRQ 0-4); no tests of significance were reported. The same trial[80] reported withdrawal of two patients in the HA group secondary to severe pain and swelling. One trial reported pseudoseptic reactions in 0% of PRP and 5% of HA recipients (Vaquerizo[281]). One trial reported treatment-related low back pain and headache (one patient each) following HA injection but none in the PRP group (Sanchez 2012[242]). One trial (Cerza[39]) and one cohort study (Kon[141]) reported that no adverse events or complications occurred at any time; data and definitions were not provided.

Knee OA, PRP vs. Saline: One trial (Patel[203]) evaluated PRP versus saline injections for the treatment of knee OA (Table 75). The study reported pain and stiffness lasting at least 2 days in 14% of PRP recipients but provided no data for HA. Systematic adverse events (syncope, headache, nausea, gastritis, sweating, and tachycardia) were reported in significantly more PRP than saline recipients (33% vs. 0%). No serious treatment-related adverse events were identified.

Knee OA, PRP vs. Exercise (±TENS): Two trials compared PRP (alone or with exercise) to exercise (alone or with TENS) for the treatment of knee OA (Angoorani[10], Rayengani[218]) (Table 75). One trial (Angoorani[10]) reported mild pain and swelling in insignificantly more PRP plus exercise versus TENS plus exercise recipients (11% vs. 4%, RR 3.0 (95% CI 0.3, 27.1)). Another trial (Rayengani[218]), noted no significant complications were observed in either the PRP or exercise groups; only transient local pain and swelling following injection were described but no data were provided.

Hip OA, PRP vs. HA: One trial comparing PRP to HA injections for hip OA (Battaglia[17]) reported no serious adverse events for either group; no statistical difference was seen between treatments regarding moderate pain during or after treatment (20% vs. 12%) (Table 75).

TMJ OA, PRP vs. HA: One trial evaluated the impact of PRP versus HA injections for OA of the temporomandibular joint (TMJ) (Battaglia[17]) (Table 75): more PRP recipients experienced injection pain (88% vs. 60%, RR 1.46 (95% CI 1.03, 2.08)) and post-intervention discomfort (76% vs. 32%, RR 2.37 (95% CI 1.28, 4.38)) compared with those who received HA injections.

Table 75. Osteoarthritis (Knee, TMJ, Hip): Harms and complications for PRP vs. Control

Adverse Event	Study	OA Location	Comparison	F/U*	PRP % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
Pain and/or swelling possibly or likely related to treatment (based on author's categorization)								
Categorical outcomes								
Postinjective pain reaction	Vaquerizo 2013	Knee	PRP vs. HA	12 mos.	17% (8/48)	14% (6/42)	1.2 (0.4 to 3.1)	NS
Severe pain, swelling; study withdrawal	Filardo 2015	Knee	PRP vs. HA	After first HA injection	0% (0/89)	2% (2/96)	0.0 (NC)	NS
Pain and mild swelling	Say 2013 (observational)	Knee	PRP vs. HA	After injection	18% (8/45)	NR	NC	NS
Temporary mild worsening of knee joint pain	Spakova 2012 (observational)	Knee	PRP vs. HA	After injection	10% (6/60)	NR	NC	NS
Pain after 3rd injection	Sanchez 2012	Knee	PRP vs. HA	6 mos.	1% (1/89)	0% (0/87)	NC	NS
Low Back Pain	Sanchez 2012	Knee	PRP vs. HA	6 mos.	0% (0/89)	1% (1/87)	0.0 (NC)	NS
Headache	Sanchez 2012	Knee	PRP vs. HA	6 mos.	0% (0/89)	1% (1/87)	0.0 (NC)	NS
Pain and stiffness lasting ≥2 days	Patel 2013‡	Knee	PRP vs. Saline	6 mos.	13.5% (7/52)	NR	NC	NC
Mild pain and swelling	Angoorani 2015	Knee	PRP vs. Exercise + TENS	2 mos.	11% (3/27)	4% (1/27)	3.0 (0.3 to 27.1)	NS
Pain during injection	Hegab 2015	TMJ	PRP vs. HA	Time of injection	88% (22/25)	60% (15/25)	1.46 (1.03 to 2.08)	0.02
Post-operative discomfort	Hegab 2015	TMJ	PRP vs. HA	12 mos.	76% (19/25)	32% (8/25)	2.37 (1.28 to 4.38)	<0.01
Moderate pain during or after treatment	Battaglia 2013	Hip	PRP vs. HA	12 mos.	20% (10/50)	12% (6/50)	1.6 (0.65 to 4.23)	NS
Continuous outcomes					**Median (IQR)**	**Median (IQR)**	**Effect size**	**p-value**
Post-injection pain (0-10 scale (worst)) x Duration §	Filardo 2015	Knee	PRP vs. HA	12 mos.	9 (0 to 20) (n = 94)	1 (0 to 7) (n = 89)	NR	NR
Post-injection swelling (0-10 scale (worst)) x Duration§	Filardo 2015	Knee	PRP vs. HA	12 mos.	6 (0 to 16) (n = 94)	1 (0 to 4) (n = 89)	NR	NR

Adverse Event	Study	OA Location	Comparison	F/U*	PRP % (n/N)	Control % (n/N)	RR (95% CI)†	p-value†
Other Events possibly or likely related to treatment								
Pseudoseptic reactions	Vaquerizo 2013	Knee	PRP vs. HA	12 mos.	0% (0/48)	5% (2/42)	NC	NS
Systemic adverse effects (syncope, headache, nausea, gastritis, sweating, tachycardia)	Patel 2013‡	Knee	PRP vs. Saline	6 mos.	33% (17/52)	0% (0/26)	NC	<0.01
Adverse effects during the second PRP injection (not specified)	Patel 2013‡	Knee	PRP vs. Saline	Time of injection	20% (5/25)	NA	NC	NC
Events not likely related to treatment								
Serious adverse events: Knee and hip pain (HA); Knee trauma (PRP)	Sanchez 2012	Knee	PRP vs. HA	6 mos.	1% (1/89)	1% (1/87)	0.98 (0.06 to 15.4)	NS
Knee pain**	Sanchez 2012	Knee	PRP vs. HA	6 mos.	8% (7/89)	2% (2/87)	3.4 (0.73 to 16.0)	NS
Back pain††	Sanchez 2012	Knee	PRP vs. HA	6 mos.	5% (4/89)	7% (6/87)	0.65 (0.2 to 2.2)	NS
Other adverse events likely not related to treatment‡‡	Sanchez 2012	Knee	PRP vs. HA	6 mos.	18% (16/89)	15% (13/87)	1.20 (0.6 to 2.4)	NS

CI: confidence interval; f/u: follow up; HA: hyaluronic acid; IQR: interquartile range; NC: not calculable; NR: not reported; NS: not statistically significant; PRP: platelet rich plasma; RR: relative risk; TMJ: temporomandibular joint

*If the timing of events was not specified, the full follow-up period of the study was assumed

†Calculated

‡Patel 2013: Two PRP injection groups were combined to create a single PRP group. One PRP group received one injection, the other received two; the saline group received a single injection

§Filardo 2015: Estimated from author Figure 3; mean post-injection pain, swelling (on a 0-10 visual analog scale) multiplied by the mean duration of the episode (in days); determination of VAS for swelling not described.

**Sanchez 2012: Comprised of acute knee pain, left/right knee pain, and other knee pain; authors do not specify if these were treated knees.

††Sanchez 2012: Comprised of sciatica, back pain, and low back pain not reported in other categories.

‡‡Sanchez 2012: Events not classified in other outcomes categories; Comprised of febrile syndrome, left knee surgery, abdominal pain and dizziness, toothache, flu, trauma, toothache, ankle sprain, renal colic, bronchitis, neck pain, itching on both outer thighs, dizziness, left hip pain, contracture lumbar, urine infection, headache, shoulder pain, left knee contusion, right shoulder pain, cold, and coxalgia.

4.3. Key Question 3: Differential Efficacy and Harms in Subpopulations

4.3.1. Number of studies retained

For this key question, RCTs that stratified on patient characteristics of interest, permitting evaluation of effect modification were considered for inclusion. Subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. All RCTs included to evaluate the efficacy or safety of PRP or ABI versus comparators of interest were assessed.

Summary of results:
In general, there was very little reporting of differential efficacy and safety; all evidence that was identified was of insufficient quality to draw firm conclusions.

4.3.2. Tendinopathies, Plantar Fasciitis, Acute Injuries, Osteochondral Lesion of the Talus, TMJ Dislocation, TMJ Osteoarthritis

Studies included
No trials of tendinopathy, plantar fasciitis, acute injury, osteochondral lesion of the talus, TMJ dislocation, or TMJ osteoarthritis provided and data (or conclusions) on differential efficacy or harms between PRP/ABI and a control group for any subgroups.

4.3.3. Knee Osteoarthritis

Studies included
One small trial reported subgroup analyses (Gormeli[95]) for PRP versus HA injections as well as PRP versus saline injections, however no formal evaluation of differential efficacy via test for interaction was reported. Authors do not state if subgroup analysis was planned *a priori* or conducted post hoc.

PRP vs. HA: Based on Spectrum's calculation of effect sizes and evaluation of the extent to which subgroup confidence intervals overlapped, stage of OA may modify the effect of treatment, such that PRP patients with early OA reported better function as evaluated by the patient-reported IKDC measure as well as better quality of life as evaluated by the patient-reported EQ-VAS scale compared with those with advanced OA following PRP (Table 76). This is based on the observation that the MD estimates are different for the early and advanced OA groups and there is little or no overlap in the confidence intervals, suggesting that these groups may respond differently. Future studies are needed to confirm and explore this further.

PRP vs. Saline: Based on Spectrum's calculation of effect sizes and evaluation of the extent to which subgroup confidence intervals overlapped, stage of OA may modify the effect of treatment, such that PRP patients with early OA reported better function as evaluated by the patient-reported IKDC measure as well as better quality of life as evaluated by the patient-reported EQ-VAS scale compared with those with advanced OA following PRP (Table 77). This is based on the observation that the MD estimates are different for the early and advanced OA groups and there is little or no overlap in the confidence intervals, suggesting that these groups may respond differently. Future studies are needed to confirm and explore this further.

Table 76. Knee OA: Differential Efficacy for PRP vs. HA

RCT	F/U	Outcome, F/U	Subgroup	PRP* Mean ± SD	HA Mean ± SD	MD (95% CI)†	p-value†
Gormeli 2015	6 mos.	**IKDC** (0-100 (best))	Early OA	59.7 ± 6.0 (n=56)	50.7 ± 5.6 (n=25)	9.6 (6.8, 12.4)	<0.01†
			Advanced OA	47.1 ± 4.4 (n=27)	44.4 ± 5.3 (n=14)	2.7 (-0.5, 5.8)	NS†
		Quality of life (EQ-VAS) (0-100 (best))	Early OA	71.5 ± 5.3 (n=56)	64.0 ± 6.0 (n=25)	7.5 (4.8, 10.1)	<0.01†
			Advanced OA	57.1 ± 4.64 (n=27)	55.1 ± 5.4 (n=14)	2.0 (-1.3, 5.3)	NS†

EQ-VAS: EuroQol visual analog scale; f/u: follow-up; IKDC: International Knee Documentation Committee Subjective Knee Form; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

*Gormeli 2015: Two PRP groups were combined (3 vs. 1 PRP injection) to create a single PRP group.

†Calculated by Spectrum Research, Inc. to compare effect sizes and overlap of confidence intervals for early and advanced OA groups.

Table 77. Knee OA: Differential Efficacy for PRP vs. Saline

RCT	F/U	Outcome, F/U	Subgroup	PRP* Mean ± SD	HA Mean ± SD	MD (95% CI)†	p-value†
Gormeli 2015	6 mos.	**IKDC** (0-100 (best))	Early OA	59.7 ± 6.0 (n=56)	36.6 ± 5.4 (n=27)	23.1 (20.4, 25.7)	<0.01†
			Advanced OA	47.1 ± 4.4 (n=27)	36.3 ± 3.5 (n=13)	10.8 (7.9, 13.6)	<0.01†
		Quality of life (EQ-VAS) (0-100 (best))	Early OA	71.5 ± 5.3 (n=56)	48.4 ± 5.1 (n=27)	23.1 (20.6, 25.5)	<0.01†
			Advanced OA	57.1 ± 4.64 (n=27)	47.2 ± 5.0 (n=13)	9.9 (6.6, 13.2)	<0.01†

EQ-VAS: EuroQol visual analog scale; f/u: follow-up; IKDC: International Knee Documentation Committee Subjective Knee Form; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

*Gormeli 2015: Two PRP groups were combined (3 vs. 1 PRP injection) to create a single PRP group.

†Calculated by Spectrum Research, Inc. to compare effect sizes and overlap of confidence intervals for early and advanced OA groups.

4.3.4. Hip Osteoarthritis

One trial reported subgroup analyses by Kellgren- Lawrence OA Grade but did not formally evaluate differential effectiveness or safety; no test for interaction was performed. Authors do not state if subgroup analysis was planned *a priori* or conducted post hoc. Based on Spectrum's calculation of effect sizes and evaluation of overlap of confidence intervals, stage of OA does not appear to modify treatment effect; however, it is unlikely that this trial was sufficiently powered to evaluate this.

4.4. Key Question 4: Cost effectiveness

4.4.1. Number of studies retained

No formal economic analyses were identified that met the inclusion criteria.

5. Strength of Evidence (SoE) Summary Tables

The following summaries of evidence have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by comparator. Details of other outcomes are available in the report.

5.1. Strength of Evidence Summary: Elbow Epicondylitis Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Elbow Epicondylitis: PRP vs. ABI									
Function success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Function (various measures)	Short-term	4 RCTs (Creaney, Raeissadat 2014a, Raeissadat 2014b, Thanasas)	N= 260	Yes[1] (-1)	No	No	Yes[3] (-1)	SMD 0.31 (95% CI 0.06, 0.56) Conclusion: Significantly greater improvement with PRP vs. ABI as evaluated by PRTEE, MMCPIE, and Liverpool elbow score.	⊕⊕○○ LOW
	Intermediate-term	3 RCTs (Creaney, Raeissadat 2014a, Thanasas)	N= 220	Yes[1] (-1)	No	No	Yes[3] (-1)	SMD 0.48 (95% CI 0.21, 0.75) Conclusion: Significantly greater improvement with PRP vs. ABI as evaluated by PRTEE, MMCPIE, and Liverpool elbow score.	⊕⊕○○ LOW
	Long-term	1 RCT (Raeissadat 2014a)	N= 61	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	MD 5.0 (95% CI -4.2, 14.2) Conclusion: No difference between groups, however insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
Pain success (≥25 VAS improve-ment)	Short-term	1 RCT (Raeissadat 2014a)	N= 61	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	RR 1.0 (95% CI 0.7, 1.4) Conclusion: No difference between groups, however insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Raeissadat 2014a)	N= 61	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	RR 1.1 (95% CI 0.8, 1.4) Conclusion: No difference between groups, however insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	Long-term	1 RCT (Raeissadat 2014a)	N= 61	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	RR 1.2 (95% CI 0.9, 1.8) Conclusion: No difference between groups, however insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain (VAS (0-10) worst))	Short-term	3 RCTs (Raeissadat 2014a, Raeissadat 2014b, Thanasas)	N= 130	Yes[1] (-1)	No	No	Yes[3] (-1)	WMD -0.8 (95% CI -1.3, -0.2) Conclusion: Significantly greater improvement with PRP vs. ABI in VAS pain.	⊕⊕◯◯ LOW
	Intermediate-term	2 RCTs (Raeissadat 2014a, Thanasas)	N= 90	Yes[1] (-1)	No	No	Yes[3] (-1)	WMD -0.6 (95% CI -1.4, 0.1) Conclusion: No difference between groups.	⊕⊕◯◯ LOW
	Long-term	1 RCT (Raeissadat 2014a)	N= 61	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	MD -0.6 (95% CI -1.8, 0.6) Conclusion: No difference between groups, however insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Elbow Epicondylitis: PRP vs. Control*									
Function Success (various measures)	Short-term	1 RCT (Lebiedzinski)	N=99	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	RR 1.0 (95% CI 0.7, 1.4) Conclusion: No difference between PRP and steroid groups in the achievement of "very good" DASH scores (i.e., scores 0-25 on 0-100 scale).	⊕⊕◯◯ LOW
	Intermediate-term	1 RCT (Lebiedzinski)	N=99	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	RR 1.0 (95% CI 0.8, 1.3) Conclusion: No difference between PRP and steroid groups in the achievement of "very good" DASH scores (i.e., scores 0-25 on 0-100 scale).	⊕⊕◯◯ LOW
	Long-term	2 RCTs (Gosens, Lebiedzinski)	N=199	Yes[1] (-1)	Yes[2] (-1)	No	Yes[3] (-1)	Conclusion: Insufficient results preclude firm conclusions, though results were inconsistent for PRP vs. steroid: • ≥25% reduction in DASH scores + no re-intervention: 73% vs. 39% (RR 1.9 (95% CI 1.3, 2.8), 1 RCT (N=100) (Lebiedzinski) • "Very good" DASH scores (i.e., scores 0-25	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								on 0-100 scale): 81% vs. 78% (RR 1.0 (95% CI 0.8, 1.3)), 1 RCT (N=99) (Gosens)	
Function (various measures)	Short-term	7 RCTs (Gautam, Krogh, Gosens, Lebiedzinski, Yadav, Behera, Mishra)	N=545	Yes[1] (-1)	Yes[2] (-1)	No	Yes[3] (-1)	Conclusion: Insufficient strength of evidence precludes firm conclusions. However, there appeared to be no difference between groups as evaluated by: • DASH, MMCPIE, ΔPRTEE disability: WMD -2.35 (95% CI -6.27, 1.58), 7 RCTs (N=545) (Gautam, Krogh, Gosens, Lebiedzinski, Yadav, Behera, Mishra) One trial included in the pooled analysis reported two additional functional outcomes: • No difference in MMCPIE: MD 0.6 (95% CI -1.6, 2.8), 1 RCT (N=30) (Gautam); • Better Oxford Elbow Scores in control (steroid) group: MD -2.4 (95% CI -4.6, -0.2), 1 RCT (N=30) (Gautam)	⨁◯◯◯ INSUFFICIENT
	Intermediate-term	5 RCTs (Gautam, Gosens, Lebiedzinski, Behera, Mishra)	N=372	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Significantly greater improvement with PRP vs. control as evaluated by: • DASH, MMCPIE, PRTEE: WMD -7.67 (95% CI –11.67, -3.67), 5 RCTs (N=372) (Gautam, Gosens, Lebiedzinski, Behera, Mishra) One trial included in the pooled analysis reported similar results with two additional functional outcomes: • Oxford Elbow Score: MD 4.9 (95% CI 1.5, 8.4), 1 RCT (N=30) (Gautam) • MMCPIE: MD 9.2 (95% CI 5.2, 12.7), 1 RCT (N=30) (Gautam)	⨁⨁◯◯ LOW
	Long-term	3 RCTs (Gosens, Lebiedzinski, Beher)	N=223	Yes[1] (-1)	No	No	Yes[3] (-1)	WMD -14.1 (95% CI -22.8, -12.3) Conclusion: Significantly greater improvement with PRP vs. control as evaluated by the DASH and MMCPIE outcome measures.	⨁⨁◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Pain Success (various measures)	Short-term	1 RCT (Mishra)	N=192	Yes[1] (-1)	Unknown	No	Yes[4] (-1)	RR 1.1 (95% CI 0.9, 1.4) Conclusion: No difference between groups in the percentage of patients achieving a ≥25% decrease in VAS scores (75% vs. 66%).	⊕⊕◯◯ LOW
	Intermediate-term	1 RCT (Mishra)	N=119	Yes[1] (-1)	Unknown	No	Yes[4] (-1)	RR 1.2 (95% CI 1.2, 2.6) Conclusion: Significantly more PRP vs. steroid patients achieved a ≥50% decrease in VAS scores (82% vs. 60%).	⊕⊕◯◯ LOW
	Long-term	1 RCT (Gosens)	N=100	Yes[1] (-1)	Unknown	No	Yes[4] (-1)	RR 0.2 (95% CI 0.05, 0.9) Conclusion: Significantly more PRP vs. steroid patients achieved a ≥25% decrease in VAS scores without re-intervention (77% vs. 43%).	⊕⊕◯◯ LOW
Pain (various measures)	Short-term	7 RCTs (Gautam, Gosens, Krogh, Behera, Stenhouse, Mishra, Yadav)	N=471	Yes[1] (-1)	No	No	No	Conclusion: No difference between groups (regardless of control treatment) as evaluated by: • VAS or PRTEE pain: SMD 0.02 (95% CI -0.22, 0.25), 6 RCTs (N=279) (Gautam, Gosens, Krogh, Yadav, Behera, Stenhouse) • VAS pain (% improvement): 55% vs. 47% (MD NR/NC, p=NS‡), 1 RCT (N=192) (Mishra) • Activity-related pain (Nirschl): SMD -0.29 (95% CI -0.86, 0.29), 2 RCTs (N=49) (Behera, Stenhouse)	⊕⊕⊕◯ MODERATE
	Intermediate-term (PRP vs. steroid or LA)	3 RCTs (Gautam, Gosens, Behera)	N=154	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Overall, there was significantly greater improvement with PRP vs. steroid or LA: • VAS pain: SMD -1.17 (95% CI -1.71, -0.62), 3 RCTs (N=154) (Gautam, Gosens, Behera) • VAS pain (% improvement) (for PRP vs. steroid): 72% vs. 56% (MD NR/NC, p=NS‡), 1 RCT (N=119) (Mishra) • Activity-related pain (Nirschl): SMD -2.06 (95% CI -3.10, -1.02), 1 RCT (N=24) (Behera)	⊕⊕◯◯ LOW
	Intermediate-term (PRP +	1 RCT (Behera)	N=25	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	Conclusion: Although insufficient strength of evidence prevents firm conclusions, there	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	DN vs. DN)							was no difference between groups as evaluated by: • VAS pain: SMD -0.09 (95% CI -0.88, 0.69) • Activity-related pain (Nirschl): SMD -0.22 (95% CI -1.01, 0.57)	
	Long-term	2 RCTs (Gosens, Behera)	N=124	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Significantly greater improvement with PRP: • vs. steroid as evaluated by VAS: SMD -0.76 (95% CI -1.17, -0.36), 1 RCT, (N=100) (Gosens) • vs. LA as evaluated by VAS: SMD -2.09 (95% CI -3.14, -1.04), 1 RCT (N=24) (Behera) • vs. LA as evaluated by activity-related pain (Nirschl): SMD -1.66 (95% CI -2.64, -0.69), 1 RCT (N=24) (Behera)	⊕⊕◯◯ LOW
Elbow Epicondylitis: ABI vs. Control†									
Function success	Any	0 RCTs						No evidence.	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	3 RCTs (Arik, Singh, Kazemi), 1 quasi-RCT (Ozturan)	N= 238	Yes[1] (-1)	No	No	Yes[3] (-1)	SMD -0.87 (95% CI -1.41, -0.33), I^2 = 74% Conclusion: Significantly greater improvement with ABI vs. steroid as evaluated by PRTEE, qDASH, and Upper Extremity Functional Scale.	⊕⊕◯◯ LOW
	Intermediate-term	1 quasi-RCT (Ozturan)	N= 37-38	Yes[1,5] (-2)	Unknown	No	Yes[3,6] (-2)	ABI vs. steroid: MD -6.4 (95% CI -11.9, -0.9) ABI vs. ESWT: MD 1.5 (95% CI -4.4, 7.4) Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 quasi-RCT (Ozturan)	N= 37-38	Yes[1,5] (-2)	Unknown	No	Yes[3,6] (-2)	ABI vs. steroid: MD -8.9 (95% CI -15.1, -2.7) ABI vs. ESWT: MD -0.9 (95% CI -6.1, 4.3) Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain (various	Short-term	3 RCTs (Arik, Singh, Kazemi),	N= 250	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Significantly greater improvement with ABI vs. steroid as	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
measures)		1 quasi-RCT (Ozturan)						evaluated by: • VAS pain: SMD -0.8 (95% CI -1.2, -0.5), 4 RCTs (N=250) • Activity-related pain (Nirschl): SMD -0.8 (95% CI -1.2, -0.1), 3 RCTs (N=170) (Dojode, Jindal, Kazemi)	
	Intermediate-term	2 RCTs (Dojode, Arik)	N= 140	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Significantly greater improvement with ABI vs. steroid as evaluated by: • VAS pain: SMD -0.8 (95% CI -1.2, -0.5), 2 RCTs (N=140) • Activity-related pain (Nirschl): SMD -0.6 (95% CI -1.13, -0.1), 1 RCT (N=60) (Dojode)	⊕⊕◯◯ LOW
	Long-term	0 RCTs						No evidence.	⊕◯◯◯ INSUFFICIENT
Pain Success	Short-term	1 RCT (Dojode), 1 quasi-RCT (Jindal)	N= 110	Yes[1,5] (-2)	Yes[2] (-1)	No	Yes[4] (-1)	Conclusion: Inconsistent results for ABI vs. steroid, insufficient strength of evidence prevents firm conclusion: • VAS improvement ≥7 points: RR 3.0 (95% CI 0.3, 27), 1 RCT (N=50) (no difference between groups) (Dojode) • Patient-reported "complete pain relief": RR 0.3 (95% CI 0.1, 0.6), 1 RCT (N=60) (better in steroid group) (Jindal)	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Dojode)	N= 60	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	RR 1.9 (95% CI 1.3, 2.9) Conclusion: Insufficient strength of evidence precludes firm conclusions regarding the percentage of patients with "complete pain relief".	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTs						No evidence.	⊕◯◯◯ INSUFFICIENT

* PRP vs. control comparators:
Gautam, Gosens, Krogh, Yadav, Lebiedzinski: PRP vs. steroid injection
Mishra, Behera: PRP vs. LA
Stenhouse: PRP + DN vs. DN

†ABI vs. control comparators:
Arik, Dojode, Jindal, Kazemi, Ozturan, Singh: ABI vs. steroid injection
Ozturan: ABI vs. ESWT
‡p-values were reported by the trial; Spectrum was unable to confirm due to missing SDs.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
5. Risk of bias downgraded an additional level (so -2) due to quasi-randomized nature of the majority of studies (patients “randomized” by alternate allocation).
6. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

5.2. Strength of Evidence Summary: Achilles Tendinopathy Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Achilles Tendinopathy: PRP vs. Control*									
Function success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Function (VISA-A (0-100 (best))	Short-term	2 RCTs (de Jonge, Kearney)	N= 73	No	No	No	Yes[3] (-1)	WMD -1.5 (95% CI -11.3, 8.4) Conclusion: No difference between groups.	⊕⊕⊕○ MODERATE
	Intermediate-term	2 RCTs (de Jonge, Kearney)	N= 73	No	Yes[2] (-1)	No	Yes[3] (-1)	WMD -6.5 (95% CI -25.7, 12.7) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Long-term	1 RCT (de Jonge)	N= 54	No	Unknown	No	Yes[3,4] (-2)	MD 6.6 (95% CI -5.1, 18.3) Conclusion: No difference between groups.	⊕⊕○○ LOW
Pain success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Pain	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Achilles Tendinopathy: ABI vs. Control†									
Function success	Any	0 RCTs						• No evidence.	⊕○○○ INSUFFICIENT
Function (VISA-A (0-100 (best))	Short-term (ABI vs. exercise)	1 RCT (Pearson)	N=28 tendons	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD 9.3 (95% CI 2.1, 16.5) Conclusion: Greater improvement with ABI; insufficient strength of evidence prevents firm conclusion.	⊕○○○ INSUFFICIENT
	Short-term (ABI vs. DN)	1 RCT (Bell)	N=50	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD 0.3 (95% CI -8.1, 8.7) • Conclusion: No difference between groups; insufficient strength of evidence prevents firm conclusion.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Bell)	N=50	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD -1.2 (95% CI -10.2, 7.8) Conclusion: No difference between groups; insufficient strength of evidence prevents firm conclusion	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	Long-term	0 RCTs						No evidence.	⨁◯◯◯ INSUFFICIENT
Pain success	Any	0 RCTs						No evidence.	⨁◯◯◯ INSUFFICIENT
Pain	Any	0 RCTs						No evidence.	⨁◯◯◯ INSUFFICIENT

* PRP vs. control comparators:
- De Jonge: PRP vs. saline injection
- Kearney: PRP vs. exercise

†ABI vs. control comparators:
- Bell: ABI vs. DN
- Pearson: ABI + exercise vs. exercise (results reported per tendon)

Reasons for downgrading:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

5.3. Strength of Evidence Summary: Patellar Tendinopathy Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Patellar Tendinopathy: PRP vs. Control*									
Function success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Function (various measures)	Short-term	2 RCTs (Dragoo, Vetrano)	N= 67	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups as evaluated by: • VISA-P: WMD 7.4 (95% CI -1.5, 16.2), 2 RCTs, N=67 • ΔLysholm: MD 2.7 (95% CI -25.4, 20.0), 1 RCT, N=21 (Dragoo) • Tegner: MD 0.9 (95% CI 0.7, 2.5), 1 RCT, N=21 (Dragoo)	⊕⊕○○ LOW
	Intermediate-term (PRP vs. ESWT)	1 RCT (Vetrano)	N= 46	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD 13.0 (3.0, 23.0)) (VISA-P) Conclusion: Significantly greater improvement with PRP vs. ESWT; insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
	Intermediate-term (PRP + DN vs. DN)	1 RCT (Dragoo)	N= 17	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: No difference between groups; insufficient strength of evidence prevents firm conclusions: • VISA-P: MD -4.3 (-24.0, 15.4) • Lysholm: MD -15.5 (95% CI -33.3, 2.3), 1 RCT, N=17 (NOTE: Due to baseline imbalances, ΔLysholm was also evaluated and favored the DN group (MD -30.7 (95% CI -50.3, -11.1)). (Dragoo) • Tegner: MD -0.6 (95% CI -2.6, 1.4), 1 RCT, N=17 (Dragoo)	⊕○○○ INSUFFICIENT
	Long-term	1 RCT (Vetrano)	N= 46	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD 13.7 (95% CI 4.6, 22.8) Conclusion: Significantly greater improvement with PRP vs. ESWT as evaluated by VISA-P; insufficient strength of evidence prevents firm conclusions:	⊕○○○ INSUFFICIENT
Pain success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Pain (VAS (0-10) (worst))	Short-term	2 RCTs (Dragoo, Vetrano)	N= 67	Yes[1] (-1)	No	No	Yes[3] (-1)	WMD -0.7 (95% CI -1.8, 0.4) Conclusion: No difference between groups.	⊕⊕◯◯ LOW
	Intermediate-term (PRP vs. ESWT)	1 RCT (Vetrano)	N= 46	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD -1.5 (-2.7, -0.3) Conclusion: Significantly greater improvement with PRP vs. ESWT; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Intermediate-term (PRP + DN vs. DN)	1 RCT (Dragoo)	N= 17	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD -0.1 (-2.2, 2.0) Conclusion: No difference between groups; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Vetrano)	N= 46	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD -1.7 (-2.9, -0.5) Conclusion: Significantly greater improvement with PRP vs. ESWT; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT

DN: dry needling; ESWT: extracorporeal shock wave therapy

* Comparators:
  - Dragoo: PRP + DN vs. DN alone
  - Vetrano: PRP vs. ESWT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

5.4. Strength of Evidence Summary: Rotator Cuff Tendinosis and/or Partial Tear Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Rotator Cuff Tendinosis and/or partial tear: PRP vs. Control*									
Function success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Function SPADI (0-100 (worst))	Short-term	2 RCTs (Kesikburun, Rha)	N= 72	No	No	No	Yes[3] (-1)	• MD -13.5 (95% CI -24.8, -2.2) (Rha) • Median 27.6 vs. 45.3, p=NS (Kesikburun) Conclusion: Greater functional improvement with PRP vs. control.	⊕⊕⊕○ MODERATE
	Intermediate-term	2 RCTs (Kesikburun, Rha)	N= 70	No	No	No	Yes[3] (-1)	• MD -11.8 (95% CI -22.5, -1.1) (Rha) • Median 21.7 vs. 40.9, p=NS (Kesikburun) Conclusion: Greater functional improvement with PRP vs. control.	⊕⊕⊕○ MODERATE
	Long-term	1 RCT (Kesikburun)	N= 40	No	Unknown	No	Yes[3,4] (-2)	Median 14.6 vs. 15.4, p=NS Conclusion: No difference between groups.	⊕⊕○○ LOW
Pain success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Pain (VAS (0-100) (worst))	Short-term	1 RCT (Rha)	N= 32	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD -5.2 (95% CI -9.5, -0.9) Conclusion: Significantly greater improvement with PRP vs. DN; insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Rha)	N= 30	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD -4.7 (95% CI -8.9, -0.5) Conclusion: Significantly greater improvement with PRP vs. DN; insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
	Long-term	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT

DN: dry needling; ESWT: extracorporeal shock wave therapy

* Comparators:

- Rha: PRP vs. DN alone (both used same technique)
- Kesikburun: PRP vs. saline injection

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials

3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

5.5. Strength of Evidence Summary: Plantar Fasciitis Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Plantar Fasciitis: PRP vs. Conservative Control*									
Function success	Short-, intermediate-term	0 RCTs						No evidence.	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Jain)	N=46 (60 heels)	Yes[1] (-1)	Unknown	No	Yes[4,5] (-2)	RR 1.8 (95% CI 1.0, 3.2), p=0.04 Conclusion: Significantly more PRP vs. steroid heels achieved functional success as measured by ≥90% improvement in AOFAS Ankle-Hindfoot scores; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT

Function (various measures)	Short-term	4 RCTs (Jain, Kim, Chew, Monto)	N= 134	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups. However:
								Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
								• AOFAS Ankle and Hindfoot scale:
								  • MD -2.7 (95% CI -11.1, 5.7), 1 RCT (N=46, 60 heels) (Jain)
								  • Median: 86 vs. 80 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT))
								  • Median: 86 vs. 80 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC))
								• FFI total score: MD 0.1 (95% CI -44, 44), 1 RCT (N=20) (Kim)
								• FFI activity limitation subscale score: MD 2.3 (95% CI -7.8, 12), 1 RCT (N=20) (Kim)
								
								In contrast, one trial reported a better outcome following PRP vs. steroid:
									⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								• AOFAS Ankle and Hindfoot scale: median 95 vs. 81, MD NR/NC†, p<0.01‡, 1 RCT (N=40) (Monto)	

	Intermediate-term	4 RCTs (Jain, Kim, Chew, Monto)	N= 134	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups. However:
								
								Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
								• AOFAS Ankle and Hindfoot scale:
								  • MD 4.7 (95% CI -3.3, 12.7), 1 RCT (N=46, 60 heels) (Jain)
								  • Median: 90 vs. 90 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT))
								  • Median: 90 vs. 87 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC))
								• FFI total score: MD -16.1 (95% CI -67, 35), 1 RCT (N=20) (Kim)
								• FFI activity limitation subscale score: MD 0.9 (95% CI -10.8, 12.6), 1 RCT (N=20) (Kim)
								
								In contrast, one trial reported a better outcome following PRP vs. steroid:
								• AOFAS Ankle and Hindfoot scale: median 94 vs. 74, MD NR/NC†, p<0.01‡, 1 RCT (N=40) (Monto)
									⊕⊕◯◯ LOW

	Long-term	2 RCTs (Jain, Monto)	N= 86	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Significantly greater improvement with PRP vs. steroid as evaluated by the AOFAS Ankle and Hindfoot scale: • MD 13.4 (95% CI 4.6, 22.3), 1 RCT (N=46, 60 heels) (Jain) • Median: 92 vs. 56 MD NR/NC†, p<0.01‡, 1 RCT (N=40) (Monto) •	⊕⊕◯◯ LOW
Pain success	Any	0 RCTs						No evidence.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality

Pain (VAS (0-100) (worst))	Short-term	4 RCTs (Jain, Kim, Chew, Tiwari)	N= 174	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups. However:
								
								Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
								• VAS pain:
								  • MD 0.7 (95% CI -1.0, 2.4), 1 RCT (N=46, 60 heels) (Jain)
								  • Median: 4 vs. 4 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT)
								  • Median: 4 vs. 4 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC)
								• FFI pain subscale score: MD -0.6 (95% CI –17, 16), 1 RCT (N=20) (Kim)
								
								In contrast, one trial reported a better outcome following PRP vs. steroid as evaluated by:
								• VAS pain: MD -0.8 (95% CI -1.1, -0.5), 1 RCT (N=60) (Tiwari)
									⊕⊕◯◯ LOW

	Intermediate-term	4 RCTs (Jain, Kim, Chew, Tiwari)	N= 174	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups. However:
								
								Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
								• VAS pain:
								  • MD 0.4 (95% CI -1.5, 2.3), 1 RCT (N=46, 60 heels) (Jain)
								  • Median: 2 vs. 3 (MD NR/NC), 1 RCT (N=32) (Chew, PRP + CC vs. ESWT)
								  • Median: 2 vs. 3 (MD NR/NC), 1 RCT (N=28) (Chew, PRP + CC vs. CC)
								• FFI pain subscale score: MD 7.7 (95% CI -29, 14), 1 RCT (N=20) (Kim)
									⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								In contrast, one trial reported a better outcome following PRP vs. steroid as evaluated by: VAS pain: MD -0.8 (95% CI -1.1, -0.5), 1 RCT (N=60) (Tiwari)	
	Long-term	1 RCT (Jain)	N=46 (60 heels)	Yes[1] (-1)	Unknown	No	Yes[3,5] (-2)	Conclusion: Although insufficient strength of evidence prevents firm conclusions, there was significantly greater improvement with PRP vs. steroid as evaluated by VAS pain: • MD -2.0 (95% CI -3.9, -0.1), 1 RCT (N=46, 60 heels)	⊕○○○ INSUFFICIENT
Plantar Fasciitis: ABI vs. Conservative Control§									
Function success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Function (AOFAS Ankle and Hindfoot)	Short-term	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Kiter)	N= 29-30	Yes[1] (-1)	Unknown	No	Yes[3,5] (-2)	Conclusion: No difference between groups, although insufficient strength of evidence prevents firm conclusions: • ABI vs. steroid: MD 0.8 (95% CI -11.2, 12.8), 1 RCT (N=29) • ABI vs. LA + DN: MD 2.7 (95% CI -7.2, 12.6), 1 RCT (N=30)	⊕○○○ INSUFFICIENT
	Long-term	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Pain success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Pain (VAS)	Short-term, ABI vs. steroid	2 RCTs (Kalaci, Lee)	N= 111	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Significantly worse improvement with PRP vs. steroid as evaluated by VAS pain: • WMD 1.68 (95% CI 0.70, 2.66)	⊕⊕○○ LOW
	Short-term, ABI vs. LA +	1 RCT (Kalaci)	N= 50	Yes[1] (-1)	Unknown	No	Yes[3,5] (-2)	Conclusion: No difference between groups as evaluated by VAS pain, although insufficient	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	DN							strength of evidence prevents firm conclusions: • MD -0.30 (95% CI -1.80, 1.20)	
	Intermediate-term, ABI vs. steroid	3 RCTs (Kalaci, Kiter, Lee)	N= 140	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups as evaluated by VAS pain: • WMD 1.09 (95% CI -0.09, 2.27)	⊕⊕◯◯ LOW
	Intermediate-term, ABI vs. LA + DN	2 RCTs (Kalaci, Kiter)	N= 80	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups as evaluated by VAS pain: • WMD 0.27 (95% CI -0.82, 1.36)	⊕⊕◯◯ LOW
	Long-term	0 RCTs						No evidence.	⊕◯◯◯ INSUFFICIENT

DN: dry needling; ESWT: extracorporeal shock wave therapy; LA: local anesthetic

* Comparators:
- Jain, Monto, Tiwari: PRP vs. steroid injection
- Kim: PRP vs. prolotherapy
- Chew: PRP vs. ESWT vs. CC

†Unable to calculate effect size (study reported median and range scores).

‡p-values were reported by the trial; Spectrum was unable to confirm due to missing SDs.

§Comparators:
- Kalaci, Kiter, Lee: PRP vs. steroid injection
- Kalaci, Kiter: PRP vs. LA + DN

Reasons for downgrading:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.6. Strength of Evidence Summary: Acute Muscle Injury Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Acute Muscle Injury: PRP vs. Control*									
Function success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Function (various)	Short-term	1 RCT (Bubnov)	N= 30	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Significantly greater improvement with PRP + CC vs. CC in subjective global function scores (0-100 (best)) (92 vs. 74, MD NR/NC, p<0.05†) although insufficient strength of evidence prevents firm conclusions.	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Reurink)	N= 80	No	Unknown	No	Yes[3,4] (-2)	MD -3 (95% CI -12, 7) Conclusion: No difference between groups as evaluated by HOS-Overall (0-100 (best)).	⊕⊕○○ LOW
	Long-term	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
Pain success	Any	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT

Pain (various)	Short-term	3 RCTs (Bubnov, Reurink, Hamid)	N= 136	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No difference between groups. However:
								
								Three trials reported no difference between groups (regardless of control treatment) as evaluated by:
								• VAS pain:
								  • MD -0.1 (95% CI -0.5, 0.3), 1 RCT (N=78) (Reurink)
								  • Mean: 0.4 vs. 1.0 (MD NR/NC, p<0.05†), 1 RCT (n=30) (Bubnov)
								• BPI-SF pain interference as assessed over time: β ± SE = -0.185 ± 0.130 (95% CI -0.44, -0.07) (NOTE: p=NS as reported by trial even though the 95% CI suggests otherwise) (Hamid)
								
								In contrast, one trial reported a better outcome
									⊕⊕○○ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								following PRP vs. steroid as evaluated by: • BPI-SF pain severity as assessed over time: β ± SE = -0.390 ± 0.142 (95% CI -0.67, -0.11) (Hamid)	
	Intermediate-term	1 RCT (Reurink)	N= 80	No	Unknown	No	Yes[3,4] (-2)	Conclusion: No difference between groups as evaluated the following HOS scales (0-100 (best)): • HOS-Soreness: MD -2 (95% CI -11, 7) (Reurink) • HOS-Pain: MD 1 (95% CI -9, 10) (Reurink)	⊕⊕◯◯ LOW
	Long-term	0 RCTs						No evidence.	⊕◯◯◯ INSUFFICIENT

BPI-SF: Brief Pain Inventory-Short Form; CC: conservative care; CI: confidence interval; HOS: Hamstring Outcome Score; MD: mean difference; NRS: numerical rating scale; PRP: platelet-rich plasma; QoL: Quality of Life; RCT: randomized controlled trial; VAS: visual analog scale.

* PRP vs. control comparators:

- Bubnov, Hamid, Hamilton: PRP + CC vs. CC
- Reurink: PRP + CC vs. Saline + CC

†p-values were reported by the trial; Spectrum was unable to confirm due to missing SDs.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

5.7. Strength of Evidence Summary: Acute Achilles Tendon Rupture Effectiveness Results

Outcome	Follow-up	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Acute Achilles Tendon Rupture: PRP + CC vs. CC									
Function success	Any	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Function (Leppilahti score)	Short-, intermediate-term	0 studies						No evidence.	⊕○○○ INSUFFICIENT
	Long-term	1 retro. cohort study (Kaniki)	N= 100	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: Insufficient strength of evidence precludes firm conclusions.	⊕○○○ INSUFFICIENT
Pain success	Any	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Pain	Any	0 studies						No evidence.	⊕○○○ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size

5.8. Strength of Evidence Summary: Ankle Sprain Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Ankle Sprain: PRP vs. placebo (saline)									
Function success	Any	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Function (LEFS (0-80 (best))	Short-term	1 RCT (Rowden 2015)	N= 33	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD 3.9 (95% CI -4.4, 12.2) Conclusion: No difference between groups, although insufficient strength of evidence prevents firm conclusions. (NOTE: Due to baseline imbalances, ΔLEFS was calculated and favored the PRP group (MD 9.6 (95% CI 4.5, 14.7))	⊕○○○ INSUFFICIENT
	Intermediate-, long-term	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Pain success	Any	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Pain (VAS (0-10 (worst))	Short-term	1 RCT (Rowden 2015)	N= 33	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	MD -0.5 (95% CI -2.0, 1.0) Conclusion: No difference between groups, although insufficient strength of evidence prevents firm conclusions. (NOTE: Due to baseline imbalances, ΔVAS was calculated and favored the PRP group (MD -1.6 (95% CI -2.6 to -0.6))	⊕○○○ INSUFFICIENT
	Intermediate-, long-term	0 studies						No evidence.	⊕○○○ INSUFFICIENT

CI: confidence interval; LEF: Lower Extremity Function Scale; MD: mean difference; PRP: platelet-rich plasma; RCT: randomized controlled trial; VAS: visual analog scale.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study.

5.9. Strength of Evidence Summary: Osteochondral Lesions of the Talus Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Osteochondral lesions of the talus: PRP vs. HA									
Function success	Any	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Function (various)	Short-term	1 quasi-RCT (Mei-Dan 2012)	N= 29	Yes[1,4] (-2)	Unknown	No	Yes[3,5] (-2)	Conclusion: While results generally favored PRP, insufficient strength of evidence precludes firm conclusions. • ΔVAS function (0-10 (worst)): MD -1.3 (95% CI -2.4, -0.2) (NOTE: Due to baseline imbalances, follow-up scores were also assessed and provided similar results (MD -2.4 (95% CI -3.9, -0.9)) • Subjective global function/disability (0-100 (best)): MD 19.0 (95% CI 6.5, 31.5) • AOFAS modified Ankle and Hindfoot Scale (0-100 (best)): MD 8.5 (95% CI -0.3, 17.0) (p=0.05)	⊕○○○ INSUFFICIENT
	Intermediate-term	1 quasi-RCT (Mei-Dan 2012)	N= 29	Yes[1,4] (-2)	Unknown	No	Yes[3,5] (-2)	Conclusion: While results favored PRP, insufficient strength of evidence precludes firm conclusions. • ΔVAS function (0-10 (worst)): MD -1.6 (95% CI -2.7, -0.5) (NOTE: Due to baseline imbalances, follow-up scores were also assessed and provided similar results (MD -2.7 (95% CI -4.3, -1.1)) • Subjective global function/disability (0-100 (best)): MD 18.0 (95% CI 5.8, 30.2) • AOFAS modified Ankle and Hindfoot Scale (0-100 (best)): MD 14.2 (95% CI 5.4, 23.0)	⊕○○○ INSUFFICIENT
	Long-term	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Pain success	Any	0 studies						No evidence.	⊕○○○ INSUFFICIENT
Pain (VAS (0-10 (worst))	Short-term	1 quasi-RCT (Mei-Dan 2012)	N= 29	Yes[1,4] (-2)	Unknown	No	Yes[3,5] (-2)	MD -2.1 (95% CI -3.4, -0.8) Conclusion: Significantly greater improvement with PRP vs. HA, however insufficient strength of evidence prevents firm conclusions. (NOTE: Due to baseline imbalances, ΔVAS was also	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								calculated and no difference was seen between groups (MD -0.6 (95% CI -1.6, 0.4)).	
	Intermediate-term	1 quasi-RCT (Mei-Dan 2012)	N= 29	Yes[1,4] (-2)	Unknown	No	Yes[3,5] (-2)	MD -2.2 (95% CI -3.6, -0.8) Conclusion: Significantly greater improvement with PRP vs. HA, however insufficient strength of evidence prevents firm conclusions. (NOTE: Due to baseline imbalances, ΔVAS was also calculated and no difference was seen between groups (MD -0.7 (95% CI -1.7, 0.3)).	⊕◯◯◯ INSUFFICIENT
	Long-term	0 studies						No evidence.	⊕◯◯◯ INSUFFICIENT

AOFAS: American Orthopaedic Foot and Ankle Society; CI: confidence interval; HA: Hyaluronic Acid; MD: mean difference; PRP: platelet-rich plasma; RCT: randomized controlled trial; VAS: visual analog scale.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Risk of bias downgraded an additional level (so -2) due to quasi-randomized nature of the majority of studies (patients “randomized” by alternate allocation)
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.10. Strength of Evidence Summary: Temporomandibular Joint Dislocation Efficacy Results

Outcome	Follow-up	RCT	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Temporomandibular Joint Dislocation: ABI vs. IMF									
Pain or function success	Any	0 studies						No evidence.	⨁◯◯◯ INSUFFICIENT
Pain or function scores	Any	0 studies						No evidence.	⨁◯◯◯ INSUFFICIENT
Recurrence of dislocation	Short-, intermediate-term	0 studies						No evidence.	⨁◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Hegab)	N= 32	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	RR 2.7 (95% CI 0.9, 8.3) Conclusion: Although more ABI patients had recurrence of dislocation through 12 months (50% vs. 19%), there was no statistical difference between groups, which is likely due to small sample size. Insufficient strength of evidence prevents firm conclusions.	⨁◯◯◯ INSUFFICIENT

ABI: autologous blood injection; IMF: intermaxillary fixation; RCT: randomized controlled trial; RR: relative risk.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.11. Strength of Evidence Summary: Knee Osteoarthritis Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Knee OA : PRP vs. HA									
Function Success (various measures)	Short-term	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT
	Intermediate –term	2 RCTs (Vaquerizo, Sanchez 2012)	N = 272	No	Yes[2] (-1)	No	Yes[4] (-1)	Conclusion: It is unclear whether functional success is more common following PRP vs. HA. OMERACT-OSARSI responders*: The proportion of responders was statistically similar between groups based on pooled analysis, however: • One trial reported no difference between groups (RR 1.07 (95% CI 0.80, 1.43)) (Sanchez 2012) • The other trial reported significantly more responders with PRP (RR 3.08 (95% CI 1.90, 4.98)) (Vaquerizo); The same trial reporting significantly more responders also reported that more PRP than HA patients achieved functional success for the following (Vaquerizo): WOMAC Physical Function • ≥30% decrease: RR 4.1 (95% CI 2.0, 7.6) 60% vs. 17% • ≥50% decrease: RR 3.8 (95% CI 1.5, 9.3) 40% vs. 11% WOMAC Stiffness • ≥ 30% decrease: RR 2.2 (95% CI 1.2, 3.9), 52% vs. 27% • ≥ 50% decrease: RR 2.3 (95% CI 1.0, 5.1), 35% vs. 16%	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								Lequesne Index • ≥ 30% decrease: RR 5.0 (95% CI 2.5, 10.1), 73% vs. 17% • ≥ 50% decrease: RR 7.0 (95% CI 1.7, 29.2), 29% vs. 4%,	
	Long-term	1 RCT (Vaquerizo)	N = 96	No	Unknown	No	Yes[4,5] (-2)	Conclusion: Significantly more PRP than HA patients achieved 30% and 50% or more decrease in the following measures, however wide CIs suggest estimate instability: WOMAC Physical Function • ≥30% decrease: RR 3.7 (95% CI 1.8, 7.7), 54% vs. 17% • ≥50% decrease: RR (NC) 31% vs. 0%, p<0.01 WOMAC Stiffness • ≥ 30% decrease: RR 4.8 (95% CI 2.0, 11.5), 52% vs. 12% • ≥ 50% decrease: RR 8.0 (95% CI 1.9, 32.9), 33% vs. 5% Lequesne Index • ≥ 30% decrease: RR 23.0 (3.2, 163.6), 48% vs. 2% • ≥ 50% decrease: RR 9.0 (1.2, 68.3), 19% vs. 2%	⊕⊕◯◯ LOW
Function (various)	Short-term	4 RCTs (Sanchez 2012, Vaquerizo, Cerza, Filardo)	N= 575	Yes[1] (-1)	No	No	No	Conclusion: No difference between groups based on the following: • Lequesne Index: MD -0.20 (95% CI -1.0, 0.60); 2 RCTs (N=272) (Sanchez 2012, Vaquerizo). • WOMAC, IKDC: SMD 0.57 (95% CI 0.60, 1.75), 2 RCTs (N=303) (Cerza, Filardo). • KOOS subscales or Tegner scores : no difference between groups in 1 trial (Filardo)	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	Intermediate-term	5 RCTs (Cerza, Vaquerizo, Sanchez 2012, Filardo, Gormeli)	N= 747	Yes[1] (-1)	No	No	No	SMD 0.84 (95% CI 0.19 ,1.48) Conclusion: Significantly better function with PRP versus HA, based on WOMAC total and IKDC scores. Note that High statistical heterogeneity (I^2=94%), may in part be due to differences in the magnitude of effect estimates, failure of two trials (Sanchez, Vaquerizo) to reach statistical significance and limitations of the random effects model.	⊕⊕⊕○ MODERATE
	Long-term	3 RCTS (Vaquerizo, Raeissadat 2015, Filardo)	N= 412	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Function may be improved following PRP as evaluated by: • WOMAC total and IKDC scores: SMD 0.66 (95% CI 0.01, 1.31), p = 0.05, 3 RCTs (N= 412) (Vaquerizo, Raeissadat, Filardo) • WOMAC Stiffness: SMD 0.90 (95 % CI 0.32, 1.49), 2 RCTs (N=229) (Vaquerizo, Raeissadat) • WOMAC Physical Function: SMD 0.93 (95% CI 0.19, 1.67), 2 RCTs (N=229) (Vaquerizo, Raeissadat) However, one trial included in the pooled analysis reported no difference for any KOOS subscale or the Tegner Score. (Filardo)	⊕⊕○○ LOW
Pain Success (≥50% or ≥20% decrease in WOMAC pain score)	Short-, long-term	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
	Intermediate-term	2 RCTs (Sanchez 2012, Filardo)	N = 272	No	No	No	Yes[4] (-1)	Conclusion: Significantly greater improvement with PRP vs. HA based on >50% decrease in WOMAC pain score: • Both trials reported significantly greater improvement with PRP: (RR 5.2 (95% CI 2.18, 12.41) in one trial (Vaquerizo) but results were marginally significant in the other (RR 1.58 (95% CI 1.0, 2.5) (Sanchez 2012).	⊕⊕⊕○ MODERATE

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								However, in one of these trials, there was no difference between treatments for ≥20% decrease in WOMAC pain score, RR 1.08 (95% CI 0.8, 1.4) (Sanchez 2012).	
Pain Success (≥30% or ≥50% decrease in WOMAC pain score)	Short-, intermediate-term	0 RCTs						No evidence.	⊕○○○ INSUFFICIENT
	Long-term	1 RCT (Vaquerizo)	N = 96	No	Unknown	No	Yes[4,5] (-2)	Conclusion: Significantly more PRP than HA patients achieved pain success: • ≥30% decrease: RR 4.9 (95% CI 2.1, 11.5) • ≥50% decrease: RR 13.3 (95% CI 1.81, 95)	⊕⊕○○ LOW
Pain (various)	Short-term	1 RCTs (Filardo)	N= 192	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD -0.1, 95% CI -5.63, 5.43 Conclusion: No difference between treatments in pain based on the KOOS Pain subscale.	⊕⊕○○ LOW
	Intermediate-term	3 RCTs (Vaquerizo, Sanchez 2012, Filardo)	N= 455	No	Yes[2] (-1)	No	No	SMD -0.45, 95% CI -1.14, 0.24 Conclusion: No difference between groups based on pooled WOMAC and KOOS pain subscales. Inconsistency and wide confidence intervals both likely stem from the smallest trial showing a significantly better results in the PRP group (Vaquerizo) while the other two trials s showed no difference between groups (Sanchez, Filardo).	⊕⊕⊕○ MODERATE
	Long-term	3 RCTs (Vaquerizo, Raeissadat 2015, Filardo)	N= 412	Yes[1] (-1)	Yes[2] (-1)	No	No	SMD -0.49 (95% CI -1.16, 0.18) Conclusion: No difference between groups based on pooled WOMAC and KOOS pain subscales. Inconsistency and wide confidence intervals both likely stem from the smallest trial showing a significantly better results in the PRP group (Vaquerizo) while the other two trials showed no difference between groups (Raeissadat, Filardo).	⊕⊕○○ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Knee OA: LR-PRP vs. Corticosteroid									
Function Success	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT
Function (KOOS Symptoms, ADL, Sporting Subscales)	Short-term	1 RCT (Forogh)	N= 41	Yes[1] (-1)	Unknown	No	Yes[3, 6] (-2)	Conclusion: No firm conclusions can be drawn, however, greater improvement with LR- PRP was seen in two measures: • KOOS Symptoms: MD 14.7 (95% CI 3.4, 25.9) • KOOS ADL: MD 20.3 (95% CI 9.5, 31.1) However, no difference in KOOS Sporting ability was seen: MD 2.7 (95% CI -3.1, 8.5)	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Forogh)	N= 41	Yes[1] (-1)	Unknown	No	Yes[3, 6] (-2)	Conclusion: No firm conclusions can be drawn, however, greater improvement was seem with LR-PRP in two measures: • KOOS Symptoms: MD 19.8 (95% CI 11.8, 27.8) • KOOS ADL: MD 12.0 (95% CI 0.93, 23.1) However, no difference in KOOS Sporting ability was seen: MD -0.3 (95% CI -3.6, 5.7)	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTS						No evidence	⊕◯◯◯ INSUFFICIENT
Pain Success	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT
Pain (KOOS pain and VAS Pain Intensity)	Short-term	1 RCT (Forogh)	N= 41	Yes[1] (-1)	Unknown	No	Yes[3, 6] (-2)	Conclusion: No firm conclusions can be drawn, however, greater improvement with PRP in two measures: • KOOS Pain relief: MD 13.5 (95% CI 3.2, 23.8) • VAS: MD -20.2 (95% CI -34.5, -5.8)	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Forogh)	N= 41	Yes[1] (-1)	Unknown	No	Yes[3, 6] (-2)	Conclusion: : No firm conclusions can be drawn, however, greater improvement in pain with PRP:	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								• KOOS Pain relief: MD 23.6 (95% CI 13.5, 33.7) • VAS : MD -27.9 (95% CI -38.4, -17.4)	
	Long-term	0 RCTS						No evidence	⊕◯◯◯ INSUFFICIENT
Knee OA: PRP vs. Saline									
Function Success	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	1 RCT (Patel)	N= 78	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: PRP resulted in significantly improved function versus saline based on percent change from baseline in • WOMAC total score (-57% versus 12%), • WOMAC stiffness score (-47% versus 2.0%) • WOMAC physical function score (-56% versus 11%)	⊕⊕◯◯ LOW
	Intermediate-term	2 RCTs (Patel 2013, Gormeli 2015)	N= 204	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: PRP resulted in improved function based on evaluation of : Percent change from baseline in the following: • WOMAC total score: -47% versus 20%, p<0.05 (Patel) • WOMAC stiffness score: -47% versus 10%, p<0.05 (Patel) • WOMAC physical function score 46% versus 20%, p<0.05 (Patel) IKDC: MD 19.0 (95% CI 16.2, 21.8) (Gormeli)	⊕⊕◯◯ LOW
	Long-term	0 RCTS						No evidence	⊕◯◯◯ INSUFFICIENT
Pain Success	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Pain	Short-term	1 RCT (Patel 2013)	N= 78	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Mean percent changes from baseline were -63% vs. 18% (p <0.05) Conclusion: LP-PRP resulted in significantly improved pain.	⊕⊕◯◯ LOW
	Intermediate-term	1 RCT (Patel 2013)	N= 78	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: LP-PRP resulted in significantly improved pain compared with saline based on: • WOMAC pain (% change): -50% vs. 25%, p <0.05 • VAS (0-10): MD -2.3 (95% CI -2.7, -1.8).	⊕⊕◯◯ LOW
	Long-term	0 RCTS						No evidence	⊕◯◯◯ INSUFFICIENT
Knee OA: PRP vs. Exercise (conservative care) or Exercise with TENS									
Function Success	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT
Function (various measures)	Short-term	1 RCT (Angoorani)	N= 54	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions, however it appears that there are no differences between PRP and exercise plus TENS based on adjusted MDs: • KOOS Symptoms: MD 8.3 (95% CI -0.42, 17.90) • KOOS ADL: MD 4.3 (95% CI -6.91, 15.48) • KOOS Sports: MD 0.5 (95% CI -12.73, 13.68)	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Rayegani)	N= 62	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions, however it appears that there are no differences between PRP and exercise (conservative care): • WOMAC Total Score: MD -0.5 (95% CI -9.73, 8.73) • ΔWOMAC Stiffness: MD 0.0 (95% CI -0.7, 0.7) • ΔWOMAC Physical: MD 0.2 (95% CI -5.7,	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								5.9)	
	Long-term	0 RCTS						No evidence	⊕◯◯◯ INSUFFICIENT
Pain Success	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT
Pain (various measures)	Short-term	1 RCT (Angoorani)	N= 54	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions, however it appears that there are no differences between LP-PRP and exercise plus TENS: • KOOS Pain: Adjusted MD 2.9 (-7.7, 13.50) • VAS Pain Scores: 47 versus 53, p = 0.900	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Rayegani)	N= 62	Yes[1] (-1)	Unknown	No	Yes[3,6] (-2)	Conclusion: Insufficient evidence precludes firm conclusions, however it appears that there are no differences between PRP and exercise (conservative care): • ΔWOMAC Pain: MD -0.9 (95% CI -2.9, 0.9)	⊕◯◯◯ INSUFFICIENT
	Long-term	0 RCTS						No evidence	⊕◯◯◯ INSUFFICIENT

* OMERACT-OSARSI responders are those who experienced a high improvement in pain or function ≥50% and absolute change ≥20; OR had improvement in 2 of the following: 1) Pain ≥20% and absolute change in ≥10; 2) Function ≥20% and absolute change in ≥10; 3) Patient's global assessment ≥20% and absolute change in ≥10.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
5. Imprecision downgraded an additional level (so -2) because the confidence intervals were extremely wide, bringing into question the stability of the estimate
6. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.12. Strength of Evidence Summary: Hip and TMJ Osteoarthritis Efficacy Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Hip Osteoarthritis : PRP vs. HA									
Function Success	Any	0 RCTS						No evidence	⊕○○○ INSUFFICIENT
Function (Harris Hip Score (0-100 (best))	Short-term	1 RCT (Battaglia)	N = 104	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD -4.3 (95% CI -10.6, 1.99) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Intermediate-term	1 RCT (Battaglia)	N = 104	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD -5.5 (95% CI -12.0, 0.92) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Long-term	1 RCT (Battaglia)	N = 104	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD -6.8 (95% CI -14.1, 0.51) Conclusion: No difference between groups.	⊕⊕○○ LOW
Pain Success	Any	0 RCTS						No evidence	⊕○○○ INSUFFICIENT
Pain VAS (0-10 (worst))	Short-term	1 RCT (Battaglia)	N = 104	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD 0.0 (95% CI -0.84, 0.84) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Intermediate-term	1 RCT (Battaglia)	N = 104	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD 0.25 (95% CI -0.59, 1.09) Conclusion: No difference between groups.	⊕⊕○○ LOW
	Long-term	1 RCT (Battaglia)	N = 104	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD 0.16 (95% CI -0.78, 1.1) Conclusion: No difference between groups.	⊕⊕○○ LOW
TMJ Osteoarthritis: PRP vs. HA									
Function Success	Any	0 RCTS						No evidence	⊕○○○ INSUFFICIENT
Function Maximum voluntary mouth opening (MVMO)	Short-term	1 RCT (Hegab)	N = 50	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Insufficient evidence precludes conclusions (no data reported for control group).	⊕○○○ INSUFFICIENT
	Intermediate-term	1 RCT (Hegab)	N = 50	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Insufficient evidence precludes conclusion, however MVMO medians appear to be similar between groups (39 vs. 40 mm).	⊕○○○ INSUFFICIENT
	Long-term	1 RCT	N =	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Insufficient evidence precludes firm	⊕○○○

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
		(Hegab)	50					conclusions; however, MVMO appears to be greater with PRP (MD 2.8mm (95% CI 0.82 mm, 3.7mm).	INSUFFICIENT
Pain Success	Any time	0 RCTS						No evidence	⊕◯◯◯ INSUFFICIENT
Pain	Short-term	1 RCT (Hegab)	N = 50	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Insufficient evidence precludes firm conclusions (inadequate data were provided to generate conclusions).	⊕◯◯◯ INSUFFICIENT
	Intermediate-term	1 RCT (Hegab)	N = 50	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Insufficient evidence precludes firm conclusions (inadequate data were provided to generate conclusions).	⊕◯◯◯ INSUFFICIENT
	Long-term	1 RCT (Hegab)	N = 50	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Insufficient evidence precludes firm conclusions. Although lower VAS pain scores were reported for the PRP group (0.4 vs. 1.6, MD -1.24 (95% CI -1.83, -0.64), it is not clear that this represents a clinically important difference.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.13. Strength of Evidence Summary: Tendinopathy Harms and Complications Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Elbow Tendinopathy: PRP vs. ABI									
Serious adverse events	Any	1 RCT (Thanasas)	N= 28	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: No serious adverse events were reported to occur; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 RCT (Thanasas)	N= 28	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Injection-site pain was slightly (but not significantly) more common with PRP vs. ABI (64% vs. 29%, RR 2.25 (95% CI 0.90, 5.6)). No other adverse events were reported; insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Elbow, Rotator Cuff, Achilles, or Patellar Tendinopathy: PRP vs. Conservative Control*									
Serious adverse events	Any	13 RCTs (Behera, de Jonge/de Vos, Dragoo, Gosens/Peerboo ms, Kearney, Kesikburun, Krogh, Mishra, Rha, Stenhouse, Vetrano, von Wehren, Yadav) 3 cohort studies (Ford, Tetschke, Tonk)	N= 913	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	13 RCTs (Behera, de Jonge/de Vos, Dragoo, Gosens/Peerboo ms, Kearney, Kesikburun, Krogh, Mishra, Rha, Stenhouse, Vetrano, von Wehren, Yadav) 3 cohort	N= 913	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Non-serious adverse events occurred relatively infrequently and similarly between treatment groups. More commonly reported events included: • Post-injection pain may be more common following PRP injection (2-13% patients in 3 RCTs) versus anesthetic injection (0% patients in 1 RCT). One trial reported significantly worse post-injection pain with PRP versus steroid when rated on a NRS pain scale (0-10 (worst))	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
		studies (Ford, Tetschke, Tonk)						(9.0 vs. 6.0, MD 3.0 (95% CI 1.5, 4.5)) (Krogh). • Adverse events (type not specified): while one trial reported than any such event occurred similarly between PRP and anesthetic injection groups (19% vs. 18%) (Krogh), 7 RCTs (Rha, Dragoo, Kearney, de Jonge/de Vos, Yadav, Behera, Stenhouse) and all three cohort studies (Ford, Tetschke, Tonk) reported that no complications or adverse events occurred.	
Elbow or Achilles Tendinopathy: ABI vs. Conservative Control†									
Serious adverse events	Any	6 RCTs (Arik, Bell, Dojode, Kazemi, Ozturan, Pearson)	N= 346	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	6 RCTs (Arik, Bell, Dojode, Kazemi, Ozturan, Pearson)	N= 346	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Non-serious adverse events occurred relatively infrequently and similarly between treatment groups. More commonly reported events included: • Post-injection pain may be more common following PRP vs. steroid injection (25-60% vs. 0-26%) as reported by 2 RCTs (Arik, Dojode). However, another trial reported 100% of ABI, steroid, and ESWT patients experienced such pain (Ozturan). Another reported post-injection pain occurred in 21% of ABI patients (and no exercise control patients) (Pearson). • One trial reported slightly fewer cases of local erythema, swelling, or nausea with PRP versus ESWT (0% vs. 16-21%) (Ozturan) (p=NS due to small sample size).	⊕⊕◯◯ LOW

*Control groups included dry needling (Rha, Dragoo, Stenhouse), saline injection (Kesikburun, de Jonge/de Vos), exercise (Kearney), steroid injection (Krogh, Gosens/Peerbooms, von Wehren, Yadav), anesthetic injection (Mishra, Behera), and extracorporeal shock wave therapy (ESWT) (Vetrano).

†Control groups included steroid injection (Kazemi, Arik, Dojode, Ozturan), extracorporeal shock wave therapy (ESWT) (Ozturan), exercise (Pearson), and dry needling (Bell).

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.14. Strength of Evidence Summary: Plantar Fasciitis Harms and Complications Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
PRP vs. Conservative Control*									
Serious adverse events	Any	4 RCTs (Chew, Jain, Kim, Tiwari) 2 cohort studies (Aksahin, Say)	N= 241 pts. & 60 heels	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	4 RCTs (Chew, Jain, Kim, Tiwari) 2 cohort studies (Aksahin, Say)	N= 241 pts. & 60 heels	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: No non-serious adverse events were reported to occur, including soft tissue injection, osteomyelitis, loss of function, stiffness.	⊕⊕◯◯ LOW
ABI vs. Conservative Control†									
Serious adverse events	Any	2 RCTs (Kalaci, Lee)	N= 135	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	2 RCTs (Kalaci, Lee)	N= 135	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Post-injection pain was more common following ABI versus steroid injection (53% vs. 13%, RR 4.1 (95% CI 1.5, 11) (1 RCT) (Lee). Otherwise, no adverse events were reported to occur, including infection, plantar fascia rupture, fat pad atrophy, skin hypopigmentation, or hematoma.	⊕⊕◯◯ LOW

*Control groups included steroid injection (Jain, Tiwari, Aksahin, Say), conservative care (Chew), extracorporeal shock wave therapy (ESWT) (Chew), and prolotherapy (Kim)

†Control groups included steroid injection (Kalaci, Lee) and anesthetic injection plus dry needling (Kalaci).

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI

5.15. Strength of Evidence Summary: Acute Injuries Harms and Complications Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Acute muscle injuries: PRP vs. Conservative Control*									
Serious adverse events	Any	3 RCTs (Hamid, Hamilton, Reurink)	N= 157	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No serious adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	2 RCTs (Reurink, Hamid)	N= 102	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Painful dermal hyperaesthesia was reported in one PRP patient (3%) over 12 months in one trial. Pain during blood draw and PRP injection was reported by "most patients" in the other trial. No other adverse events were reported.	⊕⊕◯◯ LOW
Acute Achilles tendon rupture: PRP vs. Conservative Control*									
Serious adverse events	Any	1 cohort study (Kaniki)	N=145	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: Insufficient strength of evidence precludes any firm conclusions. The incidence of repeat tendon rupture within 3 months was similar between the PRP and exercise groups: 3% vs. 4%, OR 0.65 (95% CI 0.1, 4.0). No other serious adverse events (i.e. superficial or deep infection, venous thrombosis, pulmonary embolus, numbness) were reported.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 cohort study (Kaniki)	N=145	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: No non-serious adverse events were reported to occur; insufficient strength of evidence precludes any firm conclusions.	⊕◯◯◯ INSUFFICIENT

*All control groups included standardized physical therapy programs, either alone (Hamilton, Reurink); with acetaminophen 1000 mg as needed, max. 4 x daily (Hamid); or with removable below the knee arthrosis and 2 weeks non-weight-bearing prior to commencement of exercises (Kaniki).

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI

5.16. Strength of Evidence Summary: Osteochondral Lesions of the Talus Harms and Complications Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Osteochondral Lesions of the Talus: PRP vs. HA									
Serious adverse events	Any	1 quasi-RCT (Mei-Dan 2012)	N= 29	Yes[1,4] (-2)	Unknown	No	Yes[3,5] (-2)	Conclusion: No serious adverse events were reported to have occurred; insufficient evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 quasi-RCT (Mei-Dan 2012)	N= 29	Yes[1,4] (-2)	Unknown	No	Yes[3,5] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. However, no infections occurred in either group. Acute mild pain following injection and new symptoms of mild plantar fasciitis (timing not reported) and Achilles tendinopathy (through 7 months) were reported in 7%, 29% and 7% of PRP patients, respectively, compared with no patients in the HA group (p=0.03 between groups for new plantar fasciitis symptoms).	⊕◯◯◯ INSUFFICIENT

HA: hyaluronic acid; PRP: platelet-rich plasma.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Risk of bias downgraded an additional level (so -2) due to quasi-randomized nature of the majority of studies (patients "randomized" by alternate allocation)
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.17. Strength of Evidence Summary: TMJ Dislocation Harms and Complications Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
TMJ Dislocation: ABI vs. IMF									
Serious adverse events	Any	1 RCT (Hegab)	N=32	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: No serious adverse events were reported to occur following ABI; no information was provided for the IMF group. Insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	1 RCT (Hegab)	N=32	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: Insufficient strength of evidence prevents firm conclusions. However, in the IMF group, patients complained of weight loss due to restricted diet and those who received eyelet wiring (vs. orthodontic braces) developed marginal gingivitis; no information on non-serious adverse events was provided for the ABI group.	⊕◯◯◯ INSUFFICIENT

ABI: autologous blood injection; IMF: intermaxillary fixation; TMJ: temporomandibular joint.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.18. Strength of Evidence Summary: Osteoarthritis Treatment-Related Harms and Complications Results

Outcome	Follow-up	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Knee Osteoarthritis: PRP vs. HA									
Serious adverse events	Any	4 RCTS (Filardo, Sanchez 2012, Vaquerizo, Cerza) 3 Cohort Studies (Say, Spakova, Kon)	N=944	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No serious treatment-related adverse events were reported to have occurred.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	2 RCTs (Filardo, Vaquerizo)	N=288	No	Yes[2] (-1)	No	Yes[3] (-1)	Conclusion: Non-serious treatment-related events appear to be similar for PRP and HA, but data are limited. Injection-site pain and/or swelling were the most commonly reported and may be similar between treatments. • Post-injective pain reaction was similar between treatments, 16. 6% vs. 14.2%, RR 1.2 (95% CI 0.4 to 3.1) (Vaquerizo) • Severe pain, swelling leading to withdrawal occurred only in the HA group; 0% vs. 2.1% (Filardo) Conclusions regarding pain and swelling intensity are not possible; no statistical evaluation was performed. • Pain (VAS 0-100) x duration; Median 9 (0 to 20) vs. 1 (0 to 7) (Filardo) • Swelling (VAS 0-100) x duration; Median 6 (0 to 16) vs. 1 (0 to 4) (Filardo) Pseudoseptic reaction, reported in one trial may be similar for both treatments PRP (0%) vs. HA (4.7%) (Filardo)	⊕⊕◯◯ LOW
Knee Osteoarthritis: PRP vs. Saline									
Serious	Intermediate-	1 RCT	N	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No serious treatment-related adverse	⊕⊕◯◯

Outcome	Follow-up	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
adverse events	term	(Patel)	=78					events were reported to occur.	LOW
Non-serious adverse events	Intermediate-term	1 RCT (Patel)	N =78	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: Non-serious events were fairly common following PRP; systemic events were significantly more common following PRP: • Systemic effects (syncope, headache, nausea, gastritis, sweating, tachycardia) occurred more frequently following PRP; PRP 32.6% vs. Saline 0% (RR not calculable); p<0.01 • Post-injection pain or stiffness lasting ≥2 days were only reported for the PRP group (13.5%); no comparative safety conclusions are possible.	⊕⊕◯◯ LOW
Knee Osteoarthritis: PRP vs. Exercise + TENS									
Serious adverse events	Short-term	1 RCT (Angoorani)	N= 54	Yes[1] (-1)	No	No	Yes[3.5] (-2)	Conclusion: No serious treatment-related adverse events were reported to occur, however insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Short-term	1 RCT (Angoorani)	N= 54	Yes[1] (-1)	No	No	Yes[3.5] (-2)	Conclusion: Mild pain and swelling may be more common following PRP vs. exercise + TENS (11% vs. 4%, RR 3.0 (0.3, 27.1), however insufficient strength of evidence prevents firm conclusions.	⊕◯◯◯ INSUFFICIENT
Hip Osteoarthritis: PRP vs. HA									
Serious adverse events	Any	1 RCT (Battaglia)	N= 100	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: No serious treatment-related adverse events were reported to occur.	⊕⊕◯◯ LOW
Non-serious adverse events	Any	1 RCT (Battaglia)	N= 100	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: No difference between treatment groups was observed for moderate pain during or after treatment (20% vs. 12%, RR 1.6 (95% CI 0.65, 4.23).	⊕⊕◯◯ LOW
TMJ Osteoarthritis: PRP vs. HA									
Serious adverse events	Any	1 RCT (Hegab)	N = 50	Yes[1] (-1)	Unknown	No	Yes[3.5] (-2)	Conclusion: No serious treatment-related adverse events were reported to occur, however, insufficient strength of evidence precludes	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								drawing firm conclusions.	
Non-serious adverse events	Any	1 RCT (Hegab)	N = 50	Yes[1] (-1)	Unknown	No	Yes[3.5] (-2)	Conclusion: Insufficient strength of evidence precludes drawing firm conclusions; however non-serious adverse events appear to be more common following PRP versus HA • More PRP vs. HA patients had pain during injection, RR 1.46 (95% CI 1.03, 2.08) • More PRP vs. HA patients had pain post-intervention, RR 2.37 (95% CI 1.28, 4.38)	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with PRP/ABI
4. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
5. Imprecision downgraded an additional level (so -2) because evidence was based on a single small study

5.19. Strength of Evidence Summary: Differential Efficacy and Safety Results

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Knee OA: PRP vs. HA									
Differential Efficacy or Safety	Intermediate-term	1 RCT (Gormeli)	N= 122	Yes[1, 2] (-2)	Unknown	No	Yes[3] (-1)	Conclusion: Insufficient evidence precludes firm conclusions. Patients with early OA reported better function (IKDC) and better quality of life (EQ VAS) than those with advanced OA with PRP injection. Authors do not stated if subgroup analysis was planned a priori or conducted post hoc. Outcome: IKDC (PRP vs. HA) Early OA: MD = 9/6 (95% CI 6.8, 12.4) Advanced OA: MD = 2.7 (95% CI -0.5, 5.8) Outcome: EQ-VAS (PRP vs. HA) Early OA: MD = 7.45 (95% CI 4.8, 10.1) Advanced OA: MD = 2.0 (95% CI 1.3, 5.3)	⊕◯◯◯ INSUFFICIENT
Knee OA: PRP vs. Saline									
Differential Efficacy or Safety	Intermediate-term	1 RCT (Gormeli)	N= 123	Yes[1, 2] (-2)	Unknown	No	Yes[3] (-1)	Conclusion: Insufficient evidence precludes firm conclusions. Patients with early OA reported better function (IKDC) and better quality of life (EQ VAS) than those with advanced OA with PRP injection. Authors do not stated if subgroup analysis was planned a priori or conducted post hoc. Outcome: IKDC (PRP vs. Saline) Early OA: MD = 23.1 (95% CI 20.4, 27.7) Advanced OA: MD = 10.8 (95% CI 7.9, 13.6) Outcome: EQ-VAS (PRP vs. Saline) Early OA: MD = 23.1 (95% CI 20.6, 25.5) Advanced OA: MD = 9.9 (95% CI 6.6, 13.2)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
All other conditions									
Differential Efficacy or Safety	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Serious risk of bias in evaluation of HTE failure to specify subgroup analysis *a priori*; the subgroup hypothesis was not one of a smaller number tested no formal test for interaction was done
3. Imprecise effect estimate for a dichotomous outcome: small sample size

5.20. Strength of Evidence Summary: Cost Effectiveness

No evidence.

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