Biologic Orthopedic Journal

Regenerative Rehabilitation
DOI: 10.22374/boj.v4SP1.43

THE EFFECTS OF PLATELET-RICH PLASMA IN CONJUNCTION WITH REHABILITATION FOR UPPER EXTREMITY MUSCULOSKELETAL PATHOLOGIES: A SYSTEMATIC REVIEW WITH META-ANALYSIS

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Submitted: 28 April 2022. Accepted: 2 June 2022. Published: 7 July 2022

Abstract

Background: Platelet-rich plasma (PRP) is considered in clinical practice for its role in facilitating the body's own healing processes, with the potential to complement physical therapy in managing musculoskeletal pathologies of the upper extremity.

Methods: Eligible studies must be randomized with clinical/quasi-experimental trials with complete data analysis, and published in English. They have to recruit participants aged >18 years; have at least two groups, with one intervention group receiving PRP injection alone or PRP injection and rehabilitation, and the comparison group receiving either rehabilitation alone or a control group receiving saline and rehabilitation; and finally include at least one outcome measure of pain, disability, or quality of life. An electronic search was conducted using PubMed, Embase, Cochrane, Pedro, and clinicaltrials.gov. Methodological quality was assessed using the Cochrane Collaboration Risk of Bias (RoB) tool. The grading of recommendations assessment, development, and evaluation approach was used to provide an overall assessment of the quality of evidence. Meta-analyses were conducted across outcomes within each pathology when possible.

Results: A total of 13 studies assessing adhesive capsulitis, carpal tunnel syndrome, lateral epicondylalgia, rotator cuff tendinopathy, subacromial impingement syndrome, and shoulder osteoarthritis were included with an average RoB score of 8.77 out of 12 across all studies. Meta-analyses for rotator cuff tendinopathy (n = 49) revealed a significant effect on pain (cm) (mean difference [MD] -2.53; 95% confidence interval [CI]: −5.02, −0.04; I^2 statistic = 51%; P = 0.05), quality of life (MD 16.82; 95% CI: 0.40, 33.25; I^2 = 0%; P = 0.04), and disability (standardized mean difference [SMD]: −0.64; 95% CI: −1.24, −0.04; I^2 = 0%; P = 0.04) favoring PRP and physical therapy as long-term follow-up (moderate level of evidence). All other meta-analyses for adhesive capsulitis and carpal tunnel demonstrated nonsignificant effects.

Conclusions: This systematic review demonstrated that PRP is a beneficial adjunct to physical therapy for reducing pain and improving disability and quality of life (moderate level of evidence) when compared to placebo plus physical therapy for the management of rotator cuff tendinopathy.

Keywords: *exercise; platelet-rich plasma; rehabilitation*

BACKGROUND

Musculoskeletal injuries continue to prevail in society, and are expensive.[1–3] With emphasis on the quadruple aim of healthcare (reducing costs, improving health of population, patient experience, and well-being of healthcare team),[4] physicians and allied healthcare professionals are responsible for providing cost-effective, high quality care that often involves nonsurgical management of musculoskeletal pathologies (subacromial impingement/rotator cuff tendinopathy, adhesive capsulitis, carpal tunnel syndrome, lateral epicondylalgia, and shoulder osteoarthritis) of the upper extremity (UE).[4] Physical therapy, rehabilitation, and exercise comprise the most common form of conservative management for treating musculoskeletal pathologies. More recently, regenerative medicine, such as stem cells and platelet-rich plasma (PRP) have gained popularity among orthopedic, sports medicine, and rehabilitation communities as a relatively safe adjunct to exercise and alternative treatment to surgical intervention.[5–8]

Platelet-rich plasma is the most common orthobiological used and has indicated positive effects in the management of musculoskeletal pathologies.[9–11] Recent trends have demonstrated an increase in annual expenses associated with PRP usage, indicating an ease of implementation and an increase in demand for safe, nonsurgical, and minimally invasive options.[5] Often, PRP is injected into the injured tissue or region, with the goal of initiating a cascade of local healing responses to facilitate an increase in growth hormone and anti-inflammatory cytokines that are produced as part of the normal healing process.[7,12] Therefore, PRP has been considered in clinical practice for its role in facilitating the body's own healing processes. While there is inconsistency in the literature on the dosage, histological makeup of PRP injections, and patient cohorts that are likely to improve with PRP, one consistent theme throughout is its role in treating musculoskeletal pathologies that have been recalcitrant to the normal healing process.[7,13] Based on a Cochrane Review that found insufficient evidence to support the use of PRP as a stand-alone treatment for soft tissue injuries,[14] clinicians must consider combining PRP injections with other forms of treatment such as exercise/rehabilitation. PRP injections have the potential to create a healing environment for tissues, in which subsequent loading through exercise may create positive long-term changes for various UE pathologies.

Numerous studies have been conducted assessing the role of PRP in the management of UE musculoskeletal pathologies.[10,15–26] These studies are important as they discuss the effect of PRP in comparison to or in conjunction with exercise. While previous systematic reviews examining the effectiveness of PRP exist, limitations in methodological design, lack of consistent meta-analysis, and inability to compare PRP to rehabilitation interventions prevent researchers and clinicians from drawing strong conclusions regarding its role in managing patients with UE pathologies. Therefore, the purpose of this systematic review with meta-analysis and formal grading of evidence is to assess the effectiveness of PRP alone or in addition to rehabilitation, compared to rehabilitation alone on pain, disability, and quality of life in patients with UE musculoskeletal pathologies.

METHODS

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[27] (Appendix), and registered in the International Prospective Register of Systematic Reviews (PROSPERO; #CRD42022313094).

Inclusion criteria

Studies had to meet the following inclusion criteria: (1) Randomized clinical/quasi-experimental trials with completed data analysis; (2) published in English; (3) recruited participants aged >18 years; (4) had at least two groups with one intervention group receiving PRP injection alone or PRP injection and rehabilitation, and the comparison group receiving either rehabilitation alone or a control group receiving saline and rehabilitation; and (5) included at least one outcome measure of pain, disability, or quality of life.

Exclusion criteria

Studies were excluded if (1) they were retrospective studies, or case studies/series; (2) subjects underwent surgical intervention; (3) injection was combined with dry needling or extracorporeal shockwave therapy; (4) PRP was compared to injections other than saline; (5) bone marrow aspirate or adipose grafts were used in conjunction with PRP; and (6) studies did not include physical therapy, rehabilitation, or an exercise program.

Search strategy and study selection

An electronic search was conducted by both authors in February 2022 using PubMed, Embase, Cochrane Library, Pedro, and clinicaltrials.gov for identifying all relevant articles without date restriction. Clinicaltrials.gov was included to capture gray literature not published due to nonsignificant findings. The search strategy is provided in Table 1. A hand search of reference lists of related articles was also conducted by the first author. Each author examined all titles and abstracts to screen for eligibility. Full-text articles were assessed for the inclusion criteria to determine final eligibility. If discrepancy arose, it was resolved through discussion until a consensus was reached.

Interventions

The intervention of interest in this systematic review was PRP injection. Across all the included studies, the number of injections and administration techniques vary considerably, with some details provided in Table 2 and more specifics available in the original publications. PRP alone or in conjunction with a comparison intervention was compared to rehabilitation, physical therapy, exercise, splinting, or immobilization, or to a control group that included a placebo (saline) intervention group (Table 2).

Outcomes

Primary outcomes of this review were pain, disability, and quality of life (Table 3). Electrophysiological values and cross-sectional area of the median nerve as well as shoulder external rotation range of motion (ER ROM) were included as secondary outcome measures for the carpal tunnel syndrome and adhesive capsulitis, respectively. Pain was measured using the Visual Analog

Table 1. Search Strategy

Database	Search Strategy	Yield
PubMed	((Platelet-rich plasma OR PRP) AND (clinicaltrial [Filter] OR randomizedcontrolledtrial [Filter])) AND ((physical therapy) OR (rehabilitation) AND (clinicaltrial [Filter] OR randomizedcontrolledtrial [Filter]))	163
	(Platelet-rich plasma OR PRP) AND (exercise)	78
	(Platelet-rich plasma OR PRP) AND (Physical Therapy OR Rehabilitation OR exercise) AND Musculoskeletal	77
Cochrane Library	((platelet-rich plasma OR PRP) AND (physical therapy) OR (rehabilitation) OR (exercise)):kw	54
	((Platelet-rich plasma OR PRP) AND (physical therapy OR rehabilitation OR exercise) AND musculoskeletal):kw	3
Embase	((platelet-rich plasma OR (PRP) AND (physical therapy) OR (rehabilitation) OR (exercise)):kw	23
	((Platelet-rich plasma OR PRP) AND (physical therapy OR rehabilitation OR exercise) AND musculoskeletal):kw	3
Pedro	Simple search: Platelet-rich plasma	31
	Simple search: PRP	49
Clinicaltrials.gov	Advanced search: platelet-rich plasma, studies with results, interventional studies	32

kw: keyword

Table 2. Description of Studies

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
Adhesive Capsulitis						
Thu et al., 2020[23] RCT	n = 64 48 F, 13 M Age: PRP 52.84 ± 6.92 years PT 57.17 ± 6.93 years Symptom duration: <3 months	PRP n = 32 • US-guided autologous PRP injection into the GHJ 1 Injection	Conventional PT n = 32 • SWD × 15 min • Exercise × 30 min: stretching within pain limit, AROM, PROM, pulleys 3×/week for 6 weeks	VAS DASH ER ROM	1 week 3 weeks 6 weeks	Not significant between-group differences Both groups demonstrated statistically significant improvement in VAS, DASH, and ER PROM at all time points.
Unlu et al. 2021[24] RCT	n = 34 21 F, 11 M Age, median (range): PRP 57 years (23–67 years) Placebo 57 years (45–70 years) Symptom duration, median (range): PRP 4 months (3–9 months) Placebo 6 months (3–9 months)	PRP + exercise n = 17 • PRP injection into the GHJ 3 Injections over 2 weeks • Supervised exercise program: warming, scapular stabilization, capsular stretch, pendulums, range of motion 45 min, 3×/week for 2 weeks	Placebo + exercise n = 15 • Saline injection into the GHJ 3 Injections over 2 weeks • Supervised exercise program: warming, scapular stabilization, capsular stretch, pendulums, range of motion 45 min, 3×/week for 2 weeks	VAS SPADI ER ROM	1 month 3 months	Statistically significant between-group differences in VAS, SPADI, and ER ROM favoring PRP. Both groups demonstrated statistically significant improvement in VAS, SPADI, and ER ROM.
Carpal Tunnel Syndrome						
Guven et al. 2019[15] Quasi-experimental	n = 40 hands, 30 subjects 28 F, 2 M Age, median (range): PRP 47.5 years (28–63 years) Control 50 years (31–56 years) Symptom duration: PRP 6 years (0–15 years) Control 5 years (0–13 years)	PRP + Education n = 20 • US-guided perineural PRP injection into the carpal tunnel 1 Injection • Education: activity modification, night splint, acetaminophen 4 weeks	Education n = 20 • Education: activity modification, night splint, acetaminophen 4 weeks	BCTSQ Electro-physiological values for median nerve: distal motor latency and sensory nerve conduction velocity Cross-sectional area of median nerve	4 weeks	Statistically significant between-group difference in BCTSQ change scores (not post-treatment scores) favoring the PRP group. No statistically significant between-group differences in electro-physiological values or median nerve cross-sectional area. Both groups demonstrated statistically significant improvement in BCTSQ scores and median nerve cross-sectional area, but only PRP improved in electro-physiological values of the median nerve for distal motor latency and sensory nerve conduction velocity.

Raeissadat et al. 2018[21] RCT	n = 41 41 F, 0 M Age: PRP 51.20 ± 9.82 years Splint 47.23 ± 7.11 years Symptom duration: PRP 13.74 months ± 11.5 months Splint 14.13 months ± 8.55 months	PRP + splint n = 21 • Leukocyte-poor PRP injection into the carpal tunnel 1 Injection • Pre-fabricated wrist splint at 5° wrist extension worn overnight 8 weeks	Splint n = 20 • Pre-fabricated wrist splint at 5° wrist extension worn overnight 8 weeks	VAS BCTSQ Electro-physiological values for median nerve: peak latency of sensory nerve action potential and onset latency of compound muscle action potential.	10 weeks	No statistically significant between-group differences. Both groups demonstrated statistically significant improvement in VAS, BCTSQ, and peak latency of sensory nerve action potentials, but only splint improved in median nerve onset latency of compound muscle action potential.
Wu et al. 2017[26] RCT	n = 60 52 F, 8 M Age: PRP 57.87 ± 1.51 years Splint 54.27 ± 1.34 years Symptom duration: PRP 34.43 months ± 5.67 months Splint 30.70 months ± 6.03 months	PRP n = 30 • US-guided PRP injection into the carpal tunnel 1 Injection	Splint n = 30 • Wrist splint in neutral position worn overnight for at least 8 h 6 months	VAS BCTSQ Electro-physiological values of median nerve: sensory nerve conduction velocity and distal motor latency. Cross-sectional area of median nerve.	1 month 3 months 6 months	Statistically significant between-group differences in VAS at 6 months, BCTSQ symptom at 3 and 6 months, BCTSQ function at 1, 3, and 6 months, and cross-sectional area of median nerve at 1, 3, and 6 months favoring PRP. No statistically significant between-group difference in electro-physiological values. Both groups demonstrated statistically significant differences in all outcome measures.
Lateral Epicondylalgia						
Lim et al. 2018[18] RCT	n = 120 55 F, 54 M Age: PRP 50.13 years PT 54.49 years Symptom duration: NR	PRP + physical therapy + strap n = 61 • US-guided percutaneous needle tenotomy with autologous PRP injection into the common extensor tendon 1 Injection • Tennis elbow strap • Exercise: stretching and strengthening 24 weeks	Physical therapy + strap n = 59 • Tennis elbow strap • Exercise: stretching and strengthening 24 weeks	VAS Mayo Clinic Performance Index Elbow	1 Month	Statistically significant between-group differences for VAS and Mayo Clinical Performance Index Elbow favoring PRP. PRP demonstrated statistically significant improvements in VAS and Mayo Clinic Performance Index, with PT demonstrating no significant differences.

(Continues)

Table 2. (Continued)

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
Tetschke et al. 2015[22] Quasi	n = 56 31 F, 21 M Age: PRP 51.5 ± 10.4 years Laser 53.1 ± 12.7 Symptom duration: >3 months	ACP + PT n = 27 • Intralesional ACP injections 3 Injections with 7 days interval • Manual Therapy: deep tissue massage, trigger point therapy of the forearm extensors, supinator, anconeus, brachioradialis, trapezius, supraspinatus • Exercise: AROM, stretching, strengthening, sport-specific training 2 Sessions per week for 6 weeks	Laser + PT n = 29 • Low-level laser 2 Sessions per week for 6 weeks • Manual therapy: deep tissue massage, trigger point therapy of the forearm extensors, supinator, anconeus, brachioradialis, trapezius, supraspinatus • Exercise: AROM, stretching, strengthening, sport-specific training 2 sessions per week for 6 weeks	VAS DASH	2 months 6 months 1 year	No statistically significant between-group differences
Rotator Cuff Tendinopathy						
Kesikburun et al. 2013[16]	n = 40 27 F, 13 M Age: PRP 45.5 ± 11.8 years Placebo 51.4 ± 10 years Symptom duration, median (range): PRP 8.5 months (3–36 months) Placebo 10 months (2–48 months)	PRP + PT n = 20 • US-guided autologous PRP injection into rotator cuff tendon 1 Injection • Exercise: PROM, Codman exercises, stretching of posterior capsule and pectoral muscles, strengthening rotator cuff and scapular muscles Supervised 3 weeks HEP 3 weeks	Placebo + PT n = 20 • US-guided saline injection into rotator cuff tendon 1 Injection • Exercise: PROM, Codman exercises, stretching of posterior capsule and pectoral muscles, strengthening rotator cuff and scapular muscles Supervised 3 weeks HEP 3 weeks	VAS SPADI WORC	3 weeks 6 weeks 12 weeks 24 weeks 1 year	No statistically between-group differences Both groups demonstrated statistically significant improvements in VAS, WORC, and SPADI

Kim et al. 2019[17] Quasi	n = 60 27 F, 33 M Age: PRP 55.6 ± 5.5 years PT 53.7 ± 11.5 years Symptom duration: NR	PRP n = 30 • US-guided autologous PRP injection into supraspinatus tendon 1 Injection • Provided with brochure containing exercises, but not asked to follow it.	PT n = 30 • Strengthening: scapular stabilizing, infraspinatus, subscapularis isometric, and isotonic exercises using dumbbell and thera band • Provided with brochure containing exercises Instructed by PT then performed for HEP 20 min, 4×/week	NPRS ASES CMS	6 weeks 12 weeks 24 weeks	No statistically significant between-group differences in ASES or CMS at 6 weeks or 12 weeks Statistically significant between-group differences in ASES and CMS at 24 weeks Statistically significant between-group difference in NPRS at 6 weeks, but not 12 or 24 weeks
Wesner et al. 2016[25] RCT	n = 9 3 F, 6 M Age, median (range): PRP 48 years (37–56 years) Placebo 47 and 52 years Symptom duration: PRP 75.6 months (12, 36 months) Placebo 15.5 months (13, 18 months)	PRP + PT n = 7 • US-guided PRP injection into the supraspinatus /infraspinatus tendon 1 Injection • Standardized exercise program performed at home and supervised by physical therapist 3 months	Placebo + PT n = 2 • US-guided saline injection into the supraspinatus /infraspinatus tendon 1 Injection • Standardized exercise program performed at home and supervised by physical therapist 3 months	VAS DASH WORC	3 months 6 months	Mean improvement on VAS was clinically important for PRP, but not for placebo 5/7 PRP and 1/2 placebo participants demonstrated clinically important DASH improvement 6/7 PRP and 1/2 placebo participants demonstrated clinically important WORC improvements
Subacromial Impingement Syndrome						
Nejati et al. 2017[19] RCT	n = 62 27 F, 22 M Age: PRP 52.5 ± 7.3 years Exercise 53.9 ± 10.6 years Symptom duration: >3 months	PRP n = 31 • US-guided PRP injection into injured rotator cuff tendon and subacromial space 2 Injections, 1st one on the first visit and the 2nd one after 1 month	Exercise n = 31 • Supervised exercise therapy in the hospital: aerobic activity × 10–15 min, 4 stages of progressive exercise, ice × 20 min 1×/week for 12 weeks • HEP 5×/week for 12 weeks Continued for 6 months	VAS DASH WORC	1 month 3 months 6 months	Statistically significant between-group differences in VAS favoring exercise at 1 and 3 months, but not 6 months Statistically significant between-group differences in DASH favoring exercise at 3 months Statistically significant between-group differences for WORC favoring exercise at 1, 3, and 6 months Both groups demonstrated statistically significant improvement in VAS, DASH, and ORC

(Continues)

Table 2. (Continued)

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
Pasin et al. 2019[20] RCT	n = 90 53 F, 37 M Age: PRP 49.4 ± 9.1 years PT 49.86 ± 9.0 years Symptom duration: PRP 0.77 mo ± 0.7 months PT 1.01 months ± 1.2 months	PRP + Exercise n = 30 • PRP injection into the subacromial space 1 Injection • Exercise program 3 weeks	Modalities + Exercise n = 30 • TENS • Hot pack 20 min, 5×/week for 2 weeks • US 8–10 sessions • Exercise: joint range of motion, Codman's exercises, posterior joint capsule, stretching exercises of the pectoral muscles, isotonic strengthening 5×/week for 2 weeks	VAS Quick DASH UCLA SRS SF-36	3 weeks 8 weeks	Statistically significant between-group differences in VAS, UCLA SRS, and Quick DASH favoring PRP at 8 weeks. No statistically significant between-group differences for SF-36, except body pain favoring PRP at 8 weeks Both groups demonstrated statistically significant improvement in VAS, UCLA SRS, Quick DASH, and SF-36
Shoulder Osteoarthritis						
Kothari et al. 2017[10] RCT	n = 195 63 F, 57 M Age: PRP 51.9 ± 10.1 years US 51.2 ± 11.7 years Symptom duration: PRP 4.1 months ± 2.5 months US 4.7 months ± 2.1 months	PRP + Exercise n = 65 • PRP injection 1 Injection • Exercise program: pendulums, stretching, AAROM and AROM for flexion, abduction, external, and internal rotation 10 min, 2×/day 12 weeks	US + Exercise n = 65 • US × 7 min Every other day, 7 sessions in 2 weeks • Exercise program: pendulums, stretching, AAROM and AROM for flexion, abduction, external, and internal rotation 10 min, 2×/day for 12 weeks.	VAS Quick DASH	3 weeks 6 weeks 12 weeks	Statistically significant between-group differences in VAS and Quick DASH at 6 and 12 weeks favoring PRP. Both groups demonstrated statistically significant improvements in VAS and Quick DASH

AAROM, active-assisted range of motion; AROM, active range of motion; ASES, American Shoulder and Elbow Surgeons; ACP, autologous conditioned plasma; BCTSQ, Boston Carpal Tunnel Syndrome Questionnaire; CMS, Constant–Murley Score; DASH, Disabilities of the Arm, Shoulder, and Hand; ER, external rotation; GHJ, glenohumeral joint; HEP, home exercise program; NR, not reported; NPRS, Numeric Pain Rating Scale; PROM, passive range of motion; PT, physical therapy; PRP, platelet-rich plasma; RCT, randomized controlled trial; ROM, range of motion; SF-36, Short Form-36; SWD, short-wave diathermy; SPADI, Shoulder Pain and Disability Index; TENS, transcutaneous electrical stimulation; US, ultrasound; UCLA SRS, University of California, Los Angeles Shoulder Rating Scale; VAS, Visual Analog Scale; WORC, Western Ontario Rotator Cuff Index.

Table 3. Psychometric Properties of Included Outcome Measures

Outcome measure	Description	Reliability	MDC/MCID
Pain			
Visual Analog Scale[28]	Self-reported measure of pain. Vertical or horizontal line scaled from 1–100 mm, where 1 represents "no pain" and 100 represents "worst possible pain."		MCID = 9–11 mm
Numeric Pain Rating Scale[29]	Self-reported measure of pain. 11-point scale (0–10), where 0 represents "no pain" and 10 represents "worst pain imaginable."	ICC = 0.74	MDC = 2.5 pts. MCID = 1.1 pts.
Disability			
DASH[30,31]	30-item self-reported measure of disability and symptoms in people with disorders of the upper extremity. Scored on 100% scale, with 100% indicating the maximum disability.	ICC = 0.93 (95% confidence interval [CI] 0.86, 0.97)	MDC = 10.81%
Quick DASH[29–31]	11-item self-reported measure of disability and symptoms in people with disorders of the upper extremity. Scored on 100% scale, with 100% indicating the maximum disability.	ICC = 0.93 (95% CI 0.87, 0.97) Comparison to DASH *R* = 0.98 ICC = 0.96 (95% CI 0.84, 0.98)	MDC = 11.2%, 12.85% MCID = 8%
Shoulder Pain and Disability Index[32,33]	13-item measure of shoulder pain (5 items) and disability (8 items). Each subscale scored out of 100 and an average taken across the two subscales to give a total out of 100, with higher score indicating greater disability.	ICC = 0.66, >0.89	MCIC = 8-13 pts. MDC = 18 pts.
Boston Carpal Tunnel Syndrome Questionnaire[34–36]	Self-reported questionnaire assessing symptoms and functional impairment caused by carpal tunnel syndrome. 2 subscales with 6 items each scored on a 5-point Likert scale from 1–5, with 1 representing no symptoms and 5 representing the most severe symptoms. Overall score calculated as the mean of the answered items.	ICC = 0.899 (symptom severity), 0.944 (functional status)	MCID = 0.74 MDC = 0.86 (symptoms severity), 0.75 (functional status)
Mayo Elbow Performance Index[37,38]	Functional score for evaluating elbow disorders. 4-part test based on 100-point scale.	ICC = 0.89	MDC = 12.2
American Shoulder and Elbow Surgeon[33,39]	Measure of pain and functional limitation (10 questions on 4-point scale). Scored on 0–100 scale, where 0 represents "worst" and 100 represents "best."	ICC = 0.84-0.96	MCID = 6.4 pts.

(Continues)

Table 3. (Continued)

Outcome measure	Description	Reliability	MDC/MCID
University of California Los Angeles Shoulder Rating Scale[40–42]	2 single-item subscales measuring pain and functional level of the shoulder. Likert scale 1–10 with higher scores indicating less pain and greater function.	ICC = 0.93 (pain), 0.95 (function)	MCID = 3.0, 3.5 MDC = 3.6
Quality of life			
Constant–Murley Score[42–45]	Quality of life questionnaire for shoulder assessment measured on 4 subscales. Scored on a total scale of 0–100, where 0 represents "worst" and 100 represents the "best health."	ICC = 0.80 (95% CI 0.63, 0.89), 0.93 (95% CI 0.89, 0.97)	MCID = 9.8, 6.7
Short Form-36[46–48]	36-item self-reported quality of life tool measured across 8 domains: physical functioning, bodily pain, role limitations because of physical health problems, role limitations because of emotional problems, general mental health, social functioning, energy/vitality, general health perception. Each item scored from 0–100 and then averaged to get scale score for each domain out of 100, with higher scores indicating a more favorable health state.	ICC = 0.72–0.95 (across domains)	MCID = 10 (physical functioning)
Western Ontario Rotator Cuff Index[49–51]	21-item health-related quality of life questionnaire for patients with rotator cuff disease. 5 domains, each measured on 0–100-mm scale and total score out of 2,100 converted to a percentage, with 0% representing the lowest functional status and 100% representing the highest functional status.	ICC = 0.96	MCID = 275 (converted = 13%)

ICC: intra-class correlation coefficient; MCID: minimal clinically important difference; MDC: minimal detectable change.

Scale (VAS; 0–100 mm/0–10 cm) and Numeric Pain Rating Scale (NPRS; 0–10 pts.). Disability was measured using the Disabilities of the Arm, Shoulder, and Hand (DASH; 0–100%), Quick DASH (0–100%), Shoulder Pain and Disability Index (SPADI; 0–100%), Boston Carpal Tunnel Syndrome Questionnaire (BCTSQ; 0–5 pts.), Mayo Clinic Performance Index Elbow, American Shoulder and Elbow Surgeons (ASES; 0–100 pts.), and University of California Los Angeles Shoulder Rating Scale (UCLA SRS; 0–35 pts.). Quality of life was measured using the Constant–Murley Score (CMS; 0–100 pts.), Western Ontario Rotator Cuff Index (WORC; 0–100%), and Short Form-36 (SF-36; 0–100).

Timing of outcome assessment

Outcomes were assessed in the short term (<3 months) and long term (6–12 months). When multiple time points existed, the one closest to 3-month and 12-month follow-up was used in data analyses, unless all studies had similar follow-up assessments.[52]

Methodological quality

Methodological quality was assessed using the Cochrane Collaboration Risk of Bias (RoB) tool.[52] It examines risk of bias across the following five domains of bias: selection, performance, detection, attrition, and reporting. Each item was awarded a "Yes" and received a score of one (1) if the criteria

was fulfilled, and a "No" or "Unclear" was assigned if the criteria was not fulfilled or was unclear, resulting in a score of zero (0).[52] The sum of the points represents the total risk of bias out of 12 points, with higher scores indicating lower risk of bias. Present authors independently scored each included study, with discrepancies resolved through discussion until consensus was reached (Table 4).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to provide an overall assessment of the quality of evidence across the following five domains: risk of bias, inconsistency of results, indirectness or evidence, imprecision, and publication bias.[52,53] The GRADE provides a summary rating of the quality of the body of evidence for the effect of an intervention on a particular outcome measure, providing a recommendation that may guide clinicians' decision-making in selecting the most optimal interventions. Following evidence appraisal, outcomes are classified by the level of evidence (Table 5).

Data collection

Both authors performed data extraction, and included study details and design, patient demographics, interventions, timing of assessment, outcome measures, and results (Table 2). In the event of missing data, study authors were contacted.

Data analysis

Data analysis was conducted using Revman 5.4. Post-test mean values and standard deviations (SD) were used for meta-analysis, unless articles only reported change scores. In case SD values were not provided, the authors calculated them for meta-analysis. A random-effects model with inverse variance was used to calculate mean differences (MD) for pain, disability, and quality of life in case outcomes could be converted to the same numerical scale, or standardized mean differences (SMD) and 95% CI when they could not.[52,54] Mean differences were calculated for homogenous tools of pain and quality of life so that minimal clinically important differences (MCID) could be discussed in relation to patient improvement. However, because of the heterogeneity of some measurement tools of disability, SMDs were required. Statistical heterogeneity was evaluated using the I^2 statistic, with values greater than 50% indicating high heterogeneity.[55] Effect sizes were presented in forest plots, and interpreted based on previous research: 0.2 represented small effect, 0.5 represented moderate effect, and 0.8 represented a large effect.[56]

Separate meta-analyses were conducted for each pathology, comparing PRP to a comparison or control group for their effect on pain, disability, quality of life, and electrophysiological values, and cross-sectional area of the median nerve in the short term and long term when data were available. In case statistical pooling was not possible, findings were presented in a narrative form.

RESULTS

Study selection

The search identified 485 studies, with an additional 12 identified through manual searching. In all, 41 full-text articles were assessed for eligibility, with 13 articles[10,15–26] meeting the inclusion criteria (Figure 1).

Characteristics of included studies

The average score across studies on the RoB Tool was 8.77 out of 12 (range 5–12) (Table 4). The most common sources of bias were blinding of participants, providers, and outcome assessors, leading to potential performance and detection bias.

Across studies, there were a total of 861 participants, 63% females and 37% males. All studies included patients with various UE musculoskeletal pathologies: adhesive capsulitis (2),[23,24] carpal tunnel syndrome (3),[15,21,26] lateral epicondylalgia (2),[18,22] rotator cuff tendinopathy (3),[16,17,25] subacromial impingement (2),[19,20] and shoulder osteoarthritis (1)[10] (Table 2). Of the 13 studies, 12 assessed pain[10,16–26] (VAS or NPRS), 13 assessed disability[10,15–26] (DASH, Quick DASH, SPADI, BCTSQ, Mayo Elbow Performance Index, ASES, and UCLA SRS), five assessed quality of life[16,17,19,20,25] (SF-36, WORC, and CMS), two assessed ER ROM,[23,24] three assessed electrophysiological values for the median nerve[15,21,26] (distal motor latency or onset latency of compound muscle action potential, sensory nerve conduction velocity, or peak latency of sensory

Table 4. Risk of Bias Criteria Outlined by the Cochrane Collaboration

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Providers	Blinding of Outcome Assessors	Incomplete Outcome Data – Drop Outs	Incomplete Outcome Data – ITT Analysis	Selective Reporting	Group Similarity at Baseline	Influence of Co-interventions	Compliance with Interventions	Timing of Outcome Assessments	Total
Adhesive capsulitis													
Thu et al. 2020[23]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	10/12
Unlu et al. 2021[24]	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/12
Carpal Tunnel Syndrome													
Guven et al. 2019[15]	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	7/12
Raeissadat et al. 2018[21]	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	9/12
Wu et al. 2017[26]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	10/12
Lateral Epicondylalgia													
Lim et al. 2018[18]	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	9/12
Tetschke et al. 2015[22]	N	N	N	N	N	Y	Y	Y	N	Y	Y	Y	7/12
Rotator Cuff Tendinopathy													
Kesikburun et al. 2013[16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/12
Kim et al. 2019[17]	N	N	N	N	N	N	Y	Y	N	Y	Y	Y	5/12
Wesner et al. 2016[25]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	11/12
Subacromial Impingement													
Nejati et al. 2017[19]	Y	Y	N	N	Y	N	Y	Y	Y	Y	U	Y	8/12
Pasin et al. 2019[20]	N	N	N	N	N	U	Y	Y	Y	Y	Y	Y	6/12
Shoulder Osteoarthritis													
Kothari et al. 2017[10]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	10/12

The risk of bias criteria outlined by the Cochrane Collaboration were used and results were labeled as Yes (Y) = 1; No (N) = 0; Unsure (U) = 0.[52]

Table 5. GRADE Levels of Evidence[52]

Level of Evidence	Description
High quality	Further research is very unlikely to change confidence in estimate of effect.
Moderate quality	Further research is likely to have an important impact on confidence in estimate of effect and may change the estimate.
Low quality	Further research is very likely to have an important impact on confidence in estimate of effect and is likely to change the estimate.
Very low quality	Very little confidence in estimate effect.
No evidence	No randomized controlled trials were identified that addressed this outcome.

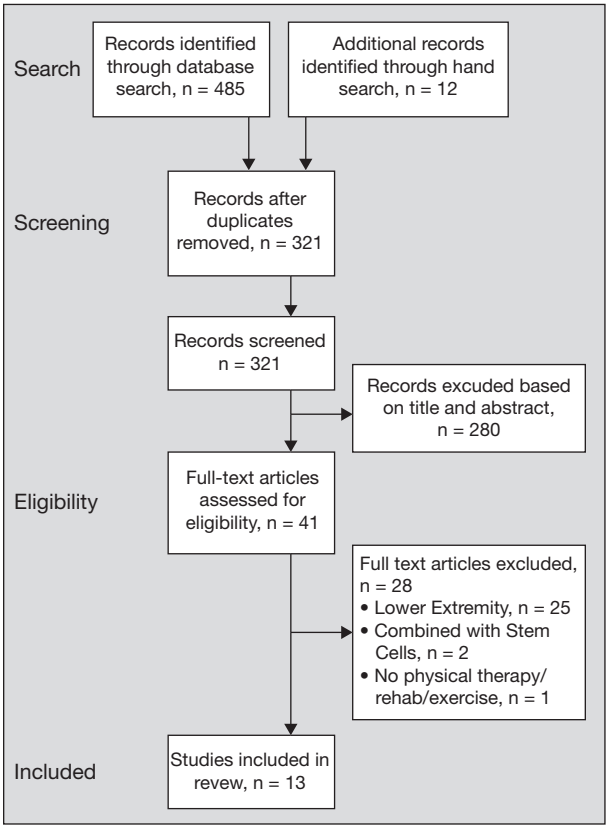

Figure 1. PRISMA flow diagram.

nerve action potential), and two assessed the cross-sectional area of the median nerve[15,26](Table 6).

Adhesive capsulitis

Two studies[23,24] included 98 participants, 74% females, with an RoB of 10 out of 12. One study[23] compared PRP alone to conventional PT, which included exercise, while the other[24] compared PRP and exercise to placebo and exercise.

Meta-analyses (n = 98) revealed a nonsignificant effect on pain (mm) (MD −10.24; 95% CI: −26.27, 5.78; I^2 = 83%; P = 0.21), disability (SMD −1.00; 95% CI: −2.17, 0.17; I^2 = 84%; P = 0.09), and ER ROM (MD 13.44; 95% CI: −9.51, 36.38; I^2 = 95%; P = 0.25) at short-term follow-up (Figures 2–4).

Carpal tunnel syndrome

Three studies[15,21,26] included 131 participants (141 hands), with 92% females. The average RoB score was 8.66 out of 12 (range 7–10). Two studies compared PRP and night splint[21] (or training to wear a night splint[15]) to the night splint/training alone, while the other[26] compared PRP alone to the night splint alone.

Meta-analysis of the two studies[21,26] (n = 101) revealed a nonsignificant effect on pain (cm) (MD −0.11; 95% CI: −1.00, 0.78; I^2 = 45%; P = 0.81) at short-term follow-up (Figure 5). Meta-analysis of three studies[15,21,26] (n = 141) revealed a nonsignificant effect on disability BCTSQ symptom (SMD −0.28; 95% CI: −0.72, 0.16; I^2 = 41%; P = 0.21) and BCTSQ function (SMD −1.74; 95% CI: −4.31, 0.83; I^2 = 97%; P = 0.19) at short-term follow-up (Figures 6 and 7). Meta-analyses of two studies[15,26] (n = 100) revealed a nonsignificant effect on distal motor latency (MD 0.03; 95% CI: −0.35, 0.42; I^2 = 22%; P = 0.87) and sensory nerve conduction velocity (MD −0.84; 95% CI: −3.57, 1.89; I^2 = 26%; P = 0.55) at short-term follow-up (Figures 8 and 9). The third study[21] demonstrated insignificant between-group differences in peak latency sensory nerve action potential or onset latency compound muscle action potential. Meta-analysis of the two studies[15,26] (n = 100) revealed a nonsignificant effect on cross-sectional area of the median nerve (MD 0.91; 95% CI: −0.63, 2.49; I^2 = 0%; P = 0.25) at short-term follow-up (Figure 10).

Table 6. Results of Included Studies

Study	Outcome	Intervention Group (Mean ± SD)		Comparison Group (Mean ± SD)		Between-group Differences	
Adhesive capsulitis							
Thu et al. 2020[23]	VAS (mm)	Pre	82.9 ± 14.42	Pre	82.67 ± 14.37		
		1 week	59.35 ± 15.48*	1 week	63.00 ± 13.17*	1 week	NS
		3 weeks	45.16 ± 16.91*	3 weeks	49.67 ± 15.20*	3 weeks	NS
		6 weeks	28.39 ± 14.63*	6 weeks	31.00 ± 14.94*	6 weeks	NS
	DASH	Pre	52.9 ± 12.18	Pre	53.8 ± 10.72		
		1 week	37.48 ± 13.93*	1 week	40.83 ± 12.24*	1 week	NS
		3 weeks	24.92 ± 13.82*	3 weeks	29.86 ± 12.82*	3 weeks	NS
		6 weeks	14.35 ± 10.74*	6 weeks	19.55 ± 12.47*	6 weeks	NS
	ER ROM (deg)	Pre	56.45 ± 15.5	Pre	52.67 ± 16.6		
		1 week	67.58 ± 15.59*	1 week	64.33 ± 14.19*	1 week	NS
		3 weeks	73.87 ± 14.65*	3 weeks	71.67 ± 12.89*	3 weeks	NS
		6 weeks	80.81 ± 11.26*	6 weeks	78.83 ± 9.16*	6 weeks	NS
Unlu et al. 2021[24]	VAS (mm)	Pre	32.0 ± 22.0	Pre	39.0 ± 36.0		
		1 month	4.0 ± 10.6*	1 month	25.0 ± 26.0*	1 month	*P = 0.045, favoring PRP
		3 months	1.7 ± 7.2*	3 months	20.0 ± 22.0*	3 months	*P = 0.004, favoring PRP
	SPADI	Pre	99.7 ± 22.8	Pre	107.8 ± 17.1		
		1 month	31.4 ± 19.5*	1 month	68.3 ± 34.4*	1 month	*P = 0.002, favoring PRP
		3 months	13.5 ± 15.2*	3 months	64.0 ± 39.8*	3 months	*P = 0.000, favoring PRP
	ER ROM (deg)	Pre	37 ± 21.1	Pre	39.3 ± 19.3		
		1 month	63.8 ± 19.2	1 month	50 ± 20.8	1 month	
		3 months	79.7 ± 13.6*	3 months	54.3 ± 11.4*	3 months	*P < 0.05, favoring PRP
Carpal Tunnel Syndrome							
Guven et al. 2019[15]	BCTSQ symptom	Pre	3.0 ± 0.7	Pre	2.3 ± 0.6		
		4 weeks	1.7 ± 0.6*	4 weeks	1.6 ± 0.5*	4 weeks	NS
	BCTSQ function	Pre	2.7 ± 0.8	Pre	2.2 ± 0.6		
		4 weeks	1.8 ± 0.6*	4 weeks	1.7 ± 0.6*	4 weeks	NS
	Distal motor latency (ms)	Pre	4.8 ± 0.8	Pre	4.5 ± 0.7		
		4 weeks	4.4 ± 0.6*	4 weeks	4.5 ± 0.6	4 weeks	NS
	Sensory nerve conduction velocity (m/s)	Pre	40.9 ± 6.5	Pre	42.4 ± 5.1		
		4 weeks	43.4 ± 5.7*	4 weeks	42.9 ± 4.7	4 weeks	NS
	Median nerve CSA (mm^2)	Pre	14.1 ± 4.9	Pre	11.5 ± 2.0		
		4 weeks	12.6 ± 4.5*	4 weeks	10.9 ± 2.2*	4 weeks	NS
Raeissadat et al. 2018[21]	VAS (cm)	Pre	6.82 ± 1.24	Pre	6.24 ± 1.17		

Study	Outcome	Intervention Group (Mean ± SD)		Comparison Group (Mean ± SD)		Between-group Differences	
		10 weeks	4.02 ± 1.92*	10 weeks	3.52 ± 2.02	10 weeks	NS
	BCTSQ symptom	Pre	2.43 ± 0.73	Pre	2.73 ± 0.40		
		10 weeks	1.72 ± 0.52*	10 weeks	1.90 ± 0.42*	10 weeks	NS
	BCTSQ function	Pre	2.36 ± 0.83	Pre	2.54 ± 0.62		
		10 weeks	1.82 ± 0.73*	10 weeks	1.82 ± 0.42*	10 weeks	NS
	Peak latency sensory nerve action Potential (ms)	Pre	4.25 ± 0.52	Pre	4.05 ± 0.22		
		10 weeks	4.12 ± 0.63*	10 weeks	3.75 ± 0.35*	10 weeks	NS
	Onset latency compound muscle action potential (ms)	Pre	4.13 ± 0.53	Pre	4.06 ± 0.55		
		10 weeks	4.15 ± 0.52	10 weeks	4.07 ± 0.55*	10 weeks	NS
Wu et al. 2017[26]	VAS (cm)	Pre	6.50 ± 1.64	Pre	6.29 ± 1.70		
		1 month	3.89 ± 1.53*	1 month	3.88 ± 1.53*	1 month	NS
		3 months	2.91 ± 1.26*	3 months	3.36 ± 1.42*	3 months	NS
		6 months	1.97 ± 1.26*	6 months	2.99 ± 1.48*	6 months	*P = 0.018, favoring PRP
	BCTSQ symptom	Pre	26.17 ± 6.02	Pre	24.93 ± 6.68		
		1 month	17.17 ± 3.45*	1 month	18.43 ± 5.09*	1 month	NS
		3 months	15.56 ± 2.74*	3 months	18.13 ± 5.59*	3 months	*P = 0.017, favoring PRP
		6 months	14.14 ± 2.46*	6 months	16.20 ± 4.71*	6 months	*P = 0.045, favoring
	BCTSQ function	Pre	19.23 ± 5.92	Pre	18.13 ± 3.56		
		1 month	12.24 ± 0.55*	1 month	14.40 ± 0.70*	1 month	*P = 0.002, favoring PRP
		3 months	10.79 ± 0.40*	3 months	13.63 ± 0.66*	3 months	*P < 0.001, favoring PRP
		6 months	10.41 ± 0.48*	6 months	12.92 ± 0.65*	6 months	*P = 0.001, favoring PRP
	Distal motor latency (ms)	Pre	5.66 ± 1.49	Pre	5.21 ± 6.90		
		1 month	5.28 ± 1.26*	1 month	4.96 ± 1.20*	1 month	NS
		3 months	5.26 ± 1.37*	3 months	4.98 ± 1.20*	3 months	NS
		6 months	5.18 ± 1.42*	6 months	4.74 ± 1.04*	6 months	NS
	Sensory nerve conduction velocity (m/s)	Pre	30.18 ± 7.07	Pre	32.35 ± 6.02		
		1 month	32.45 ± 6.85*	1 month	34.74 ± 6.63*	1 month	NS
		3 months	32.82 ± 6.96*	3 months	35.05 ± 7.01*	3 months	NS
		6 months	33.92 ± 7.34*	6 months	36.17 ± 7.34*	6 months	NS
	Median nerve CSA (mm^2)	Pre	14.01 ± 4.49	Pre	12.91 ± 4.44		
		1 month	11.86 ± 4.16	1 month	11.72 ± 4.44	1 month	*P = 0.004, favoring PRP
		3 months	11.35 ± 4.05	3 months	11.23 ± 3.94	3 months	*P = 0.003, favoring PRP

(Continues)

Table 6. (Continued)

Study	Outcome	Intervention Group (Mean ± SD)		Comparison Group (Mean ± SD)		Between-group Differences	
		6 months	10.93 ± 4.11	6 months	10.87 ± 4.16	6 months	*P = 0.004, favoring PRP
Lateral Epicondylalgia							
Lim et al. 2018[18]	VAS (mm)	Pre	64.27	Pre	44.88		
		1 month	23.67	1 month	15.68		
		Δscore	40.6*	Δscore	29.2	Δscore	*P < 0.05, favoring PRP
	Mayo Clinic Perform-ance Index Elbow	Pre	66.76	Pre	75.64		
		1 month	82.99	1 month	84.06		
		Δscore	16.23*	Δscore	8.42	Δscore	*P < 0.05, favoring PRP
Tetschke et al. 2015[22]	VAS (mm)	Pre	52.0 ± 18.0	Pre	67.0 ± 20.0		
		2 months	37.0 ± 20.0	2 months	47.0 ± 23.0	2 months	NS
		6 months	27.0 ± 16.0	6 months	36.0 ± 22.0	6 months	NS
		1 year	18.0 ± 20.0	1 year	27.0 ± 23.0	1 year	NS
	DASH	Pre	37.0 ± 18.3	Pre	47.0 ± 19.6		
		2 months	29.8 ± 21.1	2 months	38.9 ± 20.7	2 months	NS
		6 months	26.5 ± 21.2	6 months	29.0 ± 19.6	6 months	NS
		1 year	18.2 ± 19.5	1 year	26.7 ± 21.8	1 year	NS
Rotator Cuff Tendinopathy							
Kesikburun et al. 2013[16]	VAS (cm)	Pre	7.98 ± 1.18	Pre	8.63 ± 1.01		
		3 weeks	4.73 ± 2.48	3 weeks	5.93 ± 2.21	1 week	NS
		6 weeks	4.20 ± 2.67	6 weeks	4.35 ± 3.03	6 weeks	NS
		12 weeks	3.47 ± 3.03	12 weeks	4.29 ± 3.33	12 weeks	NS
		24 weeks	2.59 ± 2.73	24 weeks	4.07 ± 3.62	24 weeks	NS
		1 year	1.80 ± 2.36	1 year	3.29 ± 3.61	1 year	NS
	SPADI	Pre	70.76 ± 18.06	Pre	74.64 ± 18.32		
		3 weeks	48.61 ± 21.27	3 weeks	60.01 ± 23.20	1 week	NS
		6 weeks	37.96 ± 25.11	6 weeks	45.35 ± 26.78	6 weeks	NS
		12 weeks	31.57 ± 27.49	12 weeks	43.78 ± 31.56	12 weeks	NS
		24 weeks	25.49 ± 25.78	24 weeks	41.93 ± 33.03	24 weeks	NS
		1 year	20.24 ± 22.20	1 year	37.26 ± 34.43	1 year	NS
	WORC	Pre	34.24 ± 18.69	Pre	31.48 ± 15.31		
		3 weeks	58.51 ± 18.71	3 weeks	45.65 ± 20.15	1 week	NS
		6 weeks	65.18 ± 20.86	6 weeks	58.34 ± 26.27	6 weeks	NS
		12 weeks	69.84 ± 25.82	12 weeks	57.53 ± 31.87	12 weeks	NS
		24 weeks	77.46 ± 22.14	24 weeks	61.84 ± 32.34	24 weeks	NS
		1 year	81.15 ± 19.94	1 year	64.55 ± 34.45	1 year	NS
Kim et al. 2019[17]	NPRS	Pre	5.7 ± 2.3	Pre	4.8 ± 1.6		
		6 weeks	3.6 ± 2.6*	6 weeks	4.4 ± 1.8	6 weeks	*P = 0.031, favoring exercise

Study	Outcome	Intervention Group (Mean ± SD)		Comparison Group (Mean ± SD)		Between-group Differences	
		12 weeks	2.9 ± 2.6*	12 weeks	3.3 ± 1.1*	12 weeks	NS
		24 weeks	2.9 ± 2.7*	24 weeks	2.3 ± 1.5*	24 weeks	
	ASES	Pre	42.8 ± 18.4	Pre	59.0 ± 13.4		
		6 weeks	62.7 ± 19.4*	6 weeks	65.4 ± 16.4*	6 weeks	NS
		12 weeks	72.4 ± 17.3*	12 weeks	72.3 ± 11.0*	12 weeks	NS
		24 weeks	68.0 ± 23.8*	24 weeks	79.7 ± 14.1*	24 weeks	*P = 0.050, favoring exercise
	CMS	Pre	66.5 ± 17.7	Pre	80.9 ± 11.6		
		6 weeks	76.3 ± 14.9*	6 weeks	81.2 ± 16.1	6 weeks	NS
		12 weeks	81.6 ± 15.3*	12 weeks	82.7 ± 13.3	12 weeks	NS
		24 weeks	81.7 ± 17.4*	24 weeks	90.2 ± 9.5*	24 weeks	*P = 0.048, favoring exercise
Wesner et al. 2016[25]	VAS (cm)	Pre	4.14 ± 3.23	Pre	4.5 ± 0.71		
		6 months	1.43 ± 0.53	6 months	5.5 ± 2.12	6 months	NA
	DASH	Pre	31.29 ± 7.61	Pre	51.5 ± 21.92		
		6 months	14.0 ± 7.44	6 months	44.0 ± 46.67	6 months	NA
	WORC	Pre	47.29 ± 16.05	Pre	32.0 ± 9.89		
		6 months	85.17 ± 7.47	6 months	55.5 ± 40.31	6 months	NA
Subacromial Impingement Syndrome							
Nejati et al. 2017[19]	VAS (cm)	Pre	8.1 ± 1.7	Pre	7.0 ± 2.3		
		1 month	6.2 ± 0.4	1 month	4.8 ± 0.4	1 month	*P < 0.01, favoring EX
		3 months	6.5 ± 0.4	3 months	5.2 ± 0.4	3 months	*P < 0.01, favoring EX
		6 months	4.5 ± 0.4	6 months	4.2 ± 0.4	6 months	NS
	DASH	Pre	54.2 ± 18.6	Pre	50.5 ± 19.4		
		1 month	45.2 ± 3.9	1 month	35.0 ± 4.1	1 month	NS
		3 months	44.3 ± 3.9	3 months	30.7 ± 4.1	3 months	*P < 0.01, favoring EX
		6 months	33.0 ± 3.9	6 months	26.2 ± 4.1	6 months	NS
	WORC	Pre	33.9 ± 13.1	Pre	42.98 ± 21.0		
		1 month	45.9 ± 4.1	1 month	59.6 ± 4.4	1 month	*P < 0.01, favoring EX
		3 months	46.4 ± 4.1	3 months	68.4 ± 4.4	3 months	*P < 0.01, favoring EX
		6 months	58.7 ± 4.1	6 months	73.1 ± 4.4	6 months	*P < 0.01, favoring EX
Pasin et al. 2019[20]	VAS (cm)	Pre	4.9 ± 0.87	Pre	4.9 ± 0.5		
		3 weeks	1.3 ± 0.5	3 weeks	1.1 ± 0.5	3 weeks	NS
		8 weeks	0.8 ± 0.6	8 weeks	0.8 ± 0.6	8 weeks	*P < 0.05, favoring PRP

(Continues)

Table 6. (Continued)

Study	Outcome	Intervention Group (Mean ± SD)		Comparison Group (Mean ± SD)		Between-group Differences	
	Quick DASH	Pre	78.5 ± 6.8	Pre	77.6 ± 7.6		
		3 weeks	62.3 ± 8.7	3 weeks	56.8 ± 9.5	3 weeks	*P < 0.05, favoring PRP
		8 weeks	24.5 ± 5.2	8 weeks	29.5 ± 6.4	8 weeks	*P < 0.05, favoring PRP
	UCLA SRS	Pre	14.6 ± 4.5	Pre	15.6 ± 3.8		
		3 weeks	31.4 ± 2.5	3 weeks	32.7 ± 2.2	3 weeks	NS
		8 weeks	38.3 ± 3.3	8 weeks	34.5 ± 2.5	8 weeks	*P < 0.05, favoring PRP
Shoulder Osteoarthritis							
Kothari et al. 2017[10]	VAS (cm)	Pre	8.4 ± 1.4	Pre	8.9 ± 1.4		
		3 weeks	6.4 ± 1.6	3 weeks	6.6 ± 1.4	3 weeks	NS
		6 weeks	4.2 ± 1.9	6 weeks	4.9 ± 1.4	6 weeks	*P = 0.045, favoring PRP
		12 weeks	1.9 ± 1.8	12 weeks	4.5 ± 2.0	12 weeks	*P < 0.001, favoring PRP
	Quick DASH	Pre	83.5 ± 14.3	Pre	88.6 ± 13.6		
		3 weeks	63.7 ± 16.4	3 weeks	65.9 ± 14.0	3 weeks	NS
		6 weeks	41.6 ± 18.7	6 weeks	48.9 ± 13.6	6 weeks	P = 0.045*
		12 weeks	18.7 ± 18.2	12 weeks	45.2 ± 20.0	12 weeks	P < 0.001*

Notes. ASES, American Shoulder and Elbow Surgeons; BCTSQ, Boston Carpal Tunnel Syndrome Questionnaire; CSA, cross-sectional area; DASH, disabilities of the arm, shoulder, and hand; EX, exercise group; ER, external rotation; NPRS, Numeric Pain Rating Scale; PRP, platelet-rich plasma group; ROM, range of motion; SPADI, Shoulder Pain and Disability Index; SD, standard deviation; UCLA SRS, University of California, Los Angeles Shoulder Rating Scale; VAS, Visual Analog Scale; WORC, Western Ontario Rotator Cuff Index.

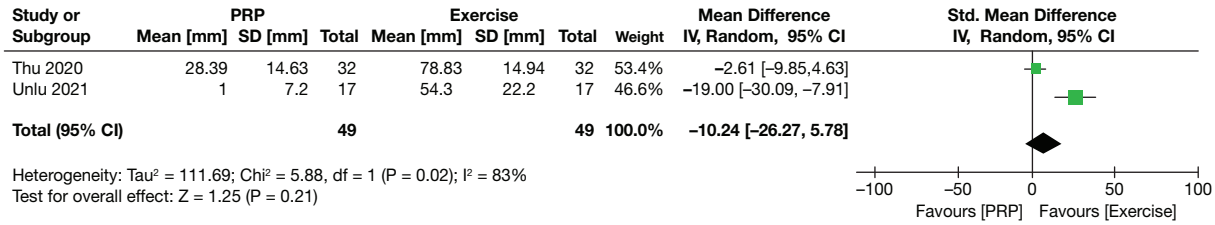

Figure 2. Meta-analysis of PRP versus exercise in adhesive capsulitis for pain (mm) in short term (<3 months).

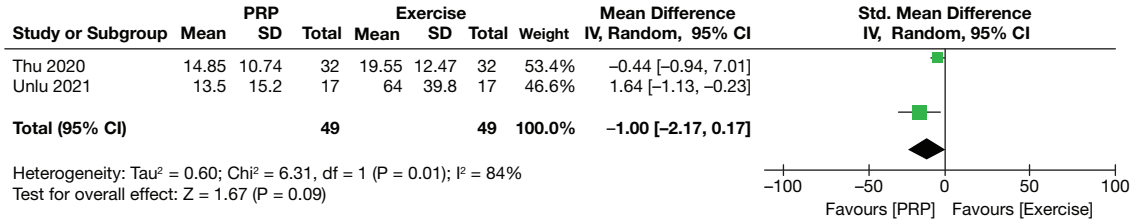

Figure 3. Meta-analysis of PRP versus exercise in adhesive capsulitis for disability in short term (<3 months).

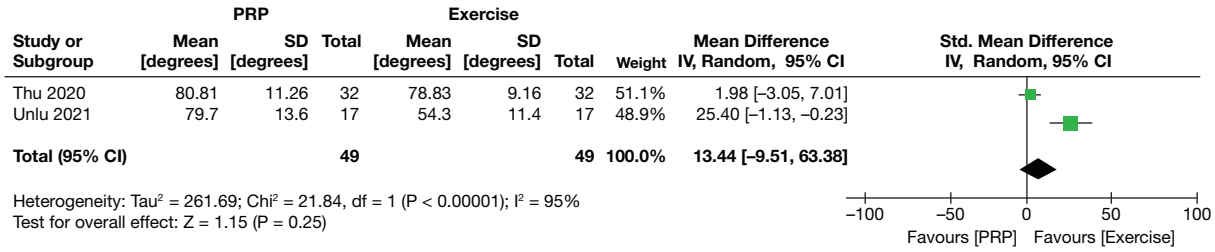

Figure 4. Meta-analysis of PRP versus exercise in adhesive capsulitis for ER ROM in short term (<3 months).

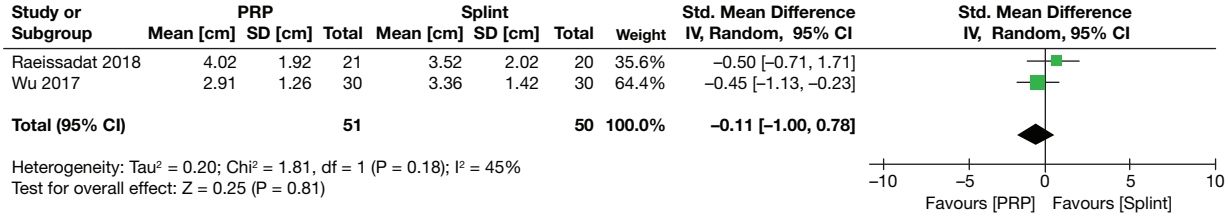

Figure 5. Meta-analysis of PRP versus splint/control in carpal tunnel syndrome for pain (cm) in short term (<3 months).

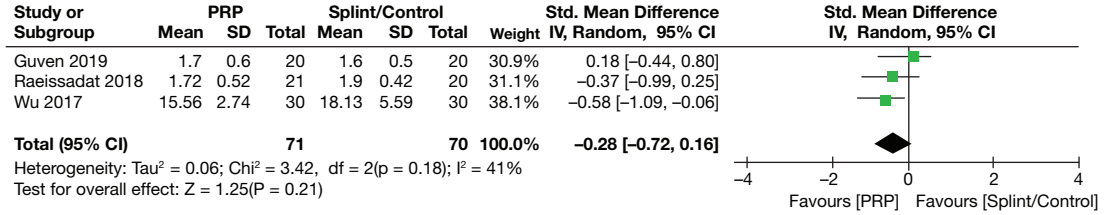

Figure 6. Meta-analysis of PRP versus splint/control in carpal tunnel syndrome for disability (BCTSQ symptom) in short term (<3 months).

Lateral epicondylalgia

Two studies[18,22] included 176 participants, with 53% females. The average RoB score was 8 out of 12 (range 7–9). One study[18] compared PRP, physical therapy, and a tennis elbow strap to physical therapy and a tennis elbow strap, while the other[22] compared autologous conditioned plasma (ACP) and physical therapy to laser and physical therapy.

One study[18] demonstrated statistically significant between-group differences on pain and disability favoring PRP, physical therapy, and a strap, while the other[22] demonstrated no significant differences when comparing ACP and physical therapy to laser and physical therapy.

Rotator cuff tendinopathy

Three studies[16,17,25] included 109 participants, with 52% females. The average RoB score was 9.33 out of 12 (range 5–12). Two studies[16,25] compared PRP and physical therapy to placebo and physical therapy, while the other[17] compared PRP and brochure exercise education to physical therapy.

Meta-analyses of the two studies[16,25] (n = 49) revealed a significant effect on pain (cm) (MD −2.53; 95% CI: −5.02, −0.04; I^2 = 51%; P = 0.05), quality of life (MD 16.82; 95% CI: 0.40, 33.25; I^2 = 0%; P = 0.04), and disability (SMD −0.64; 95% CI: −1.24, −0.04; I^2 = 0%; P = 0.04), favoring PRP and physical therapy for long-term follow-up (Figures 11–13). Kim et al. 2019[17] demonstrated statistically

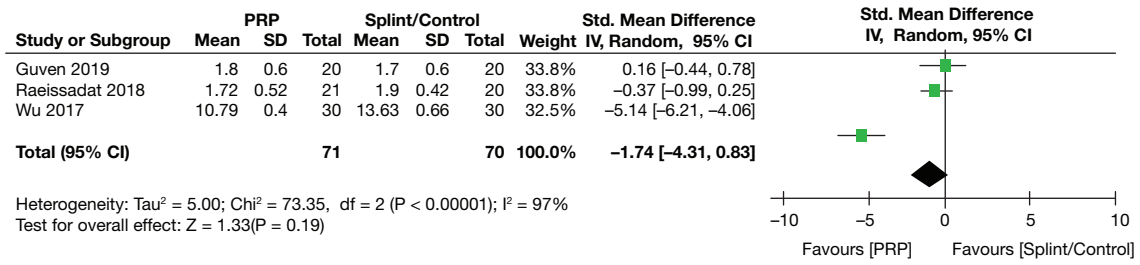

Figure 7. Meta-analysis of PRP versus splint/control in carpal tunnel syndrome for disability (BCTSQ function) in short term (<3 months).

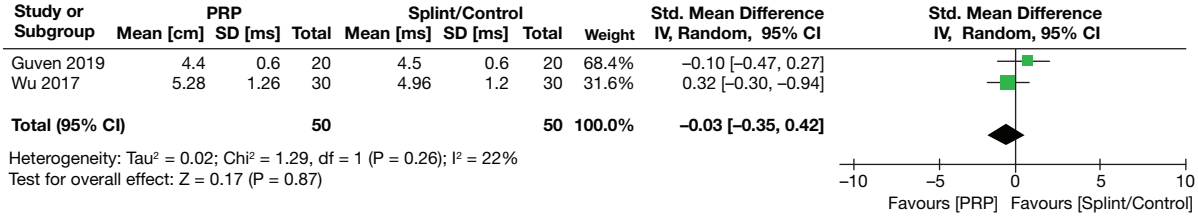

Figure 8. Meta-analysis of PRP versus splint/control in carpal tunnel syndrome for distal motor latency (ms) of the median nerve in short term (<3 months).

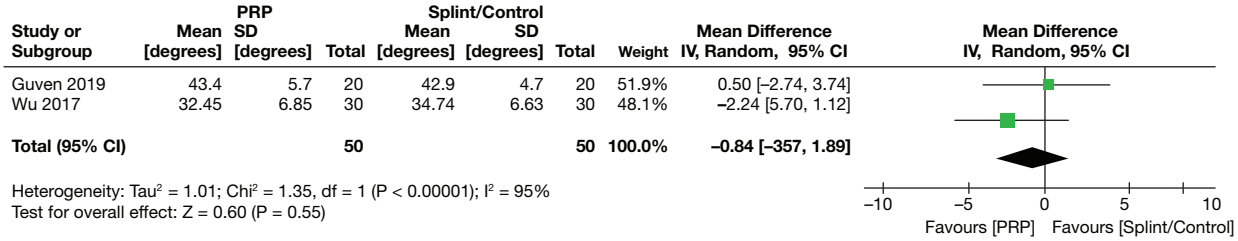

Figure 9. Meta-analysis of PRP versus splint/control in carpal tunnel syndrome for sensory nerve conduction velocity (m/s) of the median nerve in short term (<3 months).

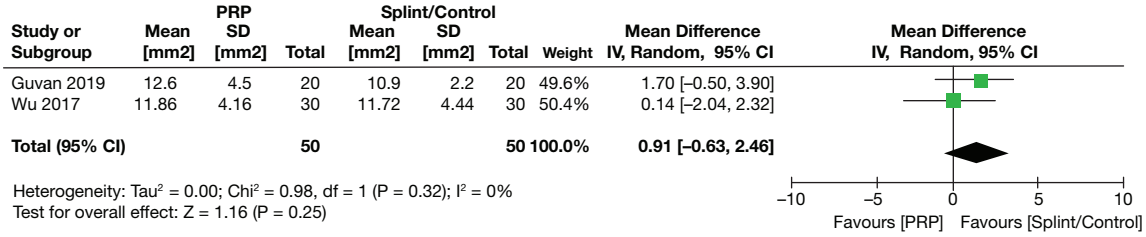

Figure 10. Meta-analysis of PRP versus splint/control in carpal tunnel syndrome for cross-sectional area (mm^2) of the median nerve in short term (<3 months).

significant between-group differences on pain at 6 weeks (P = 0.031) and quality of life (P = 0.048) and disability (P = 0.05) at 6 months favoring physical therapy.

Subacromial impingement

Two studies[19,20] included 152 participants, with 58% females. The average RoB was 7 out of 12 (range 6–8). One study[19] compared PRP alone to

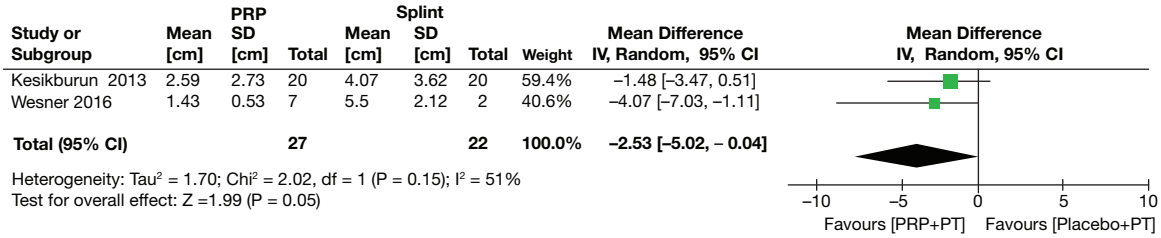

Figure 11. Meta-analysis of PRP + physical therapy versus placebo + physical therapy in rotator cuff tendinopathy for pain (cm) in long term (6 months).

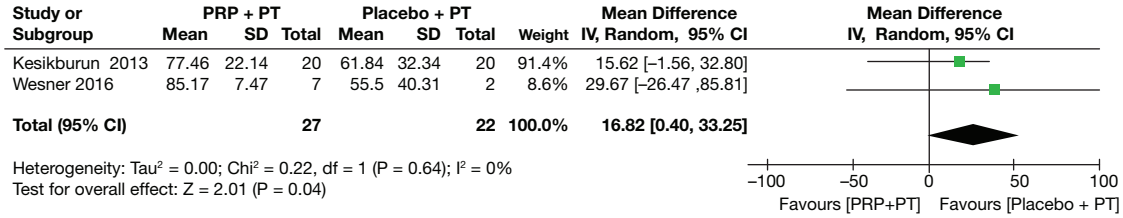

Figure 12. Meta-analysis of PRP + physical therapy versus placebo + physical therapy in rotator cuff tendinopathy for quality of life in long term (6 months).

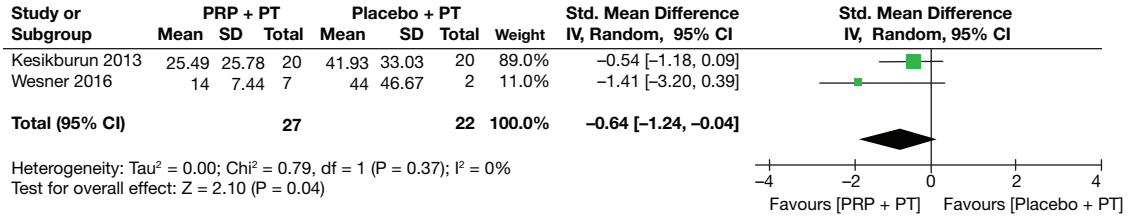

Figure 13. Meta-analysis of PRP + physical therapy versus placebo + physical therapy in rotator cuff tendinopathy for disability in long term (6 months).

exercise alone, while the other[20] compared PRP and exercise to modalities and exercise.

No meta-analysis was conducted due to heterogeneity in intervention groups. While both studies demonstrated significant between-group differences on pain and disability in the short term, results were conflicting. One study[19] demonstrated statistically significant between-group differences on pain, disability, and quality of life, favoring exercise when compared to PRP alone at 3-month follow-up ($P < 0.01$), but effects on quality of life were observed only when carried out for 6 months. Conversely, the other study[20] demonstrated statistically significant between-group differences on pain and disability favoring PRP and exercise when compared to modalities and exercise at 8-week follow-up ($P < 0.05$), but no differences in quality of life other than the bodily pain domain ($P = 0.05$).

Shoulder osteoarthritis

A study conducted by Kothari et al.[10] included 195 participants, with 53% females, and an RoB of 10 out of 12, comparing PRP and exercise to ultrasound and exercise.

The mentioned study[10] demonstrated statistically significant between-group differences on pain and disability, favoring PRP and exercise when compared to ultrasound and exercise at 6-week ($P = 0.045$) and 12-week ($P < 0.001$) follow-up.

DISCUSSION

This systematic review demonstrated that PRP is a beneficial adjunct to physical therapy for reducing pain and improving disability and quality of life (moderate level of evidence) when compared to placebo plus physical therapy for the management of rotator cuff tendinopathy (Table 7). While individual studies demonstrated significant between-group differences favoring PRP, all meta-analyses demonstrated nonsignificant effects for managing adhesive capsulitis and carpal tunnel syndrome. It

Table 7. GRADE Evidence Profile

Outcome (n = Studies)	Participants	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Level of Evidence
Adhesive Capsulitis; <3 months							
Pain [VAS] (n = 2)	98	Seriousâ€€	Serious â€€¡	Not serious	Serious Â§	None	⊕OOO Very low
Disability [DASH] (n = 2)	98	Seriousâ€€	Serious â€€¡	Not serious	Serious Â§	None	⊕OOO Very low
ER ROM (n = 2)	98	Seriousâ€€	Serious â€€¡	Not serious	Serious Â§	None	⊕OOO Very low
Carpal Tunnel Syndrome; <3 months							
Pain [VAS] (n = 2)	101	Not serious	Serious Â§¡	Not serious	Serious Â§	None	⊕⊕OO Low
Disability [BCTSQ symptoms] (n = 3)	141	Serious â€€#	Serious Â§¡	Not serious	Serious Â§	None	⊕OOO Very low
Disability [BCTSQ function] (n = 3)	141	Serious â€€#	Serious â€€¡, Â§¡	Not serious	Serious Â§	None	⊕OOO Very low
Distal Motor Latency (n = 2)	100	Seriousâ€€#	Serious Â§¡	Not serious	Serious Â§	None	⊕OOO Very low
Sensory nerve conduction velocity (n = 2)	100	Seriousâ€€#	Serious Â§¡	Not serious	Serious Â§	None	⊕OOO Very low
Median Nerve CSA (n = 2)	100	Serious â€€#	Not serious	Not serious	Serious Â§	None	⊕⊕OO Low
Rotator Cuff Tendinopathy; 6 months							
Pain [VAS] (n = 3)	109	Serious â€€#$	Serious Â§¡	Not serious	Serious Â§	None	⊕OOO Very low
Disability [WORC] (n = 2)	49	Not serious	Not serious	Not serious	Serious Â§	None	⊕⊕⊕O Moderate
Disability [DASH/ SPADI] (n = 2)	49	Not serious	Not serious	Not serious	Serious Â§	None	⊕⊕⊕O Moderate

BCTSQ: Boston Carpal Tunnel Syndrome Questionnaire; CSA: Cross-sectional area; DASH: Disabilities of the arm, shoulder, and hand; ER ROM: external rotation range of motion; SPADI: Shoulder Pain and Disability Index; VAS: Visual Analog Scale; WORC: Western Ontario Rotator Cuff Index; â€€Risk of bias associated with selection bias; â€€¡Studies demonstrate heterogeneity $I^2 > 50\%$; Â§Studies contain small sample sizes; Â§¡Studies demonstrate conflicting results; #Risk of bias associated with detection bias; $Risk of bias associated with attrition bias.

is important to observe that the overall level of evidence for nonsignificant results ranged from very low to low, which questions certainty of the findings. Meta-analyses could not be performed for lateral epicondylalgia, subacromial impingement syndrome, or shoulder osteoarthritis; however, individual studies demonstrated inconsistent results, with some favoring PRP and others favoring exercise.

Based on the overall results of this systematic review, it is observed that PRP may be a valuable adjunctive conservative option beside physical therapy for selective UE musculoskeletal pathologies. Probably both significant and nonsignificant findings could be attributed to the nature of the pathology being considered. Results of the meta-analysis comparing PRP and exercise to placebo and exercise for rotator cuff tendinopathy demonstrated a significant effect that met MCID values for pain (VAS = 0.9 cm;[28] NPRS = 1.1 pts.[29]) and quality of life (WORC = 13% converted[49]), indicating clinical importance. This is consistent with the current available literature on tendinopathy, in which tendon loading programs are considered the most effective conservative approach.[57,58] PRP intends to facilitate the body's own healing process by increasing growth hormone and anti-inflammatory cytokines, which when paired with an appropriately dosed exercise program would allow for reorganization of collagen fibers and better tolerance to loading. Similar results supporting PRP were observed in a study assessing the addition of PRP to exercise for lateral epicondylalgia probably because of similar mechanisms of healing. Conversely, no significant changes were observed in pathologies such as carpal tunnel syndrome, where the proposed mechanism is median nerve compression. While PRP is purported to induce a healing cascade of events, it is unclear whether it is capable of decompressing neural structures.

While it would have been beneficial to address the isolated role of PRP in selective UE musculoskeletal pathologies, the majority of included studies did not compare PRP and exercise to PRP alone, or PRP alone to exercise alone. This makes it difficult to draw firm conclusions on the isolated benefit of PRP, as results would only be based on individual studies included in this systematic review.[15,17,19,23,26] The results of these studies demonstrated inconsistent findings across pathologies, with no significant between-group differences for adhesive capsulitis, significant between-group differences favoring exercise for subacromial impingement syndrome, and significant between-group differences favoring PRP for both carpal tunnel syndrome and rotator cuff tendinopathy. These inconsistencies may be attributed to lack of standardization in the administration of PRP injection, or the ability of the injection to make substantial physiological changes independently in the absence of subsequent loading. Until stronger and more consistent protocols exist for the guidance of PRP delivery, definitive conclusions cannot be drawn.

CONCLUSION

This was the first systematic review to date that addressed the effectiveness of PRP combined with physical therapy, rehabilitation, or exercise. The strengths of this review include the detailed search strategy, including clinicaltrials.gov, using the Cochrane RoB tool for methodological quality, performing a GRADE analysis, and using MD to compare to MCID values to assess for clinical improvement. The results of the GRADE analysis demonstrated a moderate level of evidence supporting the addition of PRP to physical therapy for managing rotator cuff tendinopathy, suggesting that clinicians could confidently recommend PRP as an adjunctive intervention for their patients when conventional physical therapy alone is insufficient to resolve all impairments and functional limitations. While there were many strengths of this systemic review, it was not without limitations. A major limitation was the heterogeneity across trials precluding further meta-analysis. Additionally, lack of long-term follow-up in the majority of included studies made it difficult to assess long-term benefits of PRP in relation to cost and available resources. Furthermore, it was plausible that the lack of effectiveness of PRP for carpal tunnel syndrome and adhesive capsulitis could be related to the absence of standardized protocols for injection dosage and technique. Finally, and most importantly from a rehabilitation/physical therapy standpoint, heterogeneity in exercise programs across included trials might have limited the studies' ability to detect potential clinical benefits of either intervention, given the

nonsignificant findings in many studies. Therefore, the future studies should strongly consider rigorous and standardized study designs for the application of PRP in conjunction with exercise.

AUTHOR CONTRIBUTIONS

Both authors were involved in conception and design of the study. Administrative support was provided and proviso of study materials was done by both authors. Collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of the manuscript were done by both authors.

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