Impact of Platelet-Rich Plasma Use on Pain in Orthopaedic Surgery: A Systematic Review and Meta-analysis

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Context: Amid extensive debate, evidence surrounding the use of platelet-rich plasma (PRP) for musculoskeletal injuries has rapidly proliferated, and an overall assessment of efficacy of PRP across orthopaedic indications is required.

Objectives: (1) Does PRP improve patient-reported pain in musculoskeletal conditions? and (2) Do PRP characteristics influence its treatment effect?

Data Sources: MEDLINE, EMBASE, Cochrane, CINAHL, SPORTDiscus, and Web of Science libraries were searched through February 8, 2017. Additional studies were identified from reviews, trial registries, and recent conferences.

Study Selection: All English-language randomized trials comparing platelet-rich therapy with a control in patients 18 years or older with musculoskeletal bone, cartilage, or soft tissue injuries treated either conservatively or surgically were included. Substudies of previously reported trials or abstracts and conference proceedings that lacked sufficient information to generate estimates of effect for the primary outcome were excluded.

Study Design: Systematic review and meta-analysis.

Level of Evidence: Level 1.

Data Extraction: All data were reviewed and extracted independently by 3 reviewers. Agreement was high between reviewers with regard to included studies.

Results: A total of 78 randomized controlled trials (5308 patients) were included. A standardized mean difference (SMD) of 0.5 was established as the minimum for a clinically significant reduction in pain. A reduction in pain was associated with PRP at 3 months (SMD, –0.34; 95% CI, –0.48 to –0.20) and sustained until 1 year (SMD, –0.60; 95% CI, –0.81 to –0.39). Low- to moderate-quality evidence supports a reduction in pain for lateral epicondylitis (SMD, –0.69; 95% CI, –1.15 to –0.23) and knee osteoarthritis (SMD, –0.91; 95% CI, –1.41 to –0.41) at 1 year. PRP characteristics did not influence results.

Conclusion: PRP leads to a reduction in pain; however, evidence for clinically significant efficacy is limited. Available evidence supports the use of PRP in the management of lateral epicondylitis as well as knee osteoarthritis.

Keywords: platelet-rich plasma; growth factor; orthopaedics; sports medicine; regenerative medicine; arthritis

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Platelet-rich plasma (PRP), defined as autologous blood with supraphysiological concentrations of platelets, has become a popular minimally invasive biological and injectable treatment for musculoskeletal injuries. Despite a lack of evidence-based recommendations for its efficacy, the global market for PRP is projected to increase to $451 million in the next decade.[45] Support for PRP is fueled by evidence that bioactive proteins and growth factors promote healing and recovery.[4,6,32,74,76,113,129] Optimal preparation is the subject of considerable controversy and debate.[4,32,76,129] Multiple PRP preparation systems and techniques are available, each differing in final platelet concentration, presence of leukocytes and noncellular plasma clotting factors, and use of exogenous activating agents.[4,32,74,82]

Many prior systematic reviews on the use of PRP in orthopaedics have been conducted, but have been limited in their method and scope, leading to conflicting interpretations of the evidence (see Appendix Table A1, available in the online version of this article).[8,17,22,25,30,33,38,41,42,58,63,71,72,75,77,86,91,104,112,113,119,124,129] More than one-third of prior reviews were unable to perform a quantitative analysis,[30,33,38,41,58,77,119,129] and more than 60% include lower-level evidence, such as nonrandomized cohort studies or case series.[22,30,33,38,41,58,63,72,75,86,104,113,119,129] Less than half of prior reviews explored reasons for substantial variability between studies, leading to misleading effect estimates with high heterogeneity, and only 2 of the meta-analyses summarized the overall confidence in the evidence. A substantial amount of new evidence is currently available, with more than 30% of all randomized controlled trials (RCTs) being published within the past 2 years, and 60 additional RCTs being published since the last broad systematic reviews were completed.[113,129]

Despite an exponential increase in publications associated with PRP use, the evidence is far from conclusive. Trials vary in population, sample size, and methodological quality, further vindicating the need for a comprehensive updated review. Given the widespread applicability of an evidence-based recommendation, we conducted a systematic review and updated meta-analysis of RCTs to provide the current best estimate of whether PRP reduces patient-reported pain in musculoskeletal conditions, and whether particular PRP characteristics influence its treatment effect.

METHODS

Search Strategy and Criteria

A systematic review and meta-analysis was performed according to the methods of the Cochrane Handbook for Systematic Reviews and is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[59,111] A protocol for our review was registered online with Prospero (No. 42017057900; https://www.crd.york.ac.uk/PROSPERO/).

The following electronic databases were systematically searched: MEDLINE (from 1946), EMBASE (from 1974), Cochrane (from 2005), CINAHL (from 1981), SPORTDiscus (from 1800), and Web of Science (from 1976). The last updated search was conducted on February 8, 2017. Search strategies combined keywords and database-specific subject heading terms for the patient population and interventions of interest, and the highly sensitive Cochrane search strategy filter for identifying RCTs was used (see Appendix Table A2, available online).[59] Abstracts from recent (3 years) relevant annual meetings were reviewed for unpublished literature, and international trial registries were used to identify ongoing studies (see Appendix Table A3, available online). Attempts were made to contact the primary investigators of ongoing studies to collect further information. Nonindexed electronic ahead-of-print publications were identified using PubMed search filters. Additional studies were identified by reviewing the reference lists of eligible studies. After removing duplicates, 3 reviewers (HJ, NE, MK) independently screened all titles, abstracts, and full texts of potentially eligible studies for final inclusion. For full-text articles deemed ineligible, the reason(s) for exclusion were recorded. Disagreement was resolved through discussion.

Inclusion and Exclusion

We identified all English-language randomized trials comparing platelet-rich therapy with a control in patients 18 years or older with musculoskeletal bone, cartilage, or soft tissue injuries treated either conservatively or surgically, including (1) injuries to tendons or ligaments such as ruptures, tears, and sprains; (2) traumatic meniscal and labral lesions; (3) acute fractures or fractures with delayed or nonunion; (4) acute or chronic tendinopathies and fasciopathies; and (5) articular cartilage pathology, such as osteochondral defects and degenerative osteoarthritis. Treatments considered for the control groups included standard operative or nonoperative treatment, placebo, hyaluronic acid (HA), corticosteroid, local anesthetic, or whole blood injection. Platelet-rich therapies may have been used as the sole treatment or as an adjunct to surgical treatment provided to all participants in a given trial. The outcome of interest was the difference in patient-reported pain at different time intervals posttreatment. Substudies of previously reported trials or abstracts and conference proceedings that lacked sufficient information to generate estimates of effect for the primary outcome were excluded.

Assessment of Study Quality and Overall Estimate of Effect

Two independent reviewers (HJ and NE) assessed the risk of bias of the included RCTs using the Cochrane Collaboration risk of bias tool.[60] Trials were scored as *low risk, moderate risk*, or *high risk* of bias based on methodologic considerations. Differences were settled by discussion and involvement of a third reviewer as necessary.

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used to evaluate confidence in the pooled effect estimates.[10,50] According to GRADE, data from RCTs are considered high-quality evidence but can be rated down due to risk of bias, imprecision, inconsistency,

indirectness, or publication bias.[10] The quality of the evidence was graded as high, moderate, low, or very low and applied to each outcome of interest separately, organized by indication.[51]

Data Collection and Abstraction

Two teams of reviewers (HJ, MK, SE, NH) independently collected and confirmed all relevant information in duplicate using piloted data forms. Any disagreements were resolved by discussion. Collected data included study design, first author, journal, year of publication, patient characteristics, indication, target tissue, PRP preparation details/characteristics, control intervention details, surgical co-interventions, sample size and losses in each group, duration of follow-up, and patient outcomes. Several classification systems exist that define PRP products based on characteristics that may affect performance.[29,42,83] Although no single system has been validated in the literature, there is overlap among them with regard to the inclusion of leukocyte concentration, platelet concentration, and use of an exogenous activating substance. However, there is disagreement as to the contributions of each of these factors to overall efficacy.[32] To assess this, we abstracted leukocyte concentration (increased vs decreased over baseline), platelet activation (exogenous activation vs no exogenous activation), and platelet concentration (less than or greater than 5-fold over baseline) based on features and cutoffs common to previously described classification systems.[29,83] Manufacturers of the preparation systems described in the studies were contacted if PRP product characteristics were not readily available. Based on clinical significance and previous literature, pain intensity was the primary outcome of interest.[1,5,12,18,22,41,58,63,64,71,86,113] If data were provided on more than 1 scale for pain, only the most commonly reported scales across included studies (for which complete data were available) were combined. To be consistent with analyses of other reported injectable interventions, and to best capture the data presented in all studies, the time points of outcomes were grouped into 3-month, 6-month, and 1-year intervals.[11,107]

Statistical Analysis and Assessment of Heterogeneity

Continuous outcomes were calculated and expressed as the standardized mean difference (SMD), along with 95% CI. SMD was defined as the between-group differences in mean values reported at each follow-up divided by the SD. Cohen effect size criteria were used as a guide for the clinical interpretation of the SMDs.[24] An SMD of 0.2 or less represented a small effect, 0.2 to 0.8 represented a moderate effect, and greater than 0.8 represented a large effect. Based on estimates from previous authors, an SMD of 0.5 (half an SD) was used to approximate a clinically significant reduction in pain.[88]

Heterogeneity was assessed visually with inspection of the forest plots, and objectively with the χ^2 ($P < 0.10$ indicates heterogeneity) and the I^2 statistic ($I^2 < 40\%$, low heterogeneity; $I^2 \geq 75\%$, substantial heterogeneity). A random effects model was used to pool data with moderate or substantial heterogeneity ($I^2 > 40\%$); otherwise, a fixed effects model was used.

Subgroup and meta-regression analyses were carried out if significant heterogeneity was identified ($I^2 > 40\%$) to assess the influence of study characteristics on effect estimates.

A priori, we hypothesized that heterogeneity may be due to differences in population (clinical indication), PRP properties (platelet concentration, leukocyte concentration, exogenous activation), and comparator characteristics (type of control). Tests for significance were 2-tailed, and $P < 0.05$ was considered significant. Sensitivity analyses were performed to investigate heterogeneity within subgroups and the importance of study quality by omitting studies with high risk of bias.

The Cohen kappa statistic (κ) was used to evaluate agreement between reviewers with regard to study eligibility and reviewer assessments. This was interpreted using accepted cutoffs for levels of agreement.[114] All analyses were performed using STATA 14.0 software (STATA Corp) and Review Manager 5.3 (The Nordic Cochrane Center; The Cochrane Collaboration).

RESULTS

After removing duplicates, we identified 4843 potential articles, 176 of which were reviewed as full texts (Figure 1). Ninety-eight articles were excluded, and 78 RCTs that compared a platelet-rich product with a control in patients with an orthopaedic injury were included for analysis (n = 5308 randomized patients).[2,3,7,9,13-16,19-21,23,26-28,31,34-37,39,40,43,44,46-49,56,57,61,62,65,67-70,73,78,79,81,84,85,87,89,90,92-103,105,108-110,115-118,120-123,125-128,130,131,133] Interobserver agreement was substantial for screening of titles and abstracts (κ, 0.75; 95% CI, 0.72-0.78) and almost perfect for review of full texts (κ, 0.95; 95% CI, 0.92-0.98).

Figure 2 graphically depicts the cumulative number of RCTs relative to the year of publication and the number of RCTs published annually. All 78 included RCTs were published in the past decade, with 60 (73%) of them published since the last overarching systematic review on the topic in 2012.[113]

Participants averaged 47.9 years of age (range, 22.9-76 years) (Table 1). Sample sizes ranged from 9 to 380 patients, with the duration of follow-up ranging from 5 days to 72 months. The efficacy of PRP was examined across a wide range of orthopaedic indications and target tissues, and 44% of studies used PRP as an adjunct during surgical treatment (Table 1). Details of the platelet-based product preparation used in each study can be found in Appendix Tables A4 and A5 (available online) and are summarized in Table 1.

Thirty-two manufacturers were used by 64 trials that reported the PRP preparation system used, with nearly half of trials using 6 main manufacturers. Seventeen studies reported receiving funding from the manufacturer, and an additional 34 studies did not report funding source or specify conflicts of interest.

PRP Impact on Pain

The overall analysis across all indications demonstrated a statically but not clinically significant reduction in pain with PRP

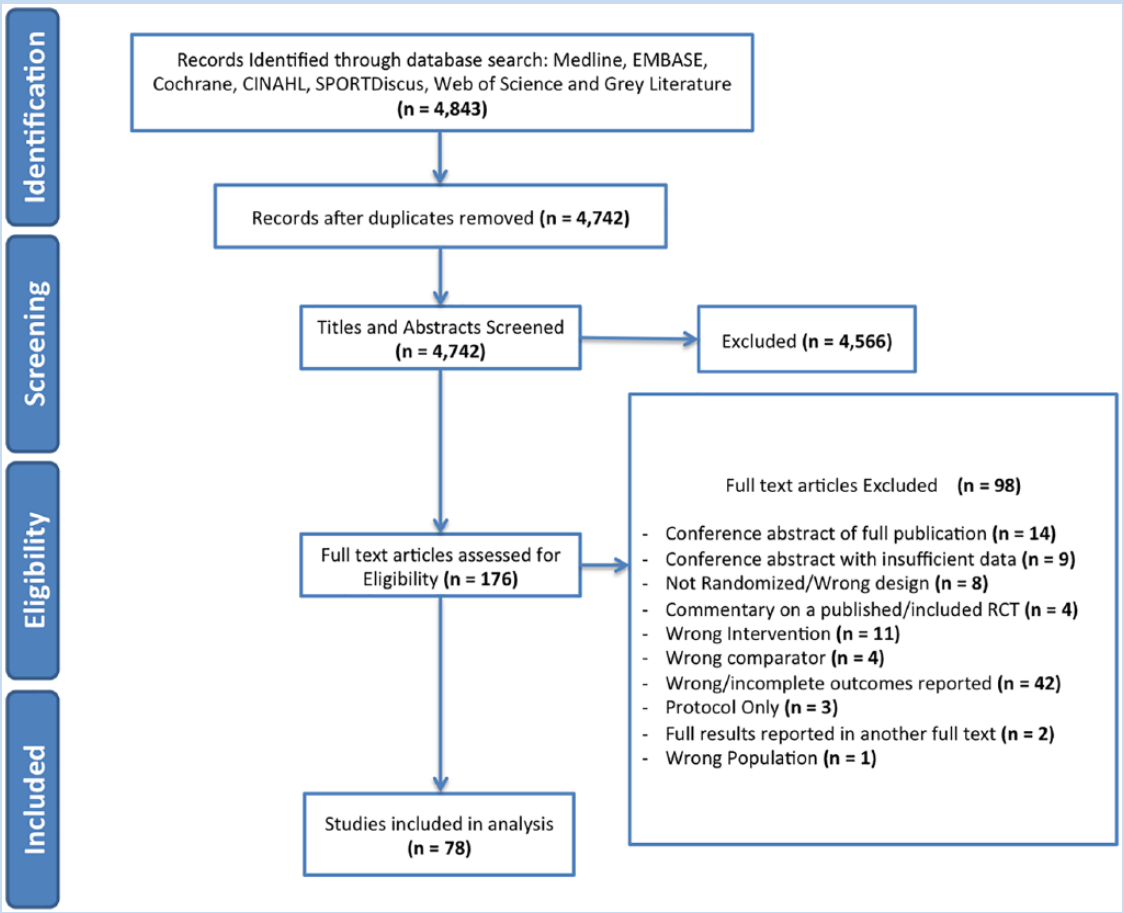

Figure 1. Study flow diagram depicting the number of studies at each stage of the systematic review, with reasons for exclusion. In the end, 78 RCTs that compared a platelet-rich product to a control in patients with an orthopaedic injury were included for analysis (n = 5308 randomized patients).

compared with controls at 3 months (SMD, –0.34; 95% CI, –0.48 to –0.20; $P \leq 0.00001$) (Figure 3). This effect grew at 6 months (SMD, –0.55; 95% CI, –0.73 to –0.36; $P \leq 0.00001$) (Appendix Figure A1, available online) and 1 year (SMD, –0.60; 95% CI, –0.81 to –0.39; $P \leq 0.00001$) (Figure 4). However, the CIs overlapped the 0.5 effect size threshold for a clinically important difference.

Heterogeneity was substantial (range, 77%-82%) and was explored further through subgroup analysis at each time point initially by clinical indication, and subsequently by comparator if there was substantial heterogeneity ($I^2 > 40\%$) (Figures 3 and 4; Appendix A1, available online). When assessing by indication, low to moderate quality evidence indicated that there was a clinically important treatment effect when PRP was used for lateral epicondylitis (compared with steroid; $I^2 = 0\%$) as well as knee osteoarthritis (compared with placebo or steroid; $I^2 = 0\%$) and talar osteochondral lesions (compared with HA, placebo, or surgery combined; $I^2 = 30\%$). The remaining indications and time points did not convincingly demonstrate an effect with use of PRP and are based on low- or very low–quality evidence due to high residual heterogeneity, high risk of bias, or inclusion of data from only a single trial (Figures 3 and 4; Appendix A1, available online). Sensitivity results were similar when assessing first by comparator, and subsequently by indication; however, the evidence for effectiveness of PRP in patients with talar osteochondral lesions came only from single studies or was no longer significant at 12 months (Appendix Figures A2-A4, available online).

PRP Characteristics and Treatment Effect

Assessment of PRP characteristics through subgroup analysis and multivariate metaregression did not reveal either leukocyte concentration, platelet concentration, or use of an exogenous activator to be associated with increased effectiveness when controlling for the indication and comparator used (Figure 5).

Risk of Bias and Summary of Evidence

Using the Cochrane risk of bias tool, 14 studies were judged to be of low risk of bias, and the remaining 64 (82%) studies were judged to be of moderate to high risk of bias, with substantial agreement between reviewers ($\kappa = 0.80$; 95% CI, 0.63-0.96).

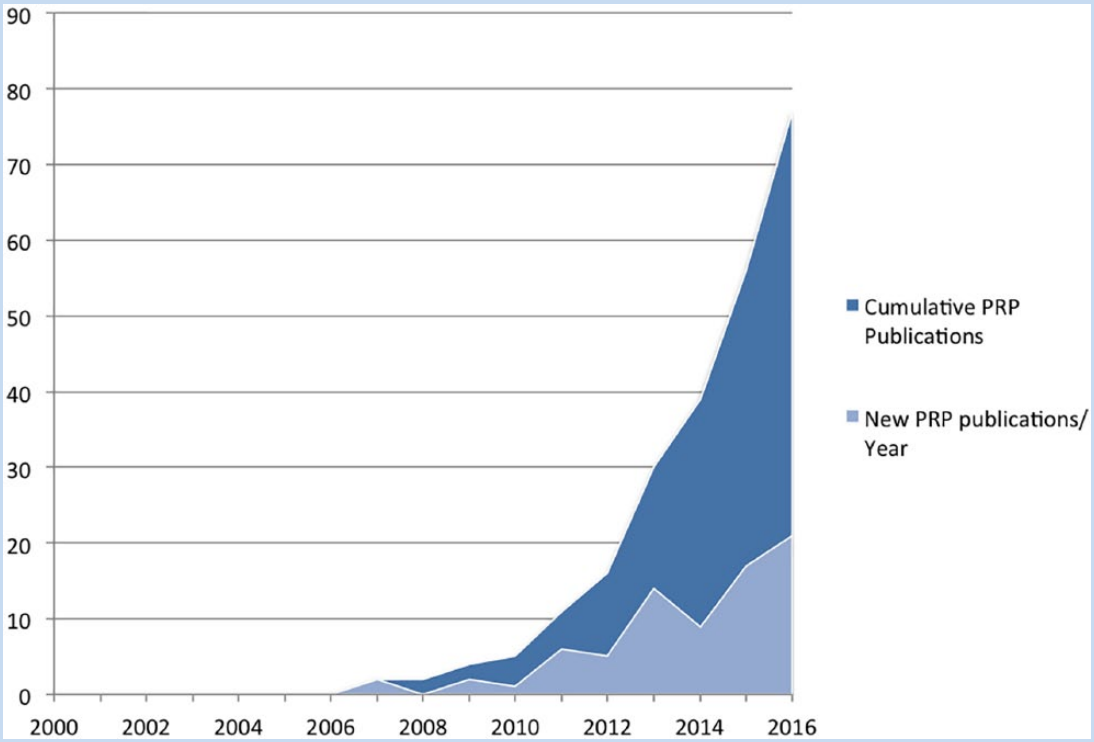

Figure 2. Graphic depiction of the number of randomized controlled trials (RCTs) published annually (light shade) as well as the cumulative number of RCTs (dark shade) relative to the year of publication since the year 2000. The number of RCTs is on the *y*-axis, with year of publication along the *x*-axis. Note the rapid rise in RCTs examining this emerging therapy over the past decade. PRP, platelet-rich plasma.

GRADE assessments of the overall quality of evidence were low at 3 months, 6 months, and 1 year (see Appendix Tables A6, A7, and A8, respectively, available online).[52-55]

DISCUSSION

This systematic review and meta-analysis of 78 trials finds PRP results in a statistically significant reduction in pain. However, evidence for clinically significant efficacy is limited. Evidence supports a statistically significant reduction in pain for lateral epicondylitis as well as for knee osteoarthritis as primary indications. The confidence in efficacy for the remaining interventions was either very low or no efficacy was noted. This includes the use of PRP in the treatment of muscle injuries, anterior cruciate ligament reconstruction, and rotator cuff tears. Leukocyte concentration, platelet concentration, or use of an activator did not influence results.

Our findings are consistent with 2 previous network meta-analyses that assessed lateral epicondylitis.[8,71] We provide an updated analysis of the lateral epicondylitis literature, with an additional 3 trials, demonstrating that 1-year PRP results suggest a clinically significant effect when compared with local anesthetic and corticosteroid injections and a similar effect to autologous whole blood and dry needling. The findings with respect to autologous whole blood and dry needling are interesting, as both present a simpler and less costly alternative for the patient. The findings may be due to 1 of 2 reasons: (1) the simple act of introducing whole blood or inciting local bleeding and inflammation to the damaged tissue may result in enough healing factors, albeit fewer than PRP, to result in a clinical improvement in pain; or (2) some component of the placebo effect may be present. Further studies with large, high-quality trials are required to delineate differences between these treatment options.

The majority of the RCTs in this analysis investigated PRP for knee osteoarthritis. Overall, moderate-quality evidence supports an early effect sustained to 1 year. Substantial heterogeneity remained, largely among trials comparing the effectiveness of PRP with HA. This is consistent with Dai et al,[25] who also noted significant heterogeneity with respect to studies comparing PRP with HA. As both interventions continue to evolve, comparison between the 2 must be done with caution. HA characteristics such as molecular weight and cross-linkage have been shown to influence this treatment's overall effectiveness in the conservative management of knee osteoarthritis,[66] and these traits must be considered when using it as a control therapy in trials. Further trials comparing PRP with HA in the nonsurgical management of knee osteoarthritis should focus on highly crosslinked, high–molecular weight HA formulations that have been shown to be the most effective.[66]

Table 1. Study characteristics

Total number of trials	78
Age, y, mean (range)	47.9 (22.9-76.0)
Sample size, mean (range)	62 (9-380)
Duration of follow-up, mean (range)	11.7 mo (5 d to 72 mo)
PRP type	
Type 1	33
Type 2	11
Type 3	13
Type 3	19
Not reported/unable to be determined	28
Orthopaedic indications	
Rotator cuff pathology	21
Lateral epicondylitis	13
Hip osteoarthritis	3
Knee osteoarthritis	19
ACL reconstruction	7
Plantar fasciitis	10
Achilles tendinopathy/rupture	5
Other	26
Target tissue	
Tendon	42
Cartilage	26
Fascia	10
Ligament	8
Bone	15
Muscle	3
Outcome measures	
Pain	78
Clinical outcome scores	95
Radiographic/MRI healing	34
Physical examination	20
PRP manufacture	
Biomet	19
Arthrex	13
Medtronic	3
Biotechnology Institute	3
Not reported	20
Other	46
PRP concentration	
≥5-fold	20
Less than 5-fold	29
Not reported	55

ACL, anterior cruciate ligament; MRI, magnetic resonance imaging; PRP, platelet-rich plasma.

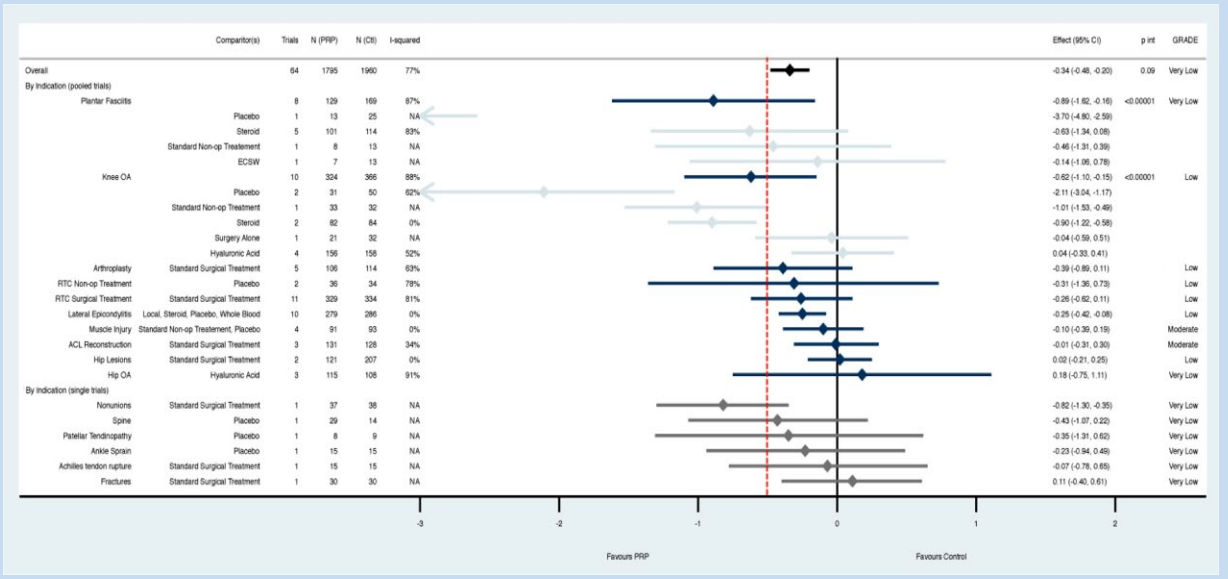

Figure 3. At 3 months, platelet-rich plasma (PRP) demonstrated a statistically but not clinically significant reduction in pain compared with controls across all indications. Subgroup analysis by clinical indication, and comparator where there were multiple trials, revealed that PRP outperformed placebo and steroid both statistically and clinically for knee osteoarthritis only. The remaining subgroups either had CIs that overlapped thresholds for minimally important difference (red line = standardized mean difference [SMD] 0.5) or statistical significance (black line = SMD 0); or were composed of only a single study. Pooled estimates by indication are in navy, with comparator subgroups in light blue. Estimates for indications with only single trials (gray) are found at the bottom; p int, p interaction for subgroup effects.

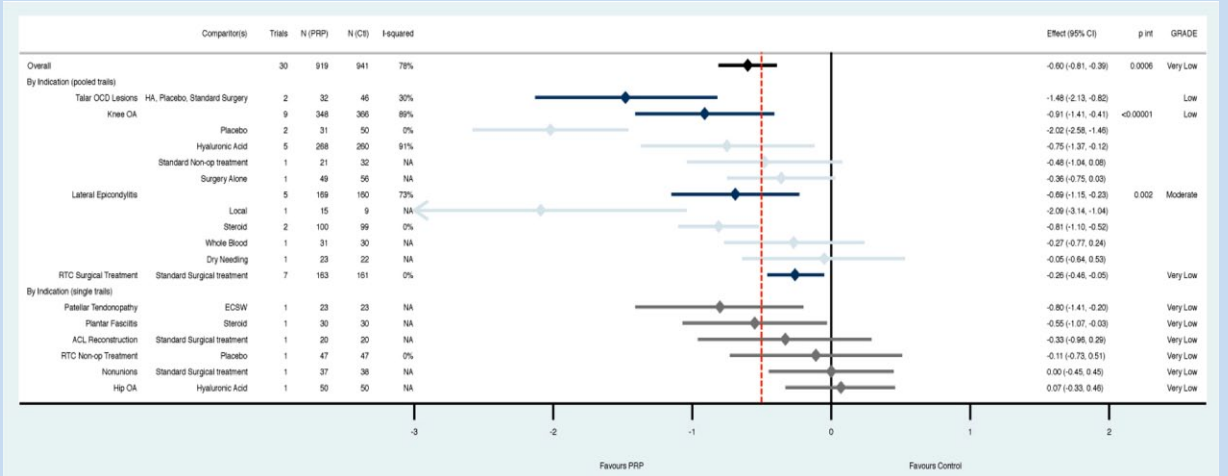

Figure 4. At 12 months, platelet-rich plasma (PRP) demonstrated a statistically but not clinically significant reduction in pain compared with controls across all indications. Subgroup analysis by clinical indication, and comparator where there were multiple trials, revealed that PRP clinically and statistically significantly improved pain compared with placebo in patients with knee osteoarthritis, compared with steroid in patients with lateral epicondylitis, and compared with hyaluronic acid, placebo, or surgery combined for patients with talar osteochondral lesions ($I^2 = 30\%$). The remaining subgroups either had CIs that overlapped thresholds for minimally important difference (red line = standardized mean difference [SMD] 0.5) or statistical significance (black line = SMD 0); or were composed of only a single study. Pooled estimates by indication are in navy, with comparator subgroups in light blue. Estimates for indications with only single trials (gray) are found at the bottom; p int, p interaction for subgroup effects.

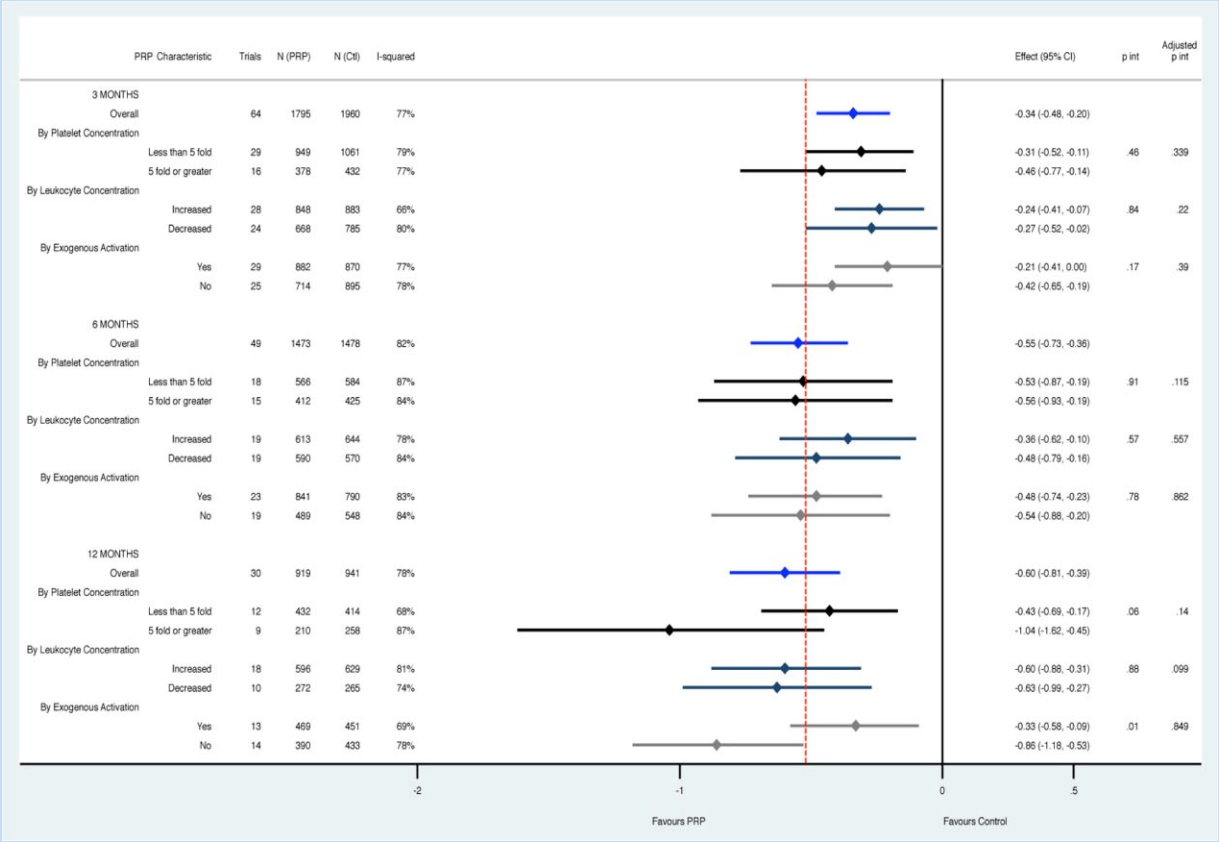

Figure 5. Assessment of platelet-rich plasma (PRP) characteristics through subgroup analysis and multivariate metaregression did not reveal any characteristic to be consistently associated with increased effectiveness when controlling for the indication and comparator used across all time points. Pooled estimates at each time point are in blue, with subanalysis below based on platelet concentration (black), leukocyte concentration (navy), and exogenous activation (gray). p int, p interaction for subgroup effects; adjusted p int, p interaction from metaregression controlling for other characteristics.

Our analysis provides insight into the role of PRP characteristics that are thought to influence effectiveness. These include leukocyte concentration, platelet concentration, and use of an exogenous activating agent, all of which can be modified using PRP preparation methods such as speed of centrifugation, number of centrifugation cycles, order of pellet and supernatant separation, and addition of products such a thrombin prior to PRP use. In separate laboratory investigations, Rubio-Azpeitia et al[106] and Zhang et al[132] each found that leukocyte-rich formulations were more proinflammatory, and the formulations with higher platelet concentrations exhibited stronger chemotactic and proliferative qualities. A further laboratory investigation showing that leukocyte-rich PRP may result in significant synoviocyte cell death and increase proinflammatory mediators has since been contradicted by an in vivo investigation of 36 patients with osteoarthritic knees who received intra-articular injections with either leukocyte-rich PRP or HA, neither of which resulted in a difference in pro- or anti-inflammatory markers compared with baseline results.[80] A recent network meta-analysis found no impact of leukocyte concentration on the overall effectiveness of PRP injections for the treatment of osteoarthritis,[104] with findings confirmed by our results for the same patient population at 1 year. Looking across other indications and at the overall cohort of 78 RCTs, the present study found no evidence that leukocyte concentration, platelet concentration, or use of an exogenous activating agent affects the overall effectiveness of PRP.

Strengths

Our review focused specifically on evidence exclusively from RCTs to limit the influence of confounding. It included substantially more trials in each indication subgroup than any other systematic review published in this area to date, many of which included evidence from nonrandomized trials, retrospective cohorts, and case series.[8,17,22,25,30,33,38,41,42,58,63,71,72,75,77,86,91,104,112,113,119,124,129] This maximized the power of our pooled analysis to detect an overall effect and allowed us to explore further where heterogeneity was a concern. Where heterogeneity was noted, a priori subgroup and metaregression analysis were conducted to assess important differences attributable to indication, PRP characteristics, comparator used, and duration of follow-up. A particular strength of this study

was the assessment of PRP product characteristics across the large body of clinical evidence regarding its use. Although postulated to be a source of considerable heterogeneity, PRP characteristics have received limited attention as an effect modifier in previous meta-analysis. We abstracted PRP characteristics as reported and derived characteristics based on PRP preparation methods described and systems used, and contacted manufacturers to confirm details as needed. Risk of bias was assessed for each study individually using a widely accepted and standardized framework,[60] and confidence in both overall evidence and specific indications was summarized using the GRADE approach.

Limitations

Our review has limitations. Between-study heterogeneity remained high and unexplained across many indications; however, we set several a priori hypotheses to explain heterogeneity and were able to identify indications where there was certainty of effect and lack of effect. Study quality was not uniformly high, and variability in comparators and design limitations were identified in nearly 50% of trials. Additionally, study sample sizes were small, further limiting inferences from individual trials.

CONCLUSION

This meta-analysis demonstrates available evidence supports the clinical efficacy of PRP in patients with lateral epicondylitis and knee osteoarthritis. PRP leads to a reduction in pain across indications; however, evidence for clinically significant efficacy is limited. Future investment of resources in high-quality research should focus on those indications with promise and aim to resolve definitively the utility of PRP in such indications.

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