Platelet-Rich Plasma Has Better Results for Long-term Functional Improvement and Pain Relief for Lateral Epicondylitis

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Corticosteroids (CS) have shown good short-term performance in terms of pain relief and functional improvement. However, the safety and long-term efficacy of this treatment remains controversial. Several studies have reported good results of platelet-rich plasma (PRP) in the treatment of tendinopathies. However, whether its use in the treatment of lateral epicondylitis (LE) is superior to that of CS remains controversial.

Purpose: To perform a systematic review and meta-analysis of original studies to determine whether the prognosis of LE patients treated with PRP is better than that of CS.

Study Design: Meta-analysis; Level of evidence, 2.

Methods: Two independent reviewers searched online databases from January 2000 to July 2022 according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to evaluate prospective studies of PRP versus CS injection for LE. A third author addressed any discrepancies. Evidence quality was assessed using the Cochrane risk of bias tool. Risk ratios for dichotomous variables and mean differences (MDs) for continuous variables were used to compare clinical outcomes. P values $<.05$ were considered statistically significant.

Results: Eleven randomized controlled trials with 730 patients were included in this review. PRP provided a significantly worse short-term (<2 months) improvement in the visual analog scale (VAS) pain score (MD, 0.93 [95% CI, 0.42 to 1.44]; $I^2 = 85\%$; $P = .0003$) and Disabilities of the Arm, Shoulder and Hand (DASH) score (MD, 10.23 [95% CI, 9.08 to 11.39]; $I^2 = 67\%$; $P < .0001$) but better long-term (≥6 months) improvement in the VAS score (MD, –2.18 [95% CI, –3.13 to −1.22]; $I^2 = 89\%$; $P < .0001$), DASH score (MD, –8.13 [95% CI, –9.87 to −6.39]; $I^2 = 25\%$; $P < .0001$), and Mayo Elbow Performance Score (MD, 16.53 [95% CI, 1.52 to 31.53]; $I^2 = 98\%$; $P = .03$) than CS. The medium-term (2-6 months) reduction in the VAS score was not significantly different between the 2 groups. After sensitivity analysis, none of the results changed except for the short-term VAS scores (MD, 0.53 [95% CI, –0.13 to 1.19]; $I^2 = 78\%$; $P = .12$).

Conclusion: Both PRP and CS injections are effective treatments for patients with LE. CS provides better short-term (<2 months) functional improvement and may be more advantageous in terms of short-term pain relief, while PRP provides better long-term (≥6 months) functional improvement and better performance regarding long-term pain relief.

Keywords: lateral epicondylitis; platelet-rich plasma; corticosteroid; meta-analysis

Lateral epicondylitis (LE), also known as tennis elbow, is a common soft tissue injury of the elbow. A population-based study published in 2015 showed[37] that the prevalence of LE in the general population ranged from 1% to 3%[37], peaking around the age of 50, with no sex

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differences.[9] This disease is characterized mainly by elbow-based pain involving the wrist and finger extensor muscles and reduced grip strength, which can place a heavy socioeconomic burden on affected individuals.[20,42] A study from the United States showed that the proportion of patients >65 years of age diagnosed with LE and treated with surgery has increased significantly in recent years, and total reimbursement and mean reimbursement per patient have steadily increased; the mean total annual reimbursement was $902,614, placing an increasing cost burden on the health care system.[10]

The specific mechanism of LE pathogenesis has not been fully elucidated, but some studies suggest that the disease may be associated with a history of repetitive activity in the affected upper extremity.[25] Past histopathological studies have suggested that LE is an inflammatory response, but in recent years, multiple studies have suggested that it is a degenerative lesion resulting from muscle overuse.[27,33,45]

Current treatment options, including activity modification, anti-inflammatory drugs, physical therapy, and local steroid injections, have been suggested as initial treatments for LE.[16,35,39] Since the introduction of glucocorticoids into the treatment of LE, multiple studies have shown good short-term performance in terms of pain relief and functional improvement. However, this treatment still has some disadvantages, such as local complications (eg, permanent damage to tendon ultrastructure) or other systemic complications.[1,5,6] Platelet-rich plasma (PRP) is an autologous blood product with platelet concentrations greater than those at baseline, and studies have suggested its possible role in accelerating tendon healing because of its ability to provide growth factors and cellular mediators.[19,21,44] Several studies have reported good results with PRP in the treatment of tendinopathies.[3,7,13] However, its use in the treatment of LE remains controversial regarding its superiority to corticosteroids (CS).[8,11,18,28,46] Our study aimed to address these controversies by conducting a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing the clinical efficacy of CS and PRP injections for LE.

METHODS

Search Strategy

The systematic evaluation and meta-analysis of this study was carried out by 2 independent evaluators (Y.X. and T.L.) who searched the PubMed, Cochrane Library, Web of Science, and Embase databases for potentially eligible literature. The following keywords were used for the search on July 29, 2022: "injections," "corticosteroid," "steroids," "platelet-rich plasma," "autologous plasma," "tennis elbow," "lateral epicondylitis," "epicondylitis, lateral humeral," "lateral elbow tendinopathy," "epicondylalgia humeri," and "epicondylitis lateral." We included only articles written in English. The keywords were restricted to the title or abstract.

Inclusion and Exclusion Criteria

The inclusion criteria for the studies were as follows: (1) the study was an RCT; (2) the focus was on participants ≥18 years of age with previously untreated LE; (3) the patients in the intervention group received PRP, and those in the comparator group received CS; (4) the article was published in English; and (5) the study published after January 2000. The exclusion criteria for studies were as follows: (1) letters, editorial materials, reviews, case reports, or basic science studies; (2) unreported function or pain outcomes; or (3) incomplete data. Per these inclusion and exclusion criteria, the titles and abstracts of eligible papers were screened, followed by a review of the full text of potentially relevant studies. Two independent evaluators determined study eligibility (Y.X. and T.L.). Disagreements were resolved by a third author (L.W.).

Data Collection and Management

Data were collected independently by 2 assessors (Y.X. and T.L.), and in cases of disagreement, consensus was reached after further discussion, or a decision was made by a third assessor (L.Y.). The extracted and summarized data included the (1) name of the first author; (2) year of publication; (3) trial design; (4) duration of follow-up; (5) patient characteristics; (6) number of participants in the intervention and control groups; (7) PRP preparation process, types of PRP, injection sites, and number and frequency of PRP injections; (8) adverse events; and (9) reported values for pain and functional scales at baseline and follow-up. The main findings were postinjection functional scores and pain scores. Functional scores included the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and the Mayo Elbow Performance Score (MEPS). Pain scores included visual analog scale (VAS) scores.

For missing parts of the data, we first tried to contact the original authors. For studies that did not explicitly mention the type of PRP used, we referred to previous studies and attempted to identify them from the preparation method and categorize them. Any differences in data collection were resolved through discussions.[26,31]

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Risk of Bias Assessment

To assess the methodological quality of eligible studies, we assessed risk using the Cochrane risk of bias tool. Sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), absence of selective reporting (reporting bias), incomplete outcome data (attrition bias), and other biases were assessed by 2 independent reviewers. Studies were considered low risk when each item was rated "low risk," and studies were considered high risk if >2 items were rated "high risk." Otherwise, the studies were considered medium risk.[29] Disagreements in the assessment were resolved through further discussion.

Statistical Analysis

Statistical analyses were performed using Manager Version 5.3.3 (Cochrane). Continuous results were calculated and are expressed as the mean difference (MD), and dichotomous results are expressed as risk ratios. Heterogeneity between studies was quantified using the I^2 statistic. I^2 values of 25%, 50%, and 75% were considered to indicate low, medium, and high heterogeneity, respectively. A fixed-effects model was used when I^2 was <50%, and a random-effects model was used when I^2 was >50%. P values <.05 were considered statistically significant. Sensitivity analysis was performed to remove studies with high-risk factors. Publication bias was assessed by funnel plot. In addition, based on previous studies, we defined short-term follow-up as <2 months, intermediate follow-up as between 2 and 6 months, and long-term follow-up as reaching or exceeding 6 months.[18]

RESULTS

Literature Search

Using the search formula, we searched 682 articles, removed 195 duplicate studies, and evaluated the titles and abstracts of the remaining 487 articles according to the inclusion and exclusion criteria. After screening, 12 clinical studies were included in this study, of which 1 article was excluded because the original data were not available. Finally, 11 studies involving 730 patients were included in this review[‡] (Figure 1). No high-risk clinical studies were included. Details of the bias assessment are shown in Figure 2.

Study and Patient Characteristics

We included 11 studies involving 730 patients. All included studies were prospective RCTs with a mean follow-up time of 6.94 months. All included studies compared the LE group receiving PRP injections with the LE group receiving CS injections. A total of 354 patients treated with PRP and 376 patients treated with CS were compared in the 11 RCTs. The main characteristics of the RCTs included in the study are shown in Table 1.

[‡]References 14, 15, 17, 23, 24, 32, 34, 36, 38, 43, 47.

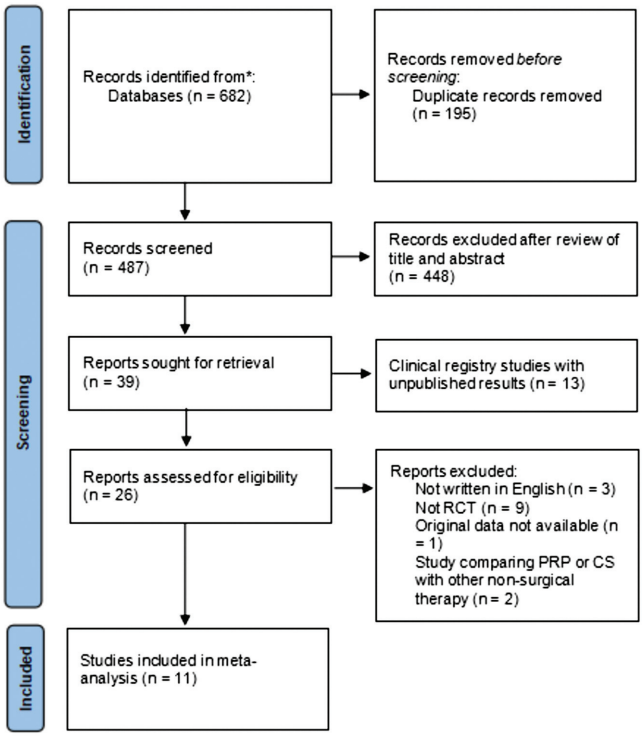

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of literature retrieval. CS, corticosteroid; PRP, platelet-rich plasma; RCT, randomized controlled trial. *The number of studies reported is the total number of studies found in all database and registry searches.

Clinical Outcomes in PRP

VAS Score. Nine of these studies reported short-term (<2 months) VAS scores, and we found that CS were more effective for pain relief in the short term than PRP (MD, 0.93 [95% CI, 0.42 to 1.44]; I^2 = 85%; P = .0003). Eight studies reported VAS scores for the CS and PRP groups in the intermediate term (2-6 months) with no significant difference between groups (MD, –0.32 [95% CI, –0.64 to 0.01]; I^2 = 87%; P = .06). Six studies reported long-term (≥6 months) VAS scores in the CS and PRP groups (MD, –2.18 [95% CI, –3.13 to −1.22]; I^2 = 89%; P < .0001) (Figure 3).

The change in short-term VAS results after sensitivity analysis by removing studies with high-risk factors from 3 trials (MD, 0.53 [95% CI, –0.13 to 1.19]; I^2 = 78%; P = .12) suggests that the results of CS and PRP for short-term pain reduction need to be treated with caution (Figure 4).

DASH Score. Six studies reported short-term (<2 months) DASH scores with statistically significant differences between the PRP and CS groups of patients (MD, 10.23 [95% CI, 9.08 to 11.39]; I^2 = 67%; P < .0001),

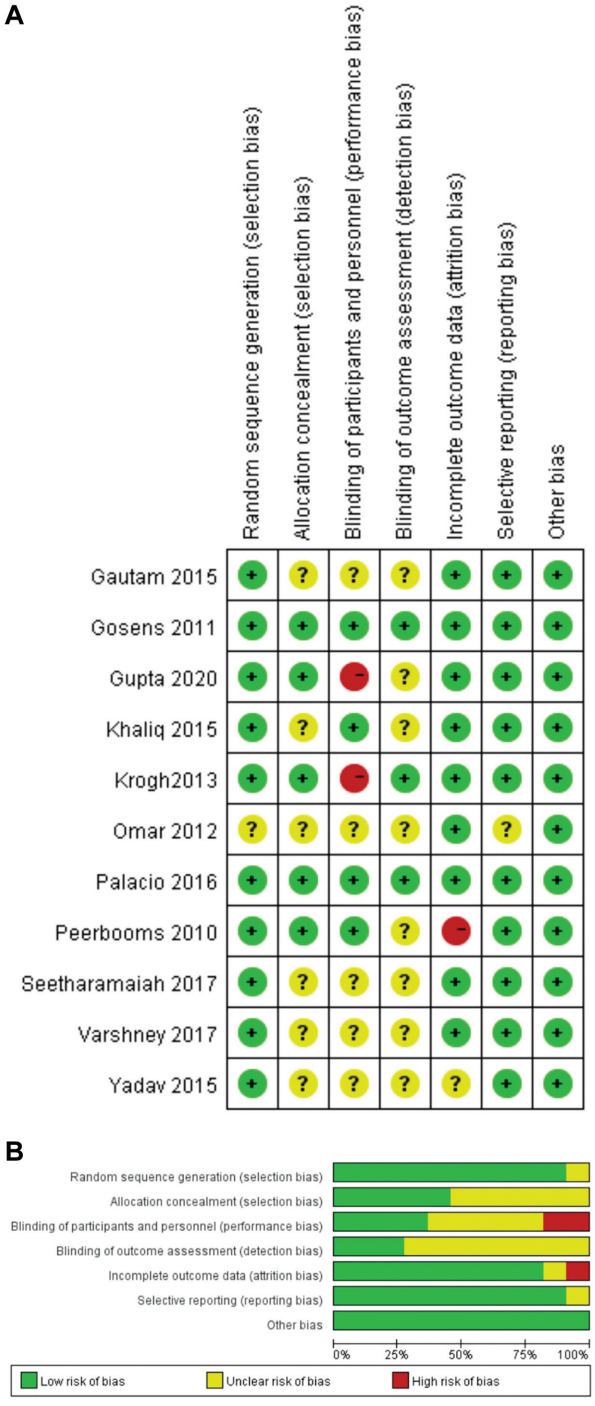

Figure 2. Risk of bias graphs. (A) Graph of the risk of bias for the included studies. (B) Graph of the risk of bias summary for the included studies.

demonstrating a greater advantage for CS patients. Six studies reported midterm (2-6 months) DASH scores in the CS and PRP groups (MD, –7.66 [95% CI, –11.36 to −3.96]; I^2 = 83%; P < .0001), and 5 studies reported DASH scores in the long-term (≥6 months) CS and PRP groups (MD, –8.13 [95% CI, –9.87 to −6.39]; I^2 = 25%; P < .0001). We noted significant differences in favor of PRP in both the medium term and the long-term observations (Figure 5). Sensitivity analysis was used to exclude studies with high-risk factors, but this did not change the results.

Mayo Elbow Performance Score. The short-term (<2 months) MEPS (MD, –4.17 [95% CI, –9.37 to 1.03]; I^2 = 90%; P = .12) and the medium-term (2-6 months) MEPS (MD, 3.31 [95% CI, –2.59 to 9.20]; I^2 = 90%; P = .27) were reported in 3 studies, with no significant differences found between the 2 groups. Three studies reported the long-term (≥6 months) MEPS (MD, 16.53 [95% CI, 1.52 to 31.53]; I^2 = 98%; P = .03), noting a significant difference in favor of PRP (Figure 6). One study with high-risk factors was excluded in the sensitivity analysis, but this did not change the results.

DISCUSSION

Several studies[4,18,22,28,40,46] have compared PRP injection with CS injection in the treatment of LE. Most studies concluded that PRP performs better in terms of long-term pain relief as well as functional improvement in patients with LE, but the merits of CS injections and PRP injections in terms of short-term and medium-term pain relief and functional improvement remain controversial. The purpose of our meta-analysis and systematic review was to compare the clinical efficacy of PRP and CS injections in improving functional scores and relieving pain in LE. With the inclusion of 11 RCTs and 730 patients, we found that CS performed better for short-term (<2 months) improvement in the VAS and DASH scores, but conversely, PRP performed significantly better for long-term (≥6 months) improvement in the VAS score, DASH score, and MEPS. After sensitivity analysis and the resulting removal of studies with a high risk of bias, none of the results changed significantly except for the short-term VAS scores; therefore, the conclusions of this study regarding the improvement of pain in the short term should be treated with caution and need to be validated by additional studies.

In terms of pain relief, 1 meta-analysis including 9 articles conducted by Huang et al[18] showed that CS injections performed better than PRP injections for short-term pain relief, whereas for long-term pain relief, the findings changed, with PRP injections being more beneficial for pain relief in patients with LE, a finding consistent with that of our study. The study also found that the change in long-term VAS pain scores exceeded the published minimal clinically important difference, indicating that PRP injections are both statistically and clinically significant for long-term pain relief in patients with LE. Another meta-analysis[46] comparing diverse injections in the treatment of LE included 7 studies, and this analysis with 6 months of follow-up at baseline found that local PRP injections were associated with better outcomes in terms of pain reduction than local CS injections, which is consistent with the long-term observations in our study. This may be because of the high overlap of RCTs included in the 2 studies and to the fact that the long-term provision was >6

TABLE 1
Main Characteristics of the Included Studies for Lateral Epicondylitis[a]

Study (Design): Diagnosis Method and Group	Enrolled (M:F)	Mean Age, y	Dominant Side, %	Symptom Duration, mo	Volume, mL	Intervention Details	Type of PRP	Injection Technique	Follow-up, mo
Gautam et al (2015): US									
PRP	15			>6	2	20 mL blood centrifuged, 15 min	LP-PRP	Peppering	6
CS	15			>6	2	2 mL methylprednisolone (40 mg/mL)		Peppering	6
Gosens et al (2011): PE									
PRP	51 (23:28)	47.3	74.5	>6	5	27 mL blood centrifuged, collected by Recover GPS II System + bupivacaine hydrochloride 0.5% with epinephrine (1:200,000)	LR-PRP	Peppering	24
CS	49 (23:26)	46.8	75.5	>6	5	Kenacort 40 mg/mL triamcinolone acetonide + bupivacaine hydrochloride 0.5% with epinephrine (1:200,000)		Peppering	24
Gupta et al (2020)									
PRP	40 (19:21)	42.4		3.8	3	18 mL blood centrifuged, 160*g* for 12 min, 460*g* for 18 min	LR-PRP	Injection at the common extensor origin	12
CS	40 (15:25)	39.4		4.1	3	40 mg triamcinolone with 2% xylocaine		Injection at the common extensor origin	12
Khaliq et al (2015)									
PRP	51 (21:30)	34			3		LR-PRP	Peppering	0.75
CS	51 (24:27)	34			3	2 mL methylprednisolone acetate + 1 mL 2% xylocaine		Peppering	0.75
Krogh et al (2013): US									
PRP	20 (9:11)	48.8	85	18.1	3-3.5	27 mL blood centrifuged, 15 min at a speed of 3.2 (× 1000 rpm), collected by Recover GPS II System	LR-PRP	US guided	12
CS	20 (11:9)	48.5	75	35.6	3	1 mL triamcinolone (40 mg/mL), 2 mL lidocaine (10 mg/mL)		US guided	12
Placebo	20 (9:11)	44.7	65	15.5	3	3 mL 0.9% NS		US guided	12
Omar et al (2012): PE									
PRP	15 (6:9)	40.5				21 mL blood centrifuged, 320*g* for 15 min, 2000*g* for 15 min			1.5
CS	15 (5:10)	37.5							1.5
Palacio et al (2016): PE									
PRP	20	47			3	60 mL blood centrifuged 10 min	LP-PRP		36
CS	20	42			3	3 mL dexamethasone			6
Peerbooms et al (2010): PE									
PRP	49 (23:26)	46.9	53.3	>6	3	27 mL blood centrifuged, collected by Recover GPS II System + bupivacaine hydrochloride 0.5% with epinephrine (1:200,000)	LR-PRP	Injection at the common extensor origin and the area of maximum tenderness	12
CS	51 (25:26)	47.3	63.3	>6	3	Kenacort 40 mg/mL triamcinolone acetonide + bupivacaine hydrochloride 0.5% with epinephrine (1:200,000)		Injection at the common extensor origin and the area of maximum tenderness	12
Seetharamaiah et al (2017)									
PRP	30 (12:18)	52			1	15 mL blood centrifuged 10 min, block with 2% lignocaine	LR-PRP		6
CS	30 (12:18)	50			1	1 mL triamcinolone, block with 2% lignocaine			6
Varshney et al (2017)									
PRP	33				3	2 mL PRP + 1 mL lignocaine	LR-PRP	Injection at most tender point	6
CS	50				3	80 mg methyl prednisolone + 1 mL lignocaine suspension)		Injection at most tender point	6

(continued)

TABLE 1
(continued)

Study (Design): Diagnosis Method and Group	Enrolled (M:F)	Mean Age, y	Dominant Side, %	Symptom Duration, mo	Volume, mL	Intervention Details	Type of PRP	Injection Technique	Follow-up, mo
Yadav et al (2015): PE									
PRP	30 (10:20)	37	70	2.3	1	Absolute platelet count of 1 million platelets/mm^3 as confirmed by manual counting	LR-PRP	Injection at the common extensor origin	3
CS	30 (7:23)	37	73	1.9	1	40 mg methylprednisolone		Injection at the common extensor origin	3

[a]CS, corticosteroid; F, female; LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma; M, male; NS, normal saline; PE, physical examination; PRP, platelet-rich plasma; RCT, randomized controlled trial; US, ultrasound. The missing data in the table is because the data were not reported in the original study and there was no response after contacting the original authors.

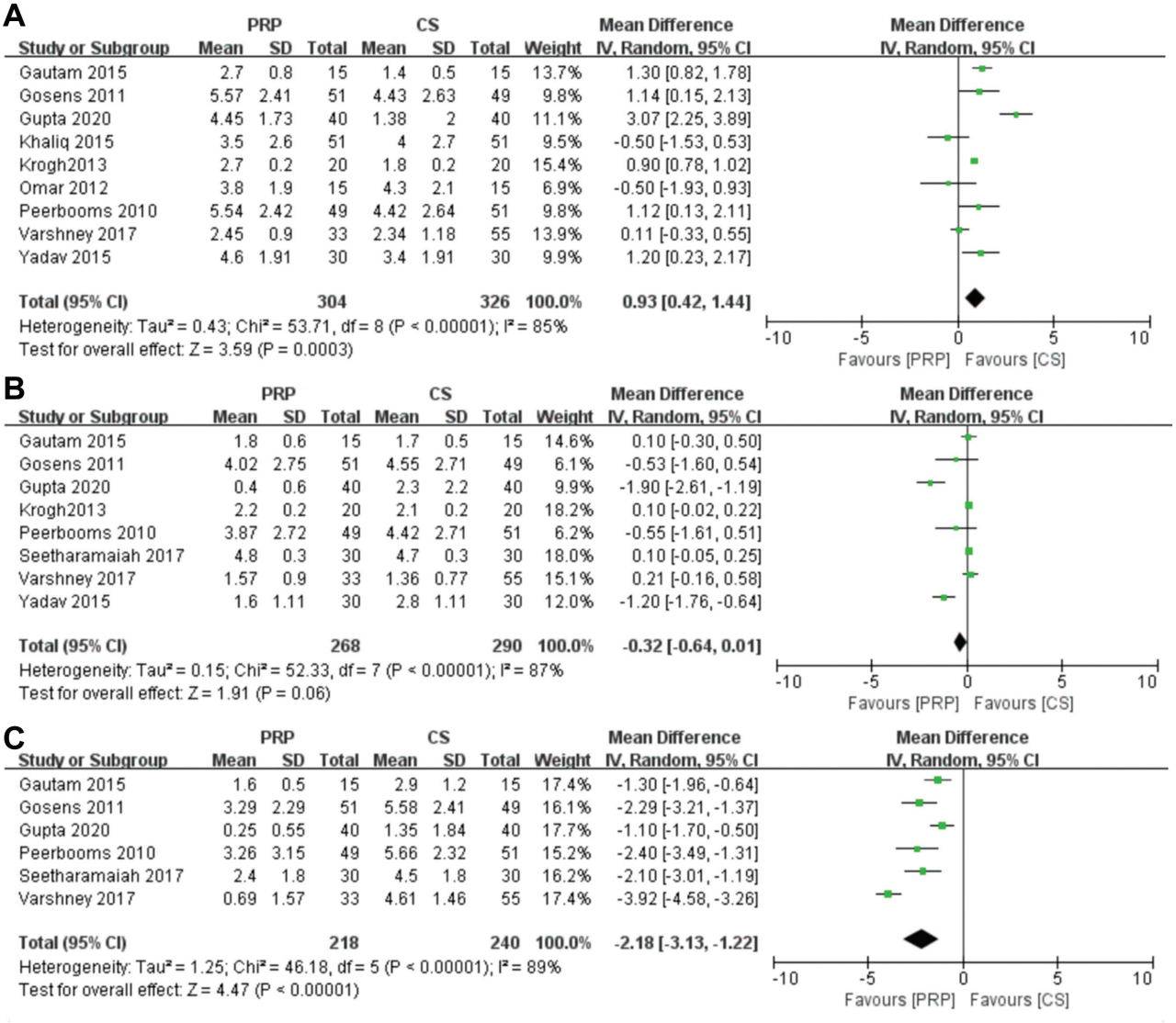

Figure 3. Meta-analysis of the effects of platelet-rich plasma (PRP) and corticosteroids (CS) on the visual analog scale score. (A) PRP versus CS in reducing pain in the short term (<2 months). (B) PRP versus CS in reducing pain in the medium term (2-6 months). (C) PRP versus CS in reducing pain in the long term (≥6 months). IV, inverse variance.

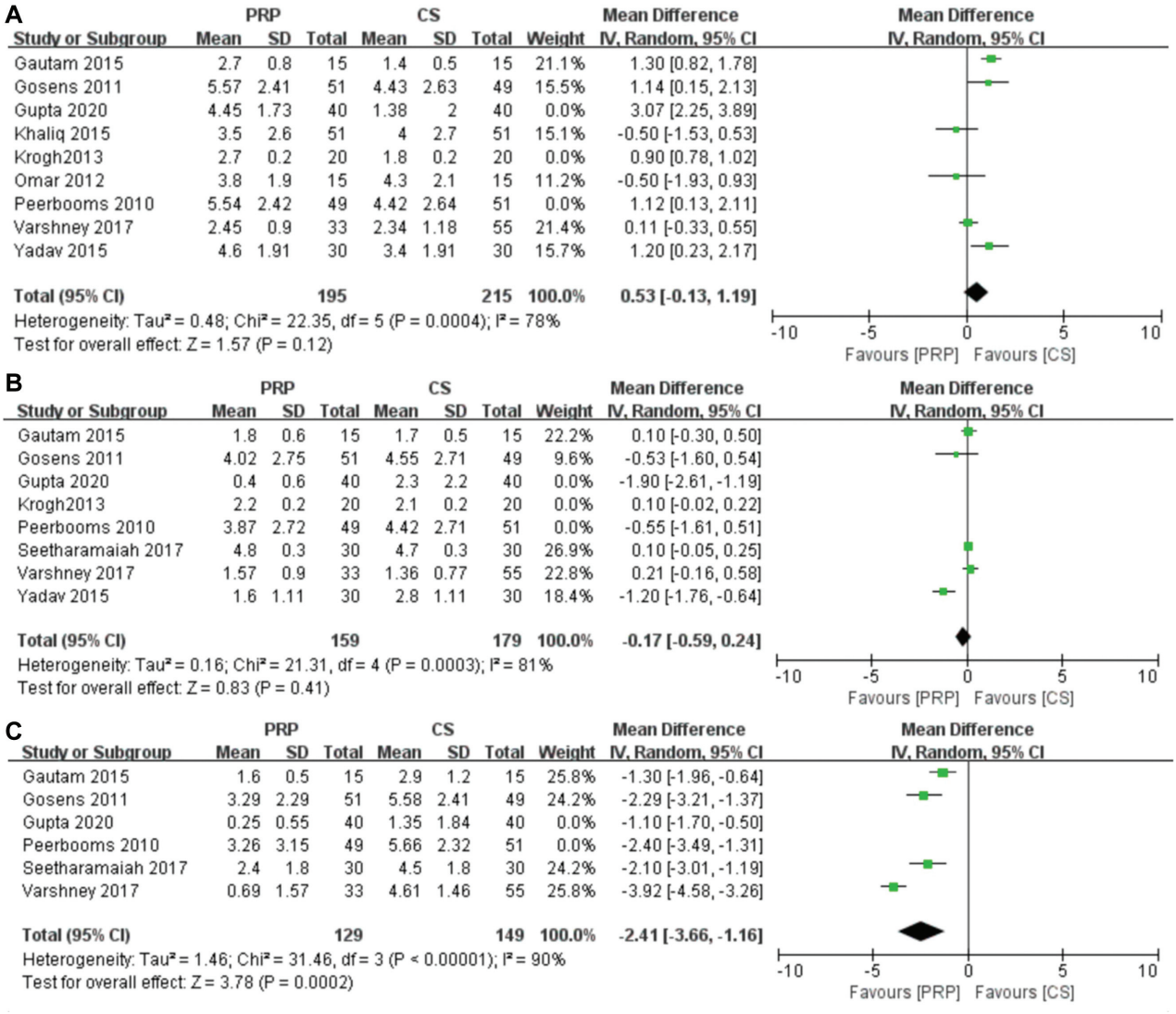

Figure 4. Sensitivity analysis of the effects of platelet-rich plasma (PRP) and corticosteroids (CS) on the visual analog scale score. (A) PRP versus CS in reducing pain in the short term (<2 months). (B) PRP versus CS in reducing pain in the medium term (2-6 months). (C) PRP versus CS in reducing pain in the long term (≥6 months). IV, inverse variance.

months. Tang et al[40] conducted a network meta-analysis with 20 documents. They compared the efficacy of local injections of PRP, CS, and autologous blood for the treatment of LE and found that PRP was more associated with long-term improvement in pain. However, in the short term, glucocorticoids were associated with the greatest improvement. This is partially consistent with our findings, and the discrepancy may be because the assessment of pain and function was not identical to the present study, which also introduced the pressure pain threshold as an assessment of pain relief, the modified Nirschl score related to activity and function.

In terms of functional improvement, the study by Huang et al[18] analyzed only short-term DASH scores and found that there appeared to be no difference in short-term DASH scores between the 2 treatment modalities. Our findings differ from those of that study. The main reason may be the different definitions of *short term*, with the criteria of the previous study defining a short-term period as ≤3 months and a long-term period as >3 months, and those of our study defining a short-term period as <2 months. Thus, some outcome indicators between 2 and 3 months may have led to the difference in the results. There are currently no strict criteria for dividing short term, medium term, and long term. Because most of the eligible trials in our study had a final follow-up of >2 months and more than half of the studies had a follow-up of >6 months, comparisons between follow-up periods were possible. For the sake of refinement, we defined 2 months as short term, 2 to 6 months as medium term, and ≥6 months as long term. In our results, the differences in treatment effects between the 3 time points justify the time point.

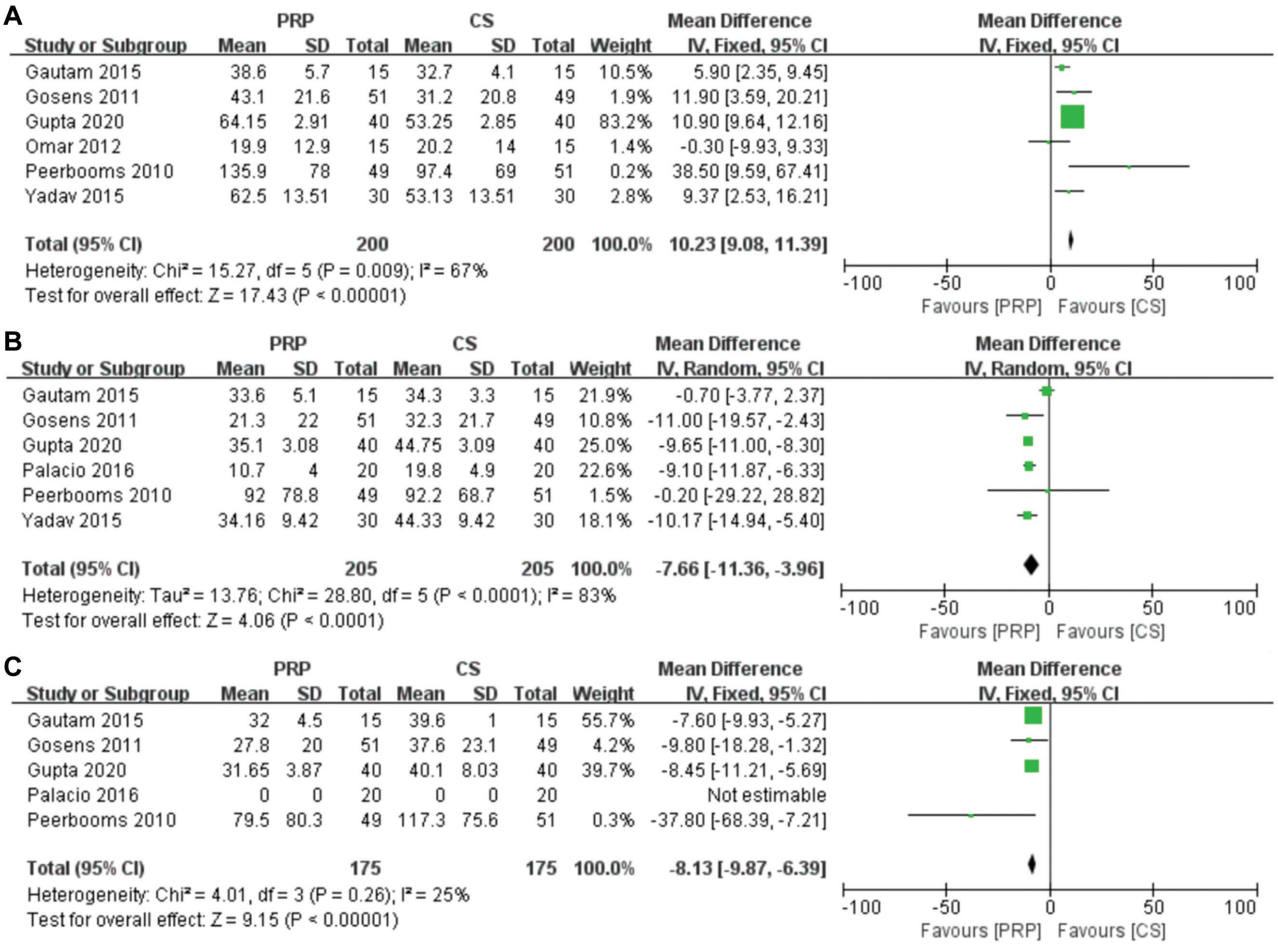

Figure 5. Meta-analysis of the effects of platelet-rich plasma (PRP) and corticosteroids (CS) on the Disabilities of the Arm, Shoulder and Hand score. (A) PRP versus CS in improving DASH scores in the short term (<2 months). (B) PRP versus CS in improving DASH scores in the medium term (2-6 months). (C) PRP versus CS in improving DASH scores in the long term (≥6 months). IV, inverse variance.

Another systematic review conducted by Kemp et al[22] concluded that PRP injections appear to be a more effective long-term treatment option than CS injections for patients with LE who have failed to respond to nonoperative therapy. The results of this study, which included 5 previous systematic reviews, found a high degree of consistency in the conclusion that previous systematic reviews showed better long-term clinical outcomes of PRP injections in patients with LE. This study was only qualitative and did not have quantitative results; therefore, conclusions should be drawn with caution. The study by Tang et al[40] also differed from our findings in that they concluded that PRP was more associated with long-term improvement in function. In the short term, glucocorticoids were associated with the greatest improvement. The discrepancy may be because that study correlated activity and function with the modified Nirschl score, as well as the Patient-Related Tennis Elbow Evaluation score, as an assessment of functional improvement. In addition, the study delineated only short- and long-term outcomes and did not discuss patients' clinical outcomes in the medium term.

The possible reason for the lack of complete agreement between the 2 functional scores in our study is the difference between the DASH score and MEPS. The DASH score is widely used and is closely related to the level of both pain and functional disability. Although the DASH score is non–organ specific, its validity for the assessment of LE has been confirmed by studies.[12,30] On the other hand, although a specific elbow scoring system, the MEPS remains controversial for assessing LE, and more studies may be needed in the future to confirm whether it is a good choice for assessing LE.[41] In summary, most of the current meta-analyses and systematic reviews on LE have shown a high degree of similarity in their conclusions regarding the clinical efficacy of CS injection and PRP injection, and there is a high degree of overlap between the included original studies. However, because of the small sample sizes in all existing original studies and the uneven quality of some of the original studies, such as specific study methods and poorly articulated

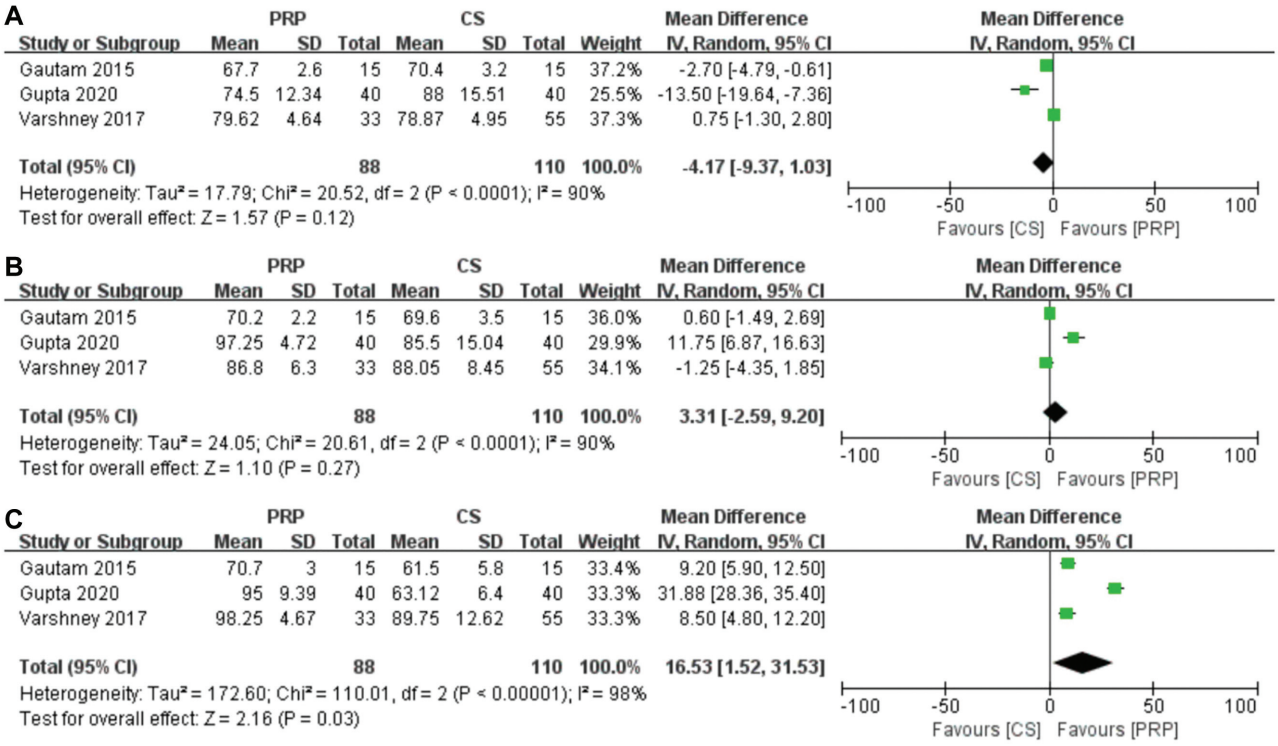

Figure 6. Meta-analysis of the effects of platelet-rich plasma (PRP) and corticosteroids (CS) on the Mayo Elbow Performance Score. (A) PRP versus CS in improving MEPS in the short term (<2 months). (B) PRP versus CS in improving MEPS in the medium term (2-6 months). (C) PRP versus CS in improving MEPS in the long term (≥6 months). IV, inverse variance.

outcome indicators, these issues may lead to weakened reliability of their conclusions.[2,18,22,40,46] Therefore, there is still a need for large, high-quality RCTs to explore questions regarding the short- to medium-term clinical efficacy of CS injections and PRP injections in patients with LE and to validate the benefits of PRP in treating patients with LE for long-term functional improvement and pain relief. The strengths of the current study include rigorous inclusion and exclusion criteria, independent data collection and analysis, and a complete assessment of study quality. We have the largest number of RCTs directly comparing PRP injections with CS injections compared with recent systematic reviews and meta-analyses, which can make good use of randomization.

Limitations

This study has several limitations. First, it included only RCTs published in English, so some non-English studies may have been missed. Second, there is no standardized treatment protocol for LE injections, and differences in treatment may lead to heterogeneity. The doses and concentrations of CS vary, and some studies also use local anesthetics for concurrent injections, which may increase bias. Similar heterogeneity exists for PRP injections, including different concentrations of platelets and leukocytes, different clutch rates and times, and whether local anesthesia was administered at the PRP injection site. Third, because of insufficient raw data, we were unable to determine whether factors such as age and sex were associated with heterogeneity. Heterogeneity in outcomes may also result from different follow-up times in the original studies because there was no consensus on the time point of follow-up. Fourth, although all 11 included studies were assessed as not having a high risk of bias, 2 were considered to have a low risk of bias, which may reduce the credibility of the conclusions of this study.

CONCLUSION

This meta-analysis and systematic review showed that both PRP and CS injections are effective treatments for patients with LE. CS provides better short-term (<2 months) functional improvement and may be more advantageous in terms of short-term pain relief, while PRP provides better long-term (≥6 months) functional improvement and better performance regarding long-term pain relief. However, the conclusions of this study regarding the improvement of pain in the short term should be treated with caution and need to be validated by additional studies.

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