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Review

Comparison of platelet rich plasma and corticosteroids in the management of lateral epicondylitis: A meta-analysis of randomized controlled trials

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ABSTRACT

Objective: To compare the clinical efficacy of platelet-rich plasma (PRP) injections with that of corticosteroids in patients with lateral epicondylitis (LE).

Methods: We searched for relevant studies on the comparison of PRP and corticosteroids in the management of lateral epicondylitis in electronic databases, including PubMed, Embase, Ovid, Cochrane Library, Web of Science, Wan Fang and China National Knowledge Internet, up to March 2019. The outcomes were pain score, elbow joint function and adverse effects after local injection. For continuous data, the weighted mean difference (WMD) and 95% confidence intervals (CIs) was used. Risk difference (RD) with a 95% CI were calculated for dichotomous outcomes. Cochrane Collaboration's tool was used to assess the risk of bias. The data were collected and input into the STATA software.

Results: A total of seven randomized controlled trials (RCTs) involving 515 patients were finally included in our study. The present meta-analysis indicated that PRP injection yielded statistically significant superior in pain scores and elbow joint function at a 6-month follow up compared with local corticosteroid injection. No significant difference was identified between two groups regarding the post-injection adverse events.

Conclusion: Local PRP injections was associated with superior outcomes for reducing pain and improving elbow joint function compared with local corticosteroids treatment for LE at a follow-up of 6 months.

1. Introduction

Lateral epicondylitis (LE), also known as tennis elbow, is one of the most common soft tissue injuries, which has been shown to affect 1%–3% of adults each year [1]. It often occurs in patients whose ages of 35 and 50 years with high demand of gripping or repetitive wrist movements [2]. The dominant arm is most frequently affected. Currently, the exact mechanism is unclear. It is believed that the lesion starts as a tear in the common extensor tendon caused by mechanical overloading which leads to abnormal microvascular responses [3]. Although it is originally thought to be an inflammation process, overuse and repetitive microtrauma of the wrist flexor and extensor tendons is thought to be the mechanism for injury of medial and lateral epicondylitis [4].

LE is associated with pain and functional disorder of elbow joint. Several methods have been used for treating LE including physiotherapy, nonsteroidal anti- inflammatory drug, and local steroid injection [5–7]. Injection with glucocorticoid was first introduced in 1950s and has shown improved outcomes for pain relief and functional recovery [8]. Although local injection of corticosteroids has considered gold standard, it may result in permanent damage within the tendon ultrastructure by intratendinous injection and injection of the mixture superficially may cause subcutaneous atrophy [9,10]. Platelet-rich plasma (PRP) is a concentrate of platelet-rich plasma protein derived from whole blood [11]. It contains several different growth factors and other cytokines that can stimulate healing and enhance the inflammatory cascade. Murray et al. [12] reported that PRP injections have an important and effective role in the treatment of LE, in cases where physiotherapy has been unsuccessful.

Currently, whether local injection of PRP is superior to corticosteroids in the management of LE remains controversial. Therefore, we conduct a meta-analysis to compare the clinical efficacy of PRP injections with that of corticosteroids in patients with LE.

2. Methods

The meta-analysis has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and

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AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines. No ethical approval was required. Ethics committee approval is not required.

2.1. Search strategy

We searched for relevant studies on the comparison of PRP and corticosteroids in the management of lateral epicondylitis in electronic databases, including PubMed, Embase, Ovid, Cochrane Library, Web of Science, Wan Fang, China National Knowledge Internet, up to March 2019. In addition, a manual search of the bibliographies of identified articles was performed to identify potentially relevant studies. A structured search was performed using the following search string: (Lateral epicondylitis OR Tennis elbow [Title/Abstract]) AND (Platelet rich plasma AND Corticosteroid OR Steroid [Title/Abstract]). Our search did not include language restrictions.

2.2. Inclusion and exclusion criteria

Two investigator identified eligible studies and extracted data independently. The titles and abstracts were screened to exclude the duplicated and apparently irrelevant ones or those that do not meet our inclusion criteria. Studies were selected if they accord with the following criteria in PICOS order: [1] Population: patients experiencing LE who were demographically alike [2]. Intervention: local injection of PRP [3]. Control: local injection of corticosteroid [4]. Outcomes: pain score, elbow function and adverse effects [5]. Study design: randomized controlled trials (RCT). Case reports, editorials, reviews, letters, experimental studies, conference articles, commentaries and other studies that failed to provide detailed results were excluded. If consensus was not reached, a third investigator would make a judgment.

2.3. Data collection

Two reviewers independently extracted data, and the third reviewer checked the consistency between them. A standard form was used; the extracted items included the following: [1] the general study information, for example, the authors, publishing date, study design, case number, age, gender and follow-up term [2]. clinical outcomes such as pain score and elbow function. The mean and standard deviation (SD) of outcomes was extracted directly from original text, if not reported, was estimated based on sample size, median and the range. Corresponding authors of the included RCTs were contacted for the missing data to ensure the integrity of the review if necessary. Consensus was finally reached between two reviewers through discussion.

2.4. Statistical methods

For continuous data, the weighted mean difference (WMD) and 95% confidence intervals (CIs) was used. Risk difference (RD) with a 95% CI were calculated for dichotomous outcomes. A P-value < 0.05 was considered statistically significant. The data were collected and input into the STATA software (version13.0; StataCorp, College Station, TX) for meta-analysis. A random-effects model was applied when statistical heterogeneity was high. Otherwise, a fixed-effects model was used. Funnel plots were performed to assess publication bias.

2.5. Quality assessment

In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, two reviewers independently assessed the risk of bias, including the following twelve items: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessor,

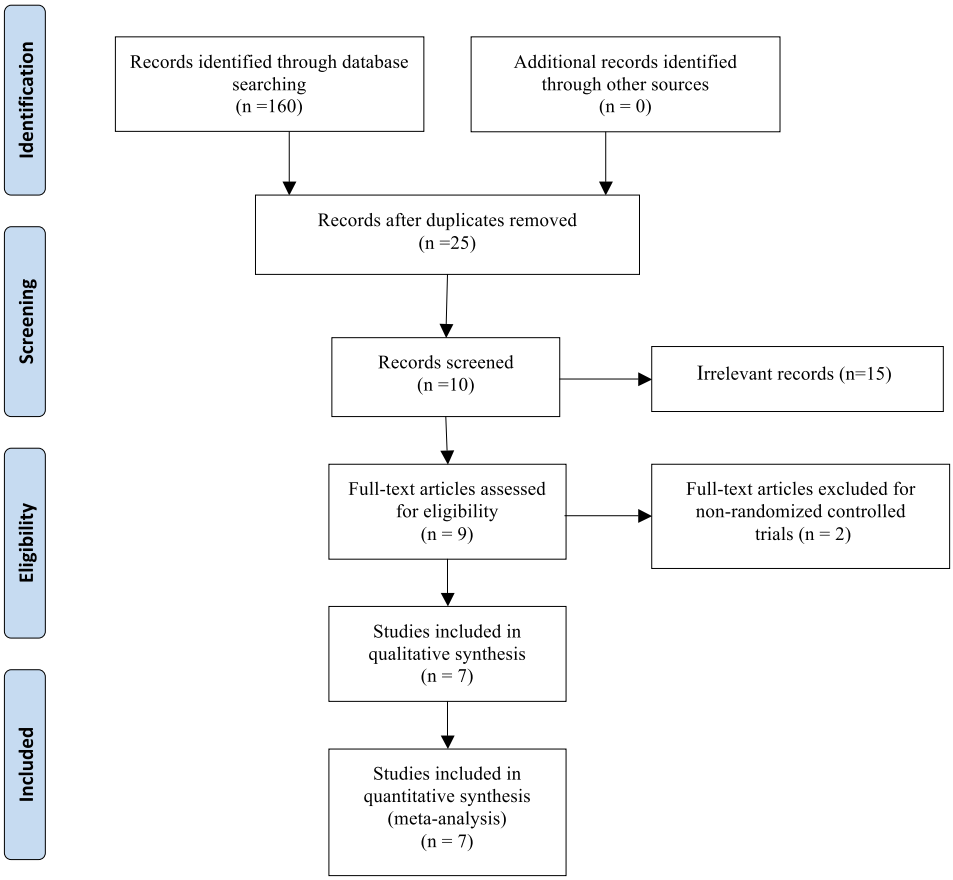


Fig. 1. Flow chart of study selection.

incomplete outcome data, reporting bias, and other bias. Each item was assessed as low, unclear, or high bias. The risk-of-bias summary and risk-of-bias graph were generated with Review Manager 5.3.0 software.

Recommendations Assessment, Development and Evaluation (GRADE) system [13] was used to grading the evidence level. Consensus was finally reached between two reviewers through discussion.

3. Results

3.1. Search results

We identified 160 potential articles by searching electronic databases. After excluding 135 duplicate articles, 15 articles were excluded based on screening titles and abstracts. A further 2 article were excluded by an assessment of full text. In addition, manual search of relevant reference did not identify any additional studies. Finally, a total of 7 RCTs [14–20] meeting all inclusion criteria were included in this meta-analysis. Progress of study selection was presented in Fig. 1.

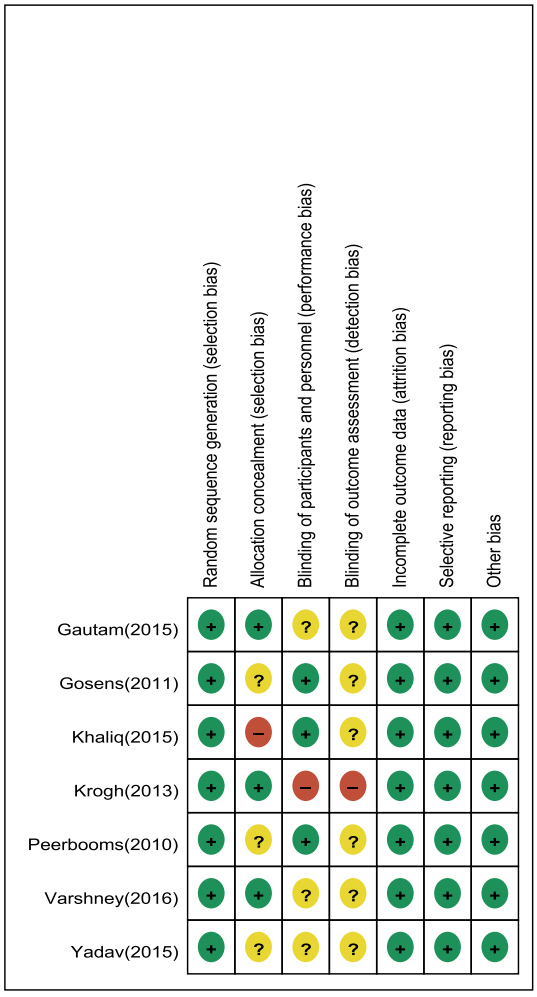
3.2. Studies characteristics

All of 7 studies were RCTs, which published between 2010 and 2016 with the sample size ranging from 30 to 102. Totally 515 participants were included, among which 251 participants were allocated in intervention groups and 264 participants in control groups. The mean age ranged from 34-year-old to 48-year-old. The duration of follow up ranged from 3 to 24 weeks (see Table 1).

3.3. Quality assessment

Table 2 and Table 3 summarized the risk of bias assessment summary and risk of bias graph. Randomization and comprehensive methodological processes were reported in all trials. Three RCTs used a sealed opaque envelope for allocation concealment. Three studies showed double blinding. However, none of them reported blinding of outcome assessment. All RCTs provided complete outcome data. Other assessment of bias was low risk.

Table 2
Risk of bias summary.



3.4. Clinical outcomes

3.4.1. Visual analogue scale (VAS) at 1st month

Six RCTs reported the outcome of VAS at 1st month after injection. There was no significant heterogeneity among studies ($I^2 = 0\%$, $p = 0.89$) and a fixed effect model was used. The present meta-analysis indicated that PRP injection yielded statistically significant superior in VAS scores after treatment at 1st month compared with local corticosteroid injection (WMD = −0.253; 95% CI: -0.403 to −0.103; P = 0.001, Fig. 2).

3.4.2. VAS at 2 nd month

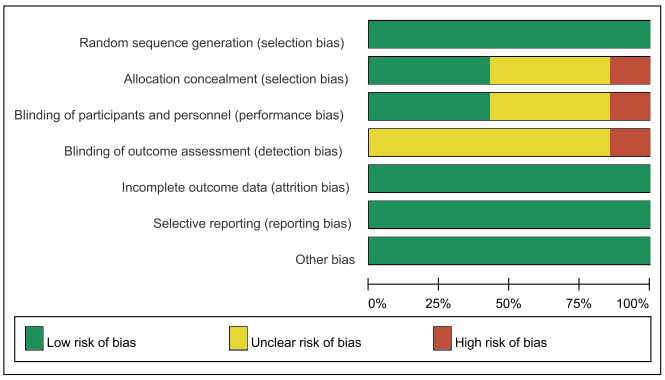
VAS at 2 nd month was reported in five studies. There was no significant heterogeneity and a fixed effect model was used ($I^2 = 0\%$,

Table 1
Characteristics of the included RCTs.

Study	Year	Design	No. of patients		Gender (Male)		Age		Doses of PRP	Doses of corticosteroids	Follow up
			RPR	corticosteroids	RPR	corticosteroids	RPR	corticosteroids			
Peerbooms et al.	2010	RCT	51	49	23	25	47	47	1 ml PRP	40 mg triamcinolone	6 months
Gosens et al.	2011	RCT	51	49	23	23	47	47	1 ml PRP	40 mg triamcinolone	3 months
Krogh et al.	2013	RCT	20	20	9	9	48	44	3–3.5 ml PRP	40 mg triamcinolone	3 months
Gautam et al.	2015	RCT	15	15	No mentioned		No mentioned	2 ml PRP	80 mg methylprednisolone	3 months	
Yadav et al.	2015	RCT	30	30	10	7	37	37	1 ml PRP	40 mg methylprednisolone	3 months
Khaliq et al.	2015	RCT	51	51	27	30	34	34	3 ml PRP	2 ml methylprednisolone acetate	3 weeks
Varshney et al.	2016	RCT	33	50	20	25	46	47	2 ml PRP + 1 ml lignocaine	80 mg methylprednisolone + 1 ml lignocaine	6 months

RCT: randomized controlled trial, PRP: Platelet-rich plasma.

Table 3
Risk of bias graph.



p = 0.506). The present meta-analysis revealed that there was significant difference between two groups regarding the VAS at 2 nd month (WMD = −0.205, 95% CI: -0.344 to −0.067, P = 0.004; Fig. 3).

3.4.3. VAS at 6th month

Four RCTs reported the VAS at 6th month after treatment. A fixed effect model was adopted (I^2 = 47.8%, p = 0.125). A significant decrease in VAS at 6th month was observed in PRP groups compared with corticosteroid groups (WMD = −0.391; 95% CI: -0.428 to −3.53; P < 0.001, Fig. 4).

3.4.4. Modified Mayo performance index (MAYO) at 1st month

A total of four RCTs showed the MAYO at 1st month after injection. There was significant heterogeneity and a random effect model was adopted (P < 0.001, I^2 = 90.1%). Our meta-analysis demonstrated that there was significant difference between groups regarding the MAYO at 1st month (WMD = 5.286; 95% CI: 3.877 to 6.694; P < 0.001, Fig. 5).

3.4.5. MAYO at 2 nd month

MAYO at 2 nd month was reported in three articles, a random effect model was used (P < 0.001, I^2 = 89.6%). Our meta-analysis demonstrated that PRP injection was associated with significant superior in MAYO at 2 nd month compared with local corticosteroid injection (WMD = 1.665; 95% CI: 0.367 to 2.962; P = 0.012, Fig. 6).

3.4.6. MAYO at 6th month

Three RCTs showed the outcome of MAYO at 6th month after treatment. A fixed effect model was used (P = 0.160, I^2 = 45.4%). The aggregated results of these studies suggest that PRP could significantly improve MAYO at 6th month (WMD = 1.666; 95% CI: 1.183 to 2.149; P < 0.001, Fig. 7).

3.4.7. Disabilities of the Arm, Shoulder and Hand (DASH) score

Three studies reported the DASH score after local injection at 1st-6th month. A random effect model was used (P = 0.036, I^2 = 58.1%). Our study demonstrated that there was significant difference between two groups in terms of DASH score (WMD = −4.885; 95% CI: -7.658 to −2.112; P = 0.001, Fig. 8).

3.4.8. Adverse effects

Four RCTs showed the incidence of infection after local injection. The present meta-analysis indicated that there was no significant difference between two groups regarding the risk of infection (RD = −0.012; 95% CI: -0.059 to 0.035; P = 0.612, Fig. 9).

3.5. Publication bias and evidence level

A low risk of publication bias was identified for the VAS at 1st month (Table 4). GRADE system was used to grading the evidence level. The overall evidence was low, which indicated that further research

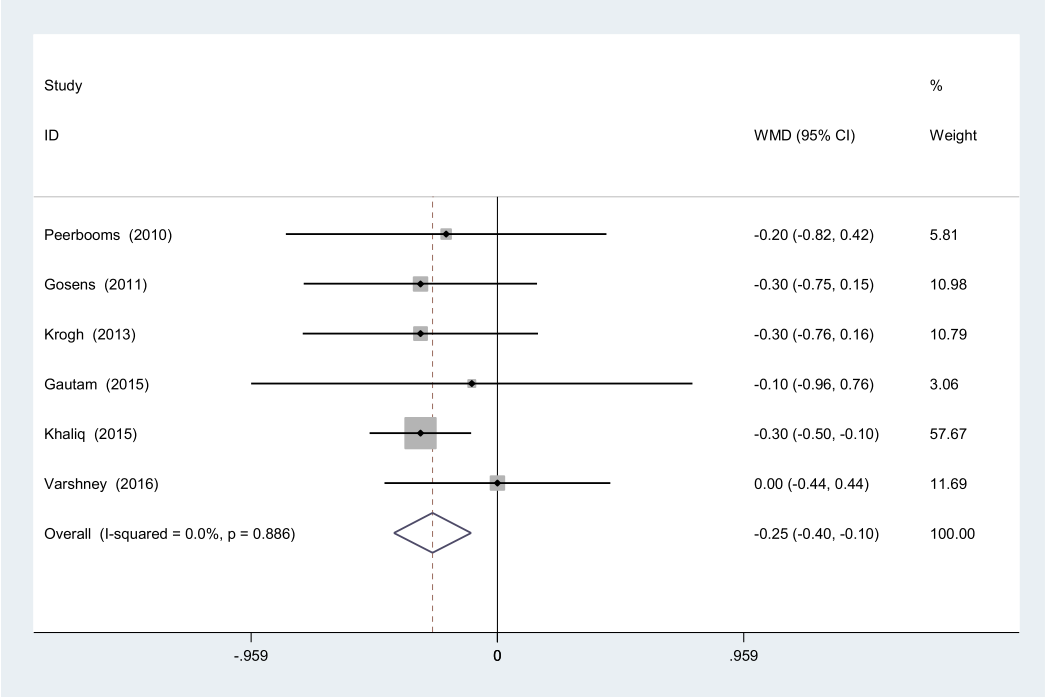


Fig. 2. Forest plot diagram of VAS at 1st month.

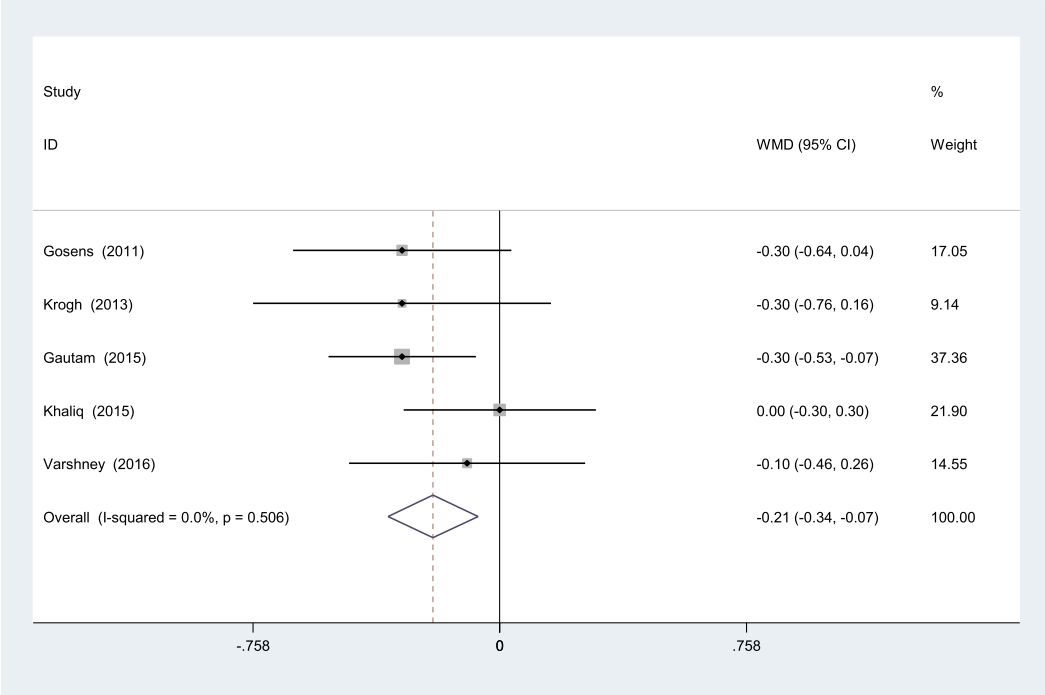


Fig. 3. Forest plot diagram of VAS at 2 nd month.

was likely to significantly alter confidence in the effect estimate and to change the estimate (Table 5).

4. Discussion

To the best of our knowledge, this was the initial meta-analysis from RCTs to compare the clinical efficacy and safety of PRP injections with that of corticosteroids in patients with LE. The most important finding was that local PRP injection yielded statistically significant superior regarding VAS score, MAYO and DASH score on the short-term follow-up period compared to local corticosteroids. The overall evidence was low, which indicated that further research was likely to significantly alter confidence in the effect estimate and to change the estimate.

LE is one of the most common soft tissue injuries in adults mainly in

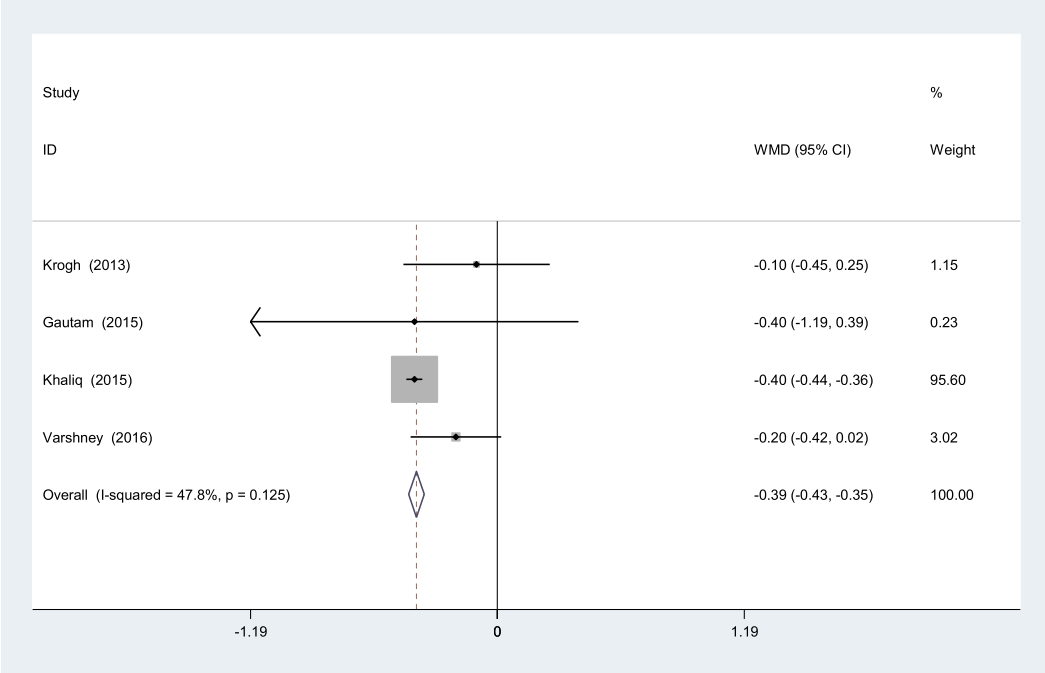


Fig. 4. Forest plot diagram of VAS at 6th month.

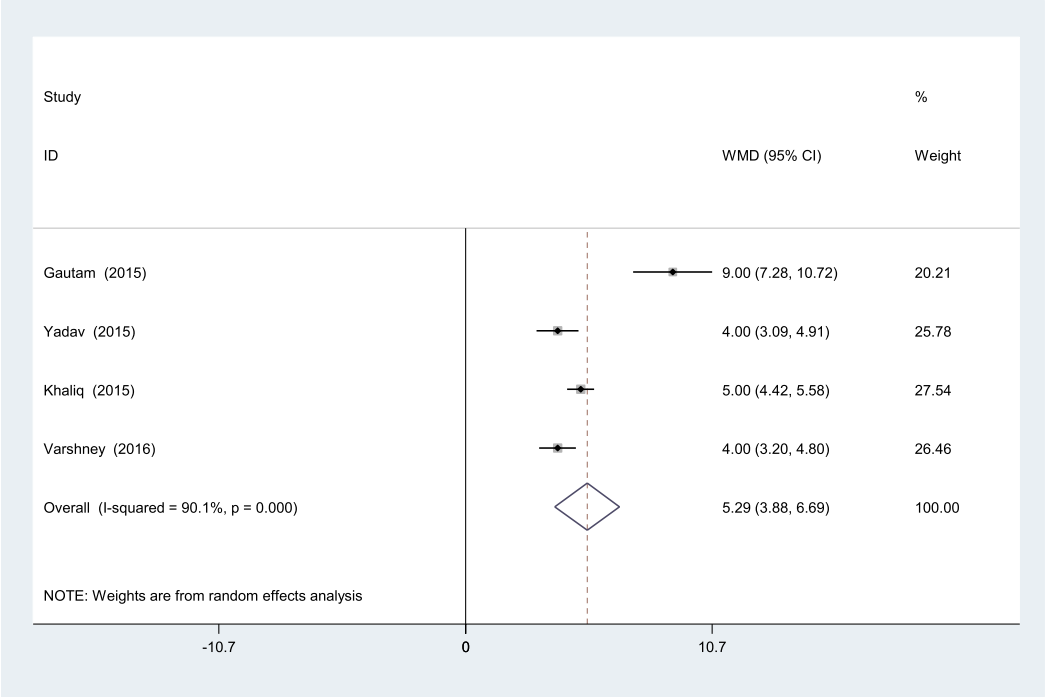


Fig. 5. Forest plot diagram of MAYO at 1st month.

the age range of 30–60 years [21]. Repetitive movements with eccentric contraction increase susceptibility to epicondylitis. The typical symptoms include lateral elbow pain, pain with wrist extension, and weakened grip strength [22]. The patients with lateral epicondylitis report lateral elbow pain that is exacerbated by grabbing objects while having the elbow in the extended position. The essential goal for treatment was to relieve pain and improve elbow joint function. Relief of pain and inflammation is the primary goal of the first phase of nonsurgical treatment.

Local injection of steroid was first introduced since the 1950s and it has been shown improved outcome for reducing pain, especially for trial in refractory cases of epicondylitis. A number of articles have

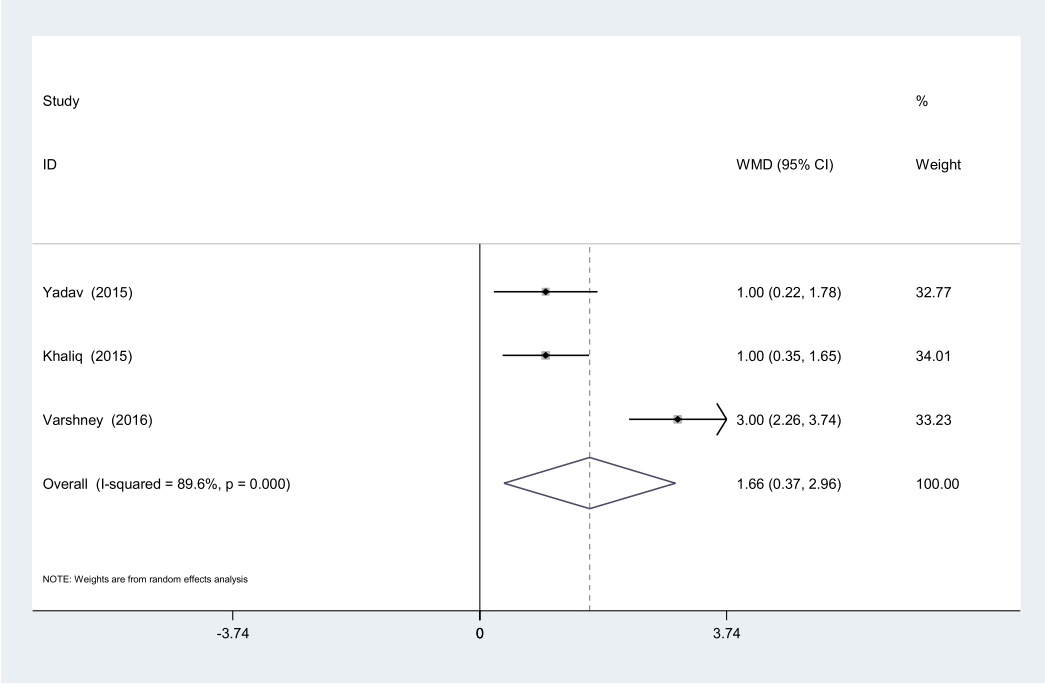


Fig. 6. Forest plot diagram of MAYO at 2 nd month.

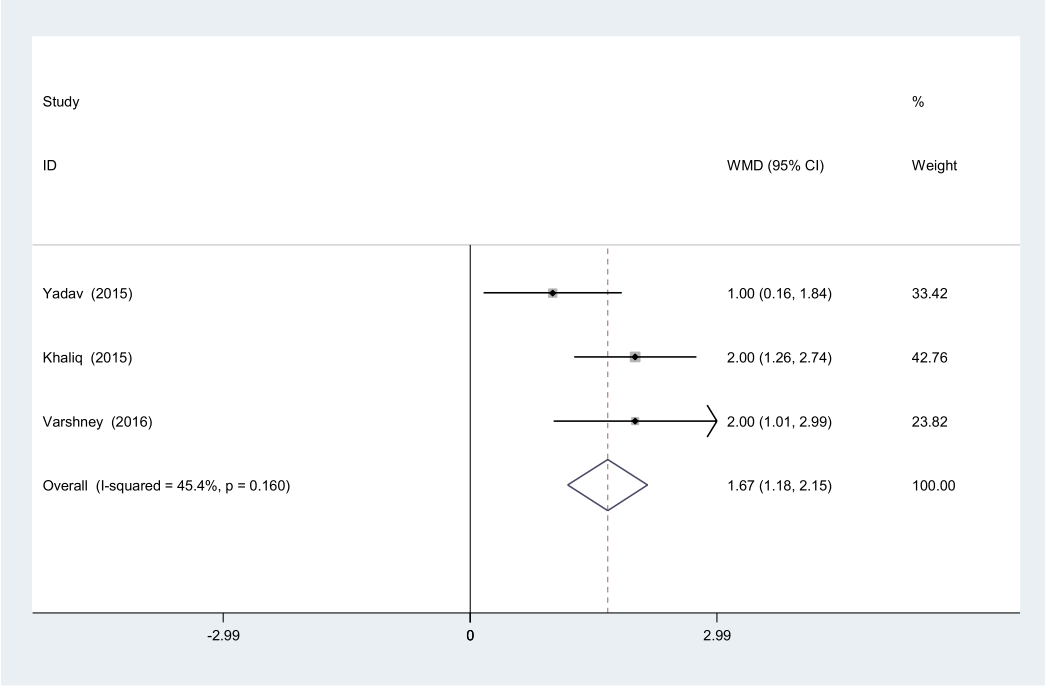


Fig. 7. Forest plot diagram of MAYO at 6th month.

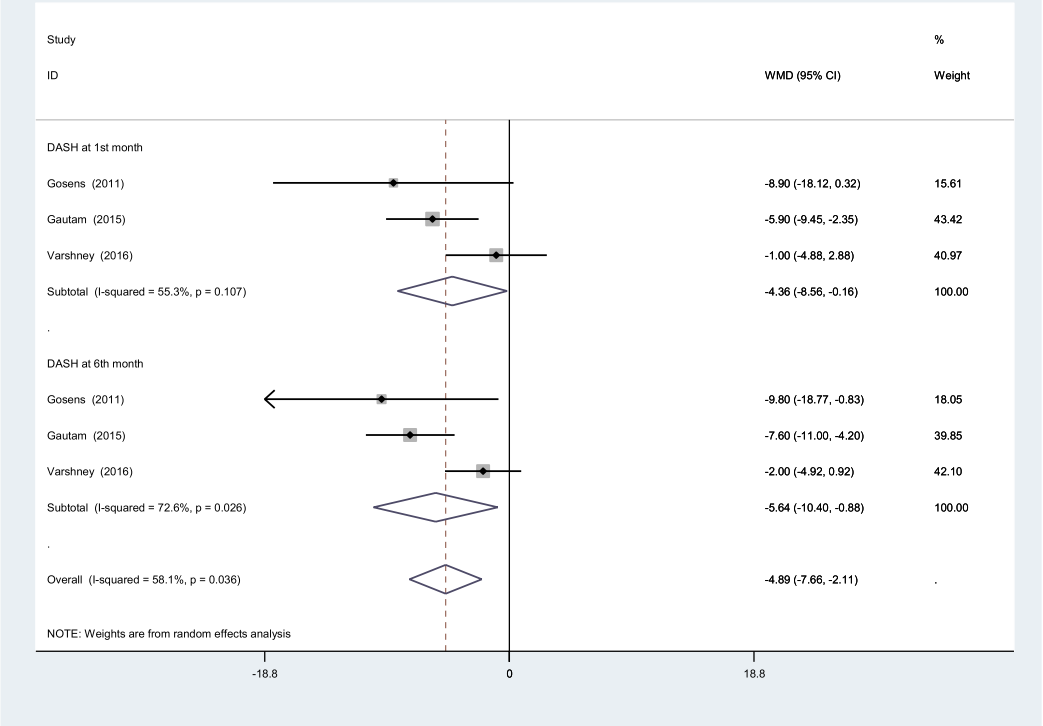


Fig. 8. Forest plot diagram of DASH score.

demonstrated the short-term efficacy of corticosteroid injections for the treatment of LE, however, no reliable evidence regarding their long-term efficacy. Besides, it may result in high rates of relapse and recurrence. Smidt et al. [23] analyzed the long-term outcomes following local injection of corticosteroid, or no treatment by RCT and demonstrated that corticosteroid injections was more effective than placebo in 6 weeks follow-up, however, corticosteroid injection was associated with worse outcome at 1 year. Krogh et al. [16] reported that there was

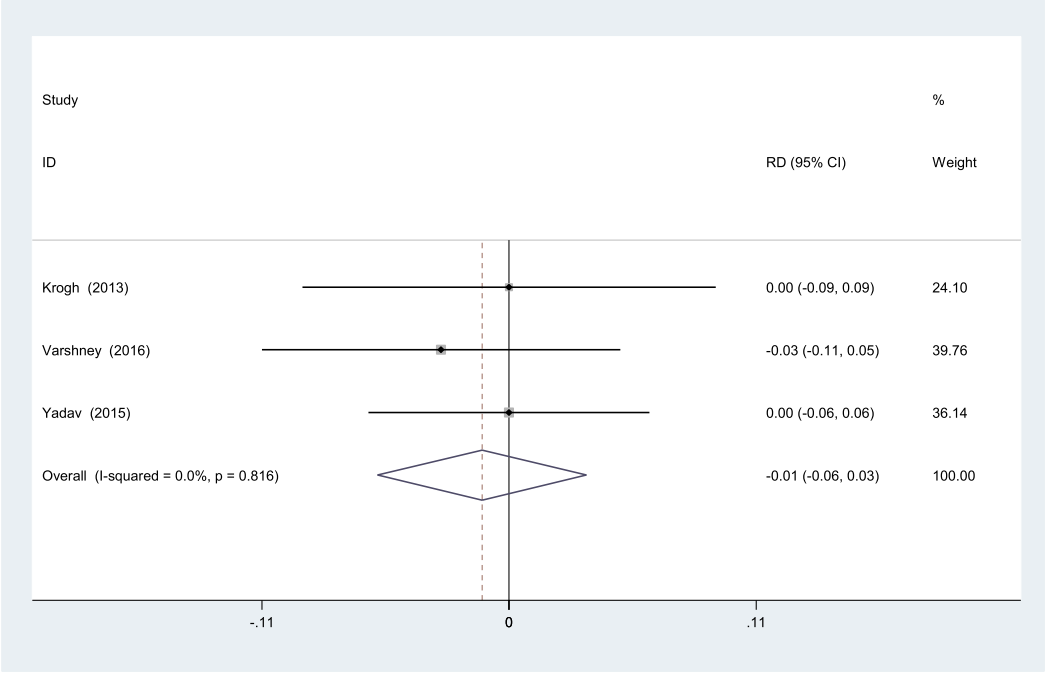
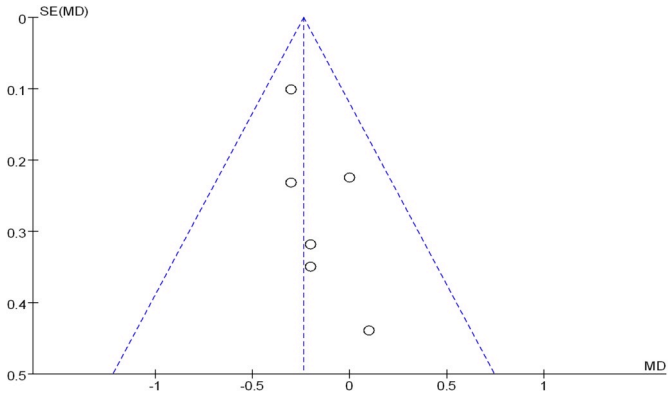


Fig. 9. Forest plot diagram of adverse effects.

Table 4
Publication bias.



no significant difference between corticosteroid group and placebo groups in terms of pain relief beyond 8 weeks. Considering to the short term action and potential complications, alternative treatment was required for improvement. Recently, several articles have reported that PRP, as a healing agent, may be efficacious in treating LE [24,25]. PRP is an autologous blood product and contains a high concentration of plate-lets. Besides the hemostatic function, PRP could release vascular endothelial growth factor and transforming growth factor-β which promotes tissue repair and fracture healing [26]. However, articles on LE with PRP treatment have shown inconclusive results. Based on the controversy, we performed a meta-analysis from RCTs, in our study, VAS (0–10 cm) from different follow up period was used to evaluate the pain after local injection treatment. The present meta-analysis indicated that PRP injection yielded statistically significant superior in VAS scores after treatment on the 6-month follow-up compared with local corticosteroid injection.

Functional recovery is also an important parameter to evaluate the various treatments. Pathophysiology of LE was under debate for a few decades. Previous studies reported that inflammation of an extra-articular radial humeral bursa was the primary cause. Recent studies demonstrated that LE was initiated as a microtear, most often within the origin of the extensor carpi radialis brevis [27]. The chronic inflammation process may affect the elbow joint function. It was well recognized that glucocorticoid had properties of anti-inflammation. Therefore, the use of glucocorticoid was associated with the improved outcome of joint function. A number of clinical trials have compared the activity and efficacy of PRP versus corticosteroids injection in patients with LE. Peerbooms et al. [14] reported that treatment of patients with chronic LE with PRP significantly increased joint function, exceeding the effect of corticosteroid injection. However, converse opinion still exited. Gautam et al. indicated that no significant difference was found regarding the function outcome between two treatment groups. The modified MAYO index is used as a valid and reliable measure to assess the functional outcome after treatment which contains motion, stability, and daily function [28]. The DASH is a 30-item, self-report questionnaire designed to evaluate physical function and symptoms in patients with any of musculoskeletal disorders of the upper limbs [29]. In our study, a total of four RCTs were analyzed for the functional outcomes after local injection. The aggregated results of these studies suggest that PRP could significantly improve elbow joint function compared with corticosteroid at a 6-month of follow up.

Adverse effects was also a major concern after local injection treatment. Fevers, rashes, local infection and exacerbation of pain were the most common. Local injection will have less clinical value if there was a relatively high incidence of adverse effects. In the present meta-analysis, a total of four RCTs reported the outcome of post-injection adverse events. Only one case occurred superficial infection and no severe adverse event was found.

There were some limitations in our meta-analysis: [1] only 7 RCTs were included in our study and sample sizes were small; [2] heterogeneity across the included studies may potentially have increased bias. Because of the small number of the included RCTs, we did not perform a subgroup analysis, therefore, source of heterogeneity was unclear; [3] dose of PRP and corticosteroids differed from each other, which may influence the results; [4] the duration of follow up was short, and there was no general consensus on follow-up time point, which led to the underestimation of complications.

Table 5
The GRADE evidence quality for each outcome.

Quality assessment					Sample size		Outcome measures	Quality	Importance
Number of RCT	Limitations	Inconsistency	Indirectness	Imprecision	PRP	Steroid			
VAS (1st month)									
6	serious limitations	serious inconsistency	no serious indirectness	no serious imprecision	221	234	WMD = −0.253; 95% CI: -0.403 to −0.103; P = 0.001	Low	CRITICAL
VAS (2 nd month)									
5	serious limitations	serious inconsistency	no serious indirectness	no serious imprecision	170	170	WMD = −0.205, 95% CI: -0.344 to −0.067, P = 0.004	Low	CRITICAL
VAS (6th month)									
4	serious limitations	no serious indirectness	no serious indirectness	no serious imprecision	119	119	WMD = −0.391; 95% CI: -0.428 to −3.53; P < 0.001	Moderate	CRITICAL
MAYO (1st month)									
4	serious limitations	no serious indirectness	no serious indirectness	no serious imprecision	129	129	WMD = 5.286; 95% CI: 3.877 to 6.694; P < 0.001	Moderate	CRITICAL
MAYO (2 nd month)									
3	serious limitations	no serious indirectness	no serious indirectness	no serious imprecision	114	114	WMD = 1.665; 95% CI: 0.367 to 2.962; P = 0.012	Moderate	CRITICAL
MAYO (6th month)									
3	serious limitations	no serious indirectness	no serious indirectness	no serious imprecision	99	99	WMD = 1.666; 95% CI: 1.183 to 2.149; P < 0.001	Moderate	CRITICAL
DASH score									
3	serious limitations	no serious indirectness	no serious indirectness	no serious imprecision	99	99	WMD = −4.885; 95% CI: -7.658 to −2.112; P = 0.001	Moderate	CRITICAL

VAS: Visual Analogue Scale, MAYO: Modified Mayo Performance Index, DASH: Disabilities of the Arm, Shoulder and Hand score.

5. Conclusion

Local PRP injections was associated with superior outcomes for reducing pain and improving elbow joint function compared with local corticosteroids treatment for LE at a follow-up of 6 months.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

No application.

Sources of funding

There is no source of funding.

Author contribution

Qiaolong Xu and Jianyang Chen: study design, data collections, data analysis, writing.
Li Cheng: writing and language editing.

Conflicts of interest

The authors declare that they have no competing interests. All authors read and approved the final manuscript.

Unique Identifying Number (UIN)

Unique Identifying Number (UIN): reviewregistry676.

Trial registry number

Not RCT.

Guarantor

Li Cheng.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.05.003.

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