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CLINICAL FEATURE
ORIGINAL RESEARCH

Platelet rich plasma versus steroid on lateral epicondylitis: meta-analysis of randomized clinical trials

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ABSTRACT

Objectives: Lateral epicondylitis (LE) is a common tendinopathy for which an effective treatment is still unknown. The purpose of this meta-analysis was to compare the effectiveness of platelet rich plasma (PRP) vs steroid in reducing pain and improving function of the elbow in the treatment of LE.

Methods: A systematic search of the literature was conducted to identify related articles published from January 1980 to September 2016 in Pubmed, Embase, the Cochrane Library and SpringerLink. All studies that compared PRP with steroid administration on LE were included. Main outcomes were collected and analyzed by the Review Manager 5.1.

Results: Eight randomized controlled trials (RCTs) that involved 511 patients met the criteria. This meta-analysis showed that there was no significant difference in pain relief in the short-term (2 to 4 weeks: SMD = 1.02, $P = .03$; 6 to 8 weeks: SMD = .73, $P = .24$) and the intermediate-term (12 weeks: SMD = -0.28, $P = .35$). Steroid exhibited a better efficacy of function in the short-term (2 to 4 weeks: SMD = .61, $P < .001$; 6 to 8 weeks: SMD = .53, $P < .001$). However, PRP was superior to steroid for pain relief in the long-term (half year: SMD = -1.6, $P < .001$; one year: SMD = -1.45, $P < .001$), and also for function improving in the intermediate-term (12 weeks: SMD = -0.53, $P < .001$) and the long-term (half year: SMD = -0.56, $P < .001$; one year: SMD = -0.7, $P < .001$). No serious adverse effects of treatment were observed in the two groups.

Conclusion: Treatment of patients with LE by steroid could slightly relieve pain and significantly improve function of elbow in the short-term (2 to 4 weeks, 6 to 8 weeks). PRP appears to be more effective in relieving pain and improving function in the intermediate-term (12 weeks) and long-term (half year and one year). Considering the long-term effectiveness of PRP, we recommend PRP as the preferred option for LE.

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Lateral epicondylitis; platelet rich plasma; steroid; meta-analysis

1. Introduction

Lateral epicondylitis (LE), also known as tennis elbow, is one of the most common lesions of the arm, which affected approximately 1% to 3% of the population[1,2]. However, the cause of LE is still unclear. It is generally a work related or sport related pain disorder usually caused by local injury, overuse, hypovascularity and gripping activities of the wrist and finger[3–5]. As time goes on, the symptoms of LE will reduce. According to reports, approximately 80% of patients' symptoms improved within 1 year[6,7]. Although the LE occurs at all ages, the high risk age of LE is 35–60 years old. The dominant arm is most frequently affected and females appears to be of longer duration and severity[8].

Although the signs and symptoms of LE are clear and its diagnosis is easy, there is no ideal treatment approved by all clinicians. Various methods have been recommended for treating LE, including rest, physical therapies, steroid, platelet rich plasma (PRP), autologous blood and operative treatment[9–14]. These treatments have different theoretical mechanisms, but all the treatments aim to reduce pain

and improve function. It is widely accepted that LE is a fibroblastic and vascular response, pathologically known as angiofibroblastic degeneration[15]. It has been considered that steroid was a gold standard treatment for patients with LE. However, several studies have shown that steroid focused on presumed inflammatory process which was not exist in epicondylitis and steroid has no long-term efficacy on LE, then, the search for alternative treatments has been intensified[16,17]. PRP is prepared from the autologous whole blood which contains an increased concentration of autologous platelets. It has been applied to various tissues such as tendon injury, muscle strain, osteoarthritis, bone healing[18–20]. The theory is that PRP can deliver various growth factors and cytokines, thereby affecting cell proliferation, cell differentiation and angiogenesis.

Recently, several clinical trials have been conducted to compare the efficacy between PRP and steroid in patients with LE. However, there is still no consensus on which method is the preferred treatment for LE[21–23]. The purpose of this study was to compare the efficacy of PRP and steroid in treatment of LE.

2. Materials and methods

2.1. Search strategy

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines were used to conduct our meta-analysis. The databases used for the electronic search included Pubmed, Medline, The Cochrane Library, OVID and Springerlink from January 2000 to September 2016. The following search terms were used: steroid or methylprednisolone or platelet rich plasma or PRP or lateral epicondylitis or LE or tension elbow.

2.2. Data selection

Two investigators independently screened the titles and abstracts of the articles to evaluate eligibility for inclusion. Any disagreements were resolved by discussion among the authors. A third researcher was the adjudicator when there was debate among two investigators. Related articles should be to meet the following criteria: (1) the studies should be designed as randomized controlled trials (RCTs); (2) the articles should compare the efficacy between PRP and steroid for LE; (3) the articles were restricted to English language; (4) the major outcome involved the efficacy of pain relief or functional restoration. The exclusion criteria were as follows: (1) articles were included the same data set; (2) subjects have systemic disorder such as diabetes, rheumatoid arthritis and hepatitis.

2.3. Data extraction

From each eligible study, two authors independently extracted the following data study design, type of study population, age, number of participants, pain scores and disability of function scores. Further information about the main characteristics of intervention or control protocols was also extracted. We contacted with the trial authors by e-mail when the required information was obscure or missing.

2.4. Quality and risk of bias assessments

Modified Jadad scale was used to assess quality of studies. The Cochrane Handbook for Reviews of Interventions (Revman version 5.3) was used to assess the risk of bias. Two authors subjectively reviewed all included articles and assigned a value of 'high', 'low' or 'unclear' based on following items: selection bias; performance bias; detection bias; attrition bias; reporting bias and other bias. Any disagreements were resolved by discussion between authors.

2.5. Statistical analysis

This meta-analysis was conducted using the RevMan statistical software (Revman version 5.3). The standardized mean difference (SMD) was used to compare PRP with steroid group. Heterogeneity was tested using the I^2 statistic. Studies with an I^2 value $<25\%$ were considered to have low

heterogeneity and those with an I^2 statistic $>75\%$ were considered to have high heterogeneity. Statistical significance was indicated by a P value $<.01$.

3. Results

3.1. Literature search and study characteristics

After comprehensive search from the databases, we finally identified eight eligible studies. There were 253 patients in the PRP group and 258 patients in the steroid group. The flowchart of literature search was displayed in Figure 1. The demographic characteristics and quality scores of the studies were summarized in Table 1 and Table 2.

3.2. Risk of bias in included studies

Figure 2 shows the risk of bias assessment in the studies. All trials were described as randomized trial design, while three of the six trials did not show the detail information about random sequence generation[21,27,29] and three trials did not describe the methods of allocation conceal [21,24,29]. Blinding of patients were considered to be unclear in three trials[27–29] and had high risk in one trial [21]. Blinding of doctors were considered to be unclear in three trials[27–29] and had high risk in four trials[21–23,26]. Blinding of outcome assessment were considered to be unclear in three trials[27–29] and had high risk in one trial[21].

3.3. Pain scores

Six of the eight trials reported data on pain relief. As shown in Figure 3, there was no significant difference in relieving pain in 2–4 weeks (SMD = 1.02, $I^2 = 92\%$, $P = .03$), 6–8 weeks (SMD = .73, $I^2 = 90\%$, $P = .24$) and 12 weeks (SMD = -0.28 , $I^2 = 78\%$, $P = .35$). However, PRP exhibited a better efficacy in terms of pain relief than steroid in half year (SMD = -1.6 , $I^2 = 0\%$, $P < .001$) and 1 year (SMD = -1.45 , $I^2 = 0\%$, $P < .001$).

3.4. Disability of function scores

Seven of the eight trials reported data on the efficacy of functional restoration. As shown in Figure 4, there was significant difference in disability of function scores between PRP and steroid group. The details were as follows: PRP group had a higher disability of function scores in 2–4 weeks (SMD = .61, $I^2 = 82\%$, $P < .001$) and in 6–8 weeks (SMD = -0.53 , $I^2 = 67\%$, $P < .001$). However, PRP group had a better function in 12 weeks (SMD = -0.55 , $I^2 = 7\%$, $P < .001$), half year (SMD = -0.56 , $I^2 = 96\%$, $P < .001$) and 1 year (SMD = -0.7 , $I^2 = 97\%$, $P < .001$).

3.5. Adverse events

Of the eight trials, three reported data on adverse events. Krogh et al.[23] and Lebidzinski et al.[28] reported a higher rate of postinjection pain at the injection site in the PRP group than the in the steroid group. Krogh et al.[23] also reported

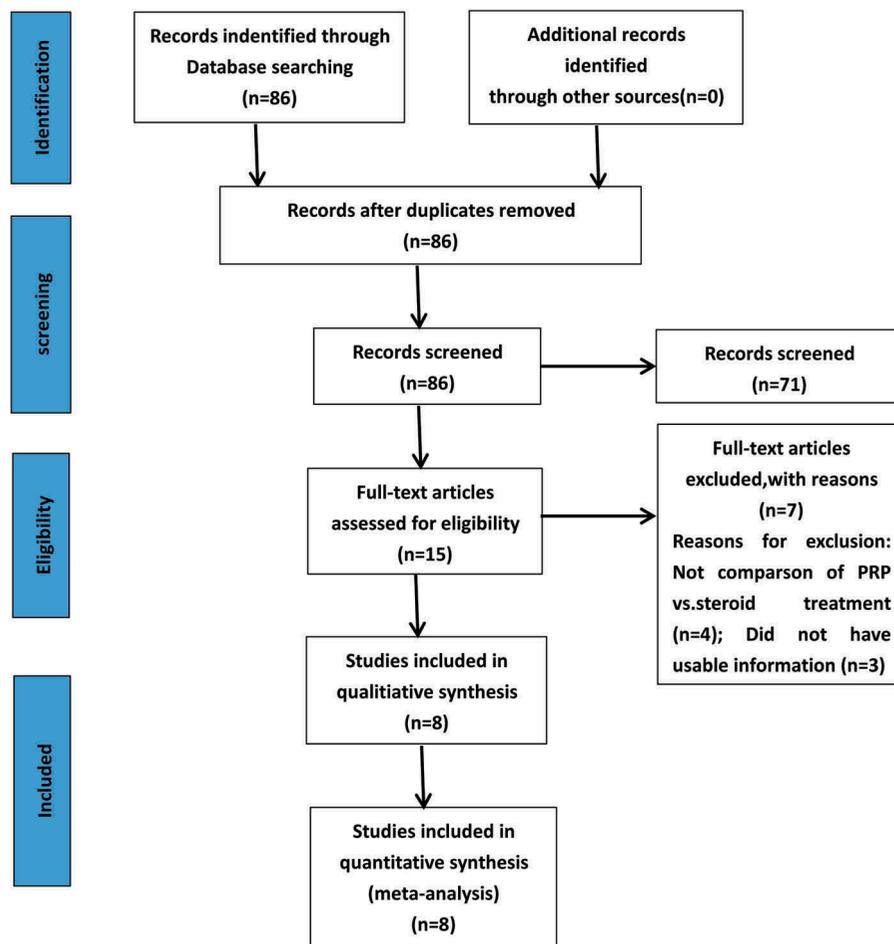


Figure 1. Flow chart showing study identification, inclusion and exclusion.

Table 1. The characteristics of included studies.

Study	Year	Country	Patients(n)		Age (Years)		Gender				Study design	Quality scores
			PRP	Steroid	PRP	Steroid	PRP		Steroid			
							Male	Female	Male	Female		
Gautam VK[21]	2015	India	15	15	18–60	18–60	15		15		RCT	2
Khaliq A[26]	2015	Peshawar	51	51	33.6 ± 10.5	34.2 ± 10.2	21	30	24	27	RCT	4
Krogh TP[23]	2013	Denmark	20	20	47.6 ± 7.1	43.9 ± 8.7	9	11	11	9	RCT	7
Lebiedzinski R[28]	2015	Poland	53	46	47 (25–67)	54 (21–96)	28	25	12	34	RCT	5
Omar AS[27]	2012	Egypt	15	15	Above 18	Above 18	15		15		RCT	3
Palacio EP[24]	2016	Brazil	20	20	46.6 (26–61)	46.2 (19–61)	20		20		RCT	5
Peerbooms JC[22]	2010	Netherlands	49	51	46.96 ± 8.4	47.3 ± 7.6	23	26	25	26	RCT	7
Yadav R[29]	2015	India	30	30	36.6 (25–50)	36.67 (25–50)	10	20	7	23	RCT	2

that there was local skin atrophy and minor rash in steroid group. In addition, Peerbooms et al.[22] reported a higher rate of reinterventions in the steroid group than PRP group. There were no systemic adverse effects in all studies. The details of adverse effects were shown in Table 3.

4. Discussion

Pain with local elbow tenderness is the characteristic complaints of patients with LE. This kind of people is often considered to inject steroid. Several studies have demonstrated that by steroid injection, the patients can get short-term pain relief and functional improvement[21,25]. Unfortunately, steroid injection may result in high rates of relapse and recurrence

[22]. Considering to the disadvantages of steroid, alternative injection treatment options was arisen. Recently, a growing number of studies and meta-analysis have confirmed that injection of PRP could effectively either relieve pain or advance elbow function of patients with LE[26,30,31]. However, there remains no consensus regarding the effectiveness of PRP than steroid in LE[23,27,28]. Therefore, a study focus on comparing PRP with steroid in LE was considered. We want to investigate if PRP was superior to steroid for LE.

Our primary concern was the pain relief and functional improvement, which was also mostly concerned by patients. In this meta-analysis, we found that PRP has no significant difference in pain relief in short-term (≤ 8 weeks) and intermediate term among the PRP and steroid group. However,

Table 2. Characteristics of the eight trials selected showing general intervention information.

Study	Duration of symptoms (months)	Interventions			Injection protocol	Outcome measures	Postintervention rehabilitation exercises
		PRP	Steroid				
Gautam VK[21]	At least 6	2 mL of PRP collected from 20 mL of whole blood	2 mL of methylprednisolone (40 mg/mL)		Peppering technique	VAS, DASH	–
Khaliq A[26]	–	3 mL of PRP	2 mL of methylprednisolone acetate + 1 mL of 2% xylocaine		Peppering technique	VAS	–
Krogh TP[23]	At least 3.8	3–3.5 mL of PRP collected from 27 mL of whole blood	1 mL of triamcinolone 40 mg/mL +2 mL of lidocaine 10 mg/ mL		Ultrasound-guided injection technique	Pain scores, PRTEE scores	Standard tennis elbow stretching and training program
Lebiedzinski R[28]	At least 1.5	Autologous conditioned plasma	1 mL betamethasone injections and 2 mL of 1 % lignocaine		Same physician in the same way	DASH	–
Omar AS[27]	At least 1	Concentrated platelet	Corticosteroid		–	VAS, DASH	–
Palacio EP[24]	–	3 mL of PRP	3 mL of dexamethasone acetate		–	DASH	–
Peerbooms JC[22]	At least 6	1 mL of PRP + bupivacaine hydrochloride 0.5% with epinephrine (1:200000)	40 mg/mL kenacort with bupivacaine hydrochloride 0.5% with epinephrine (1:200000)		A 22-gauge needle and a peppering technique	VAS, DASH	A standardized stretching protocol
Yadav R[29]	1–6	1 mL of PRP	40 mg/mL methylprednisolone		–	VAS, DASH	–

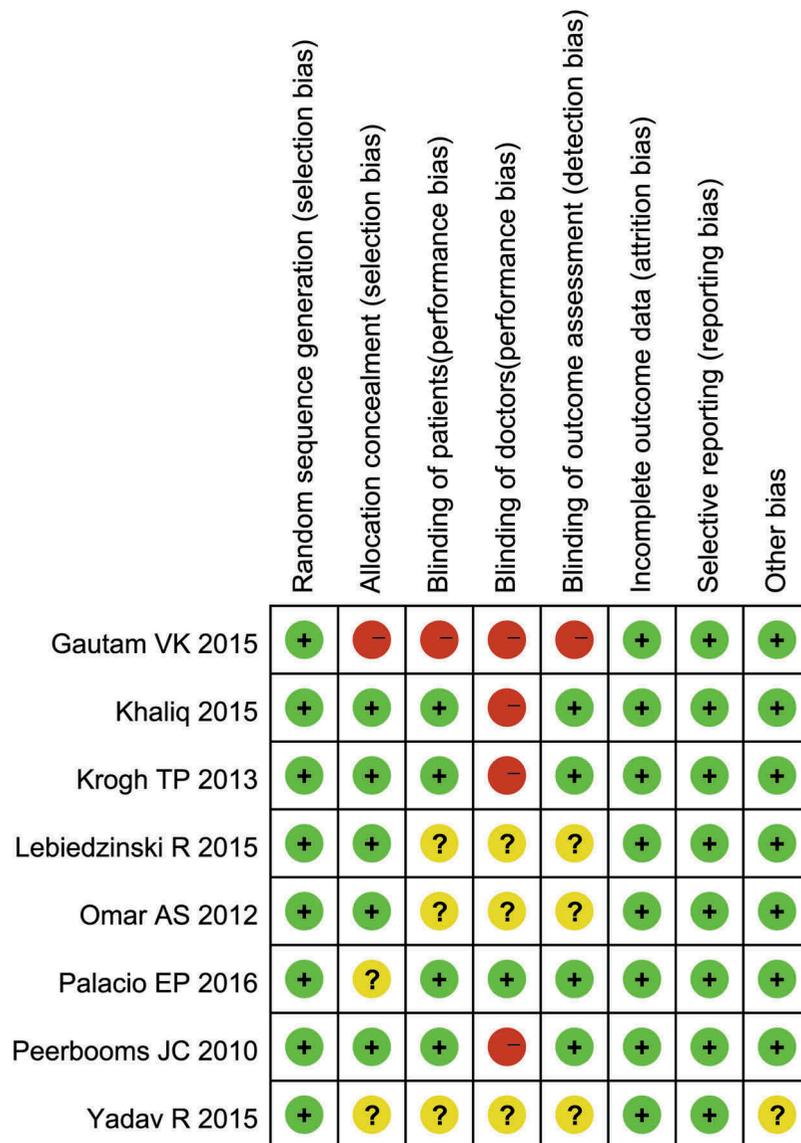


Figure 2. Risk of bias summary.

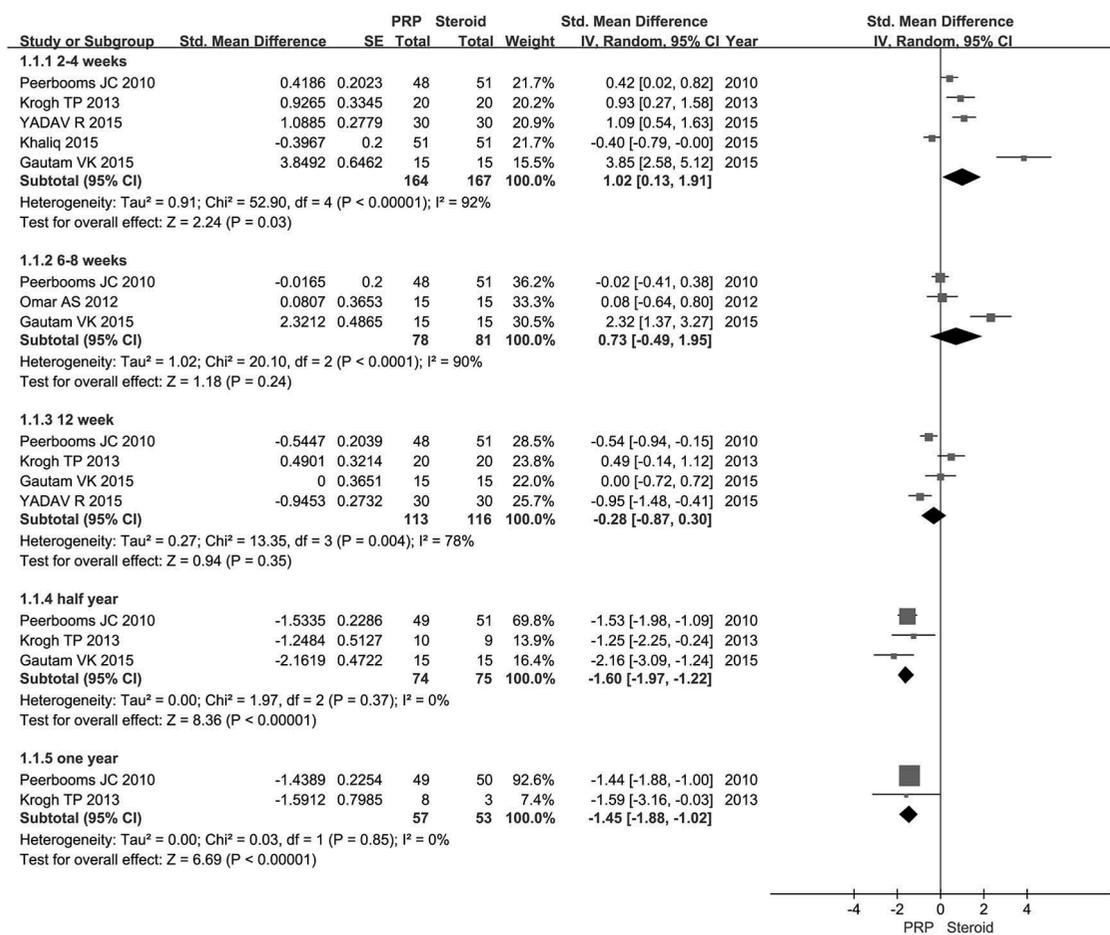


Figure 3. Forest plot of pain score when comparing PRP group with steroid group.

there was a trend that steroid group had better efficacy on pain relief in short-term (2–4 weeks: SMD = 1.02; 6–8 weeks: SMD = .73). Combined that steroid group has a higher efficacy on functional improvement in short-term (2–4 weeks: SMD = .61, $P < .001$; 6–8 weeks: SMD = .53, $P < .001$), it can be concluded that local steroid injection appears to be the most effective treatment for LE in short-term. The observed short-term effect of steroid and PRP in our meta-analysis matches the results of previous studies that steroid injection had better short-term outcomes of pain relief and functional improvement.

Interestingly, from 12 weeks onwards, there was a trend that PRP group exhibited a better efficacy on pain relief and functional improvement. As shown in Figure 3, PRP group showed a lower pain scores in 12 weeks, although there was no statistical difference between the two groups (SMD = -0.28 , $P = .35$). However, PRP group has better pain relief in long-term (half year and 1 year) and functional improvement in intermediate term (12 weeks: SMD = -0.55 , $P < .001$) and long-term (half year: SMD = -0.56 , $P < .001$; 1 year: SMD = -0.7 , $P < .001$). There was three possibly reasons to explain these results for pain reduction and functional improvement in intermediate term and long-term. First of all, high concentrations of platelets included in PRP can improve the early neotendon properties so that the cells are able to perceive and respond to mechanical

loading at an early time point[32,33]. Secondly, the regeneration of the tendon tissue might take more than 3 months[23]. Thirdly, steroid injection may lead to the permanent adverse changes within the structure of the tendon. As a result of direct pain relief, patients tend to overuse the arm after steroid injection[6,34].

People began to inject steroid for LE since the 1950s because steroid can inhibit the inflammatory molecular release which could induce pain. However, an increasing number of studies reported that steroids can disrupt tendon healing through inhibiting the migration, proliferation of the cell and induce the differentiation of the nontenocyte [35,36]. Besides, recent studies found that the pathogenesis of LE is closely related with degeneration (such as abnormalities of the cellularity, vascularity, and collagen arrangement within the tendon), whereas inflammation has little impact on LE[37]. These may explain why steroid has better short-term efficacy and worse long-term efficacy on LE. PRP can enhance tendon healing by delivering various growth factors and cytokines, then increasing expression of the collagen gene and production of vascular endothelial growth factor and type-I collagen [38]. These advantages may be the reasons why PRP has long-term efficacy on LE. Considering to the advantages of steroid's short-term efficacy and PRP's long-term efficacy, it is logical to suggest that combined using of steroid and PRP may be a better

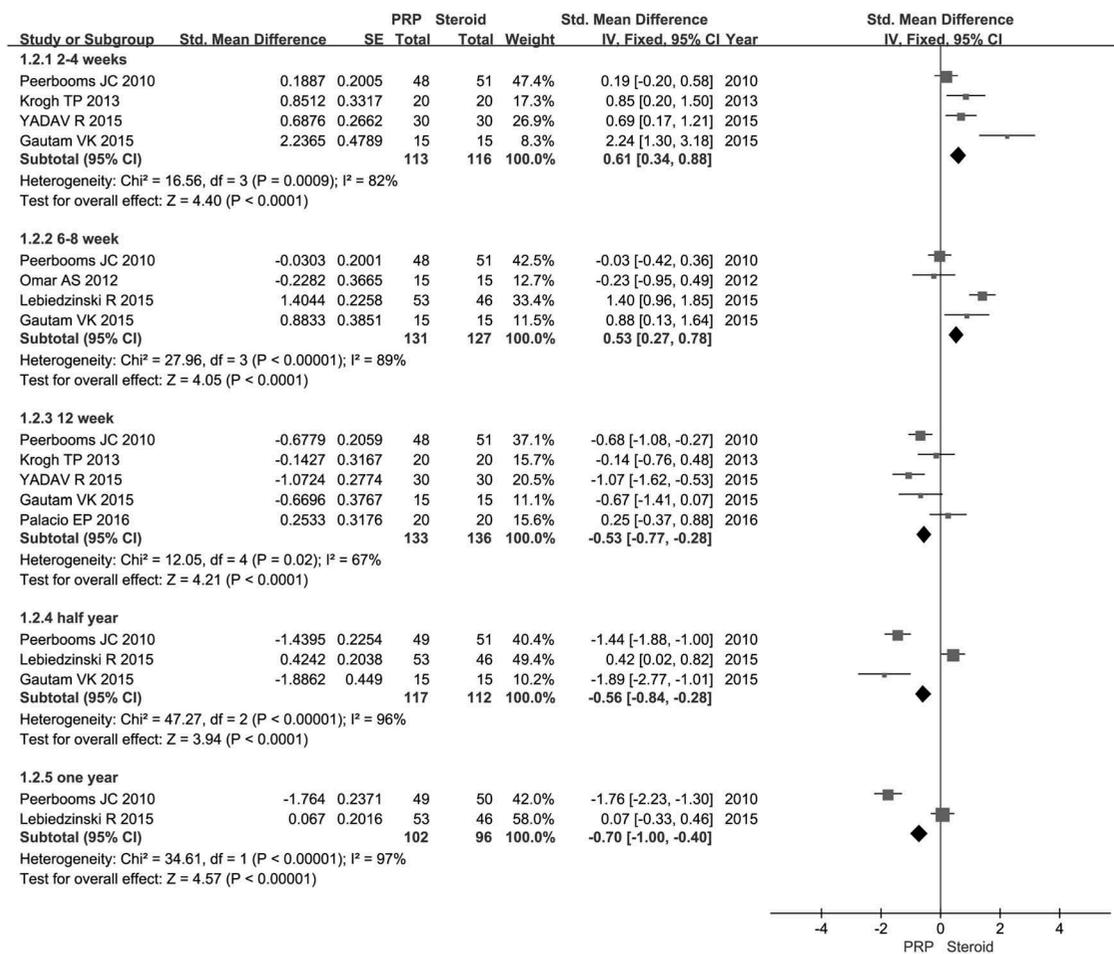


Figure 4. Forest plot of disability of function score when comparing PRP group with steroid group.

Table 3. Adverse events of the eight trials.

Study	Reinterventions		Postinjection pain		Skin atrophy		Minor rash	
	PRP	Steroid	PRP	Steroid	PRP	Steroid	PRP	Steroid
Gautam VK[21]	—	—	—	—	—	—	—	—
Khaliq A[26]	—	—	—	—	—	—	—	—
Krogh TP[23]	—	—	4/20	1/20	—	3/20	—	1/20
Lebiedzinski R[28]	—	—	11/53	2/46	—	—	—	—
Omar AS[27]	—	—	—	—	—	—	—	—
Palacio EP[24]	—	—	—	—	—	—	—	—
Peerbooms JC[22]	5/51	13/49	—	—	—	—	—	—
Yadav R[29]	—	—	—	—	—	—	—	—

therapy method for LE. Therefore, more randomized clinical trials are needed to test this hypothesis.

Serious side effects of PRP and steroid injection should be highly concerned when assessing safety. In this meta-analysis, we found that there was a higher postinjection pain of PRP when compared with steroid[23,28]. This may be related to the physiological effect of the platelets. Fortunately, the duration of postinjection pain after PRP injection did not last longer without special intervention. One trial[22] in our meta-analysis shown a higher number of reintervention in steroid group, this may be attributed to the fact that steroid suppress the viability of tenocytes. At the same time, some patients overuse their elbows because of the temporary pain relief after the steroid injection[6,21,39]. Other side effects of

steroid including local skin atrophy and minor rash[23]. The major limitations of adverse events were that the other five trials had failed to concern those complications, which should be paid more attention by clinicians.

Several limitations of the present study should be acknowledged. First of all, the nonuniformity among trials which was related to PRP concentration and various dose of PRP and steroid make it difficult to compare the main outcome of trials. A second limitation was the high statistical heterogeneity across trials and limited trials focused only on English publications. In addition, a variety of outcome types of pain scores and disability of function scores may also have influence to the end results. Therefore, more high-quality RCTs are needed to verify our results.

5. Conclusion

Our meta-analysis found that there was no statistical difference in pain relief in short-term (2–8 weeks) and intermediate term (12 weeks). However, the steroid group was superior to PRP group in terms of functional improvement in the short-term (2–8 weeks). In addition, PRP had a better efficacy on pain relief and functional improvement than steroid in intermediate term (12 weeks) and in long-term (half year and 1 year). Considering to the long-term effectiveness of PRP, we recommend to use PRP as the preferred treatment option for LE. Further high-quality RCTs with more patients and that take a uniform scoring standard are needed to confirm the effectiveness and safety of PRP and steroid on LE.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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