Corticosteroid injections for the treatment of lateral epicondylitis are superior to platelet rich plasma at 1 month but platelet rich plasma is more effective at 6 months. An updated systematic review and meta-analysis of level 1 and 2 studies.

Running Title: PRP Tennis Elbow Meta-Analysis

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Abstract

Background

The purpose of this study was to perform a systematic review and meta-analysis of studies comparing local injections of either platelet-rich plasma (PRP) or corticosteroid for the treatment of lateral elbow epicondylitis.

Methods:

A systematic review of Medline, Embase, Scopus, and Google Scholar was performed, and all level 1 and 2 randomized studies from 2000 to 2022 were included. Clinical symptoms, patient perceived outcomes, and pain were assessed by the DASH (disabilities of the arm, shoulder and hand questionnaire) and pain by the VAS (visual analog scale). Publication bias and risk of bias were assessed using the Cochrane Collaboration's tools. The modified Coleman Methodology Score (CMS) and the GRADE system were used to assess the quality of the body of evidence. Heterogeneity was assessed using χ^2 and I^2 statistics.

Results:

Thirteen studies were included in the analysis. Five studies had a high risk of bias, and the risk of bias across studies was assessed as unclear. There was no publication bias identified. Two of the four GRADE domains (inconsistency of results, imprecision of results) were downgraded to low quality, and the final GRADE assessment was downgraded to a low quality of evidence. The mean CMS score was 62.8, indicating fair quality. The pooled estimate for VAS at 1 month favored corticosteroids (p=0.75), but favored PRP at three (p=0.003) and six months (p=0.0001). The pooled estimate for the DASH score favored corticosteroids at 1 month (p=0.028), but favored PRP at three (p=0.01) and six months (p=0.107)

Conclusion:

The results of this meta-analysis suggest that PRP has no advantage over steroid injections within the first month of treatment, but that it is superior to steroids at both 3 and 6 months. These results also suggest that corticosteroids have a short-term beneficial effect during the early treatment period, although the quality of the available evidence is not very robust in support of this finding. However, these findings must all be viewed with caution as the high risk of bias and moderate to low quality of the included studies may not justify a recommendation of one treatment over another.

Keywords:

Tennis elbow; lateral epicondylitis; PRP; platelet-rich plasma; meta-analysis; systematic review

Level of evidence

Level II; systematic review and meta-analysis

Introduction

Chronic lateral epicondylitis, or "tennis elbow", affects 1-3% of adults annually. [17] It commonly involves the extensor carpi radialis brevis at its origin, and normally presents with lateral elbow pain, pain with wrist extension, and weak grip strength. [10,49] The exact mechanism of this disease is unclear, but is believed to be caused by repetitive microtrauma resulting in tendon degeneration. [16]

Several non-invasive treatment options have been proposed including physiotherapy, nonsteroidal anti-inflammatory medication, rest, bracing, and extracorporeal shock wave therapy. Alternatively, injection therapy with various agents has been advocated, using autologous blood, dextrose, corticosteroids, or platelet rich plasma. [4,10,33,48,49] Corticosteroid injections have been used routinely since 1953. [10] They have been widely considered to be safe and effective, and have been regarded as the most accepted standard of injection therapy for decades. [10,11] However, injections may result in subcutaneous atrophy and skin depigmentation, or damage to the tendon structure locally. [8] In addition, corticosteroid injections downregulate inflammatory cells and decrease collagen type I synthesis, potentially retarding the healing response. [10,11,46] The possible lack of inflammation in tendinopathy and the concomitant inhibition of collagen synthesis by corticosteroid treatment may explain why the treatment effect is disputed by some. [8,11] In fact, a recent meta-analysis could not demonstrate any differences in pain intensity between corticosteroid and placebo injections. [8] This suggests corticosteroid injections do not modify the disease process, and despite a possible short-term palliative effect they may not have any clinical benefit. [11]

In contrast, platelet-rich plasma (PRP) promotes collagen synthesis and theoretically enhances tendon and tissue healing. [24] Several studies have demonstrated pain reduction following local injection, and regard PRP as an effective treatment for chronic lateral elbow epicondylitis. [28,39,43,50] However, the issue as to whether PRP is superior to corticosteroid injections remains controversial. The purpose of this study was, therefore, to perform a systematic review and meta-analysis of studies comparing local injections of either PRP or corticosteroid for the treatment of lateral elbow epicondylitis.

Methods

The study was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines statement [37], and the guidelines from the Cochrane Handbook were used to conduct this research. [14,25]

Eligibility criteria

All comparative level of evidence randomized 1 and 2 studies comparing corticosteroid to PRP injections in patients with lateral epicondylitis from 2000 until 2022 were included. Studies with multiple treatment arms were also considered for inclusion if they incorporated a treatment group with corticosteroids and PRP. For these studies the data was extracted for the treatment arms of interest only. A minimum follow-up of 3 months was required for inclusion, but longer-term and shorter-term follow-up studies were also eligible if the authors reported 3 months follow-up data. Studies comparing PRP or corticosteroids with normal saline, whole blood, prolotherapy, or any other analgesics were not considered for inclusion. Level II non-randomized studies and both level III and IV studies were also excluded. To be included in the meta-analysis, studies had to evaluate at least one validated pain measure, such as VAS (Visual Analogue Scale), [32] and at least one validated patient reported outcome measure, such as DASH (disabilities of the arm, shoulder and hand symptom scale) [6] or Patient-Rated Tennis Elbow Evaluation (PRTEE). [44] Furthermore, included studies must have had complete documentation of all data in the tables, main text, or supplementary documentation, outlining the demographic information and treatment details. The reason for the selection of the short-term follow-up was that injection therapy in general has only short-term effects, [10,11] and growth factors and cytokines are generally released within 1 hour, thereby reducing

the likelihood of long-term effects. [18] However, if the studies also included longer-term data, pooling was performed, and this data was meta-analyzed. Abstracts or conference proceedings, *in-vivo* and *ex-vivo* basic science studies, and case reports were excluded. It is acknowledged that the omission of these "grey" data sources could potentially result in publication bias.

Literature research

A systematic review of the literature was performed on 30 September 2022 in the German and English literature to identify all publications reporting on injection therapy for the treatment of lateral elbow epicondylitis. Medline, Embase, Scopus, and Google Scholar were systemically searched using the terms and Boolean operators: "PRP" AND/OR "platelet plasma" AND/OR "cortisone" AND/OR "corticosteroid"; AND/OR "injection" AND/OR "infiltration" AND/OR "lateral epicondylitis" AND/OR "tennis elbow" AND/OR "elbow pain" AND/OR "elbow epicondylitis". Two reviewers conducted independent title and abstract screening. Disagreements between reviewers were resolved by consensus, and if no consensus was reached, they were carried forward to the full text review. All eligible articles were manually cross-referenced to ensure that other potential studies were included.

Data extraction and quality assessment

An electronic data extraction form was used to obtain the following data from each article: age, gender, level of evidence, length of follow-up, disease duration, PRP and steroid preparation and injection technique, outcome scores, country, and sample size. The senior author independently completed data extraction, and a second reviewer verified the data.

Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias Tool. [12,23] The Modified Coleman Methodology Score (CMS) was used as a valid instrument to assess study quality. [13] The CMS was categorized as follows: 85-100 excellent quality; 70-84 good quality; 55-69 fair quality; <55 poor quality. Any disagreement between reviewers was resolved by consensus and/or by arbitration between the two senior authors. [13]

The GRADE system was used by two reviewers to assess the certainty of evidence for each outcome measure. [14] The recommendations from the Cochrane Handbook were followed, and an initial level of certainty assigned. Outcomes were downgraded if there was a high risk of bias, inconsistency and imprecision of the results, and indirectness of evidence. Studies were upgraded if there were large treatment effects, a dose-response, or reasons to oppose plausible residual bias and confounding effects. Any disagreement between reviewers was resolved by consensus and/or arbitration between the two senior authors.

Statistical analysis

Inter-observer differences for study eligibility and risk of bias were measured using Cohen's kappa coefficient. Heterogeneity of the data was assessed using χ^2 and I^2 statistics. Outcomes were pooled using a random effects model if the I^2 statistic was >50%; however, if it was <25% then a fixed effect model was utilized. Similar improvements in outcome scores were calculated from baseline scores and pooled. Subgroup analysis for VAS, DASH, and PRTEE for the same time period and different follow-up intervals was performed if more than three studies utilized these scores. If standard deviations were not reported the standard deviation was

calculated using the following formula: SD = max-min/4. [29] Hozo et al. have shown that this formula reliably provides a good estimate of the standard deviation. [29] All tests of significance were two-tailed, and an α of less than 0.05 was considered significant. Publication bias was assessed using funnel plots and Egger's test. Funnel and forest plots, and all statistical analyses, were performed using STATA SE (Version 12.0; StataCorp, College Station, Texas, USA) for Windows, and the comprehensive meta-analysis software package (CMA), version 3 (Biostat Inc, Englewood, NJ, USA).

Results

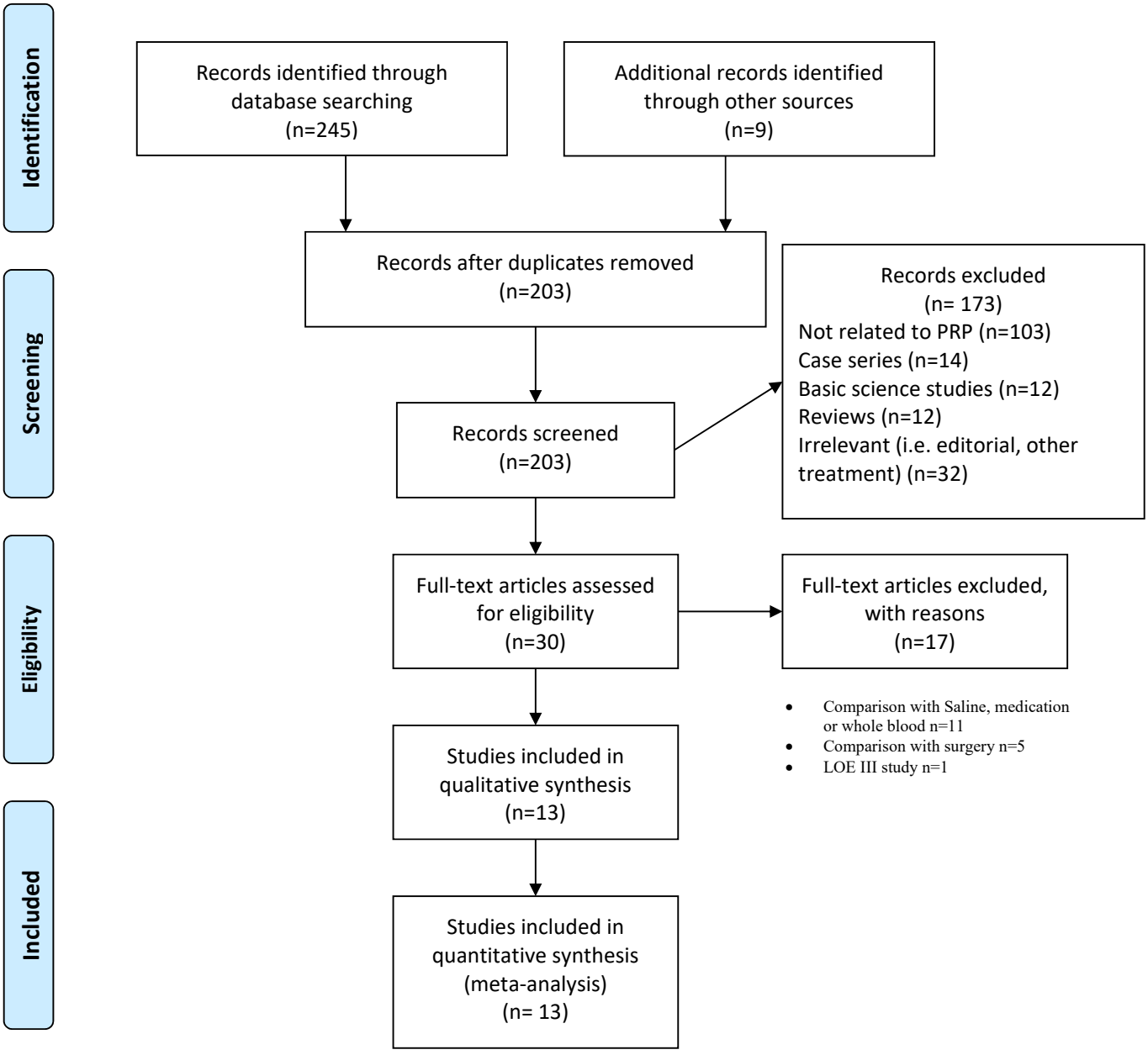
Study selection and characteristics

The initial literature search identified 253 publications. Of these, 203 were screened and 173 were excluded. The full text versions of the remaining 30 articles were assessed and another 17 publications were excluded. Only 13 studies met all of the eligibility criteria and were included in the final analysis (Figure 1). [7,20,22,23,31,33,34,40,41,42,45,51,53] Agreement between the two reviewers for final eligibility was excellent (kappa value 0.94, 95% CI 0.89-0.99). All 13 studies were published in English between 2010 and 2019, with an aggregate total of 846 cases. This total includes 415 patients treated with PRP, and 431 with corticosteroid injections. All studies included in this meta-analysis received an injection containing either one dose of PRP or one dose of corticosteroids at point zero. The study characteristics are summarized in table 1.

Authors	LOE	Country	Patients (PRP-Steroid)	Age (PRP-Steroid)	Gender	Follow-Up	Disease duration	PRP Preparation	Steroid
Peerbooms 2010	I	Netherlands	49-51	46.9 -47.3	PRP: M23:F26 S: M25:26	1,2,3,6,12 months	>6 months	Recover GPS II (Biomet) 27 ml blood, 3 ml sodium citrate Dose: 3 ml PRP+4ml 0.5% bupivaine	1ml triamcinolone 4ml 0.5% bupivaine
Krogh 2013	I	Denmark	20-20	47.6-43.9	PRP: M9:F11 S: M11:F9	3,6,12 months	>3 months	27 ml blood + 3 ml sodium citrate Recover GPS II (Biomet) Does: 3-3.5 ml PRP	1ml triamcinolone 40 mg 2 ml lidocaine (10 mg/ml)
Lebiedzinzki 2015	I	Poland	53-46	53-46	PRP: M28:F25 S: M12:F34	6 weeks 6 months 1 year	>6 weeks	Dose: ACP volume unknown	1ml bethamethasone 2 ml lignocaine 1%
Gupta 2019	I	India	43-47	42.4-39.4	PRP: 22:F21 S: M12:F25	6 weeks 3 month 1 year	>3 months	20 ml blood 12min@160g then 18min@460g Dose 4ml PRP	3 ml triamcinolone (40 mg) 2% Xylocaine
Güngör 2021	II	Turkey	24-24	40.9 – 43.9	PRP M8:F165 S M9: F15	3 months	1-3 months	Arthrex ACP	1ml Methylprednisolone (40 mg)
Arora 2022	II	India	20-20	34.6-33.8	PRP: M11:F9 S: M9:F11	6 weeks 3months	>3 months	30 ml blood 15 min@3000rpm, then 5min@2000rpm Dose 3ml PRP	1 ml methylprednisolone (40 mg) 2 ml 1% lignocaine
Omar 2012	II	Egypt	15-15	40.5-37.5	PRP: M6:F9 S: M5:F10	6 weeks	Not reported	150 ml blood + 63 ml citrate phosphate 15min@320g then 15min@2000g Dose: not reported	Not reported
Kahliq 2015	II	Pakistan	51-51	33.6-34.2	PRP: M21:F30 S: M24:F27	4 weeks	Not reported	Dose: 3 ml PRP	2ml Methyprednisolone 1 ml Xylocaine (2%)
Yadav 2015	II	India	30-30	36.6-36.7	PRP: M10:F20 S: M7:F23	2 weeks 1,3 months	1.93-2.26 months	Not described Dose: 1 ml PRP (1 mill platelets/mm^3	1ml Methylprednisolone (40 mg)
Palacio 2016	II	Brazil	36-36	46.6-46.2	Not reported	3,6 months	Not reported	60 ml blood + sodium citrate 10min@400g then 10 min@800g Dose: 3 ml PRP	3ml dexamethasone
Seetharamaiah 2017	II	India	30-30	20-40	PRP:M12:F18 S: M12:F18	3,6 months	Not reported	15 ml blood + sodium citrate 15min@1500 rpm then 10min@2500 rpm Dose: 1ml PRP	1 ml 40 mg triamcinolone
Varshney 2017	II	India	33-50	20-40:40% 40-60:53% >60: 7%	M39:F44	1,2,6 months	Not reported	200 ml blood + 21 ml anticoagulant 10min@1400 rpm then 10 min@3500 rpm Dose: 2 ml + 1 ml lignocaine	80 mg Methylprednisolone 1 ml lignocaine
Gautam 2015	II	India	15-15	18-60	Not reported	2,6 weeks 3,6 months	>6 months	20 ml blood + acid citrate dextrose 15min@1500 rpm Dose: 2 ml PRP	

Table 1: Summary of the study characteristics

Figure 1: PRISMA Flow Diagram. From the initial 253, 13 studies were included.



Risk of bias

The findings of the risk of bias assessment are summarized in table 2. Five studies were identified that had a high risk of bias. [20,31,33,45,53] Three of the studies had bias from randomization; [20,31,53] one study [33] had bias due to missing data and one study [45] had bias in measurement of the outcome. Six studies [22,23,34,40,41,51] had some bias and of those five studies [23,34,40,41,51] all had bias due to bias in measurement of the outcome. Only two studies were assessed as having a low risk of bias. [7,42] The risk of bias across all studies was assessed as unclear (table 2). Overall, 50% across the domain were either high risk or unclear, which raises further doubt about the results and can be considered as plausible bias across studies. [14,25] Publication bias was not detected. The funnel plot was symmetric and Egger's regression intercept (Intercept 7.211, t-value 0.901, p-level 0.397) did not suggest publication bias (figure 2).

Quality Assessment

None of the included studies were assessed as high quality. Three studies [23,34,42] had good quality, eight studies fair quality, [7,22,31,33,40,41,45,53] and two studies [20,51] low quality (table 3). [20,51] The mean score of all studies was 62.8, indicating overall fair quality. Applying the GRADE criteria to the individual studies, all included studies were categorized with an initial high quality of evidence (table 4). Four studies [7,23,33,42] were downgraded to moderate quality either due to limitations in study design or imprecision of results. The other nine studies [20,22,31,34,40,41,45,51,53] were downgraded to low quality because of both limitations in study design and imprecision of results. The overall GRADE domains were assessed individually. Limitations in the study design domain was downgraded to moderate quality, as most studies had either some or high risk of bias, and these limitations are likely to lower the confidence in the

Table 2: Risk of Bias Cochrane Risk of Bias Assessment Tool Version 2 for Randomized Controlled Trials

Authors	LOE	Bias from Randomization	Bias from Deviations from Intended Interventions	Bias due to Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the Reported Results	Overall Risk of Bias
Peerbooms 2010	I	Low	Low	Low	Low	Low	Low
Krogh 2013	I	Low	Low	High	High	Low	High
Lebiedzinzki 2015	I	Low	Low	Low	Some	Low	Some
Gupta 2019	I	Low	Low	Low	Low	Some	Some
Omar 2012	II	Low	Some	Low	Some	Low	Some
Gautam 2015	II	High	Low	Low	Low	Low	High
Kahliq 2015	II	High	Low	High	Some	Low	High
Yadav 2015	II	High	Low	High	Some	Low	High
Palacio 2016	II	Low	Low	Some	Some	Low	Some
Seetharamaiah 2017	II	Some	Low	Low	High	Low	High
Varshney 2017	II	Low	Low	Low	Some	Low	Some
Güngör 2021	II	Some	Low	Low	Some	Low	Some
Arora 2022	II	Low	Low	Low	Low	Low	Low

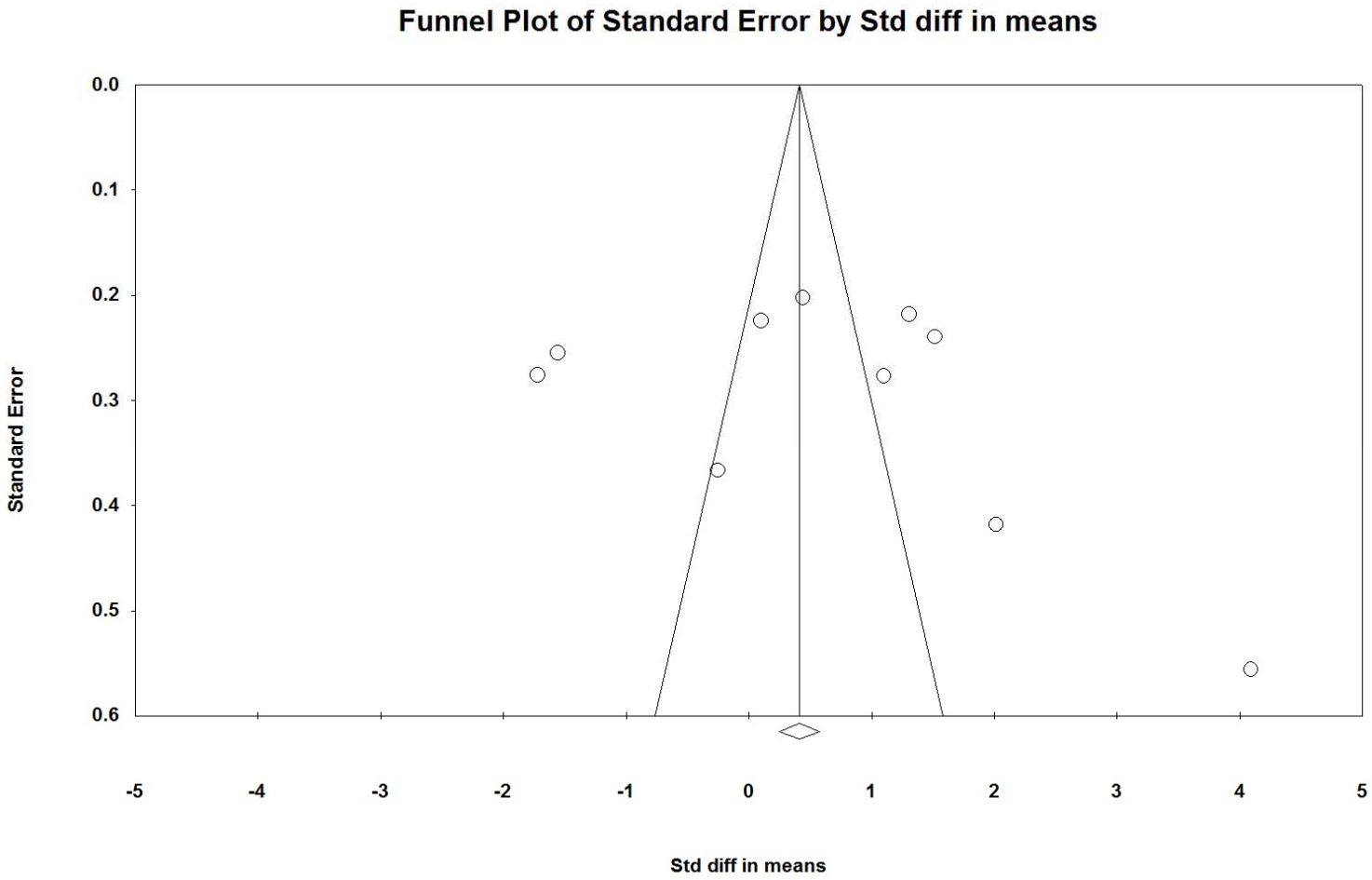


Figure 2: Publication bias: The funnel plot for publication bias was symmetric and Eggers' test did not suggest publication bias.

Table 3: Modified Coleman Methodology Score

Authors	**Total Points**	**Study Size**	**Mean Follow-Up**	**Percent of patients with follow-up**	**Number of Interventions**	**Type of Study**	**Diagnostic Certainty**	**Description Surgical Technique**	**Description Post Op Rehabilitation**	**Outcome Criteria**	**Procedures for Assessing Outcomes**	**Description of Subject Selection**
Peerbooms 2010	**71**	**7**	**0**	**3**	**10**	**15**	**5**	**5**	**5**	**8**	**8**	**5**
Krogh 2013	**60**	**7**	**0**	**5**	**10**	**5**	**5**	**5**	**5**	**10**	**3**	**5**
Lebiedzinzki 2015	**83**	**7**	**0**	**5**	**10**	**15**	**5**	**5**	**5**	**10**	**11**	**10**
Gupta 2019	**68**	**4**	**0**	**5**	**10**	**15**	**5**	**5**	**5**	**8**	**6**	**5**
Omar 2012	**63**	**4**	**0**	**3**	**10**	**15**	**5**	**5**	**0**	**10**	**6**	**5**
Gautam 2015	**44**	**0**	**0**	**3**	**10**	**10**	**5**	**5**	**0**	**8**	**3**	**0**
Kahliq 2015	**64**	**7**	**0**	**3**	**10**	**15**	**5**	**5**	**0**	**8**	**6**	**5**
Yadav 2015	**56**	**4**	**0**	**3**	**10**	**10**	**5**	**5**	**0**	**8**	**6**	**5**
Palacio 2016	**63**	**4**	**0**	**5**	**10**	**15**	**5**	**5**	**0**	**8**	**6**	**5**
Seetharamaiah 2017	**58**	**4**	**0**	**5**	**10**	**15**	**5**	**5**	**0**	**8**	**6**	**0**
Varshney 2017	**51**	**7**	**0**	**3**	**10**	**10**	**5**	**5**	**0**	**8**	**3**	**0**
Güngör 2021	**75**	**4**	**0**	**5**	**10**	**15**	**5**	**5**	**5**	**10**	**6**	**10**
Arora 2022	**61**	**4**	**0**	**3**	**10**	**10**	**5**	**5**	**5**	**8**	**6**	**5**
Total Score	**62.8**	**4.8**	**0**	**3.9**	**10**	**12.7**	**5**	**5**	**2.3**	**8.6**	**5.8**	**4.6**

Authors	Initial Quality of Evidence	Final Quality of Evidence	Limitations in Study design	Inconsistency of Results	Indirectness of evidence	Imprecision of Results	Increase Quality of Evidence
Peerbooms 2010	High	Moderate				No sample size calculation, 95% CI missing	
Krogh 2013	High	Moderate	Risk of bias: some concerns				
Lebiedzinzki; 2015	High	Low	Risk of bias: some concerns			No sample size calculation, 95% CI missing	
Gupta 2019	High	Low	High Risk of Bias			No sample size calculation, 95% CI missing	
Omar 2012	High	Low	Quasi RCT, automatic downgrade			No sample size calculation	
Gautam 2015	High	Low	High risk of bias			No sample size calculation, 95% CI missing	
Kahliq 2015	High	Low	Quasi RCT, automatic downgrade High risk of bias			No sample size calculation, 95% CI missing	
Yadav 2015	High	Low	Quasi RCT, automatic downgrade High risk of bias			No sample size calculation, 95% CI missing	
Palacio 2016	High	Low	Quasi RCT, automatic downgrade High risk of bias			No sample size calculation, 95% CI missing	
Seetharamaiah 2017	High	Low	High risk of bias			No sample size calculation, 95% CI missing	
Varshney 2017	High	Low	Quasi RCT, automatic downgrade High risk of bias			No sample size calculation, 95% CI missing	
Güngör 2021	High	Moderate	Risk of bias: some concerns				
Arora 2022	High	Moderate				No sample size calculation, 95% CI missing	

Table 4: Quality Assessment using the Cochrane GRADE system

estimate of the effect. The inconsistency of results domain was downgraded to low quality, as the heterogeneity of the I^2 statistic for all pooled comparisons were above 90%. The indirectness of evidence domain was not downgraded, as the authors did not detect any evidence of differences in patient population, interventions, and outcome measures. The imprecision of results domain was downgraded to low quality, as the majority of the included studies did not perform sample size analysis and the 95% confidence intervals were not reported. None of the studies had any factors that increased the quality of the evidence. The final GRADE quality assessment was downgraded to low level of certainty. This was based on the downgrading of two of the four domains and the final quality of evidence of the included studies. Of the thirteen included studies, nine had a low final quality of evidence.

Clinical outcomes

The clinical outcomes for all studies are summarized in table 5. Eleven studies [7,20,22,23,31,33,40,41,42,51,53] reported the 1-month results for the VAS score. The pooled estimate for these studies demonstrated significant differences in favor of corticosteroids (SMD 0.727, 95% CI: 0.123 to 1.415, p=0.038, I^2= 96%; figure 3). Ten studies [7,20,22,23,31,33,41,42,51,53] reported the 3-month results for the VAS score. The pooled estimate for these studies demonstrated significant differences between the two groups in favor of PRP (SMD -0.875, 95% CI: -1.321 to -0.429, p=0.0001, I^2= 95%; figure 4). Only four studies [20,42,45,51] reported the 6-month results for the VAS score. The pooled estimate for these studies demonstrated significant differences between the two groups (SMD -2.174, 95% CI: -3.440 to -0.908, p=0.0001, I^2= 93%; figure 5), favoring PRP injections.

	LOE		
		PRP	Steroid
Peerbooms 2010	I	**VAS** 1/12: 55.4+24.2 3/12: 38.7+27.2 6/12: 32.6+31.5 12/12: 25.3+31.2 **DASH** 1/12: 135.9+78 3/12: 92.0+78.8 6/12: 79.5+80.3 12/12: 54.7+73.2	**VAS** 1/12: 44.2+26.4 3/12: 44.2+27.1 6/12: 56.6+23.2 12/12:50.1+28.1 **DASH** 1/12: 97.4+69 3/12:92.2+68.7 6/12:117.3+75.6 12/12: 108.4+82.2
Krogh 2013	I	**VAS** 1/12: 2.7+0.22 3/12: 2.15+0.33	**VAS** 1/12: 1.8+0.22 3/12: 2.28+0.22
Lebiedzinzki 2015	I	**DASH** 6/52: 32.3+18.2 6/12: 14.2+13.4	**DASH** 6/52: 20.6+21.5 6/12: 14.7+22
Gupta 2019	I	**VAS** 6/52: 4.45+1.731 3/12 4.0+5.98 12/12: 2.5+5.5 **DASH** 6/52: 64.15+2.91 3/12: 35.1+3.08 12/12: 31.65+3.87	**VAS** 1/12: 2.46+0.74 3/12: 6.46+0.9 6/12: 6.88+0.68 **DASH** 6/52: 53.25+2.85 3/12: 44.75+3.09 12/12: 40.1+8.03
Omar 2012	II	**VAS** 6/52: 3.8+1.9 **DASH** 6/52: 19.9+12.9	**VAS** 6/52: 4.3+2.1 **DASH** 6/52: 20.2+14.0
Gautam 2015	II	**VAS** 6/52: 2.7+0.8 3/12: 1.8+0.6 6/12: 1.5+0.5 **DASH** 6/52:38.6+5.7 3/12:33.6+5.1 6/12: 32.0+4.5	**VAS** 6/52: 1.4+0.5 3/52: 1.7+0.5 6/12: 2.9+1.2 **DASH** 6/52: 32.7+4.1 3/12: 34.3+3.3 6/12: 39.6+1.0
Kahliq 2015	II	**VAS:** 1/12: 3.5+2.61	**VAS** 1/12: .0+2.6
Yadav 2015	II	**VAS** 1/12: 4.6 3/12:1.6 **DASH** 1/12: 62.5 3/12: 34.16	**VAS:** 1/12: 3.4 3/12: 2.8 **DASH** 1/12: 53.13 3/12: 44.33
Palacio 2016	II	**PRTEE** 3/12: 13.0+4.7 **DASH** 3/12: 10.7+4.0	**PRTEE** 3/12: 21.8+5.5 **DASH** 3/12: 19.8+4.9
Seetharamaiah 2017	II	**VAS** 3/12: 0.8 6/12: 0.8	**VAS** 1/12: 1.5 3/12: 2.8
Varshney 2017	II	**VAS** 1/12: 2.45+0.9 3/12: 1.57+0.9 6/12: 0.69+1.57	**VAS** 1/12: 2.34+1.18 3/12: 1.36+0.77 6/12: 4.61+1.46
Güngör 2021	II	**VAS** 3/52: 2.25+0.60 3/12: 1.58+0.77 **DASH** 3/52: 30.75+4.6 3/12: 32.41+4.79	**VAS** 3/52: 2.34+0.64 3/12: 0.75+060 **DASH** 3/52: 32.0+5.05 3/12: 26.66+3.23

Arora 2022	II	**VAS** 1/52: 50.5 3/12:30.5 **DASH** 1/12: 56.2 3/12: 29.1	**VAS** 1/52: 50.9 3/12:40.5 **DASH** 1/12: 42.0 3/12: 32.0

Table 5: Clinical Outcomes for VAS and DASH Scores

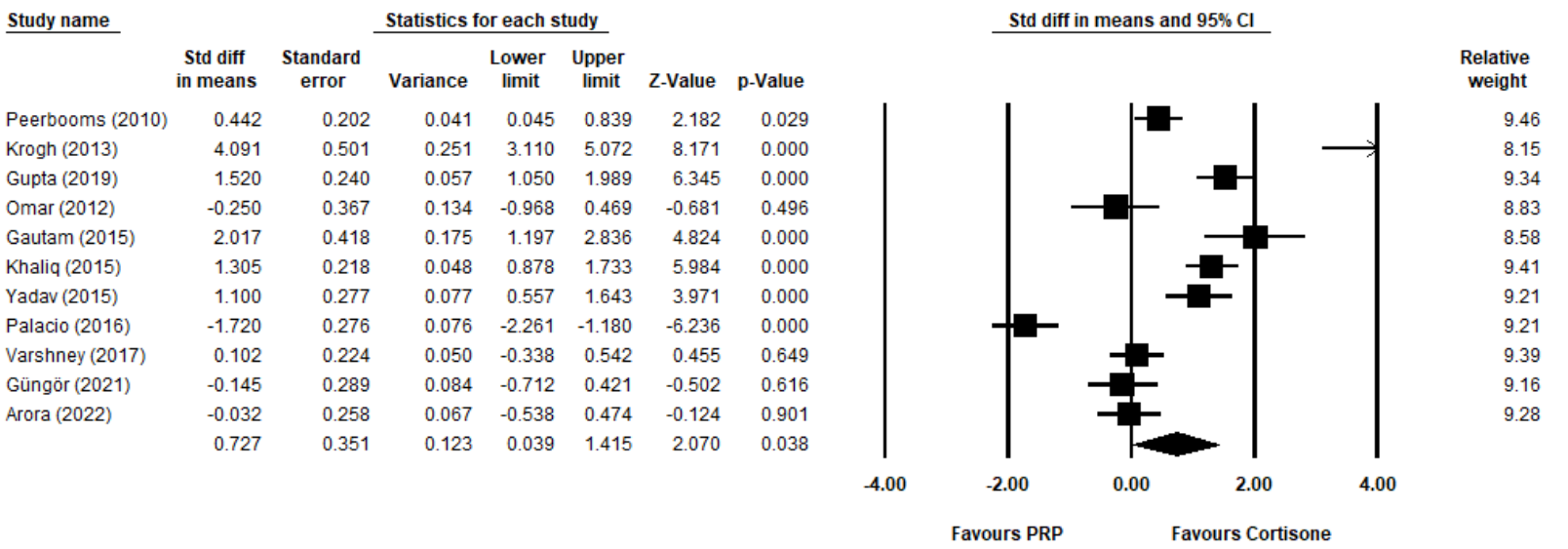


Figure 3: Forest Plot for VAS at 1 month. The pooled estimate for all studies demonstrated significant differences in favor of CSI (p=0.038).

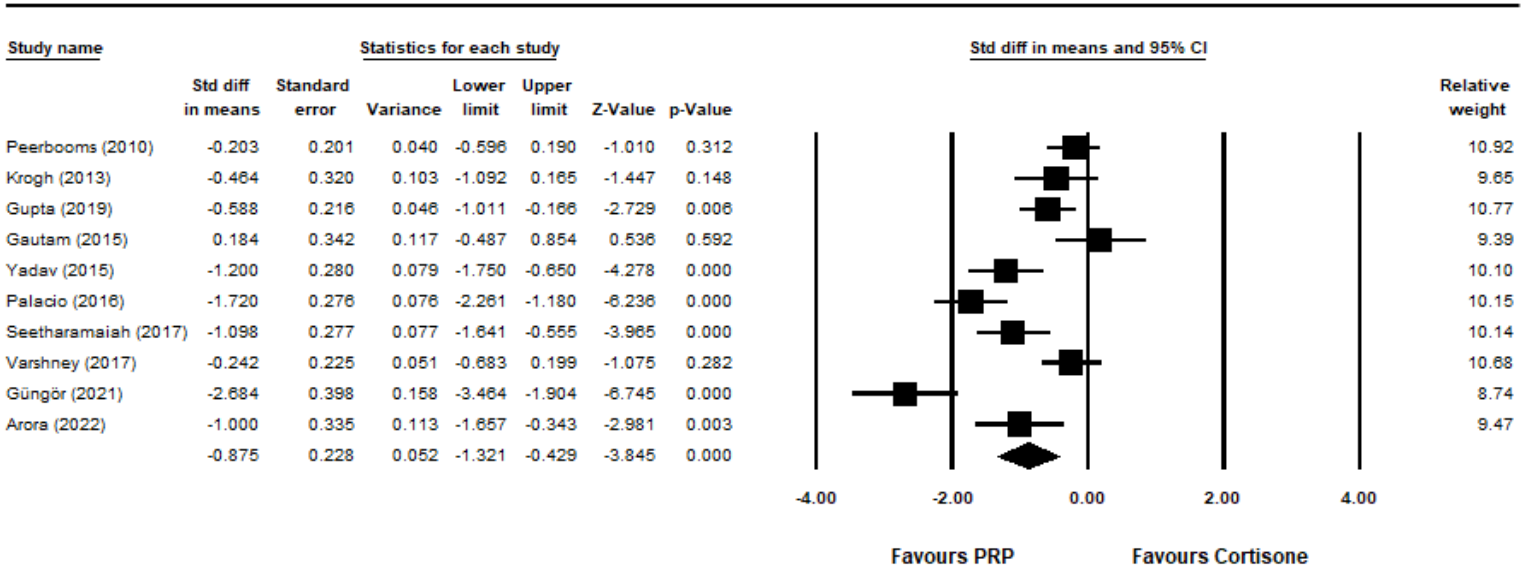


Figure 4: Forest Plot for VAS at 3 months. The pooled estimate for all studies demonstrated significant differences in favor of PRP (p=0.0001).

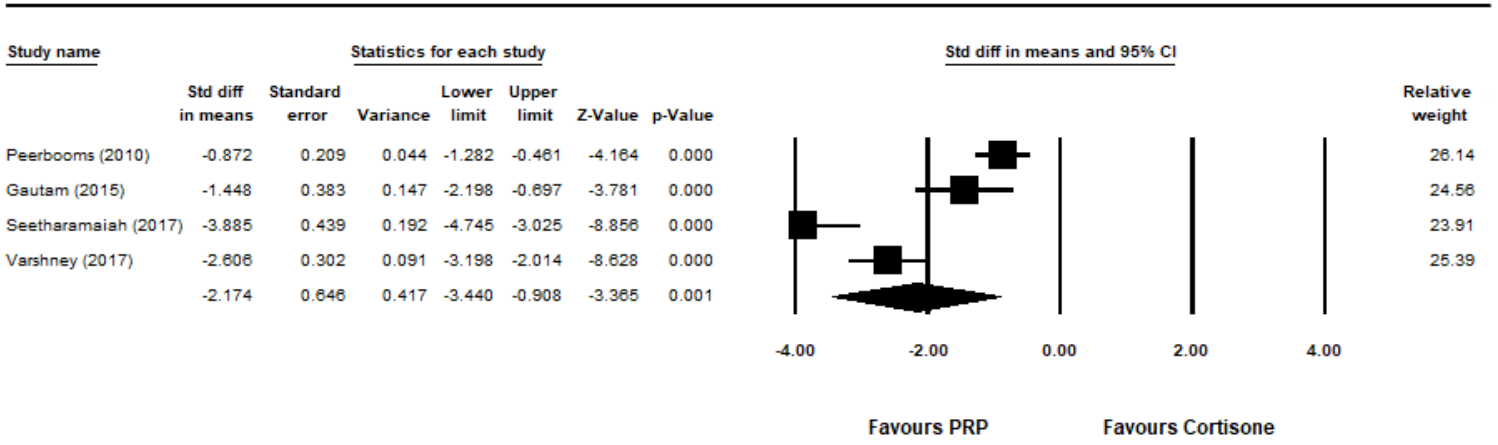


Figure 5: Forest Plot for VAS at 6 months. The pooled estimate for all studies demonstrated significant differences in favor of PRP (p=0.001).

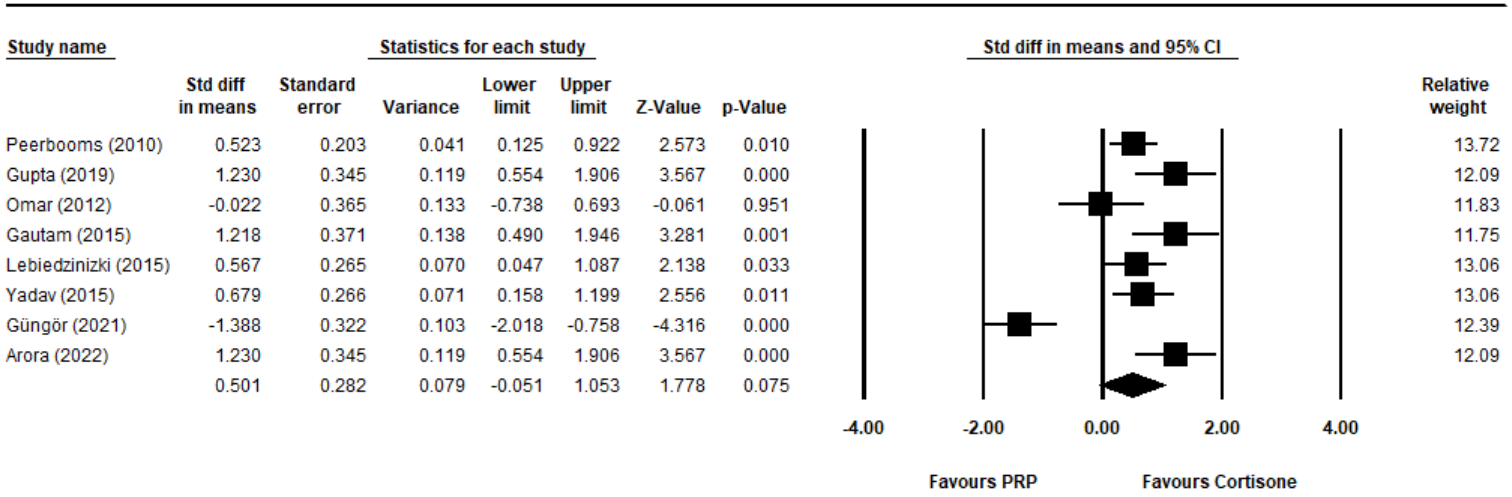


Figure 6: Forest Plot for DASH at 1 month. The pooled estimate for all studies demonstrated no significant differences but favored CSI (p=0.075).

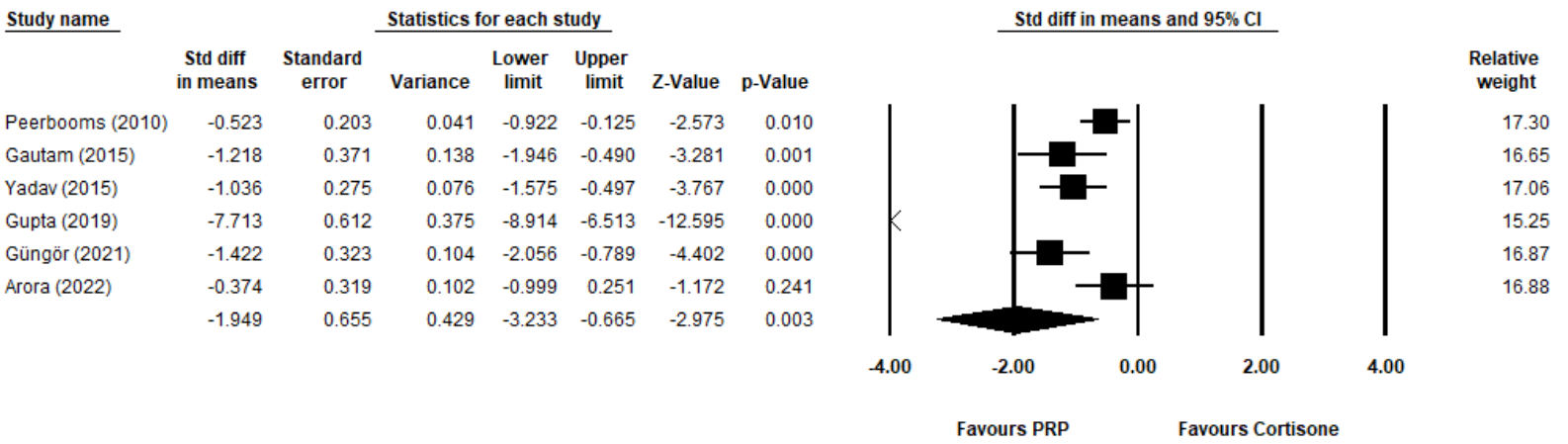


Figure 7: Forest Plot for DASH at 3 months. The pooled estimate for all studies demonstrated significant differences in favor of PRP (p=0.003).

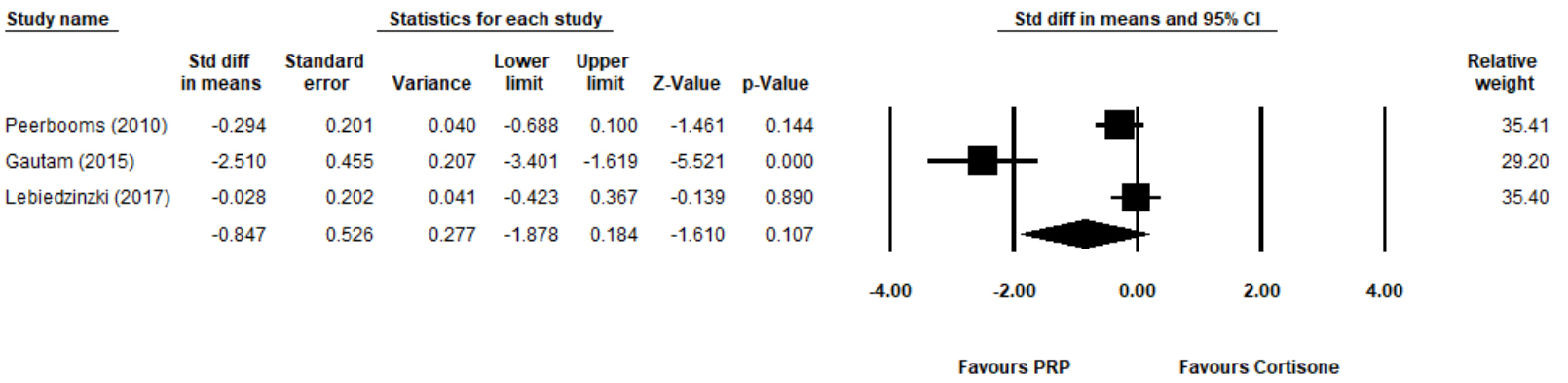


Figure 8: Forest Plot for DASH at 6 months. The pooled estimate for all studies demonstrated no significant differences but favored PRP (p=0.107).

Eight studies [7,20,22,23,34,40,42,53] reported the 1-month results for the DASH score. The pooled estimate for these studies demonstrated non-significant differences between the two groups in favor of corticosteroids (SMD 0.501, 95% CI: -0.051 to 1.053 p=0.075, I^2= 96%; figure 6). Six studies [7,20,22,23,42,53] reported the 3-month results for the DASH score. The pooled estimate for these studies demonstrated significant differences between the two groups favoring PRP (SMD -1.949, 95% CI: -3.233 to -0.665, p=0.003, I^2= 97%; figure 7). Only three studies [20,34,42] reported the 6-month results for the DASH score. The pooled estimate for these studies demonstrated non-significant differences between the two groups, but favored PRP (SMD -0.847, 95% CI: -1.878 to 0.184, p=0.107, I^2= 97%; figure 8).

Discussion

The results of this meta-analysis demonstrate that steroid injections are superior to PRP within the first month of treatment. At both three and six months, patients injected with PRP had significantly lower disability (DASH) and lower pain scores (VAS). Although the VAS pain scores are significantly lower at one month in the patient group who were injected with steroids, the standard difference in means lower limit is close to zero and the between group variance is also quite low, suggesting the treatment effects are possibly not clinically relevant. Similarly, the between group differences for disability and function (DASH) favor steroid injections. Although these differences did not reach significance, the standard difference in means lower limit was negative and the variance was again low, suggesting the treatment effects are unlikely to be clinically relevant.

In meta-analysis, weighted and standard mean differences (SMD), risk ratios, and odds ratios are measures of effect size. [5] SMD values between 0.2-0.5 are considered small, values between 0.5- 0.8 are considered medium, and values above 0.8 are considered large effect sizes. [12] Medium and large effect sizes suggest significant between group differences, and provide an indication that these changes are clinically relevant. [5] When interpreting the results of this meta-analysis in the light of effect size using the definition of Cohen, [12] the effect sizes for both VAS and DASH at 1 months were medium and clearly favor corticosteroid injections. The 95% confidence interval for VAS does not cross zero and the p-value is significant, together suggesting the between group differences are clinically relevant. In contrast, the DASH score is not statistically significant and the 95% confidence intervals cross over zero, suggesting that, despite a medium effect size, the statical differences are not clinically relevant. One could interpret these findings as follows: although the pain is substantially reduced early after corticosteroid injections, the subjective feeling of disability in comparison to PRP is not clinically different. At both 3 and 6 months, the analyzed data strongly supports the use of PRP over corticosteroid injections. The effect sizes were large and ranged between 0.85 and 2.17, clearly favoring PRP over corticosteroids and indicating these findings are also likely to be clinically relevant.

These results are consistent with other recently published meta-analyses. [8,28,35,36,52] For instance, Mi et al. reported a short-term advantage for CSI up to 8 weeks, but PRP was more efficacious regarding both pain relief and function in the intermediate and longer term, and thus recommended using PRP as the preferred option. [36] Moreover, they [36] included eight studies that were also included in our meta-analysis. [20,31,33,34,40,41,42,53] They [36] have only included studies until 2016 and used the Cochrane

Risk of Bias Tool and the modified Jadad scale for quality assessment. Unfortunately, the modified Jadad scale should not be used for assessing study quality because it only appraises randomization, blinding, and patient attrition, and is considered a less robust version of the Cochrane Risk of Bias Tool. In addition, they have not reported the results of the Jadad appraisal. The addition of five more recent studies [6,20,21,43,49] reinforces the findings of Mi et al. [36] However, given that the between group differences in our analysis were only significant for VAS but did not reach significance for the DASH score, superiority of CSI over PRP at 1 month is doubtful.

Similarly, Barnett et al. suggested that regenerative injections are more useful in the long-term, with both PRP and CSI providing pain relief in the short-term. [8] Unfortunately, they combined both autologous blood and PRP injections within the treatment arm, and therefore introduced systematic error. In addition, the PEDro scale was used for quality assessment. The construct validity of the PEDro scale has recently been questioned, and it has been suggested that the PEDro summary scores should not be used. [2] Furthermore, there was only moderate agreement between PEDro and the Cochrane Risk of Bias Tool, particularly when assessing unclear risk of bias. [38] The conclusion of the Barnett et al. [8] meta-analysis must, therefore, be viewed with caution due to these multiple biases.

Li et al. reported that CSI demonstrated favorable outcomes in the short-term (2-4 weeks), with PRP being more effective with regards to improved pain and function at longer-term (24 weeks) follow-up. [35] Although seven studies were included, [20,21,31,33,42,51,53] their meta-analysis regarding the VAS, Mayo, and DASH scores contained only two studies for ten of the eleven items. As a result, this study has

serious methodological flaws and is, therefore, misleading and of limited benefit. [30] Xu et al. [52] included the same seven studies [20,21,31,33,42,51,53] from 2010 to 2016 in their meta-analysis, and used the Cochrane Risk of Bias Tool and GRADE for quality assessment. They concluded that PRP injection was statistically superior in the short-term for up to 6 months. [52] However, they admitted that the overall quality of evidence was low and indicated that further research is required to confirm these findings. [52] The addition of six clinical studies in our meta-analysis added 323 patients, increasing the sample size by 38%. Despite the substantial increase in patient numbers, arguments supporting the superiority of CSI in the short-term or PRP in the longer-term could not be strengthened. In fact, the trend towards more effective treatment with CSI in the short-term (4-12 weeks) and superiority in the longer-term (26 weeks) was substantially weakened.

As per the GRADE handbook, [14] the initial quality of evidence of all included studies was high, but was downgraded to moderate in four studies [7,23,33,42] and low in nine studies. [20,22,31,34,40,41,45,51,53] Similarly, CMS assessment resulted in only three studies [23,34,42] achieving good quality and nine studies achieving fair quality [7,22,31,33,40,41,45,53] supporting the GRADE quality assessment. The final GRADE assessment was downgraded to a low level of certainty. This suggests that the true effect might be markedly different from the estimated effect, and future studies may change the direction of the treatment effect. However, it could be argued that the results of this meta-analysis confirm the trend that was previously shown by other published studies, [8,35,36,52] confirming that PRP may be more effective in the longer term.

Currently, the available evidence cannot fully explain the potentially prolonged PRP effects observed. Several studies have demonstrated that at the cellular level the effect is immediate. For example, Foster et al. reported that 70% of growth factors are released from platelets within 10 minutes, and the remaining growth factors are released within 1 hour. [18] Furthermore, the half-life of plasma and platelet released cytokines is less than 2 hours. [55] Consequentially, the prolonged effect of PRP may reflect the inhibition of catabolic and inflammatory cytokines such as IL-1β, TNF-α, fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β). [8] These modulators act as signaling molecules, mediating cell responses by binding to specific cell receptors to initiate the healing process. [54,55] This might suggest that PRP has a more profound influence locally, downregulating pro-inflammatory cytokine receptors and upregulating endogenous anti-inflammatory cytokines. This can theoretically reduce pain dramatically over a prolonged period of time, [54] aiding in the tissue healing process. It is possible that prolonged growth factor activity is unnecessary, and is instead needed only to activate specific molecular pathways during the first several hours.

The aetiogenesis of lateral epicondylitis is characterized by angiofibroblastic degeneration. [3,10] Corticosteroids down regulate inflammatory cells and mediators, [3,47] and the lack of inflammation in tendinopathy may explain the short duration of efficacy of corticosteroids used for lateral epicondylitis.

The limitations of this meta-analysis are directly related to the limitations of the included studies. The combination of high risk of bias, moderate to low study quality, the discrepancies in the preparation protocols for PRP, and differences in the dosage

and preparations for the corticosteroid arm all decrease the external validity substantially, and therefore, reduce and limit the value of any meta-analysis. In addition, randomized clinical trials have other weaknesses such as limited external validity including a specific study population, and non-specific measures not correlating with the outcome of interest. Although the included studies have utilized validated outcome scores, only one study [33] used the Patient-Rated Tennis Elbow Evaluation (PRTEE). [44] Therefore, this meta-analysis relied on pooling the results of general pain and upper extremity disability scales. In theory, patients may have had additional symptoms influencing results. Unfortunately, only three of the four studies reported whether the applied PRP-preparation was leukocyte-rich or leukocyte-poor. As such, subgroup analysis was not possible. Systematic reviews and meta-analysis are, out of necessity and by design, heavily dependent on the quality of the primary studies. The quality and limitations of the included studies may not allow any valid conclusion to be reached. In contrast, this may be a valid conclusion in itself, and would demonstrate that treatment recommendations should not be made based on poor evidence. Ultimately, care must be exercised when interpreting the conclusions of any meta-analysis, and under some circumstances the application of certain evidence-based recommendations may not be beneficial. [19,26,27]

Conclusions

The results of this meta-analysis suggest that PRP has no advantage over steroid injections within the first month of treatment, but that it is superior to steroids at both 3 and 6 months. These results also suggest that corticosteroids have a short-term beneficial effect during the early treatment period, although the quality of the available evidence is not very robust in support of this finding. However, these

findings must all be viewed with caution as the high risk of bias and moderate to low quality of the included studies may not justify a recommendation of one treatment over another.

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