

Effect of Platelet-Rich Plasma Injections on Pain Reduction in Patients with Temporomandibular Joint Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials

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Submitted February, 11, 2019;
accepted September 5, 2019.
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Aims: To study the effect of platelet-rich plasma (PRP) injections on pain reduction in patients with temporomandibular joint osteoarthritis (TMJ OA). **Methods:** The authors performed a comprehensive search of the MEDLINE, PubMed, and Web of Science databases to retrieve RCTs published up to July 2018. Pain outcomes (visual analog scale scores) were extracted to assess the effect of PRP injections on TMJ OA. All data analyses were conducted using RevMan 5.3. **Results:** Six studies were included. According to the results of these trials, intra-articular injections of PRP were more effective than placebo for pain reduction (6 months postinjection: mean difference [MD] -2.82 , 95% CI -3.39 to -2.25 , $P < .00001$; 12 months postinjection: MD -3.29 ; 95% CI -4.07 to -2.52 , $P < .00001$). Additionally, the comparison between PRP and hyaluronic acid injections showed a statistically significant difference in pain reduction in support of PRP (MD -0.81 ; 95% CI -1.22 to -0.40 ; $P = .0001$) at 12 months postinjection. All trials revealed a moderate risk of bias. **Conclusion:** Based on current evidence, PRP injections may reduce pain more effectively than placebo injections in TMJ OA at 6 months (level of evidence: moderate) and 12 months (level of evidence: moderate) postinjection. This significant difference in pain reduction could also be seen when PRP was compared to hyaluronic acid at 12 months postinjection (level of evidence: low). It can be cautiously interpreted that PRP has a beneficial effect on the relief of TMJ OA pain. Large-scale, low-bias RCTs are needed to test whether PRP injection should be a routine treatment for patients with TMJ OA. *J Oral Facial Pain Headache* 2020;34:149–156. doi: 10.11607/ofph.2470

Keywords: meta-analysis, myofascial, pain, platelet-rich plasma, temporomandibular disorders

Osteoarthritis (OA) is a continuous physiologic adaptation process. In the state of joint degeneration, balance in the joint is disrupted, and the joint synovium, cartilage, joint capsule, tendon, bone, etc begin to show inflammatory changes.¹ The occurrence of OA in the temporomandibular joint (TMJ) is mainly due to chronic degenerative inflammatory disease of the articular cartilage and condyle caused by an imbalance of metabolism.² The current principles of treatment for TMJ OA are based on nonsurgical methods, including physical therapy, bite plates, joint cavity irrigation, intra-articular injection of corticosteroids, and hyaluronic acid (HA). The effect of joint arthrocentesis is temporary and does not restore the microstructure of the TMJ. Injecting some biologic or nonbiologic agents that have a tissue regeneration ability into the TMJ can help initiate and maintain the regeneration process; therefore, intra-articular injections of different agents, such as HA and corticosteroids, are used to treat TMJ OA.³

Injection of HA into the joint cavity has potential benefits for the recovery of bone, cartilage, and TMJ structure. Maximum mouth opening during the treatment and follow-up period, pain in the TMJ area, and chewing efficiency were significantly improved in a trial testing two HA drugs.⁴ Recently, platelet-rich plasma (PRP) has been introduced as an injection treatment for TMJ OA. The rationale for PRP use in the treatment of OA is that platelet-releasing growth factor stimulates the secretion of HA from synovial fibroblasts.⁵ Transforming growth factor- β 1 (TGF- β 1) and platelet-derived growth factor (PDGF) are the main

secretory products of platelets, and platelet-released growth factors regulate endogenous growth factors and restore HA levels, thereby enhancing joint lubrication and protection.⁶ Leukocyte-free PRP containing specific doses of platelets and growth factors is called plasma rich in growth factors (PRGF).

PRP treatment of OA is an innovative clinical application that stimulates the repair and replacement of damaged tissues.⁷ PRP can not only accelerate tissue healing, but may also play a potential role in pain relief. The analgesic effect of PRP may be due to its ability to promote an increase in the number of cannabinoid receptors CB1 and CB2.⁸ Although PRP has achieved good results in the treatment of knee osteoarthritis, it has been found that the effect of four injections of PRP into the TMJ cavity is not significantly different from the effect of injecting HA once.⁹ PRP might also present potential complications.^{10,11} Therefore, a meta-analysis was necessary to further determine the safety and effectiveness of PRP.

One of the main clinical symptoms of TMJ OA is pain. After searching a large amount of the literature, it was found that the effect of PRP on pain relief in patients with TMJ OA was controversial. Due to these mixed results, a systematic search of the literature with meta-analysis was performed to assess the safety and effect of PRP injections in patients with TMJ OA.

Materials and Methods

Eligibility Criteria

Studies written in the English language that fulfilled the following eligibility criteria were included: compared PRP or a similar product containing platelets (eg, PRGF) to a control treatment (eg, placebo or HA) in patients with TMJ OA; and was a published or unpublished (ie, presented at a society meeting) randomized controlled trial (RCT).

Literature Selection and Data Extraction

An electronic search of the MEDLINE, PubMed, and Web of Science databases was performed for papers published in English up to July 2018. In addition, relevant journals covering TMJ disorders were examined, and a manual search of the reference lists from primary studies was performed to identify additional results. The following terms were used in the search strategy: [(temporomandibular OR (temporomandibular AND joint) AND (temporomandibular joint osteoarthritis)) AND (platelet OR plasma OR (plasma rich in growth factor) OR (platelet AND rich AND plasma))].

Two reviewers (L.F.L. and S.H.J.) independently screened the literature, extracted the data, and

checked the cross sections to ensure consistency of the data extracted. First, the reviewers read the titles and abstracts of the literature and then evaluated the studies by downloading and reading the full texts. During the screening process, the literature was strictly screened according to the eligibility criteria. When the two reviewers had different opinions, they solved the problem by discussion or by consulting experts. The following data were extracted: first author; date of publication; study design; sample size; intervention; pain at various time points; and adverse reactions.

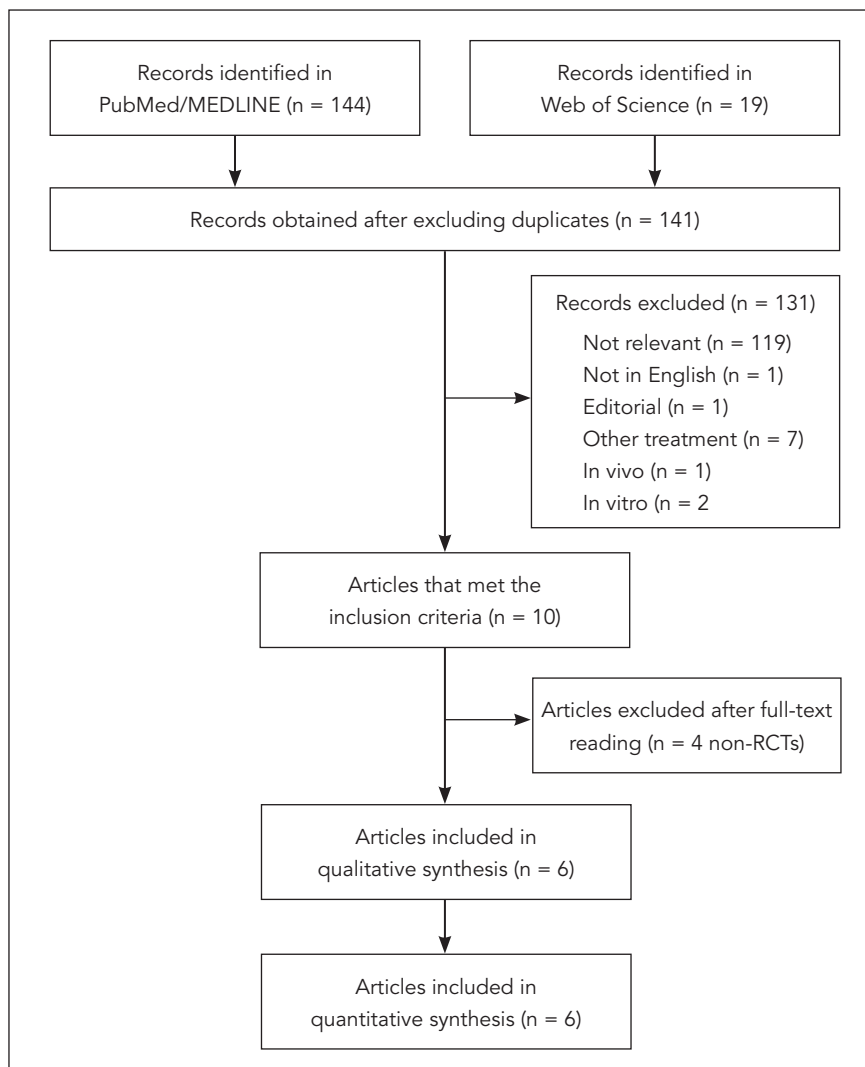
Methodologic Quality Assessment

The same two independent reviewers assessed the quality of the included studies using the Cochrane Collaboration Risk of Bias tool.¹² This tool contains the following domains: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias. The risk of bias was assessed in each domain for all included studies using a risk of bias table. All items were determined to be at low, high, or unclear risk of bias.¹² Trials were considered to be at low risk when every single item of bias was scored with a low rating. If studies scored high or unclear on one or two items of bias, a moderate bias was considered. Studies with more than two high or unclear scores were considered to be at high risk of bias. Differences were settled by discussion, and in case of disagreement, a third reviewer made the final decision.

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was developed to classify the strength of clinical recommendations on the basis of the quality of evidence. The GRADE system works on the principle that "all relevant clinical studies and observations provide evidence, the quality of which varies."¹³ Quality of evidence is determined on the basis of four key factors: (1) methodologic limitations, (2) heterogeneity, (3) indirectness, and (4) imprecision. The basic study design is the most important determinant of how the evidence is graded. Randomized trials are assumed to be of higher quality than observational studies and are downgraded according to analysis of the four previously mentioned factors. The quality of the evidence is graded as high, moderate, low, or very low.

Data Syntheses

The results of the studies were analyzed using RevMan 5.3, and these findings were summarized in a meta-analysis. Continuous outcomes were calculated and expressed as mean difference (MD).

Fig 1 Study flowchart.

To determine the heterogeneity among studies, χ^2 ($P < .10$ indicates heterogeneity) and I^2 ($< 40\%$ represents low heterogeneity, and $\geq 75\%$ or more indicates high heterogeneity) statistics were used. When $I^2 > 50\%$, the outcomes were pooled using random-effects models. Fixed-effects models were used when fewer than five studies were included. Additionally, subgroup analyses were performed to explore possible differences in reagents used in the control groups and in duration of follow-up.

Results

Search Results

The search strategy identified 163 records, 144 from MEDLINE/PubMed and 19 from Web of Science. After deleting duplicates, 141 studies remained. The remaining articles were filtered according to the inclusion criteria, and 10 articles were selected for

further analysis. Of the 10 full-text articles examined, only 6 fulfilled the inclusion criteria (Fig 1).

Six studies^{9-11,14-16} were reported to be RCTs. Three of these trials^{10,14,16} compared PRP to placebo for pain, whereas the other three trials^{9,11,15} compared PRP to HA. Two studies^{10,11} mentioned some complications after PRP injections.

Characteristics of the Included Studies

The characteristics of the included studies^{9-11,14-16} are shown in Table 1. Three of these studies treated patients with TMJ OA^{9,11,16} and reported patient characteristics, including disc displacement with reduction or disc displacement without reduction and degenerative changes in the condyle surface^{10,14,15} (broadly considered as OA). The types of PRP used in all six studies according to the Mishra et al¹⁷ classification system are presented in Table 1. Before Mishra et al proposed classifying PRP, it was rare to classify it on the basis of platelet and leukocyte

Table 1 Basic Characteristics of Included Studies

Study, y	Study type	Study population characteristics/ Mean age (y)	No. of patients (women/ men)	Injections (n)/ interval (wk)/ volume (mL)	PRP type (Mishra classification)	Intervention measures in experimental group	Measures given in control group	Follow-up time (mo)/overview of intervention effect
Cömert Kiliç and Güngörmüş, ⁹ 2016	RCT	TMJ OA/ 30.48	31 (26/5)	4/4/1	3B	Intra-articular injection of PRP	Intra-articular injection of HA	12/-
Hancı et al, ¹⁰ 2015	RCT	DDwR with functional disability and pain/ 27.2	20 (18/2)	1/NA/0.6	4A	Intra-articular injection of PRP	Intra-articular injection of placebo (Ringer's lactate solution)	3/NA, 6/+
Hegab et al, ¹¹ 2015	Single-blind RCT	TMJ OA with mild to severe degenerative changes/ 38.6	50 (29/21)	3/1/1	NA	Intra-articular injection of PRP	Intra-articular injection of HA	12/+
Fernández Sanromán et al, ¹⁴ 2016	Single-blind RCT	DDwoR and OA of the mandibular condyle/ 35.8	92 (86/6)	1/NA/5	4B	Intra-articular injection of PRP after arthroscopy	Intra-articular injection of placebo (saline) after arthroscopy	3/-, 6/+, 12/+, 18/-, 24/-
Fernández-Ferro et al, ¹⁵ 2017	Single-blind RCT	DDwR/DDwoR and condylar OA/ 35.5	100 (88/12)	1/NA/5	4B	Intra-articular injection of PRP after arthroscopy	Intra-articular injection of HA after arthroscopy	3/NA, 6/NA, 12/NA, 18/+
Cömert Kiliç et al, ¹⁶ 2015	RCT	OA of the mandibular condyle/ 37.37	30 (27/3)	4/4/1	3B	Intra-articular injection of PRP	Intra-articular injection of placebo (Ringer's lactate solution)	12/-

SD = standard deviation; DDwoR = disc displacement without reduction; OA = osteoarthritis; DDwR = disc displacement with reduction; TMJ OA = temporomandibular joint osteoarthritis; NA = not available/applicable; PRP = platelet-rich plasma; HA = hyaluronic acid; + = beneficial effect on pain (visual analog scale) derived from *P* value (< .05); - = no beneficial effect on pain derived from *P* value (> .05).

concentrations and on whether the PRP had been activated. Mishra et al believed that this classification method could improve study comparisons and better reveal how to use PRP. The types are as follows:

- Type 1: increased white cell count and no activation
- Type 2: increased white cell count with activation
- Type 3: minimal/no white cell count and no activation
- Type 4: minimal/no white cell count with activation
- A: contains an increased platelet concentration at or above five times the baseline (extracted venous blood)
- B: contains an increased platelet concentration less than five times the baseline (extracted venous blood)

An overview of the intervention effect per study and follow-up time can also be seen in Table 1.

Quality Assessment

All of the included RCTs achieved a moderate risk of bias according to the Cochrane Collaboration Risk of Bias tool. The quality of the existing evidence

for each subgroup (PRP vs placebo or HA, 6- vs 12-month follow-up) according to the GRADE system is summarized in Table 2.

Pain Measures

The visual analog scale (VAS) is a continuous scale composed of horizontal lines (10 cm [100 mm] in length) ranging from a score of 0 to a score of 10 (100 mm), which is different from the numeric rating scale (NRS). Ten pain VAS outcomes (PRP vs placebo or HA at 3-, 6-, 12-, 18-, and 24-month follow-up times) from the six randomized trials^{9-11,14-16} served as the primary outcomes of this review. Of the 10 outcomes, 5 combinations showed that PRP provided a significant benefit of pain relief, and 5 demonstrated no difference between PRP and the control (Table 1).

There was a significant difference in VAS scores between the PRP and control groups across the six RCTs (MD -0.93, 95% confidence interval [CI] -1.75 to 0.10, *P* = .03; *I*² = 80%) (Fig 2); however, this result showed high heterogeneity. To analyze whether the high heterogeneity might result from different interventions in the control groups and the different follow-up times, subgroup analyses were performed to determine the effect of these two factors on the

Table 2 GRADE Quality Assessment of Evidence for Platelet-Rich Plasma (PRP) Injections

Study design	No. of studies, no. of participants	Methodologic limitations	Consistency	Directness	Precision	Quality of evidence (GRADE)
PRP vs placebo, 6 mo postinjection	2 (Hancı et al, ¹⁰ and Fernández Sanromán et al ¹⁴), 112	Serious limitations (-1) ^a	Not serious	Not serious	Not serious	+++ Moderate
PRP vs placebo, 12 mo postinjection	2 (Cömert Kilic et al ¹⁶ and Fernández Sanromán et al ¹⁴), 122	Serious limitations (-1) ^a	Not serious	Not serious	Not serious	+++ Moderate
PRP vs HA, 12 mo postinjection	3 (Fernández-Ferro et al, ¹⁵ Hegab et al, ¹¹ and Cömert Kilic and Güngörmüş ⁹), 181	Serious limitations (-1) ^a	Serious (-1) ^b	Not serious	Not serious	++ Low

All studies used a 0- to 100-mm visual analog scale for pain assessment at 6 and 12 months postinjection.

Methodologic limitations: Limitations that result in downgrading include lack of blinding with subjective outcomes, lack of concealment, failure to use intention-to-treat analysis, large loss to follow-up, or early cessation of the study.

Consistency: If the widely different estimates of treatment effects (ie, heterogeneity) among studies cannot be explained, the quality of the evidence will be reduced.

Directness: The population, interventions, comparisons, and outcomes among studies should be similar; if there is a difference among studies, the quality rating will be downgraded.

Precision: In the absence of patients and events, the results provide no information and are therefore considered imprecise. The data are also inaccurate if no confidence intervals are reported or if they are so wide that the estimates are consistent with the conflicting recommendations.

^aLack of blinding with a subjective outcome.

^b $I^2 > 75\%$.

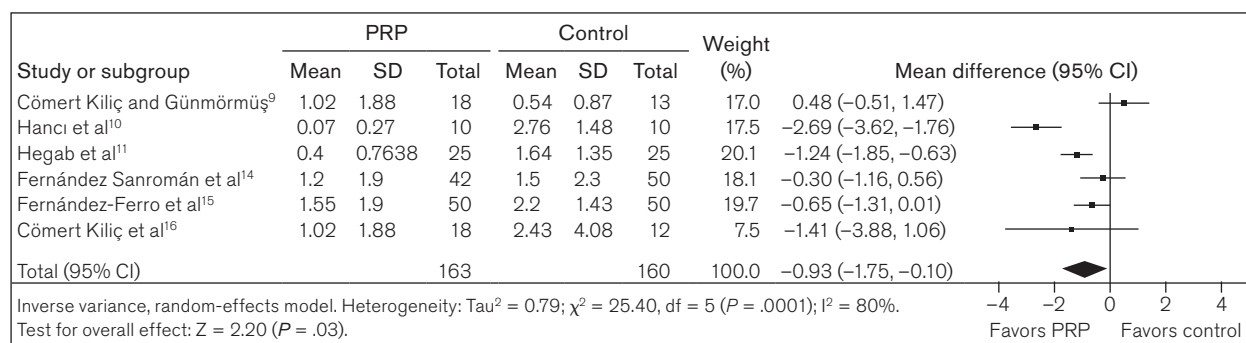


Fig 2 Forest plot of comparison of pain outcomes between PRP and control groups in all six included RCTs.

PRP assessment. In the three studies in which the control groups were treated with placebo,^{10,14,16} the pain scores from 6 and 12 months after PRP administration were pooled. The pooled estimates demonstrated a significant difference between the PRP and placebo groups at 6 months^{10,14} (MD -2.82, 95% CI -3.39 to -2.25, $P < .00001$; $I^2 = 0\%$) and 12 months^{14,16} (MD -3.29, 95% CI -4.07 to -2.52, $P < .00001$; $I^2 = 0\%$) (Fig 3a). In the three RCTs in which the control groups were treated with HA,^{9,11,15} pain scores from 12 months after PRP administration were pooled (no data were given for PRP vs HA at 6 months postinjection). The pooled estimates confirmed a significant difference between the PRP and HA groups at 12 months (MD -0.81, 95% CI -1.22 to -0.40, $P = .0001$; $I^2 = 76\%$) (Fig 3b). However, high heterogeneity was still present in this analysis and was likely related to the different types of PRP used in the three studies,^{9,11,15} as well as whether arthroscopic surgery was performed.

Complications

Of the six included studies, two^{10,11} reported complications after TMJ injection. Hancı et al¹⁰ noted that there was momentary swelling and pain on the day after injections. Hegab et al¹¹ evaluated pain during injection and discomfort after injection, and the results showed that the incidence of complications in the PRP group was significantly higher than in the control group ($P < .05$). However, the remaining four studies^{9,14-16} showed no significant complications during injection or follow-up.

Discussion

This systematic review and meta-analysis assessed the effect of PRP on pain reduction in TMJ OA, studied in six RCTs. A generally beneficial effect on pain reduction was found in favor of PRP injections compared to control treatments; however, the level of

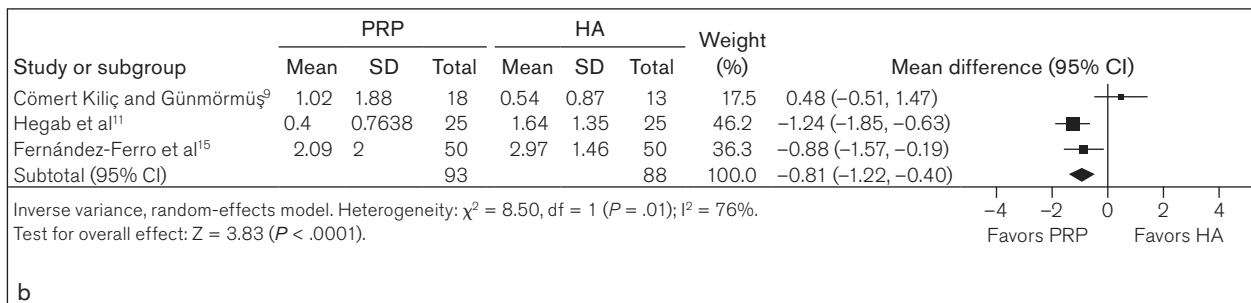
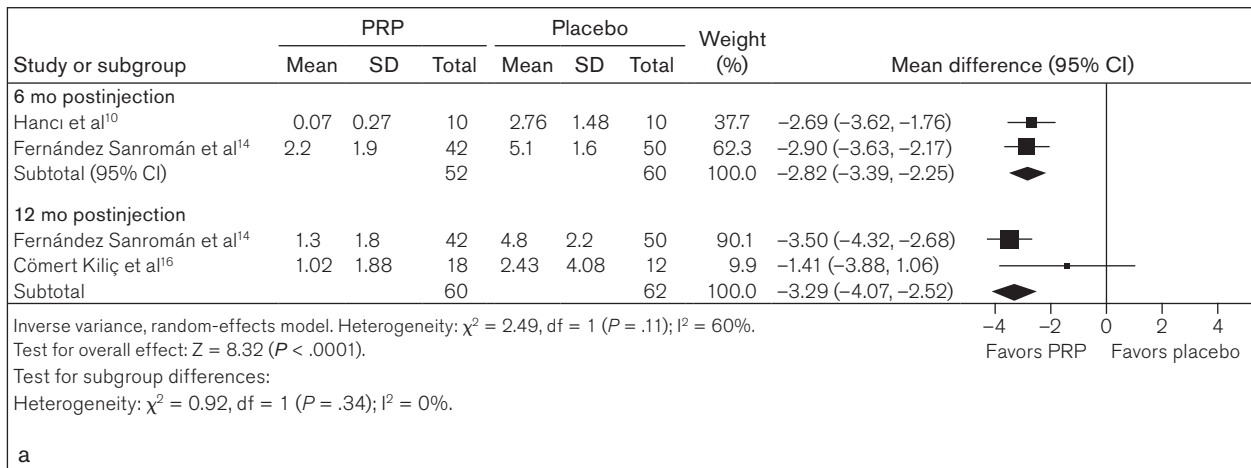


Fig 3 Forest plot of comparison of pain outcomes for (a) PRP vs placebo at 6 and 12 months postinjection and (b) PRP vs HA at 12 months postinjection.

evidence was limited to moderate or low. Three RCTs compared PRP to placebo, reporting data from 142 patients^{10,14,16} and showing evidence of a benefit in pain reduction at 6 months and 12 months postinjection. In comparisons between PRP injections and HA, a beneficial effect regarding pain reduction was found in favor of PRP at 12 months postinjection.^{9,11,15} The subgroup analyses could not provide evidence for pain reduction effects of PRP vs HA at 6 months postinjection due to lack of data.

The most common initial symptom of TMJ disorders is pain.¹⁸ Patients suffering from TMJ OA (including disc displacement with or without reduction) were included in this review, and the most common outcome measure across all six studies—VAS pain—was used. However, PRP injection not only has a role in pain relief, but also protects bone and cartilage.⁶ Of the six RCTs included, only two^{9,16} reported significant differences in reparative remodeling of TMJ bone tissue observed using CBCT (two-fold better reparative remodeling of osteoarthritis) compared to the control group. This finding requires a larger number of clinical studies and samples to confirm the effect of PRP injection on the condylar bone. The reference points of the TMJ injection were similar to the points used in arthroscopic examination (lateral

canthus-tragus). The entry point was located along the canthus–tragus line 10 mm from the middle of the tragus and 2 mm below the line.¹⁹ Some scholars believe that the relief of symptoms after intra-articular injection of PRP may be due to inflammatory regulation in the TMJ caused by removal of the inflammatory inducing factor and subsequent repair in the micro-environment of the articular disc, joint capsule, and double plate area.¹⁰

All RCTs presented performance bias due to the impossibility of blinded personnel, participants, and outcomes (Fig 4). This situation led to the downgrading of methodologic limitations in the GRADE quality assessment. When comparing PRP to HA, I^2 was greater than 75%, revealing the existence of heterogeneity, and the quality rating of consistency was subsequently downgraded.

Two RCTs^{14,15} studied PRP injections following arthroscopy. With arthroscopy, the procedures joint cavity lavage, lysis of pre-articular crypt adhesion, articular disc reduction, and joint capsule contraction could be performed under direct vision. Although the condylar bone of the TMJ was not changed due to arthroscopic surgery, the present authors believe that arthroscopic surgery to restore the articular disc before PRP injection was one of the sources of heterogeneity. At the

same time, whether exogenous activators should be added to PRP and whether PRP after centrifugation should contain white blood cells are currently controversial topics. Some authors believe that white blood cells are the source of cytokines and play a positive role in preventing infection,²⁰ while others believe that PRP without leukocytes is more conducive for bone regeneration.²¹ Some animal experiments in New Zealand white rabbits have also proven that PRP-containing leukocytes should not be used for the treatment of chronic inflammation or chronic degenerative fascial damage.^{22,23} The PRP used by the six RCTs was classified according to the Mishra classification system. The preparation method for PRP used in each study, the PRP content, whether the PRP was activated, and the amount and frequency of injection were different, and these factors were considered to be the main sources of heterogeneity. Although many studies showed that the injection of PRP into the TMJ was safe, Hancı et al¹⁰ reported that PRP had a higher complication incidence rate than HA. Moreover, the cost of PRP was approximately 1.5 times higher than that of HA.

Conclusions

Based on current evidence, PRP injections might be effective in reducing pain in TMJ OA. However, the safety and clinical feasibility of PRP still need further research to be confirmed. Larger, randomized, high-quality, low-bias studies are needed to test whether PRP injection should be a routine part of pain management in patients with TMJ OA.

Acknowledgments

L.F.L. and W.C.B. participated in the design of this study; L.F.L. and S.H.J. carried out the literature search, data acquisition, and data analysis; L.F.L. drafted the manuscript; and Z.Q. performed the manuscript review. All authors have read and approved the content of the manuscript. The authors report no conflicts of interest.

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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (detection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other
Cömert Kiliç and Güngörmüş ⁹	+	+	-	-	+	+	+
Hancı et al ¹⁰	+	+	-	-	+	+	+
Hegab et al ¹¹	+	+	?	-	+	+	+
Fernández Sanromán et al ¹⁴	+	+	?	-	+	+	+
Fernández-Ferro et al ¹⁵	+	+	?	-	+	+	+
Cömert Kiliç et al ¹⁶	+	+	-	-	+	+	+

Fig 4 Risk of bias summary. + = low; - = high; ? = unclear.

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