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Effect of platelet-rich plasma on meniscus repair surgery

A meta-analysis of randomized controlled trials

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Abstract

Background: Studies have shown that platelet-rich plasma (PRP) can enhance the effect of meniscus repair, but some studies have suggested different views on the role of PRP. Therefore, a meta-analysis was conducted to determine whether PRP can enhance the effect of meniscus repair with respect to pain reduction and improved functionality and cure rate in patients with meniscus injury.

Methods: PubMed, EMBASE, Cochrane Library Databases, clinicaltrials.gov, and the CNKI Database were searched from their inception till December 1, 2020. The RCTs reporting the outcomes of the Pain Visual Analog Scale (VAS), Lysholm score, healing rate, and adverse events were included. The risk of bias was assessed using Cochrane collaborative tools. The simulated results were expressed with effect size and 95% confidence interval, and sensitivity and subgroup analysis were performed.

Results: The meta-analysis included 8 RCTs and 431 participants. Compared with the control group, use of PRP during meniscus surgery significantly improved the VAS (SMD: –0.40, *P* = .002, 95%CI: –0.66 to –0.15) and Lysholm score (MD: 3.06, *P* < .0001, 95%CI: 1.70–4.42) of meniscus injury, but the PRP showed no benefit in improving the healing rate of meniscus repair (RR: 1.22, *P* = .06, 95%CI: 0.99–1.51). No serious adverse events were reported in any study.

Conclusions: PRP is safe and effective in improving the effect of meniscus repair as augment. High quality RCTs with long follow-up and definitive results are needed in the future to confirm the use and efficacy of PRP in meniscus tears.

Abbreviations: CI = confidence intervals, MD = mean difference, MRI = magnetic resonance imaging, PRP = platelet-rich plasma, RCTs = randomized controlled trials, RR = risk ratio, SMD = standard mean difference, VAS = visual analogue scale.

Keywords: augmentation, meniscus injury, meniscus repair, platelet-rich plasma

1. Introduction

The meniscus, an important structure of the knee joint, is located between the tibia and the femoral condyle. Its functions include transferring load and stabilizing the knee joint.[1] Meniscus injury is a common disease of the knee joint and often leads to knee joint dysfunction, swelling, pain, bounce, etc, which affect the knee function and quality of life of patients.[2] According to reports, nearly 4 million patients worldwide undergo arthroscopic meniscus surgery every year.[3]

Total or partial meniscectomy is 1 method of treating meniscus injuries. However, 1 fatal disadvantage of this technique is that it reduces the tissue of the meniscus, which can increase knee contact stress and decrease knee joint stability.[4,5] In recent years, multiple randomized controlled trials (RCTs) have shown that In recent years, several randomized controlled trials have shown that there is no additional benefit to meniscectomy compared to sham surgery, so surgeons should try to preserve meniscus as much as possible rather than remove it.[6–8] Due to the presence of the avascular zone in the meniscus, meniscus repair can preserve meniscus tissue but still not restore the anatomy and function of the meniscus.[9] Interestingly, a large number of studies have evaluated the potential of augments to promote meniscus repair.[10–13] Platelet-rich plasma (PRP), as a kind of the augments, contains a variety of proteins and cytokines, such as platelet-derived growth factor, vascular endothelial growth factor and fibrinogen, which increase meniscus activity and

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promote cartilage precursor cell adhesion and revascularization, thereby safeguarding tissue repair.[14,15] PRP has been applied extensively to treat muscle, ligament, tendon and cartilage based disorders.[16] Previous studies have shown that PRP combined with surgery could enhance the effect of meniscus repair and no adverse events were reported.[13,17–23] However, some studies are still controversial about some clinical outcomes such as the visual analogue scale (VAS), Lysholm score, and healing rate.[18,19,23–25] Current evidence suggests that the ability of PRP to promote meniscus repair may not be as strong as previously thought.[26,27]

Therefore, a meta-analysis of RCTs of patients with meniscus tears undergoing meniscus repair combined with PRP versus meniscus surgery alone was conducted to assess the safety and efficacy of PRP-enhanced meniscus repair and to provide evidence-based decisions for clinical application.

2. Methods

This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA-P).[28] Ethical approval is not required for this study, as it relies on secondary data.

2.1. Literature search and data extraction

PubMed, EMBASE, Cochrane Library Databases, clinicaltrials.gov, and the CNKI Database were searched from their inception till December 1, 2020, with the following string: (platelet-rich plasma)AND(meniscus). References in the relevant literature were reviewed as well, to find additional relevant studies to increase the outputs. There were no language restrictions.

All of the search and included studies were conducted by 2 independent reviewers.If there was any objection, the third reviewer made the final decision.The following data were extracted from the final included research: research title (first author name and publication date), participants (sample size), sex ratio, age range of participants, follow-up time, meniscus injury degree, surgical procedure, evaluation indicators, and effect values.

2.2. Inclusion criteria

Studies meeting the following criteria were included: (1) RCTs; (2) Comparison of the efficacy of meniscus repair combined with PRP versus meniscus repair alone in the treatment of meniscus injuries; (3) Studies of using PRP only during meniscus repair; (4) Studies with a follow-up time > 6 months. The exclusion criteria for this study were as follows: (1) Studies of using PRP after surgery; (2) nonRCTs; (3) redundant report.

If data were repeated or shared in multiple studies, the study that best met the above criteria were considered. All published or unpublished studies were found. If the necessary information could not be obtained from the publication, the authors were contacted to obtain the details.

2.3. Types of outcome measures

The primary outcomes included the VAS at the end of the follow-up, and the secondary outcomes were the Lysholm scores at the 6-month follow-up.The Healing rate was recorded at 24 to 33 weeks' follow-up. We also evaluated the adverse reactions of applying PRP in meniscus repair.

2.4. Risk of bias assessment

Two authors independently assessed the methodological quality of the included studies. Any disagreements were resolved through discussions with a third reviewer. Each RCT used Cochrane collaborative tools to assess the risk of bias, including the following criteria: adequacy of sequence generation, concealment of allocation, blinding of participants and personnel, blinding of result evaluators, incomplete results' data, selective reporting, and other biases.[29,30]

2.5. Statistical analyses

All statistical analyses were performed using methods published by Cochrane, with overlapping confidence intervals and chi-square tests to test for heterogeneity of outcome results of included studies. Fixed-effect model was used when there was no heterogeneity, but when there was heterogeneity, a random-effect model was used. This meta-analysis utilized risk ratio (RR) to assess dichotomous outcomes and calculated 95% confidence intervals (CIs) as the effect size.

If substantial heterogeneity was detected ($I^2 > 50\%$), subgroup analysis or sensitivity analysis would be further performed to determine the source of heterogeneity (e.g., dosage and preparation of PRP, location of the research institution, average age of the participants, different regions and study quality, and the length and severity of the meniscus injury).

3. Results

Eight studies[17–19,23,24,31–33] met the inclusion criteria (Fig. 1). Initially, 199 articles were identified after before-mentioned search strategy, and no articles were retrieved when searching other sources. According to the inclusion and exclusion criteria, 35 duplicate articles were excluded first, subsequently 150 articles that did not meet the criteria based on the inclusion and exclusion criteria were excluded. Finally, after viewing the full text of the 14 remaining articles, 6 studies were excluded due to the use of PRP after meniscus repair and nonRCT design.

3.1. Study characteristics

The 8 RCTs included had a total of 431 participants aged 19 to 75 years (PRP, n = 217; nonPRP, n = 214). There was no difference between the PRP and nonPRP groups at baseline. Six studies[18,19,24,31–33] were performed in China and the remaining 2 were from America.[17,23]The average follow-up time of the included studies range from 6 to 42 months. Two studies by Kaminski et al had the longest follow-up time of 23 months[23] and 42 months,[17] respectively. The degrees of meniscus injury were assessed by magnetic resonance imaging (MRI) before treatment in all studies. Four studies[18,19,31,32] utilized the Stoller level to evaluate the degree of meniscus injury and included participants with meniscus injury of Stoller level II or above, and the other 4 studies[17,23,24,33] included participants with meniscus tear diagnosed by MRI. However, these included studies did not clearly state whether participants had degenerative meniscus tears or acute meniscus injuries. After examining the details of the type of meniscus repair in all studies and found that 4 studies[17,18,23,31] used FasT-Fix or Outside-in Suture to suture the meniscus; 2 studies[19,32] only repaired the meniscus without suturing the meniscus and the remaining studies[24,33] did not mention details of meniscus repair. The results of all included studies at least 2 of the following 3 items: VAS, Lysholm score, and healing rate (Table 1).

The preparation process of PRP varied slightly among the included studies. Only 2 studies[17,23] mentioned that the type of PRP was Leukocyte-Poor platelet-poor plasma (LP-PRP). No studies described the amount of platelets in the PRP. All studies used PRP during meniscus repair surgery.

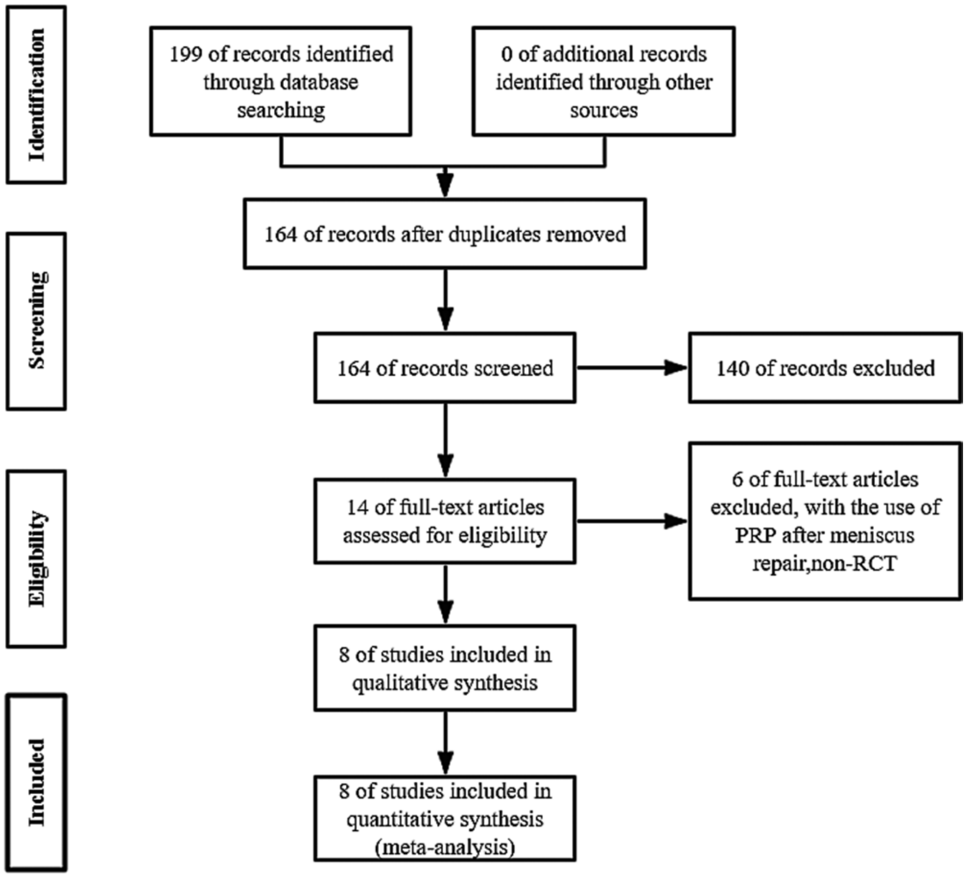


Figure 1. PRISMA flowchart of the study selection process. PRP, platelet-rich plasma.

3.2. Risk of bias

Figures 2 and 3 showed the results of the risk of bias for the all included studies. All studies had some methodological strengths and limitations. Most studies had a high risk of selection bias, except for the studies by Kaminski et al[17,23] and Liu et al,[18] because these trials were not clearly described in terms of allocation concealment. Performance bias was a high risk in 2 studies in which the surgeons were aware of the grouping of participants.[19,33] Except for He et al,[31] other studies showed low risk of detection bias. Of all studies, only Liu et al[18] performed a high risk of attrition bias and reporting bias.

The number of studies included in this meta-analysis was small, therefore, funnel plots could not be used to assess publication bias. However, this did not mean that this meta-analysis was free from publication bias.

3.3. VAS

Five articles[17,19,23,24,32] evaluated VAS from 6 months to 42 months after surgery (Fig. 4), which included 250 participants, with 126 in the PRP group and 124 in the control group. There was no significant heterogeneity among these studies (I^2 = 9%), so the fixed-effects model was used. The simulated result revealed that compared with the control group, intraoperative application of PRP could significantly decrease VAS of participants(standard mean difference [SMD]: –0.40, *P* = .002,95% CI: –0.66 to –0.15).

3.4. Lysholm scores

The Lysholm scale was commonly used as an assessment tool to reflect knee function. Six studies[18,19,23,31–33] evaluated Lysholm scores at 6 months of follow-up (Fig. 5), which included 322 participants, with 156 in the PRP group and 166 in the control group. There was significant heterogeneity among these studies (I^2 = 84%), so the random-effect model was used. The simulated result revealed that PRP group showed a higher improvement on Lysholm scores compared with control group(mean difference [MD]: 4.86, *P* = .0009, 95%CI: 1.98–7.75).

Considering the presence of significant heterogeneity, a sensitivity analysis subsequently was performed. Analysis after excluding each trial in turn revealed heterogeneity originating from the study of Liu et al.[18] After exclusion of this study, the heterogeneity of 5 studies[19,24,31–33] became insignificant (I^2 = 15%). The simulated result revealed that PRP combined with surgery significantly enhanced knee joint function(MD: 3.06, *P* < .0001, 95%CI: 1.70–4.42) (Fig. 5).

3.5. Healing rate

Five studies[17,18,23,31,33] evaluated the healing rate at 24–33 weeks of follow-up (Fig. 6), which included 156 participants, with 134 in the PRP group and 132 in the control group. There was significant heterogeneity among these studies (I^2 = 66%), so the random-effect model was used. The simulated result revealed there was no significant difference on healing rate between groups(RR: 1.22, *P* = .06, 95%CI: 0.99–1.51).

Further, a subgroup based on the nationality was conducted. There was no obvious heterogeneity within the subgroups and subgroup analysis of China (I^2 = 34%, RR: 1.15, *P* = .01, 95%CI: 1.03–1.30) and American (I^2 = 0%, RR: 1.77, *P* = .01, 95%CI: 1.15–2.73) both showed that PRP combined with surgery showed significant efficacy than surgery alone (Fig. 7). This result indicated that nationality may be the source of heterogeneity.

Table 1

Studies on PPR combined with meniscus repair included in meta-analyses.

Reference	No. of patients		Basic date: M/F(n)		Basic date: age						
Lead author (year)	PRP	NonPRP	PRP	NonPRP	PRP	NonPRP	Follow-up (mo)	Meniscus injury degree by MRI	Types of menisci treated	Outcome measure	*P* value
He (2015)[31]	14	14	NR	NR	31.6 (19–40)	31.6 (19–40)	6	≥Stoller level II	FasT-Fix or Outside-in Suture	1.Lysholm 2.Healing rate	1.$P > .05$ 2.NR
Kaminski (2018)[23]	19	18	15/3	15/3	30 (18–43)	26 (19–44)	42	1.Complete vertical longitudinal tear > 10 mm in length on MRI 2.Unstable peripheral tear	FasT-Fix or Outside-in Suture	1.Healing rate 2.VAS	1.$P = .048$ 2.$P = .15$
Li (2019)[19]	20	20	4/16	5/15	62 (50–74)	64 (52–75)	6	= Stoller level III	Only repair the meniscus without suturing the meniscus	1.Lysholm 2.VAS	1.$P<.05$ 2.$P<.05$
Kaminski (2019)[17]	42	30	22/20	19/11	44 (18–67)	46 (27–68)	23	1.Chronic horizontal tears on MRI 2.Tear located in the vascular or avascular portion of the meniscus 3.Single tear of the medial and/or lateral meniscus	FasT-Fix or Outside-in Suture	1.Healing rate 2.VAS	1.$P = .04$ 2.$P = .39$
Liu (2019)[18]	40	40	NR	NR	34.7 (NR)	34.7 (NR)	6	≥Stoller level II	FasT-Fix or Outside-in Suture	1.Healing rate 2.Lysholm	1.$P = .009$ 2.$P = .001$
Zhou (2019)[24]	24	34	14/10	12/22	64.1 (NR)	64.3 (NR)	12	Meniscus tear visible under MRI	NR	1.Lysholm 2.VAS	1.$P = .007$ 2.$P = .163$
Shi (2020)[33]	34	34	24/10	22/12	49 (NR)	49 (NR)	6	Meniscus tear visible under MRI	NR	1.Lysholm 2.Healing rate	1.$P < .05$ 2.NR
Wu (2020)[32]	24	24	10/14	9/15	71.3 (60–75)	69.3 (61–73)	6	= Stoller level III	Only repair the meniscus without suturing the meniscus	1.Lysholm 2.VAS	1.$P < .01$ 2.$P < .05$

Values are expressed as mean with range or SD.

F = female, M = male, PRP = platelet-rich plasma, VAS = the visual analogue scale.

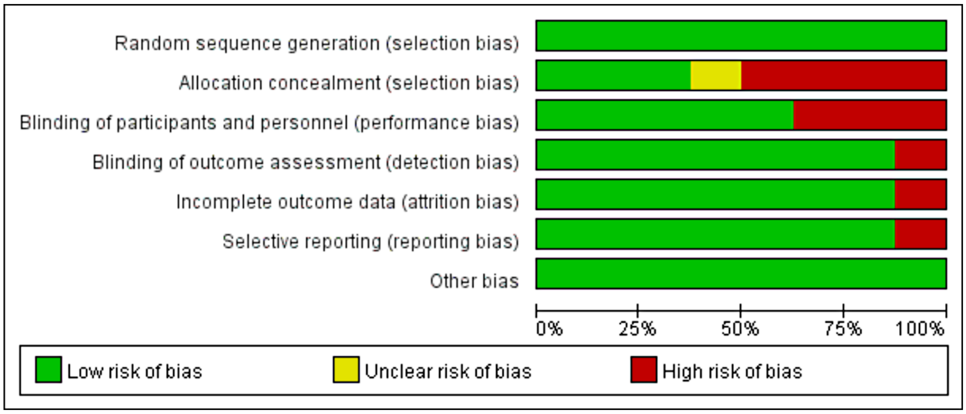


Figure 2. Assessment of the risk of bias.

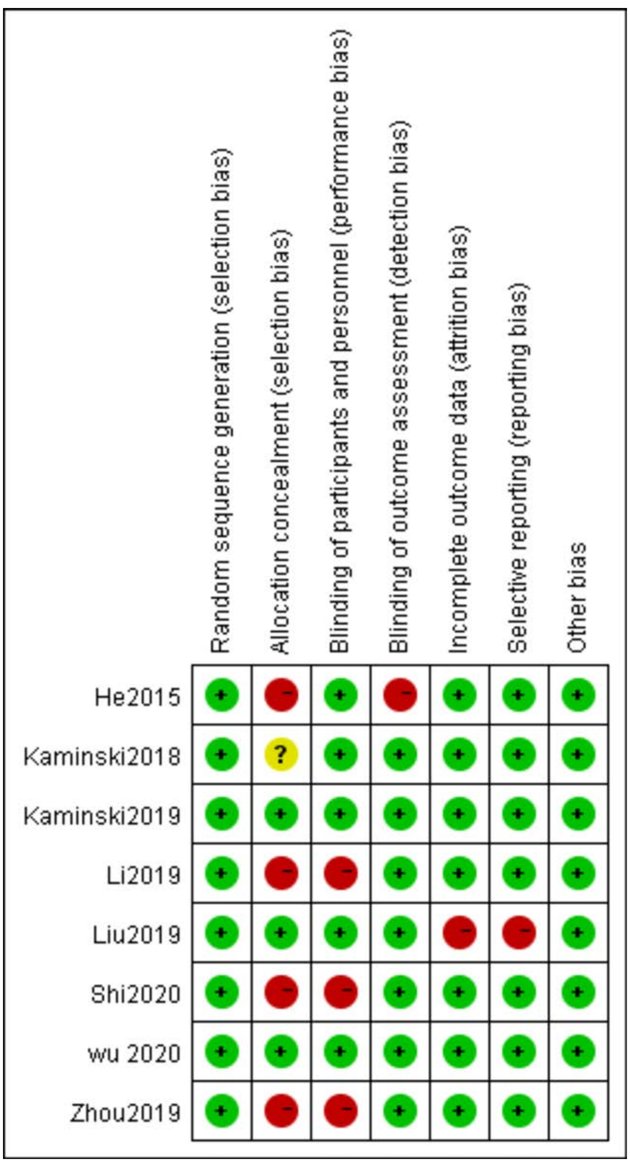


Figure 3. Distribution of each type of bias.

3.6. Adverse reactions

Only 1 study reported adverse events.[19] During the study, 2 participants presented with mild postoperative joint swelling and pain with restricted movement, and the above symptoms were eliminated after 3 days of local ice, restricted movement, and oral analgesia. Unfortunately, this study did not clarify how these adverse events were determined.

4. Discussion

Based on the simulated results of 8 studies, the application of PRP in meniscus injury repair had a positive impact on VAS scores, Lysholm scores and healing rate. Meanwhile, all included participants were well-tolerated to PRP.

PRP, a concentrated platelet obtained by centrifugation of peripheral blood, consists mainly of platelet-associated leukocyte aggregation, high-density fibrous network structures, platelet-derived growth factors, transforming growth factor-beta, insulin-like growth factor, epidermal growth factor and vascular endothelial growth factor.[34,35] PRP releases a large number of growth factors to promote cell proliferation and regulate cell behavior and antiinflammatory factors to reduce local inflammation.[36] In recent years, its role in cartilage injury repair has drew increasing attention. Vitro study suggested that chondrocytes exhibit a significant dose- and time-dependent increase in cell number and metabolic cell activity in response to PRP.[37] In this meta-analysis, some studies[17,23,24] showed that PRP did not decrease the VAS score,which contradicts our simulated result. This might be related to the long-term follow-up of 12–42 months of these studies, but the follow-up time of the other studies[19,32] was 6 months, suggesting that PRP may have a limited effect in relieving long-term pain after meniscus repair. There was a significant heterogeneity in the Lysholm score, after sensitivity analysis to exclude 1 study,[18] simulated result showed that PRP improved Lysholm scores after meniscus repair. A full-text review of the Liu et al study revealed that sex ratio, mean age and random sequence generation were not reported between 2 groups, which may account for the high degree of heterogeneity between this study and the other studies. For healing rate, simulated result indicated that PRP combined with surgery could not improve the healing rate of meniscus repair with high heterogeneity. Therefore, a subgroup analysis based on the nationality was conducted and suggested that PRP could improve the healing rate in the subgroups without significant heterogeneity. The reasons for the differences in healing rates in the subgroup analysis may be related to the different types of PRP used and follow-up time in different countries. Previous articles have manifested that even small changes in the centrifugation setup could alter the content of each PRP component, which emphasizes the importance of describing the composition before using PRP products.[38] However, only 2 studies[17,23] verified PRP content by ELISA and hematology analyzer. The inconsistent levels of each component of PRP used across studies may be an important reason for the inconsistent outcome measures.

Study or Subgroup	PRP Mean	PRP SD	PRP Total	non-PRP Mean	non-PRP SD	non-PRP Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Kaminski2018	0.84	0.42	18	0.89	0.33	17	14.6%	-0.13 [-0.79, 0.53]	2018
Zhou2019	1.4	0.6	24	1.6	0.8	34	23.3%	-0.27 [-0.80, 0.25]	2019
Li2019	0.9	0.5	20	1.4	0.6	20	15.1%	-0.89 [-1.54, -0.23]	2019
Kaminski2019	1.97	0.32	40	2.05	0.43	29	28.0%	-0.21 [-0.69, 0.27]	2019
Wu2020	2.37	0.56	24	3.03	1.25	24	18.9%	-0.67 [-1.25, -0.09]	2020
Total (95% CI)			**126**			**124**	**100.0%**	**-0.40 [-0.66, -0.15]**	

Heterogeneity: Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 3.12 (P = 0.002)

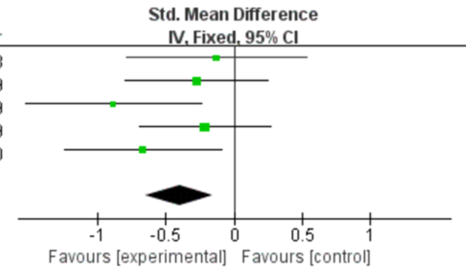
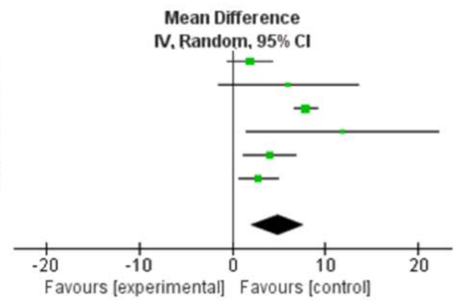


Figure 4. Forest plot for visual analogue scale (VAS).

Lysholm scores at 6 months

Study or Subgroup	PRP Mean	PRP SD	PRP Total	non-PRP Mean	non-PRP SD	non-PRP Total	Weight	Mean Difference IV, Random, 95% CI	Year
He2015	92.4	1.8	14	90.5	4.3	14	20.7%	1.90 [-0.54, 4.34]	2015
Li2019	93	14	20	87	10	20	9.1%	6.00 [-1.54, 13.54]	2019
Liu2019	94.5	3.1	40	86.6	2.7	40	23.2%	7.90 [6.63, 9.17]	2019
Zhou2019	77.5	19.8	24	65.6	19.9	34	5.9%	11.90 [1.53, 22.27]	2019
Shi2020	94	6	34	90	6	34	19.6%	4.00 [1.15, 6.85]	2020
Wu2020	84.05	2.43	24	81.23	4.71	24	21.5%	2.82 [0.70, 4.94]	2020
Total (95% CI)			**156**			**166**	**100.0%**	**4.86 [1.98, 7.75]**	

Heterogeneity: Tau² = 8.91; Chi² = 30.57, df = 5 (P < 0.0001); I² = 84%
Test for overall effect: Z = 3.31 (P = 0.0009)



After sensitivity analysis

Study or Subgroup	PRP Mean	PRP SD	PRP Total	non-PRP Mean	non-PRP SD	non-PRP Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
He2015	92.4	1.8	14	90.5	4.3	14	31.1%	1.90 [-0.54, 4.34]	2015
Li2019	93	14	20	87	10	20	3.3%	6.00 [-1.54, 13.54]	2019
Zhou2019	77.5	19.8	24	65.6	19.9	34	1.7%	11.90 [1.53, 22.27]	2019
Wu2020	84.05	2.43	24	81.23	4.71	24	41.2%	2.82 [0.70, 4.94]	2020
Shi2020	94	6	34	90	6	34	22.8%	4.00 [1.15, 6.85]	2020
Total (95% CI)			**116**			**126**	**100.0%**	**3.06 [1.70, 4.42]**	

Heterogeneity: Chi² = 4.71, df = 4 (P = 0.32); I² = 15%
Test for overall effect: Z = 4.41 (P < 0.0001)

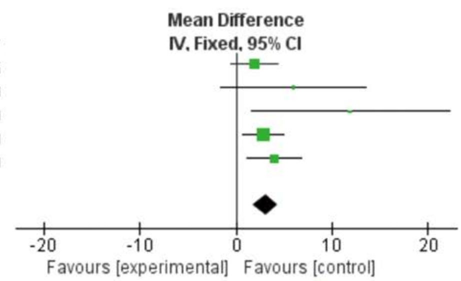


Figure 5. Forest plot for Lysholm scores at 6 months and after sensitivity analysis.

Study or Subgroup	PRP Events	PRP Total	non-PRP Events	non-PRP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
He Hanliang2015	13	14	13	14	26.8%	1.00 [0.81, 1.23]	2015
Rafal Kaminski2018	16	19	8	17	10.8%	1.79 [1.04, 3.07]	2018
Liu Jia2019	39	40	35	40	31.8%	1.11 [0.98, 1.27]	2019
Rafal Kaminski2019	14	27	8	27	7.5%	1.75 [0.88, 3.47]	2019
Shi Yuhui2020	30	34	23	34	23.1%	1.30 [1.00, 1.70]	2020
Total (95% CI)		**134**		**132**	**100.0%**	**1.22 [0.99, 1.51]**	
Total events	112		87				

Heterogeneity: Tau² = 0.03; Chi² = 11.73, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 1.86 (P = 0.06)

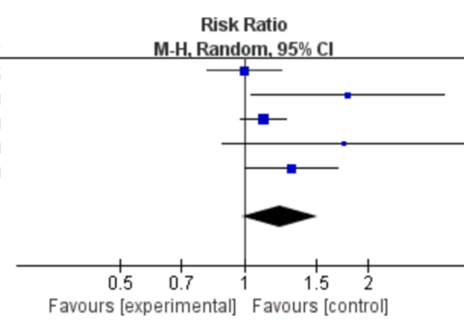


Figure 6. Forest plot of healing rate.

The cause of meniscus injuries is usually related to the age of the patient. The most common causes of meniscus tears and/or injuries in young and older patients are related to acute trauma and degenerative changes of the joint, respectively.[39] The red area of the meniscus is rich in blood vessels, and the abundant blood supply to the mesenchymal cells can induce healing of the meniscus.[40] In contrast, the white area is not covered by blood vessels and the healing of the meniscus depends on the repairability of its own tissue and is often difficult or impossible to heal.[41] meniscus repair has a 90% cure rate for injuries to the red region of the meniscus, but is not as effective for injuries to the white region.[42] In fact, in meniscus injuries, both regions are often torn at the same time. Different types of meniscus tears and different age levels result in different healing abilities. Also, different methods of meniscus repair result in varying degrees of meniscus motion and popliteal fossa tear size, leading to different biomechanics and kinematics of the lateral knee region, which in turn leads to different degrees of meniscus repair.[43] However, the studies in this meta-analysis did not directly refer to the age stratification of the participants, the areas of the meniscus tear, or the types of meniscus tear; in addition, the method of meniscus repair varied among these studies. Consequently, a broader subgroup analysis to elucidate the augmentation of PRP in different meniscus repair procedures could not be performed.

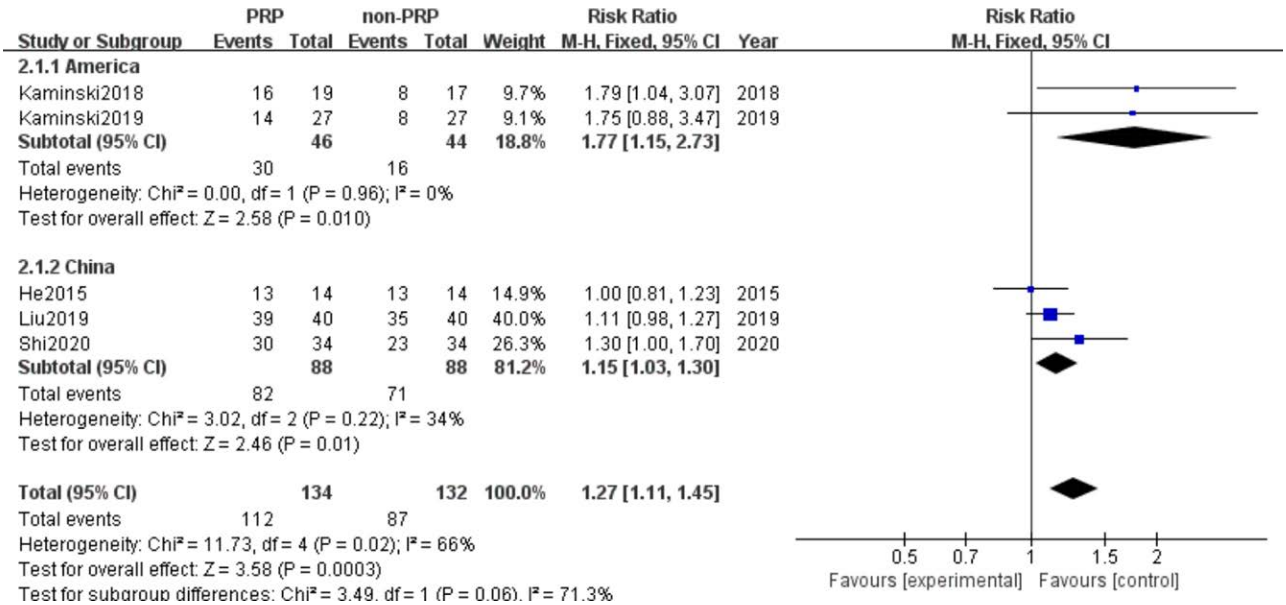


Figure 7. Forest plot of subgroup analysis of healing rate.

The function of the knee joint after meniscus repair requires long-term follow-up. Most studies generally choose a 6-month follow-up period, with few studies having a follow-up period of more than 12 months. This may also be the reason why the results of this meta-analysis differ from previous studies.[16,44] Based on the evidence in this study, PRP improved the ability of meniscus repair and no adverse events were reported, suggesting that PRP was generally well tolerated. Future clinical studies with multicentre, large samples and long-term follow-up are needed to more fully explore the effect of PRP as augmentation.

There were some limitations in this meta-analysis. First, potential confounding variables in the included studies, such as age, gender, cause and type of meniscus injury, type of meniscus tear, surgical procedure, method of PRP preparation and platelet content in PRP, have not been reported in detail. Secondly, all participants included in the study were American or Chinese and were not a true representation of patients with meniscus injuries worldwide; therefore, the conclusions drawn from the simulations need to be interpreted with caution.

5. Conclusions

This meta-analysis demonstrated that PRP is safe and effective in improving the effect of meniscus repair as augment. Due to the limited data analyzed in this study and poor methodological quality, the results should be interpreted with caution. High quality RCTs with long follow-up and definitive results are needed in the future to confirm the use and efficacy of PRP in meniscus tears.

Author contributions

Conceptualization: Yu-lei Xie.
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Supervision: Yu-lei Xie, Shan Wang.
Validation: Qing Wu.
Visualization: Yu-lei Xie.
Writing - original draft: Yu-lei Xie, An-li Hu.
Writing—review & editing: Shan Wang, Qing Wu, Hong Jiang.

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