Can platelet-rich plasma enhance the effect of meniscus repair?: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.

Purpose: 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: By searching PubMed, EMBASE, Cochrane Library databases, clinicaltrials.gov, and the CNKI database from their inception till December 1, 2020, we performed a meta-analysis of RCTs reporting the results of the Pain Visual Analog Scale (VAS), Lysholm score, healing rate, and adverse events. The risk of bias is assessed using Cochrane's collaborative tools. The summary results are expressed with effect size and 95% confidence interval, and sensitivity and subgroup analysis were performed.

Results: The meta-analysis included eight RCTs and 431 patients. In general, compared with the control group, use of PRP during meniscus surgery significantly improved the VAS (SMD: -0.40, P=0.002, 95%CI: -0.66 to -0.15) and Lysholm score (MD: 4.86, P=0.0009, 95%CI: 1.98–7.75) of patients with meniscus injury, but the PRP enhancement technique showed no benefit in improving the cure rate of meniscus repair (risk ratio [RR]: 1.22, P=0.06, 95%CI: 0.99–1.51). No serious adverse events were reported in any study.

Conclusion: PRP deserves further consideration as an enhancement program for meniscus repair. However, the evidence still needs to be interpreted carefully because of the quantity and quality of the included studies.

Introduction

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

Meniscus or partial meniscus resection is a method of treatment for meniscus injuries. However, this technique has a fatal disadvantage, in that it will reduce the tissue of the meniscus, which increases knee contact pressure and decreases knee joint stability[4–5]. In recent years, several randomized controlled trials (RCTs) have shown that meniscus resection has no additional benefit to sham surgery, so surgeons should preserve meniscus damage as much as possible instead of removing the meniscus[6–8]. Owing to the presence of the avascular area of the meniscus, meniscus repair can preserve the meniscus tissue as much as possible but still cannot restore the anatomy and function of the meniscus after repair[9]. Therefore, multiple studies have evaluated the potential of certain augments such as the extracellular matrix, fibrin, hyaline, and growth factors to enhance meniscus repair[10–13]. Recently, many studies have shown that adding platelet-rich plasma (PRP) during surgery can enhance the effect of meniscus repair[14–20]. However, some studies are still controversial regarding some clinical outcomes such as the visual analogue scale (VAS), Lysholm score, and healing rate[19–23]. Current evidence indicates that PRP may not be as strong as previously thought[24–25].

In this study, we conducted a meta-analysis of RCTs that compared meniscus repair combined with PRP versus only meniscus surgery in patients with meniscus tears, evaluated the safety and effectiveness of this technology to enhance meniscus repair, and provided evidence-based decisions for clinical applications.

Methods

Literature search and Data extraction

We searched PubMed, EMBASE, Cochrane Library databases, clinicaltrials.gov, and the CNKI database from their inception till December 1, 2020 for RCTs. The following string was used: (platelet rich plasma) AND (meniscus). We also checked the references of related articles to identify additional relevant research to increase the output of related studies. No language restrictions were employed.

All searches and included studies were conducted by two 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 treatment, evaluation indicators, and effect values.

Criteria for considering studies

Clinical studies that meet the following criteria were included: (1) RCTs; (2) compared the use of meniscus repair combined with PRP therapy versus only meniscus repair in patients with a meniscus injury; (3) only those studies that used PRP during meniscus repair but not after surgery; and (4) the studies had a follow-up period of > 6 months.

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 investigated. If the information required for the analysis could not be obtained from the publication, the author was contacted to obtain the necessary details.

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 24–33 weeks' follow-up. We also evaluated the adverse reactions of applying PRP in meniscus repair.

Risk of bias assessment

Two review authors independently assessed the methodological quality of the included studies. We recorded and resolved any disagreements through discussions with a third reviewer. Each RCT used Cochrane's 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[26–27].

Statistical analyses

All statistical analysis used the methods released by Cochrane, and the heterogeneity of different research results were tested by overlap of confidence intervals and chi-square tests. When there was no heterogeneity in the test results, fixed effects model was used for the meta-analysis, and when the test results were heterogeneous, the random effects model was used. For enumeration data, the risk ratio (RR) was used as the statistical tool for the efficacy analysis, and 95% confidence intervals (CIs) were used for the effect size.

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

Results

We identified eight studies[18–21, 23, 28–30] that met the inclusion criteria (Fig. 1). Initially, 199 articles were identified by searching the databases, and no articles were retrieved by searching other sources. According to the inclusion and exclusion criteria, we first excluded 35 duplicate articles, followed by 150 articles that did not meet the inclusion criteria. Finally, we checked the full text of the 14 remaining articles and excluded six for reasons being the use of PRP after meniscus repair and non-RCT design.

Study Characteristics

The eight included RCTs for in the meta-analysis had a total of 431 participants aged 19–75 years (PRP, n = 217; non-PRP, n = 214). There was no difference in baseline between the PRP and non-PRP groups. Six studies[19–21, 28–30] were performed in China and the remaining two were from America [18, 23]. The average follow-up period of the included study was 6–42 months. The two studies by Kaminski et al. had the longest follow-up times, namely 23 months [23] and 42 months[18], respectively. In all studies, the degree of meniscus injury of the participants was assessed by magnetic resonance imaging (MRI) before treatment. Four studies[19–20, 28–29] used the Stoller level to evaluate the degree of meniscus injury. Participants with a meniscus injury of Stoller level II or above were included in the study, and the other four studies[18, 21, 23, 30] included participants with meniscus tear under MRI. However, these studies did not clearly indicate whether the participants had acute meniscal injuries or degenerative meniscal tears. We checked the details on the types of meniscus repairs for all studies and found that four studies[18–19, 23, 28] sutured the meniscus using FasT-Fix or Outside-in Suture; two studies[20, 29] only repaired the meniscus without suturing the meniscus; and the remaining studies[21, 30] did not mention the details of meniscus repair. The results of all studies included at least two of the VAS, Lysholm score, and healing rate (Table 1).

Table1.Studies on PPR combined with meniscus repair included in meta-analysesa

Reference	No. of Patients		Basic date:M/F(n)		Basic date:Age		Follow-up (month)	Outcome measure	P value
Lead Author (Year)	PRP	Non-PRP	PRP	Non-PRP	PRP	Non-PRP			
He(2015)	14	14	NR	NR	31.6(19-40)	31.6(19-40)	6	1.Lysholm 2.Healing rate	1.P>0.05 2.NR
Kaminski(2018)	19	18	15/3	15/3	30(18-43)	26(19-44)	42	1.Healing rate 2.VAS	1.P=0.048 2.P=0.15
Li(2019)	20	20	4/16	5/15	62(50-74)	64(52-75)	6	1.Lysholm 2.VAS	1.P□0.05 2.P□0.05
Kaminski(2019)	42	30	22/20	19/11	44(18-67)	46(27-68)	23	1.Healing rate 2.VAS	1.P=0.04 2.P=0.39
Liu(2019)	40	40	NR	NR	34.7(NR)	34.7(NR)	6	1.Healing rate 2.Lysholm	1.P=0.009 2.P=0.001
Zhou(2019)	24	34	14/10	12/22	64.1(NR)	64.3(NR)	12	1.Lysholm 2.VAS	1.P=0.007 2.P=0.163
Shi(2020)	34	34	24/10	22/12	49(NR)	49(NR)	6	1.Lysholm 2.Healing rate	1.P□0.05 2.NR
Wu□2020□	24	24	10/14	9/15	71.3(60-75)	69.3(61-73)	6	1.Lysholm 2.VAS	1.P□0.01 2.P□0.05

[a] F, female;M, male;PRP, platelet-rich plasma;VAS,the visual analogue scale;Values are expressed as mean with range or SD.

The preparation process of PRP was slightly different in the included studies. Only two studies[18, 23] mentioned that the type of PRP used was leukocyte- or PRP. No study described the content of platelets in PRP. All studies used PRP in meniscus repair surgery, and no study used PRP after surgery.

Risk of bias

Figures 2 and 3 present the results of the risk of bias graph of all eight RCTs. All included trials had some methodological advantages and limitations. Most studies had a high risk of selection bias, except for Kaminski et al's study, which had a low risk of bias for random sequence generation. Except for the studies by Kaminski et al.[18, 23], most studies had a high risk of selection bias, because these trials were not explicitly described in allocation concealment. In the two studies[20, 30], the surgeons knew the grouping of participants, and performance bias was a high risk. The detection bias of most studies showed low risk except for that by He et al. Among all the studies, only study by Liu et al[19] showed the high risk of attrition bias and reporting bias.

The meta-analysis included in the number of studies is very small, and we could not use funnel plots to assess publication bias. Therefore, publication bias could not be completely eliminated.

VAS

A pooled analysis of five articles[18, 20–21, 23, 29] had evaluated VAS from 6 months to 42 months after surgery (Fig. 4). There were 250 patients, 126 in the PRP group and 124 in the control group. There was no significant heterogeneity in any study (I^2 = 9%), so the fixed effects model was used. The statistical difference was conducive to PRP enhancement (standard mean difference [SMD]: -0.40, P = 0.002, 95% CI: -0.66 to -0.15).

Lysholm scores

A pooled analysis of six studies[19–21, 28–30] had evaluated Lysholm scores at 6 months of follow-up (Fig. 5). There were 322 patients in these studies, 156 in the PRP group and 166 in the control group. There was significant heterogeneity in all studies (I^2 = 84%), so the random effects model was used. The statistical difference was conducive to PRP enhancement (mean difference [MD]: 4.86, P = 0.0009, 95%CI: 1.98–7.75).

Therefore, taking into account the obvious heterogeneity, we conducted a sensitivity analysis that excluded every trial in turn, and the analysis revealed that the heterogeneity originated from the study of Liu et al.[19] After excluding this study, five studies[20–21, 28–30] were re-incorporated (Fig. 6). There was no significant heterogeneity in all studies (I^2 = 15%), so the fixed effects model was used. The statistical difference remained the same as before the sensitivity analysis, which was conducive to PRP enhancement (MD: 3.06, P < 0.0001, 95%CI: 1.70–4.42).

Healing rate

In a pooled analysis of five studies[18–19, 23, 28, 30] that had evaluated the healing rate at 24–33 weeks' follow-up (Fig. 6), there were 156 patients in all, with 134 in the PRP group and 132 in the control group. There was significant heterogeneity in all studies (I^2 = 66%), so the random-effects model was used. In the 24–33 weeks of follow-up, compared with the control group, the PRP enhancement technique showed no benefit in improving the cure rate of meniscus repair

A subgroup analysis of American versus Chinese studies revealed a significant benefit of using PRP in meniscus repair (Fig. 7). The test for subgroup differences attained significance, indicating that countries may be the source of heterogeneity. Both subgroups showed significant effectiveness of PRP in improving the symptoms of meniscus injury, and there was no obvious heterogeneity within the subgroups (America/China: RR, 1.77/1.15; P = 0.01/0.01).

Adverse reactions

Adverse events were reported in only one study[20]. During the treatment, two patients developed mild postoperative joint swelling and pain and limited mobility, which were eliminated within 3 days after local ice compress, restricted mobility, and oral analgesics. Unfortunately, this study did not indicate how these adverse events were determined.

Discussion

Based on eight RCTs conducted in America and China, the application of PRP in meniscus repair might have a positive effect on patients' VAS, Lysholm score, and the healing rate. However, these results should be interpreted carefully. We only included randomized, placebo-controlled trials. Most studies had explained their randomization methods, and only a few studies had explained allocation concealment methods. The experiments reported varying results. Most studies reported were adequate. There were a small number of cases where there was no standard deviation or graphic representation. There was significant heterogeneity in a part of our analysis, and we therefore used sensitivity analysis or subgroup analysis to address this concern.

Some studies[18, 21, 23] have shown that PRP cannot reduce the VAS score after meniscus repair, although our meta-analysis demonstrates that this was effective. This might be linked to the long follow-up events of these studies (12–42 months), while the follow-up time of the other two studies[20, 29] was 6 months, indicating that PRP may have a limited effect on alleviating long-term pain after meniscus repair. There was significant heterogeneity in the Lysholm score after the sensitivity analysis; the pooled analysis, after excluding a study[19], still suggested that PRP could improve the Lysholm score after meniscus repair. Analysis of the full text of Liu et al's study[19] showed that the sex ratio, mean age, and random sequence generation between the two groups were not reported, which might be the reason for the high heterogeneity between this and other studies. In general, PRP could not further improve the healing rate of patients after meniscus repair, but due to the high heterogeneity of the included studies, we conducted a subgroup analysis and compared studies in America and China. We found that PRP could increase the healing rate in the subgroups, and there was also significant clinical heterogeneity between the subgroups. The reason for the above difference in healing rate in the subgroup analysis is likely related to the different follow-up time and types of PRP used in different countries. A few trials have adverse events and found that there may be no difference in the incidence of adverse events between participants receiving and not receiving PRP treatment.

All participants in the included studies were either American or Chinese; thus, this review is limited to representing the Chinese or American population. Many potentially confounding variables such as the age, sex, cause and of meniscus injury, categories of meniscus tear, surgical approach, and platelet content in PRP had not been reported in detail. Routine postoperative treatment varies by research included active/passive activities and weight training, among others.

The cause of meniscus tear is often related to the patient's age. The most common cause of meniscus tear and/or deterioration in young and elderly patients is typically related to acute trauma to the joints and degenerative changes, respectively[31]. Due to the uniqueness of the meniscus structure, there are two different mechanisms for the healing of injuries. In the red area of the meniscus (vascular area), the abundant blood supply provides nutrients for mesenchymal cells to induce healing[32]. In the white area (avascular area), the healing of the meniscus depends on its own tissue repairability, which leads to difficult healing or even non-healing[33]. Meniscus repair is effective in treating meniscus injuries in the red area, with a healing rate as high as 90%, but it has a poor effect on injuries in the white area[34]. In

young men with meniscus injuries, there are often simultaneous tears in two areas. Different types of meniscus tears and age-related causes of meniscus tears can lead to different healing abilities. At the same time, different meniscus repair methods have different repair capabilities. The all-inside meniscus repair systems are safer, faster, and more convenient and hence, more popular than other meniscus repair systems such as meniscus arrows, Fast-Fix, and RAPIDLOC meniscus repair[35]. In addition, different repair methods result in different movement of meniscus and sizes of popliteal hiatus, which further leads to different biomechanics and kinematics of the lateral knee joint compartment. However, the research included in this meta-analysis did not directly mention the age stratification of the participants, area of the meniscus where the tear was located, and the type of meniscus tear; furthermore, the meniscus repair methods used were also different. Therefore, more extensive subgroup analysis could not be performed to clarify the enhancement ability of PRP on different meniscus repair procedures; moreover, it was also not possible to judge whether PRP is age-related or tear type-related for enhanced meniscus repair procedures.

PRP is a platelet concentration obtained after centrifugation of peripheral blood, and its role in the repair of cartilage damage has gradually attracted attention in recent years. PRP mainly includes platelet-related leukocyte aggregates, high-density fibrous network structure, platelet-derived growth factor, transforming growth factor-β, insulin-like growth factor, epidermal growth factor, and vascular endothelial growth factor[36–37]. PRP can release a large number of anti-inflammatory factors to reduce local inflammation and can release a variety of growth factors to promote cell proliferation and regulate cell behavior[38]. In vitro studies have shown that chondrocytes and PRP exhibit a significant dose- and time-dependent increase in cell number and metabolic cell activity[39]. It has already been shown that even small variation in centrifugation settings can alter the content of the PRP product, which underlines the importance to describe the ingredients before applying PRP product[40]. However, only two studies[18, 23] verified the PRP contents by using enzyme-linked immunosorbent assays and blood analyzers. The PRP content used in various studies is inconsistent, which may be an important reason for the inconsistent clinical results. Thus, future studies should not only be carried out in a randomized placebo-controlled fashion but also characterize the applied PRP product to compare results revealed in different studies.

The recovery of knee joint function after meniscus repair requires long-term follow-up. Most studies generally chose a follow-up period of 6 months, and only some studies had a follow-up period of more than 12 months. This may also be the reason for the difference between the results of this review and previous studies[41–42]. According to the evidence in this review, PRP enhances the meniscus, and no side effects were reported, which indicates that PRP is generally well tolerated. However, we cannot draw conclusions about the safety of PRP based on limited data. Further multi-center, large-sample, and long-term follow-up clinical studies are needed to address these questions.

Future trials of PRP-enhanced meniscus repair need to establish standardized protocols and report in detail the application of randomization, allocation concealment procedures, and blinding. The basic characteristics of the participant, cause of the meniscus injury, types of meniscus tears, meniscus repair methods, and the PRP preparation method should also be listed in detail. Platelet content in PRP should also be tested. Conventional treatment regimens should be specified in each group. Outcome measurements should include not only VAS, Lysholm score, and healing rate for a longer follow-up time but also MRI data of the meniscus and serious adverse reactions. Upcoming trials of PRP-enhanced meniscus repair will also need to be conducted in people outside of China and the United States.

Conclusion

Platelet-rich plasma deserves further consideration as an enhancement program for meniscus repair. However, due to the limited data analyzed in this paper and poor methodological quality, the results should be interpreted with caution. Therefore, future trials should be designed as high-quality RCTs with longer follow-up time and clearly defined outcomes to confirm the use and efficacy of PRP in meniscus tears.

Abbreviations

PRP: Platelet-rich plasma;

VAS: Visual Analog Scale;

RCT: randomized controlled trials;

RR: risk ratio;

CI: confidence intervals;

MRI: magnetic resonance imaging;

MD: mean difference;

SMD: standard mean difference;

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XY was a major contributor in writing the manuscript. YJ and WS carried out all searches and included research, HA made the final decision for any objection. WQ reviewed the content of the article, and he was the corresponding author. All authors read and approved the final manuscript.

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Figures

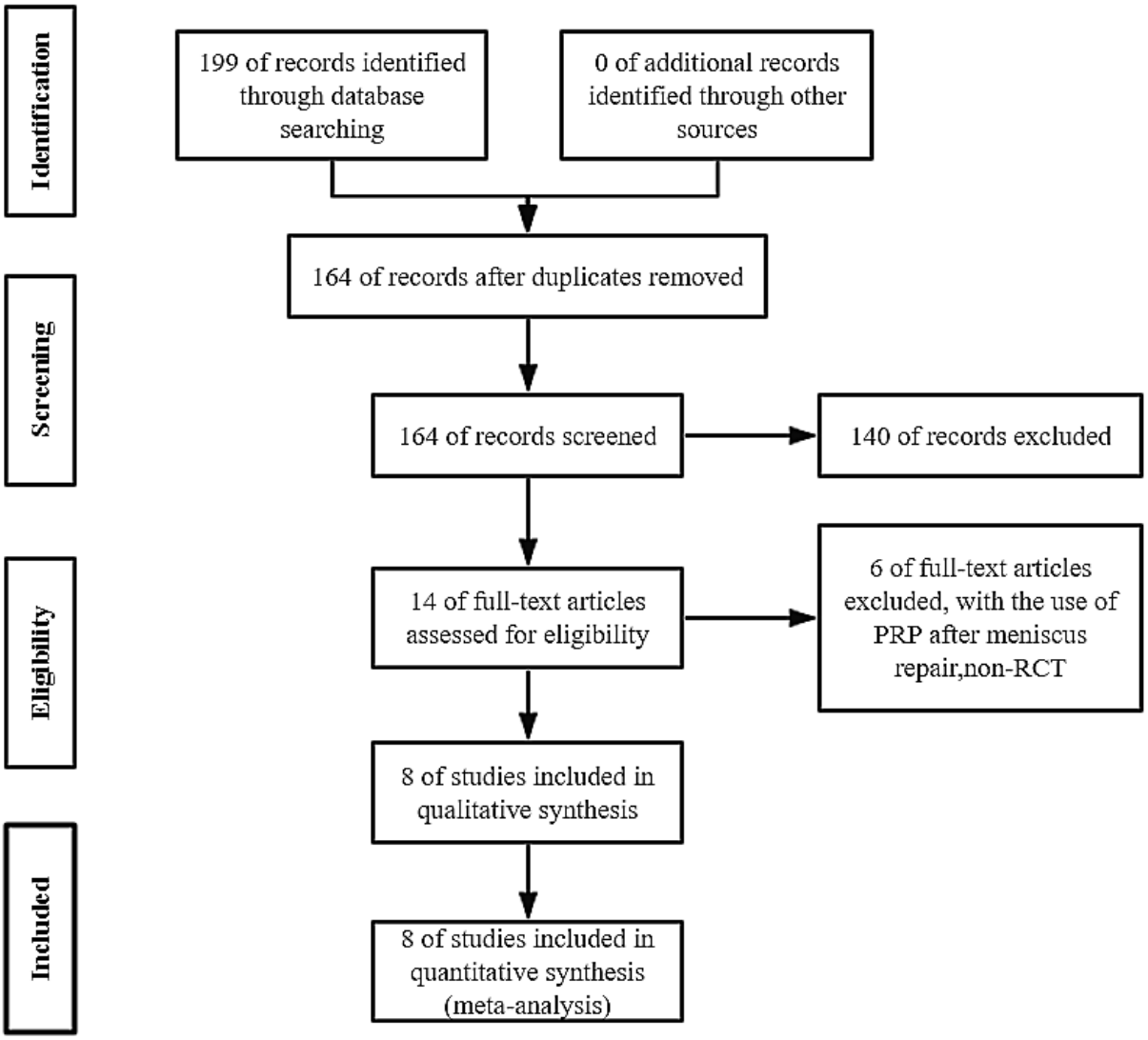

Figure 1

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

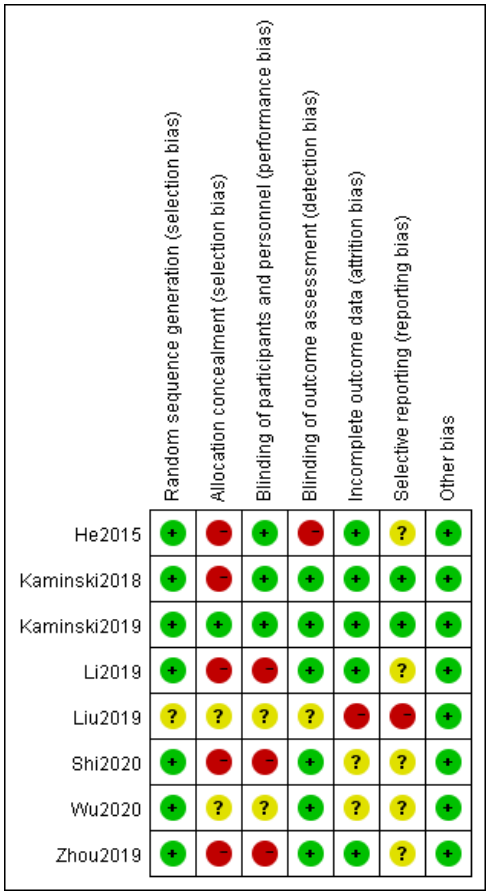

Figure 2

Assessment of the risk of bias.

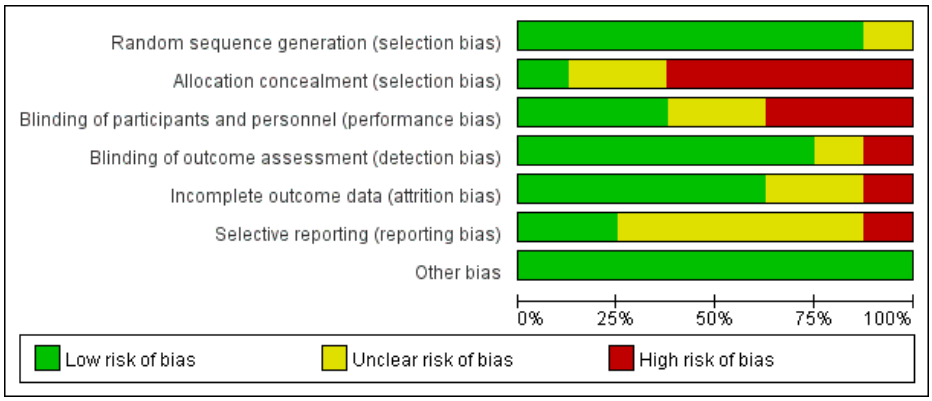

Figure 3

Distribution of each type of bias.

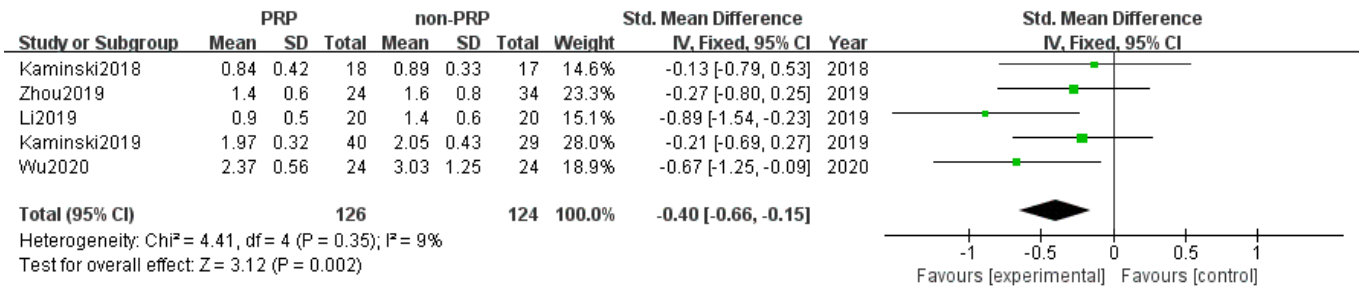

Figure 4

Forest plot for visual analogue scale (VAS).

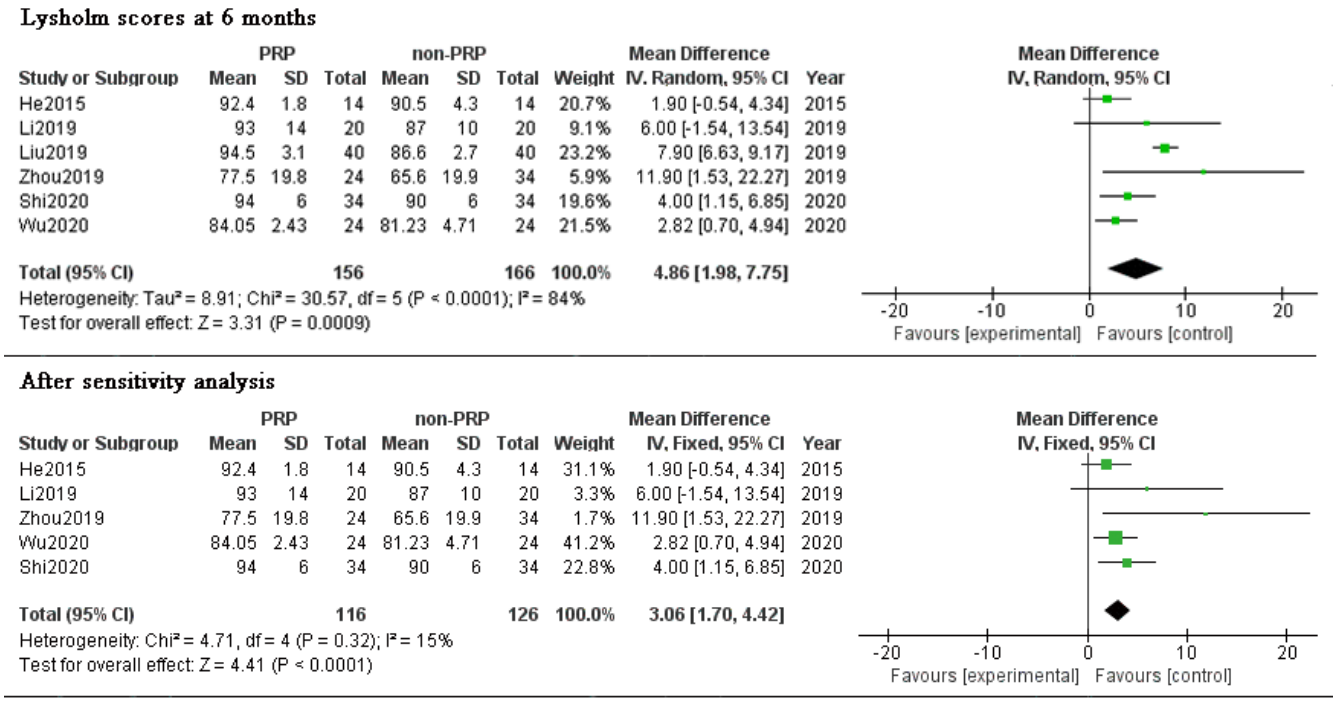

Figure 5

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

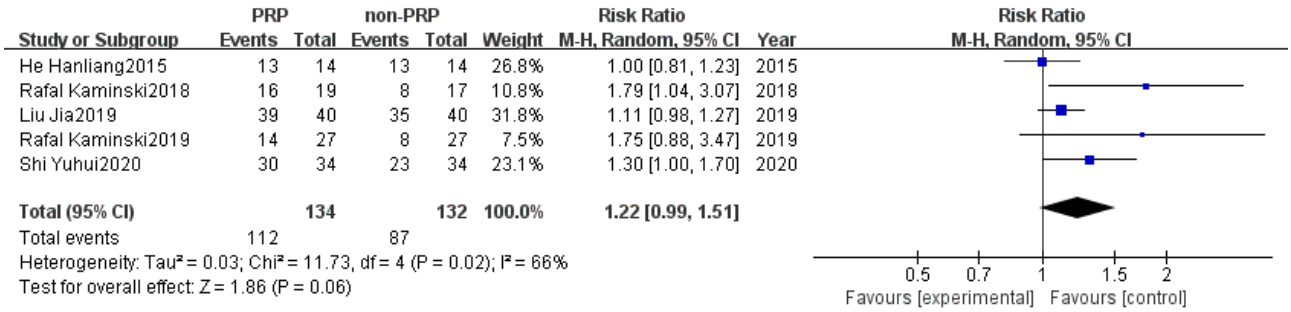

Figure 6

Forest plot of healing rate.

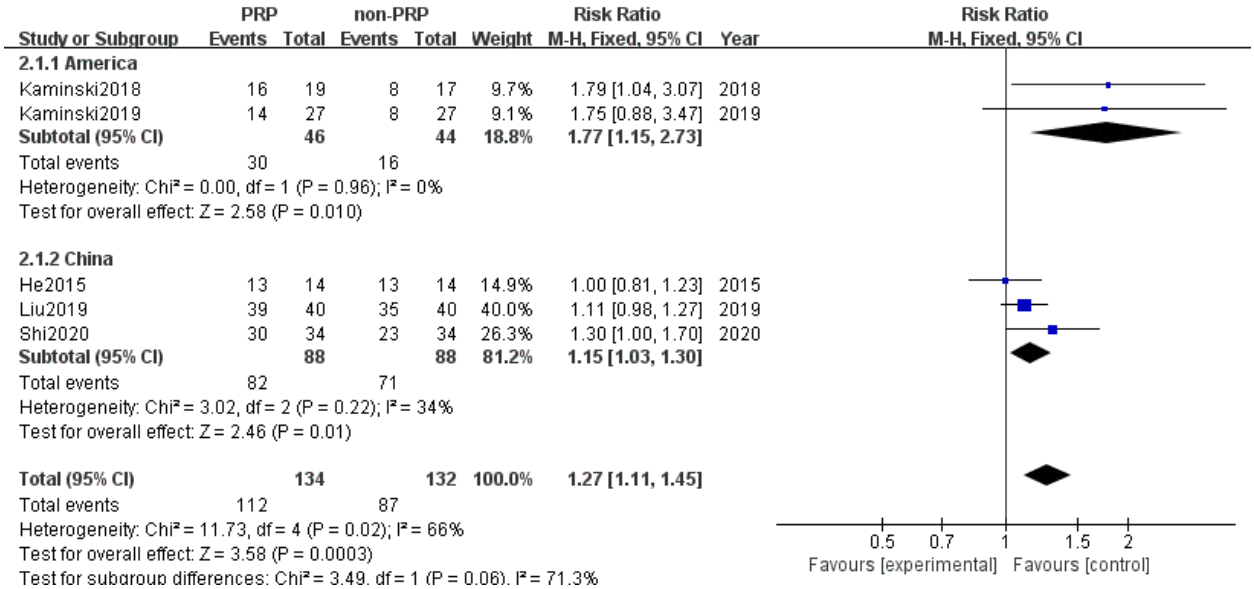

Figure 7

Forest plot of the subgroup analysis for healing rate.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009flowdiagram.doc