Systematic Review and Meta-Analysis

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Effectiveness of platelet-rich plasma injections for the treatment of acute Achilles tendon rupture

A systematic review and meta-analysis

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Abstract

Background: The effect of platelet-rich plasma (PRP) on patients with acute Achilles tendon rupture is still controversial. The purpose of this systematic review is to assess the efficacy of PRP injections treating acute Achilles tendon rupture.

Methods: A comprehensive electronic literature search was performed in the PubMed, Embase, Cochrane Library, and Web of Science databases to identify relevant studies that were published prior to April 29, 2021. Randomized controlled trials evaluating the efficacy of PRP injections in treating patients with acute Achilles tendon rupture were included. Statistical analyses were conducted using RevMan software.

Results: Five randomized controlled trials were included in this systematic review. The results of the meta-analysis showed that PRP has positive effects on ankle dorsiflexion angle, dorsal extension strength of the ankle, and calf circumference compared with that in controls. However, the current evidence failed to show that PRP effectively improves ankle plantar flexion angle, plantar flexion strength of the ankle, and pain.

Conclusions: PRP injections for the treatment of acute Achilles tendon rupture significantly improved ankle dorsiflexion angle, dorsal extension strength of the ankle, and calf circumference compared with that in controls. Additional studies with larger sample sizes, more rigorous designs and standardized protocols are needed to draw more reliable and accurate conclusions.

Abbreviations: CI = confidence interval, MD = mean difference, PRP = platelet-rich plasma, RCT = randomized controlled trial, ROM = range of motion, VAS = Visual Analogue Scale.

Keywords: acute Achilles tendon rupture, function, pain, platelet-rich plasma, systematic review

1. Introduction

A tendon is a kind of connective tissue, in which almost no cell division occurs; however, they are the basic organ of the musculoskeletal system, and they transfer energy and connect muscles and bones.[1,2] The Achilles tendon is the strongest and largest tendon in the body and connects the plantaris muscle, soleus muscle, gastrocnemius muscle, and calcaneus bone.[3] However, tendons are prone to excessive mechanical stretching in daily life and sports, which can lead to rupture. Studies[4–7] have shown that risk factors for Achilles tendon rupture include high activity levels, weak tendon elasticity, obesity, long-term low blood supply, long-term strain, and weak muscle strength. Acute Achilles tendon rupture is one of the most commonly occurring ligament ruptures.[8,9] With population, the incidence of acute Achilles tendon rupture continues to rise. Acute Achilles tendon rupture seriously affects people's quality of life and increases the economic burden on society. Therefore, it is desirable to accelerate recovery and improve the quality of tissue repair.

A new biological treatment, a platelet-rich plasma (PRP) injection, is increasingly being used in clinical practice. PRP is a platelet concentrate that typically contains various growth factors in its α-granules. Under certain circumstances, these growth factors, including platelet-derived growth factor, epidermal growth factor, transforming growth factor-β1, insulin-like growth factor, vascular endothelial growth factor, basic fibroblast growth factor, and hepatocyte growth factor, can be released at higher than physiological levels.[10] Thus, PRP has garnered the interest of many researchers as a source of induction factors for tissue regeneration.[11–14] A number of recent studies have shown that PRP is effective in treating orthopedic injuries such as carpal tunnel syndrome,[15–17] rotator cuff injuries,[18–20] and chronic Achilles tendinopathy.[21,22] Animal models have

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shown that PRP promotes the histopathological recovery of the Achilles tendon, increases its structural strength, shortens the inflammatory phase, and accelerates Achilles tendon healing.[23–25]

However, the role of PRP in human Achilles tendon healing is still controversial. For example, in some studies[21–26] ankle joint function significantly improved in the PRP group compared with that in the control group. Conversely, in some trials,[27,28] there were no significant differences between the PRP and control groups in heel function. In summary, the effects of PRP on patients with acute Achilles tendon rupture need to be analyzed and explored further to guide clinical practice. Furthermore, to the best of our knowledge, no systematic reviews have evaluated the effects of PRP in patients with acute Achilles tendon rupture. Two recently published systematic reviews in this field were about the effects of PRP on chronic Achilles tendinopathy, rather than the effects of PRP on acute Achilles tendon rupture.[11,29] Thus, we performed this systematic review and meta-analysis to elucidate the efficacy of PRP in treating acute Achilles tendon rupture.

2. Methods

We conducted this systematic review and meta-analysis of randomized controlled trials (RCTs) in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[30] In preparation for this meta-analysis, we registered the protocol in PROSPERO (CRD42020205118). Ethics approval is not required as this study is a meta-analysis based on published studies.

2.1. Search strategy

A comprehensive electronic literature search was performed in the PubMed, Embase, Cochrane Library, and Web of Science databases to identify relevant studies that were published prior to April 29, 2021. Two investigators conducted the literature search independently. The reference lists of the included studies and previous related systematic reviews were searched for additional relevant studies. The search strategy were modified specifically for each database. For example, the key search terms used for PubMed were a combination of medical subject heading (MeSH) terms and entry terms: ("Platelet-Rich Plasma"[Mesh] OR Platelet Rich Plasma[Title/Abstract] OR PRP[Title/Abstract] OR Platelet-Rich Plasma[Title/Abstract] OR thrombocyte rich plasma[Title/Abstract] OR platelet-rich plasma cell[Title/Abstract]) AND ("Achilles Tendon"[Mesh] OR Achilles tendon [Title/Abstract] OR heel tendon[Title/Abstract] OR chorda magna[Title/Abstract] OR tendo calcaneus[Title/Abstract]). More detailed information about the search strategies of each database is available in Supplemental Digital Content (Appendix A, http://links.lww.com/MD2/A572).

2.2. Inclusion criteria and exclusion criteria

Studies were included in this review if they met the following population, intervention, comparison, outcome, and study design (PICOS) criteria: P: patients diagnosed with acute Achilles tendon rupture were included; I: injections of PRP around the tendon were administered; C: placebo injections (such as normal saline or glucose injections) or no injections (such as dry needle) were administered; O: results on ankle and leg function (such as the isokinetic strength of the ankle, ankle range of motion [ROM], calf circumference), or pain were reported. The isokinetic strength of the ankle will be measured by the Multi-Joint Isokinetic Dynamometer. ROM will be measured by the goniometer. Calf circumference will be measured by a measuring tape, 10 cm below the tibial tuberosity. Pain will be measured by the Visual Analogue Scale (VAS); and S: the study design was that of an RCT. The exclusion criteria will be as follows: less than 10 samples in the intervention group or control group; no non-PRP controls were included; the article was incomplete (e.g., conference abstracts); or the article reported duplicate data (e.g., early and final papers of a clinical trial).

2.3. Literature quality evaluation

Two independent investigators evaluated the quality of the included studies by using the approach recommended by the Cochrane handbook for systematic reviews of interventions.[31] Seven recommended types of bias, namely, random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias, were assessed. Each item was judged as having "high risk", "unclear risk", or "low risk" on the basis of the data presented in the article. If the article provided sufficient and accurate information, it was considered to have "low risk". If the article provided insufficient or missing information, it was considered to have "unclear risk". If the article reported inaccurate data, it was considered to have "high risk". If disagreements occurred between the 2 investigators, a third investigator joined the discussion until a consensus was reached.

2.4. Study selection and information extraction

All of the searched records were imported into EndNote X9 (Thomson Reuters, Albuquerque, United States) to eliminate duplicate studies. The 2 investigators worked independently to identify studies that met the inclusion criteria. The titles and abstracts of identified articles were screened first by 2 investigators. To further evaluate the eligibility of potential studies, we obtained full-text articles and discussed any disagreements with the third investigator. If necessary, corresponding authors of the reviewed articles were contacted to obtain missing data. Data were extracted from the included studies by 2 independent investigators using the standardized data extraction tool. From each included study, we extracted information including the author, publication year, country, sample size, participants' mean age, participants' sex, intervention methods, follow-up times, and outcome measurement tools.

2.5. Statistical analysis

The standardized mean difference with the 95% confidence interval (CI) was used when studies used different outcome scales, and the mean difference (MD) with the 95% CI was used when studies used the same outcome scale. The level of heterogeneity was evaluated by the I^2 method, and a value of $I^2 > 50\%$ was considered to indicate significant heterogeneity.[32] A fixed-effects model was used to calculate the pooled effect size if the data were not significantly heterogeneous. Otherwise, a random-effects model was used. RevMan 5.3 (Cochrane Collaboration, Oxford, England) provided by the Cochrane Collaboration was used for

all statistical calculations, and a P value $<.05$ was considered statistically significant.

3. Results

3.1. Study Selection

A total of 916 studies from 4 databases were identified in the final search. There were 138 duplicates, and 778 studies for screening. No additional studies were identified by manual reference list screening. The studies were first screened by the titles and abstracts, and studies were excluded according to certain parameters, such as the interventions or outcomes reported. Following this screening, 17 full texts were retrieved and evaluated according to these same parameters. Eventually, 5 studies met all the inclusion and exclusion criteria and were included. See the flowchart for a more detailed overview (Fig. 1).

3.2. Characteristics of the included publications

The main characteristics of the included studies are shown in Table 1. All 5 articles[26–28,33,34] that were included were RCTs. Two of the included trials were conducted in the UK,[28,33] and 1 study each was conducted in Sweden,[27] Denmark,[34] and China.[26] In total N = 363 patients were included in these 5 trials: 70 women (19.28%) and 293 men (80.72%). The mean age of the included patients ranged from 28.9 ± 5.7 years[26] to 45.9 ± 13.74 years.[28]

All PRPs were prepared from patients' whole blood. In one of the studies,[26] the platelet concentration in the PRP was 6 times the normal physiological level. The concentration of leukocytes in PRP was 4 times the normal physiological level. The mean concentration of PRP platelets in one of the studies was 36,736 ± 1051 × 109 platelets per mL.[27] In 1 study, the prepared PRP had a platelet concentration that was 4.1-fold (95% CI 3.6–4.5) larger than that in whole blood and a leucocyte concentration that was 2.2-fold (95% CI 2.0–2.5) larger than that in whole blood.[28] Platelet concentration was not mentioned in the remaining study.[33,34]

Regarding the PRP injection volume and injection site, in one of the studies, 3 to 4 mL of PRP was injected into the paratenon sheath and the surrounding lacerated tissue.[26] In one of the studies, 4 mL of PRP was injected into the center of the tendon gap.[28] In one of the studies, after the tendon was sutured, 2 mL of PRP was injected in liquid form without activation near the

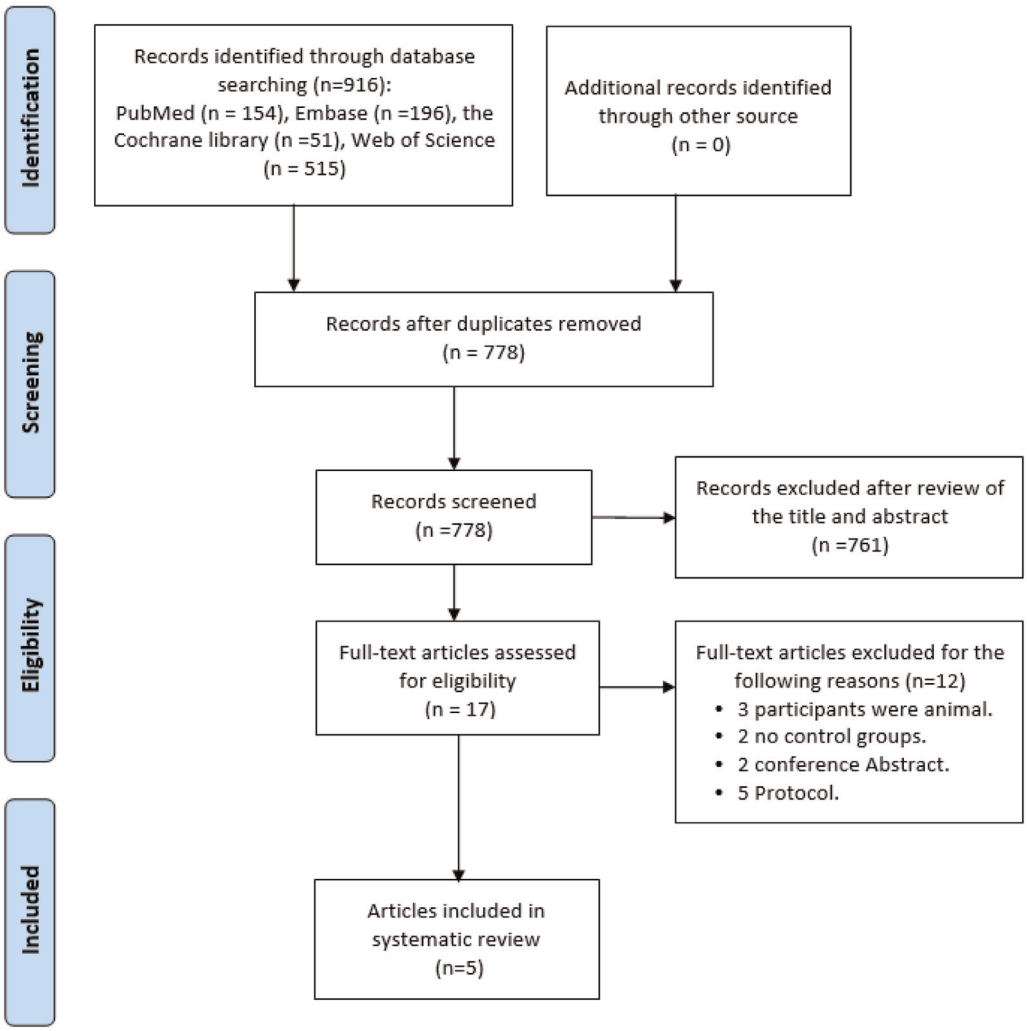

Figure 1. Flow diagram for the search and selection processes for the included studies.

Table 1

Characteristics of the studies included in this meta-analysis.

Study, year, country	Study design	Participants: Number PRP	Number Control	Age (yrs) PRP	Age (yrs) Control	Male/female PRP	Male/female Control	PRP Intervention	Control	Follow up	Outcomes
Zou et al, 2016, China	RCT	16	20	30.2±5.8	28.9±5.7	16/0	19/1	Composition: platelet concentration 6 times, leukocytes concentration 4 times. Inject volume: 3–4 mL PRP	No PRP	3 wk, 6 wk, 12 wk, 24 wk	Isokinetic evaluation; Ankle range of motion; Calf circumference; Leppilahti score.
Schepull et al, 2011, Sweden	RCT	16	14	39.8±6.2	39.4±8.3	13/3	11/3	Composition: platelet concentration 36736±1051 × 109 per mL. Inject volume: 10 mL PRP	No PRP	7 wk, 19 wk, 59 wk	Calf circumference; Achilles tendon rupture score.
Keene et al, 2019, UK	RCT	113	116	45.9±13.7	45.2±12.4	88/25	84/32	Composition: platelet concentration 4.1-fold, leucocyte concentration 2.2-fold. Inject volume: 4 mL PRP	Placebo	4 wk, 7 wk, 13 wk, 24 wk	Ankle range of motion; Pain visual analogue score; Achilles tendon rupture score.
De Carli et al, 2015, UK	RCT	15	15	No available	No available	13/2	11/4	Composition: no available. Inject volume: 4 mL PRP	No PRP	1 mo, 3 mo, 6 mo, 24 mo	Isokinetic evaluation; Jumping evaluation.
Boesen et al, 2020 Denmark	RCT	19	19	39.3±7.4	41.7±8.9	19/0	19/0	Composition: no available. Inject volume: 4 mL PRP	No PRP	8 wk, 3 mo, 4.5 mo, 6 mo, 9 mo, 12 mo	Achilles tendon rupture score Heel-Rise Work and Height Achilles Tendon Length Calf Circumference Ankle Dorsiflexion ROM

PRP = platelet-rich plasma, RCT = randomized controlled trial, ROM = range of motion.

sutured tendon. In addition, gelatinized form of PRP (2 mL), created by the addition of thrombin and 10% Ca-gluconate a few minutes before its use, was injected by suturing it to the peritoneum before skin closure. The patients received a second injection of 4 mL of PRP at 14 days postoperatively with the same preparation procedure.[33] In the remaining studies, 4 mL[34] or 6 mL[27] of PRP was injected into the rupture site.

3.3. Risk of bias

The risk of bias results for the included studies are presented in Figures 2 and 3. Four included studies reported their randomization procedures clearly,[26–28,34] so the risk of random sequence generation bias was judged determined to be low. Three studies reported allocation concealment in detail; allocation numbers were kept in "sealed envelopes"[27,34] or allocation concealment was performed on the basis of a randomization allocation system developed by the Oxford Clinical Trials Research Unit.[28] In another 2 studies,[26,33] allocation concealment was not reported adequately. Four studies[27,28,33,34] were determined to have a low risk of performance bias because the participants and personnel in the trials were blinded. There was no evidence of detection bias, attrition bias, or reporting bias in any of the included studies; therefore, the risk of bias for these items was determined to be low. The risk of other bias was categorized as unclear in 2 studies[27,33] because it was difficult to identify whether the baseline characteristics were balanced.

3.4. Effects of PRP among patients with acute Achilles tendon rupture

3.4.1. Ankle ROM. Three studies[26,27,34] provided detailed data on ankle ROM, which were used to evaluate the effect of PRP injections on the dorsal extension angles[26,27,34] and plantar flexion angles[26,27] at 6 months and 12 months. The dorsal extension angles and plantar flexion angles are expressed in degrees, and the differences between the healthy side and the

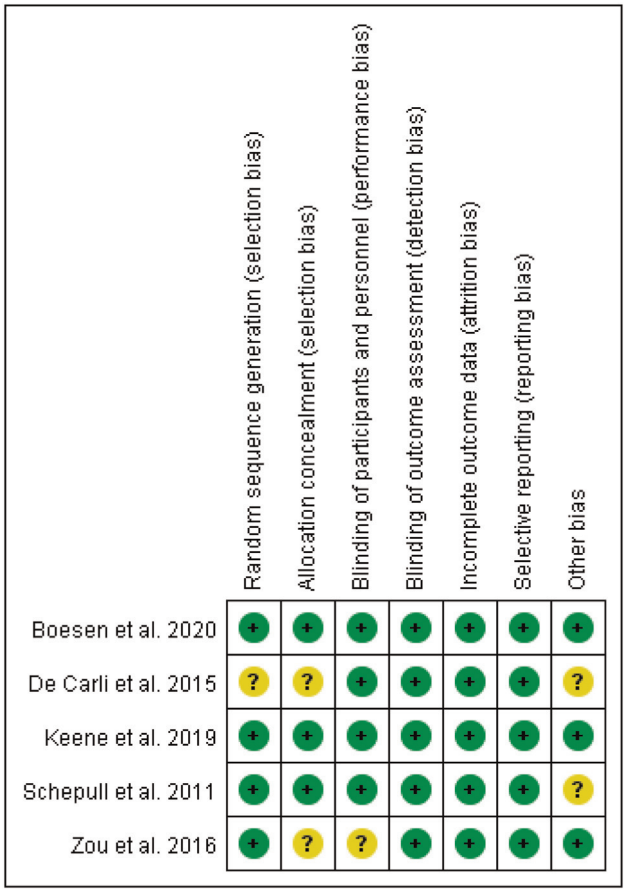

Figure 2. Risk of bias summary review of the authors' judgments about each risk of bias item for each included study.

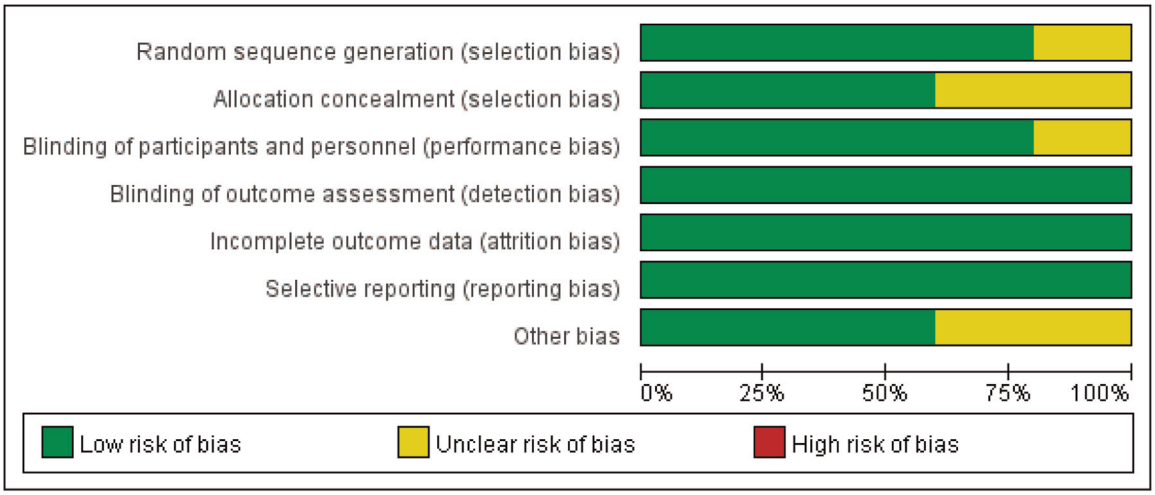

Figure 3. Risk of bias graph: review of the authors' judgments about each risk of bias item, presented as percentage of included studies.

affected side were calculated. Because the same measuring tool was used, we reported the MD as the pooled effect size.

3.4.1.1. Dorsiflexion angle. The results of the first meta-analysis showed that PRP significantly improved ankle dorsiflexion angle compared with that in controls at 12 months (n = 104, MD = –0.70, 95% CI [–1.36, –0.04], $P = .04$, $I^2 = 85\%$, the random-effects model; Fig. 4). However, when at 6 months, there was no obvious significant difference (n = 104, MD = –0.52, 95% CI [–1.84, 0.80], $P = .44$, $I^2 = 96\%$, the random-effects model; Fig. 4).

3.4.1.2. Plantar flexion angle. For the ankle plantar flexion angle, the meta-analysis indicated that there were no significant differences between the PRP and control groups at 6 months (n = 66, MD = –0.82, 95% CI [–3.00, 1.35], $P = .46$, $I^2 = 53\%$, the random-effects model; Fig. 5) or at 12 months (n = 66, MD = 1.41, 95% CI [–4.26, 7.08], $P = .63$, $I^2 = 93\%$, the random-effects model; Fig. 5).

3.4.2. Isokinetic strength of the ankle. Two studies[26,33] provided detailed data on isokinetic strength of the ankle, in which the effect of PRP injections on dorsal extension and plantar flexion strength in the ankle were evaluated after Achilles tendon repair was performed. Because the same measuring tool was used, we reported the MD as the pooled effect size.

3.4.2.1. Dorsal extension strength. The results of the meta-analysis showed that PRP significantly improved dorsal extension strength compared with that in controls when the angular speed was 60°/s (n = 66, MD = 4.00, 95% CI [1.69, 6.31], $P = .0007$, $I^2 = 0\%$, the fixed-effects model; Fig. 6). However, when the angular speed was 120°/s, there was no obvious significant difference (n = 66, MD = 1.78, 95% CI [–0.33, 3.90], $P = .10$, $I^2 = 0\%$, the fixed-effects model; Fig. 6).

3.4.2.2. Plantar flexion strength. The results from 2 studies showed that the effect of PRP injections on plantar flexion

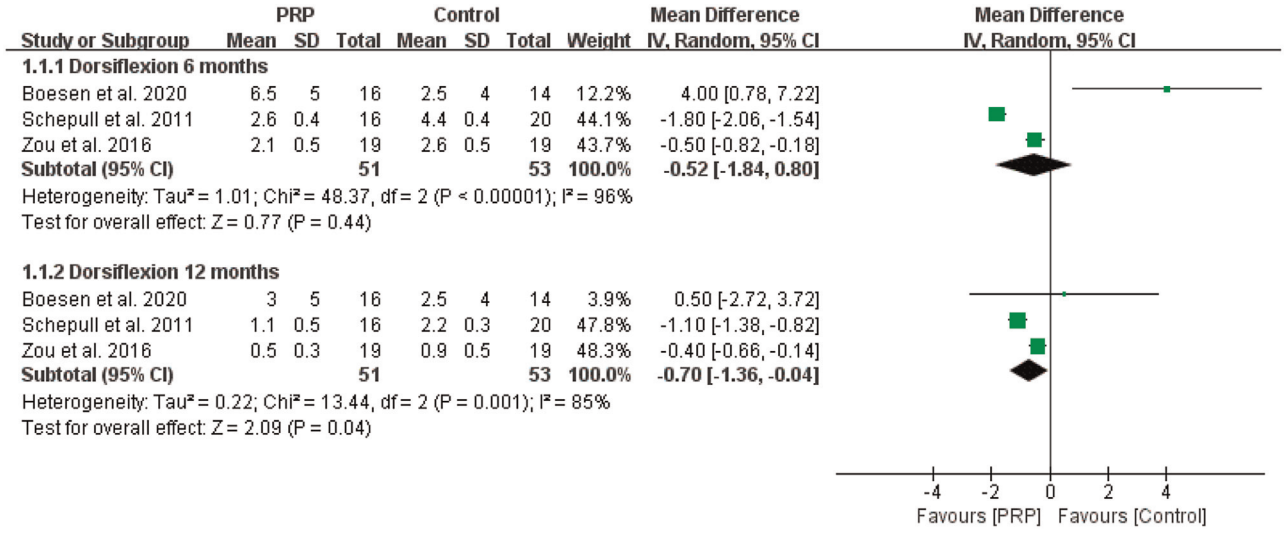

Figure 4. The effect of PRP on ROM— dorsiflexion angle. PRP = platelet-rich plasma, ROM = range of motion.

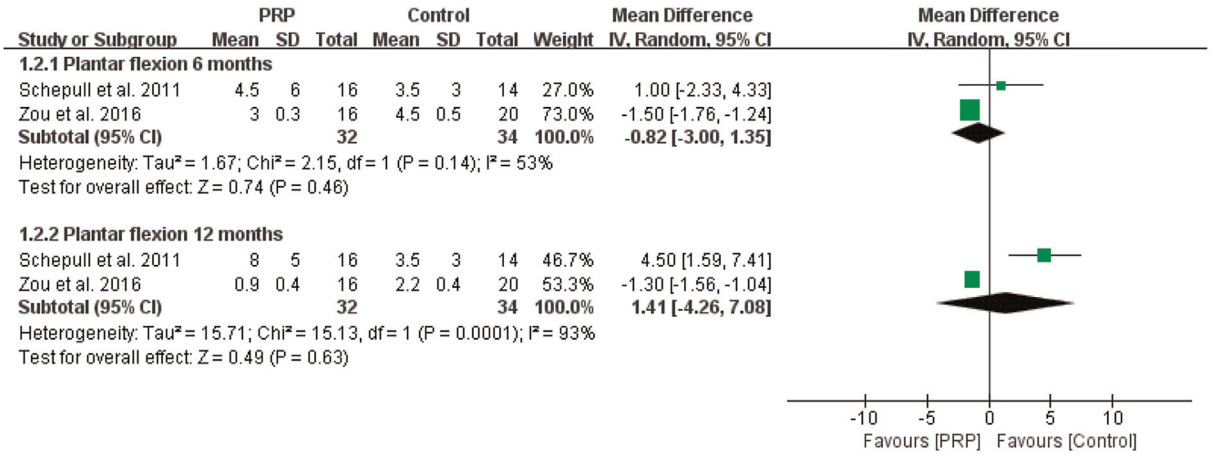

Figure 5. The effect of PRP on ROM— plantar flexion angle. PRP = platelet-rich plasma, ROM = range of motion.

strength was not statistically significant when the angular speed was 60°/s (n = 66, MD = –0.48, 95% CI [–8.22, 7.26], $P = .90$, $I^2 = 92\%$, the random-effects model; Fig. 5) or 120°/s (n = 66, MD = 0.48, 95% CI [–3.92, 4.87], $P = .83$, $I^2 = 87\%$, the random-effects model; Fig. 7).

3.4.3. Calf circumference. The results from 3 studies[26,27,34] revealed that there was significant difference in calf circumference at 6 months (n = 104, MD = 0.20, 95% CI [0.10, 0.30], $P < .0001$, $I^2 = 33\%$, the fixed-effects model; Fig. 8) and at 12 months (n = 104, MD = 0.20, 95% CI [0.10, 0.30], $P = .0001$, $I^2 = 0\%$, the fixed-effects model; Fig. 8).

3.4.4. Pain. Two studies[28,33] reported the effects of PRP on pain, as measured by the VAS. Because the same measuring tool was used, we reported the MD as the pooled effect size. The meta-analysis results showed that PRP had no significant effect on the VAS score (n = 210, MD = –0.27, 95% CI [–1.13, 0.59], $P = .54$, $I^2 = 28\%$, the fixed-effects model; Fig. 9).

4. Discussion

4.1. Summary and interpretation of results

This systematic review and meta-analysis identified 5 RCTs investigating the use of PRP injections to treat acute Achilles tendon rupture. The meta-analysis showed that PRP injections for the treatment of acute Achilles tendon rupture significantly improved ankle dorsiflexion angle (at 12 months), dorsal extension strength of the ankle (when the angular speed was 60°/s), and calf circumference compared with that in controls. However, the current evidence failed to show that PRP effectively improves ankle plantar flexion angle, plantar flexion strength of the ankle, and pain.

The meta-analysis showed that PRP injections had positive effects on the ankle dorsiflexion angle, dorsal extension strength of the ankle, and calf circumference compared with that in controls. The results were consistent with that in Sanchez et al's[35] study, which proved that injections of PRP help

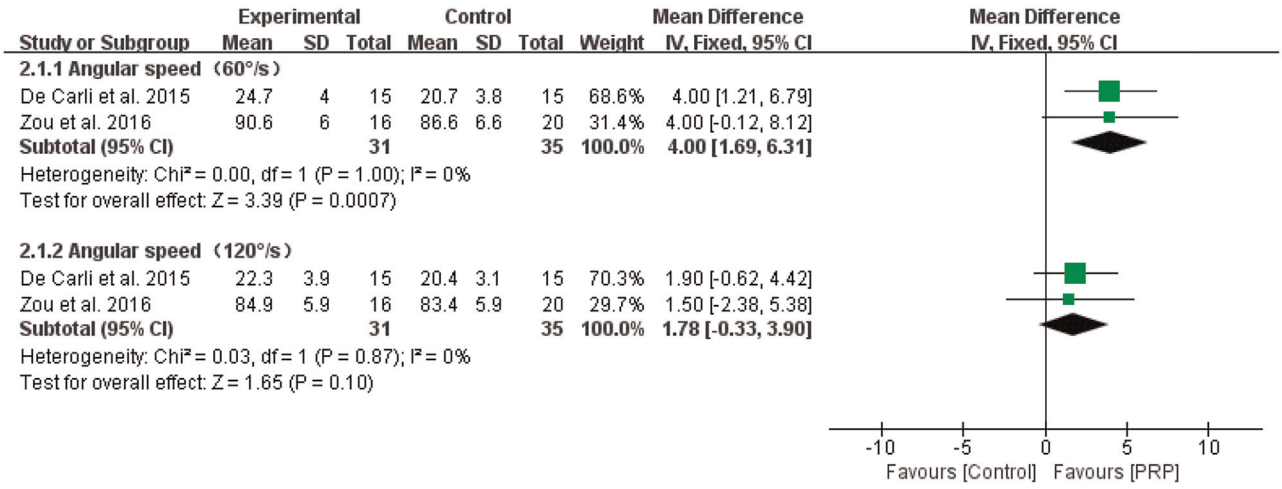

Figure 6. The effect of PRP on dorsal extension strength of the ankle. PRP = platelet-rich plasma.

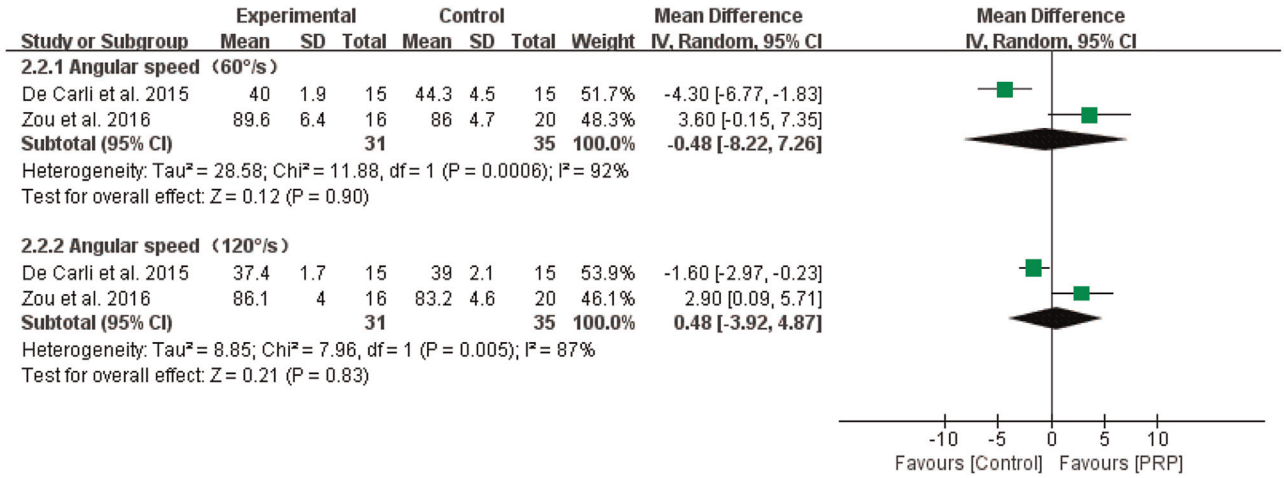

Figure 7. The effect of PRP on plantar flexion strength. PRP = platelet-rich plasma.

individuals enhance Achilles tendon healing and recover Achilles tendon function. Zou et al's[26] study showed that PRP has a positive effect on ankle joint function, as measured by the Leppilahti score, in the short to medium term. However, this result is inconsistent with that in the study by De Carli et al. In De Carli et al's[33] study, the Foot and Ankle Outcome Score and Victorian Institute of Sports Assessment Achilles score were not different between the PRP and control groups at 1, 3, 6, or 24 months after surgery for acute Achilles tendon rupture. This inconsistency in results may be caused by differences in the concentration of PRP, the content of the ingredients, the injection time, and the injection site. Rapid healing of tendons requires a rich blood supply, and the generation of blood vessels requires the supply of growth factors.[36] Lyras et al[37] found that early PRP injections for tendon injury can significantly increase angiogenesis and that PRP can reduce the tendon healing time. Some studies have shown that PRP can induce tendon cell proliferation and can also promote angiogenesis factor produc-

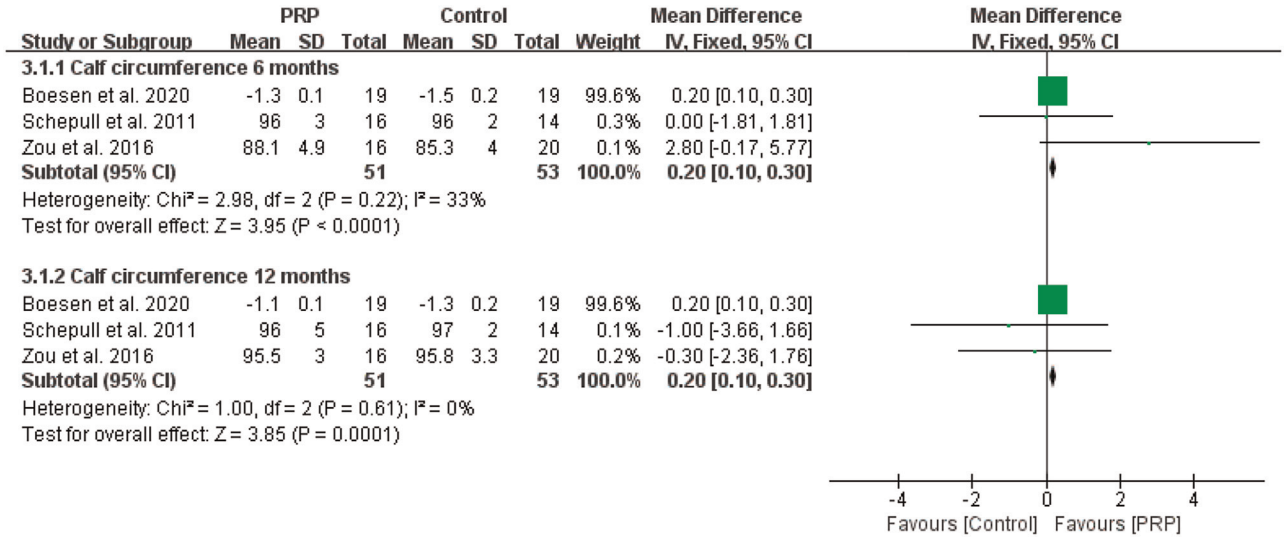

Figure 8. The effect of PRP on calf circumference. PRP = platelet-rich plasma.

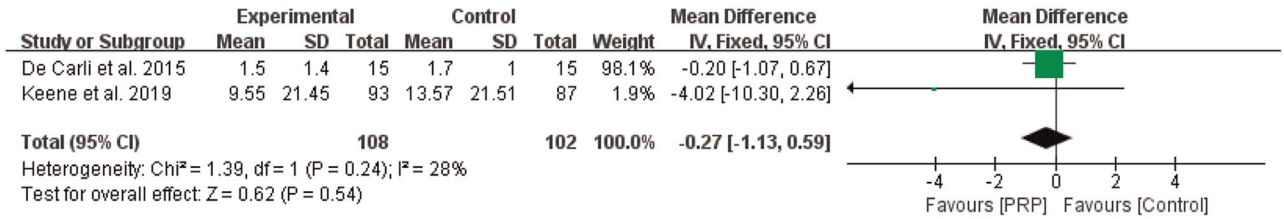

Figure 9. The effect of PRP on pain. PRP = platelet-rich plasma.

tion.[38,39] Some in vitro experiments have also shown that platelet-rich clot release induces rabbit TSCs to differentiate into active tenocytes.[40,41] In rat experiments, it has been shown that immediate injection of PRP for tendon injury improves tendon healing in rats.[42] In contrast, Delos et al[43] found no significant differences in tendon healing between immediate injections of PRP and delayed injections. Zhou et al found that white blood cell-rich platelets may be harmful to the healing of tendon injuries in rabbits. White blood cell-rich platelets cause catabolism gene expression, increase protein production, and promote increased inflammatory mediators. This inflammatory mediator induces the differentiation of non-tendon cells.[44,45] Some studies have found that leukocyte-reduced PRP is more effective and safer than traditional PRP for the differentiation of normal cells in lesions within the joint.[46–48] Therefore, the most appropriate concentration, injection time, and injection site of PRP in the treatment of acute Achilles tendon rupture need to be explored further.

However, we found no statistically significant effects of PRP on ankle plantar flexion angle, plantar flexion strength of the ankle, or pain. Several systematic reviews have also explored the effect of PRP injection on bone and joint diseases.[49–51] Our results are consistent with the findings reported in a systematic review[52] showing that for the repair of full-sheared rotator cuffs, there was no significant difference between the clinical outcome scores of groups in which PRP was and was not used. Another systematic review[49] of the effects of PRP injections on pain and function in patients with rotator cuff tendinopathy revealed that the efficacy of PRP injections and placebos is indistinguishable in terms of pain relief and functional improvement in the short-term (3–12 weeks). Nevertheless, PRP injections led to significant long-term (>24 weeks) reduction in pain. For functional improvement in the long-term, there was no significant difference between the PRP injection and placebo groups. However, our results are inconsistent with those in a recent systematic review conducted by Catapano et al[50] who indicated that there was a statistically significant improvement in the carpal tunnel functional status and pain between PRP and control groups. Another systematic review[51] investigated the effect of PRP on postoperative failure rates following rotator cuff repair, and the results demonstrated that intra-operative PRP reduces the failure risk and has a significant protective effect on tears. In summary, the effectiveness of PRP injections among patients with bone and joint diseases remains unclear. Nevertheless, due to the insufficient evidence in the studies included in our review on the effectiveness of PRP injections in treating acute Achilles tendon rupture, additional research should be performed to determine the effects of PRP infections in patients with acute Achilles tendon rupture.

4.2. Issues that require attention and directions for future research

Several issues should be considered when the effects of PRP on the repair of acute Achilles tendon rupture is studied. First, it is important to inject PRP with containing the appropriate concentrations and amounts of relevant components, such as white blood cells.[52] Belk et al[53] found that leukocyte-poor PRP may be superior to leukocyte-rich PRP for treating knee arthritis over leukocyte-rich PRP. Therefore, additional studies are needed to directly compare the efficacy of PRP injections with varying leucocyte content in treating acute Achilles tendon rupture. Second, when PRP injections are used to treat acute Achilles tendon rupture, the injection time, injection volume, and injection site should be strictly controlled. In a study by Vilchez-Cavazos et al,[54] a single PRP injection was as effective as multiple PRP injections in relieving pain; however, multiple PRP injections seemed more effective in improving joint function than was a single PRP injection. Because the available evidence is still insufficient in this field, more research needs to be conducted in the future to verify these results. Third, there is heterogeneity among patients, and PRP injections needs to be developed with the patient's own blood to maximize the effect of PRP and guarantee the safety of patients.

4.3. Strengths and limitations

A strength of this meta-analysis is that only RCTs were included, which implies that the included studies had a rigorous study design. This study also has some limitations. First, only 5 studies were included in this systematic review, and the limited number of trials limits the strength of the evidence and generalizability of the findings. Second, the types of outcome indicators varied considerably across studies, resulting in some outcome indicators not being included in the meta-analysis. Third, the cause of acute Achilles tendon rupture and heterogeneity in the types of PRP in the included studies are factors to be considered.

5. Conclusion

Five articles on PRP injections as a treatment for acute Achilles tendon rupture were included in our systematic review. The results of the meta-analysis showed that PRP has positive effects on ankle dorsiflexion angle (at 12 months), dorsal extension strength of the ankle (when the angular speed was 60°/s), and calf circumference compared with that in controls. However, the current evidence failed to show that PRP effectively improves ankle plantar flexion angle, plantar flexion strength of the ankle, and pain. Currently, there is a relative paucity of high-quality studies in this field, and the body of evidence supporting those results is insufficient. Additional studies with larger sample sizes and more rigorous designs and standardized protocols are needed to draw more reliable and accurate conclusions.

Author contributions

Conceptualization: Qingsan Zhu.
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Funding acquisition: Zhuo Zhang.
Methodology: Chenglong Wang, Hua Fan.
Project administration: Qingsan Zhu, Zhuo Zhang.
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Software: Zhuo Zhang, Zhihe Yun.
Validation: Qingsan Zhu, Zhuo Zhang.
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