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GENERAL REVIEW

Platelet-rich plasma in chronic Achilles tendinopathy

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Abstract

Introduction Achilles tendinopathy [AT] is a functional problem characterised by swelling and pain above the Achilles tendon insertion region. In individuals with AT, PRP or platelet-rich plasma can be used as an alternative modality of treatment with an aim to lessen the discomfort and enhance functional recovery. We assessed the available data supporting the effectiveness of PRP in treating chronic AT.

Materials and methods We did a literature search for randomised controlled trials [RCTs] that contrasted the effectiveness of PRP with that of eccentric exercise and placebo injections as treatment for AT in databases such as the Cochrane Library, Web of Science, PubMed, and EMBASE. The Visual analogue scale [VAS] score, Victorian Institute of Sports Assessment-Achilles [VISA-A] score, and Achilles tendon thickness were used to measure the results. We used the RevMan 5.3.5 software for statistical analysis.

Results We included five RCTs in this meta-analysis. There was no significant difference in the VISA-A between the PRP and placebo groups at 12 weeks, 24 weeks and 1 year after treatment. However, at 6 weeks after treatment, PRP exhibited better efficacy than the placebo treatment. Two studies in our meta-analysis included VAS scores and tendon thickness. There was no significant difference in VAS scores at 6 weeks and 24 weeks after treatment. However, VAS scores at 12 weeks and tendon thickness were significantly different.

Conclusion PRP injection is an effective treatment for chronic AT. It has a unique potential for increasing function and reducing discomfort in AT patients.

Keywords Achilles tendinopathy · Platelet-rich plasma · VAS score · Tendon thickness · Randomised controlled trial

Introduction

Achilles tendinopathy (AT) is a functional problem characterised by swelling and pain above the Achilles tendon insertion region [1]. It is common among recreational runners as well as the general population, with incidences of 9% and 5–6%, respectively [2]. The aetiology is complex and poorly understood. This condition has serious complications and is mostly treated with conservative measures. However, this treatment method has a poor curative effect, and the condition recurs frequently [3].

Excessive exercise or long-term overuse causes the Achilles tendon and its surrounding tissues to stretch beyond the repair capability of the tendon, causing inflammatory changes in the periorbital tissue and the tendon. Chronic inflammation causes degeneration of the tendon's hyaline and fatty tissues. This effect weakens and even causes the Achilles tendon to rupture spontaneously [4].

The first-line treatment in AT is a conservative approach that includes exercise therapy and patient education which includes resistance and eccentric training [5]. If adequate relief is not obtained, other additional therapies may be considered. Invasive interventions, such as surgery, can have negative consequences and are sometimes unsuccessful [6]. As a result, non-invasive therapies should be prioritised. These are further classified as a pharmaceutical which includes injection therapy and Glyceryl Tri-nitrate [GTN] patches and non-pharmaceutical like extracorporeal shock-wave therapy [ESWT] [7]. The most commonly used treatment methods in clinical practice are lidocaine and

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steroid injection therapy, which have strong analgesic and anti-inflammatory effects. However, repeated injections can cause collagen necrosis which leads to degradation of the mechanical properties of the Achilles tendon [8]. Also, the long-term use of nonsteroidal anti-inflammatory drugs can easily result in gastrointestinal ulcers. As a result, the long-term clinical use of these drugs in the treatment of AT has been controversial [9].

PRP or platelet-rich plasma is derived from autologous whole blood via centrifugation. Platelet-derived growth factor [PDGF], Transforming growth factor-beta 1 [TGF-1], epidermal growth factor [EGF] and insulin-like growth factor [IGF] are all growth factors that can be released by highly concentrated platelets. PRP stimulates the vascular endothelial cell division which leads to vascular proliferation, collagen synthesis and capillary growth in the transplant area, which in turn speeds up wound healing [10]. PRP has piqued the interest of researchers due the large number of benefits associated with its use, such as self-sufficiency, ease of extraction, and high safety [11]. The local injection of autologous PRP has been used clinically to treat chronic AT based on the findings of a large number of basic research and animal experiments. However, the findings of numerous clinical studies on the efficacy and safety of PRP are inconclusive.

In this study, we searched the clinical literature for information on the use of PRP injections locally to treat AT. We used a systematic review and meta-analysis to combine relevant literature. We wanted to understand the efficacy of local PRP injections in AT treatment and compare it to the efficacy of conservative treatments.

Material and methods

Before beginning the study, we developed a prospective protocol that included objectives, literature-search strategies, inclusion and exclusion criteria, outcome measurements, and statistical analysis methods based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis [PRISMA] criteria [12].

Literature search

Systematic searches were conducted in Cochrane Library, Web of Science, EMBASE and PubMed. “plasma,” “platelet-rich,” “platelet-rich plasma,” “PRP,” “plasma/platelet-rich,” “plasma/platelet-rich fibrin,” “tendon, Achilles,” “calcaneal tendon,” “tendo calcaneus” were searched in the title and abstract. The last search was done in December 2022. By reading the retrieved literature, we manually retrieved eligible references.

Inclusion criteria

The following eligibility criteria were established based on patient, intervention, comparison, outcome, and study design (PICOS): P: At diagnosis; I and C: PRP injection around the tendon; O stands for the Victorian Institute of Sport Assessment-Achilles (VISA-A), VAS, and Achilles tendon thickness measurement; S stands for a randomised controlled clinical trial.

The following are the specifics of the outcomes: The VISA-A score was between 0 and 100, with 0 indicating no activity and maximum pain and 100 indicating maximum activity and no pain [13]. The secondary outcome measures were pain during activity as measured by a VAS score where 0 represents no pain and 100 represents the worst pain imaginable; 0–100 mm [14]. Ultrasonography was used to determine the thickness of the tendons.

Exclusion criteria

The following exclusion criteria were used: PRP combined with surgery; a lack of non-PRP controls; insufficient literature (such as only meeting summaries); and duplication of literature (such as early and final papers of a clinical trial).

Evaluation of literature

Two independent reviewers assessed the quality of the included studies using the Newcastle–Ottawa Scale [NOS] [15]. The following items were evaluated: comparability, selection and outcome measurement. It consisted of an eight item scale. Based on the data presented in the article, each item was assigned a “strong evidence,” “medium evidence,” or “limited evidence” rating.

Extraction of data and analysis

The relevant data were extracted independently by the two researchers. The mean difference and 95% confidence interval (CI) were calculated and analysed as the effect amounts based on the ankle function scores of each study treatment group and control group. In the case of complete data, the priority sequence of VISA-A, VAS, and Achilles tendon thickness was calculated if multiple ankle joint function scores were used in the study. Methods for data extraction, transformation, and analysis were carried out following the Cochrane system evaluation manual.

Statistical analysis

The Cochrane Collaboration provided Review Manager 5.3 software for meta-analysis, which was supplemented by Graphpad Prism 5.1 software for calculation and plotting. I2 was calculated to test for heterogeneity across studies. When I2 was less than 50%, the study's heterogeneity was low, and the random-effect model (random effect) was used. I2 values greater than 75% indicated heterogeneity. As a result, heterogeneity was investigated using the random-effect model (random effect). By removing an article, sensitivity analysis was performed. $P < 0.05$ was deemed statistically significant.

Results

Selection of study

Our initial search yielded a total of 608 articles. Following the screening and application of inclusion and exclusion criteria, we included 5 articles with 189 patients with chronic AT in our meta-analysis (Fig. 1). Table 1 details the general information included in the study. According to the NOS, one study had a score of 8, two studies had score of 7, and two studies had score of 6, thus having high risk of bias (Table 2).

Main outcome indicators, VISA-A score

VISA-A scores were included in four articles at 6 weeks after treatment while scores at 12 and 24 weeks after

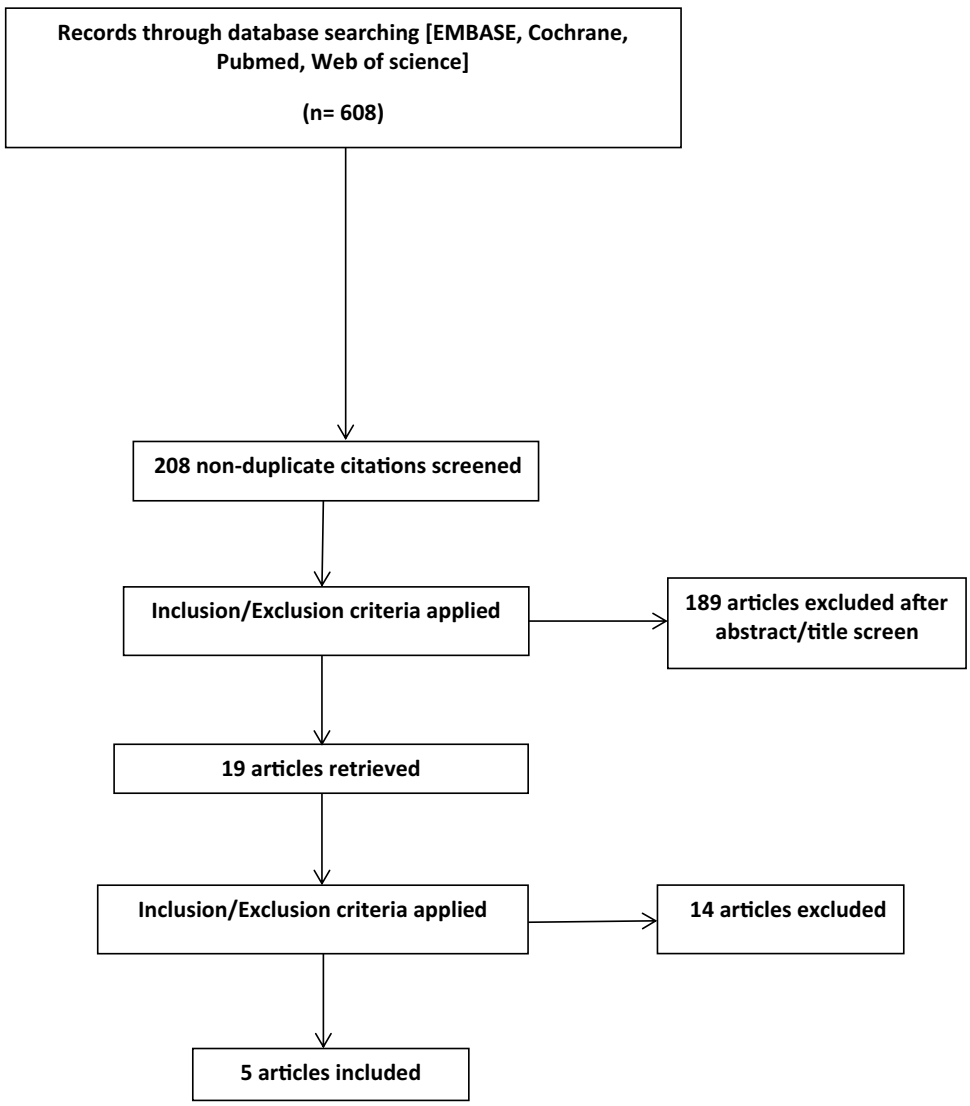

Fig. 1 PRISMA flow chart of the systematic review

Table 1 Characteristics of the included studies in the meta-analysis

Included study	Year	Sample size		Male/Female		Mean age /Years		Interventions		Follow-Up, Months	Study Design	Outcomes
		PRP	Control	PRP	Control	PRP	Control	PRP	Control			
De Jong et al. [16]	2011	27	27	Not Provided		49.7	49.7	4 ml, 1 time	Saline, 1 time	12	RCT	VISA-A
De Vos et al. [17]	2010	27	27	13/14	13/14	49	50	4 ml, 1 time	Saline, 1 time	6	RCT	VISA-A
Boesen et al. [18]	2017	19	19	19/0	19/0	43.1	40.9	4 ml, 4 times	Saline, 4 times	6	RCT	VISA-A, VAS, TT
Krogh et al. [19]	2016	12	12	5/7	6/6	46.7	51.8	6 ml, 1 time	Saline, 1 time	6	RCT	VISA-A, TT
Kearney et al. [20]	2013	9	10	4/5	3/7	47.8	49.9	4 ml, 1 time	Eccentric loading	6	RCT	VISA-A, VAS

PRP Platelet-rich plasma
VISA-A Victorian Institute of Sports Assessment-Achilles
VAS Visual analogue scale
TT Tendon thickness

Table 2 Quality assessment for the studies included in the meta-analysis by the Newcastle–Ottawa scale

Study	Selection	Comparability	Exposure or outcome	Total score
De Jong et al. [16]	★★★	★★	★★	7
De Vos et al. [17]	★★★	★★	★★	7
Boesen et al. [18]	★★★	★★★	★★	8
Krogh et al. [19]	★★	★★	★★	6
Kearney et al. [20]	★★	★★	★★	6

★★★—Strong level of evidence
★★—Moderate level of evidence
★—Limited level of evidence

treatment were included in five articles, respectively. The other time points showed high heterogeneity, except for the results at 6 weeks, and the random-effect model was used for combined analysis. The random-effect model and the heterogeneous $I^2 < 40\%$ were combined. Standard mean difference [SMD], 95% Confidence interval [CI], Z score, and I^2 at 6 weeks, 12 weeks and 24 weeks after treatment was demonstrated on a forest and funnel plot diagram (Figs. 2, 3 and 4). Although there was no significant difference in improvement, the VISA-A score of the PRP group was significantly higher than that of the control group 6 weeks after treatment. Patients were followed up 1 year after the procedure in only 2 studies, which was shown on a forest and funnel plot diagram (Fig. 5). No significant difference existed between the experimental PRP and control groups.

VAS score

Two studies used VAS scores at 6, 12, and 24 weeks following treatment. The results were sufficiently dissimilar that combined analysis was done using a random-effect model. The results were shown on a forest and funnel plot diagram in terms of SMD, 95% CI Z score and I^2 (Fig. 6, 7 and 8). At 6 and 24 weeks following treatment, there was no discernible difference between the VAS scores of the PRP and control groups. At 12 weeks after treatment, the PRP group's VAS scores were much higher than the control group, and the improvement was statistically significant.

Measurement of Achilles thickness

At 12 weeks after treatment, measures of the Achilles tendon thickness were statistically analysed in two investigations. The

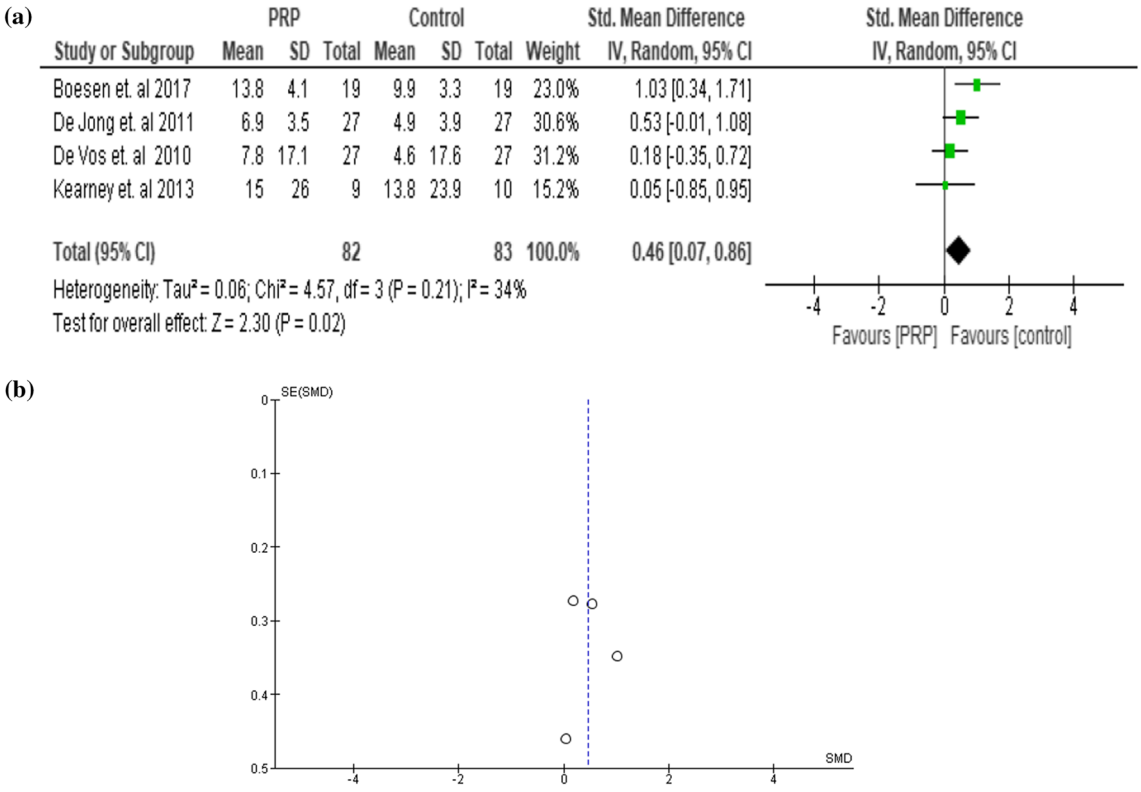

Fig. 2 Forest plot and Funnel plot for VISA-A score between PRP and placebo injections plus eccentric training at 6 weeks after treatment

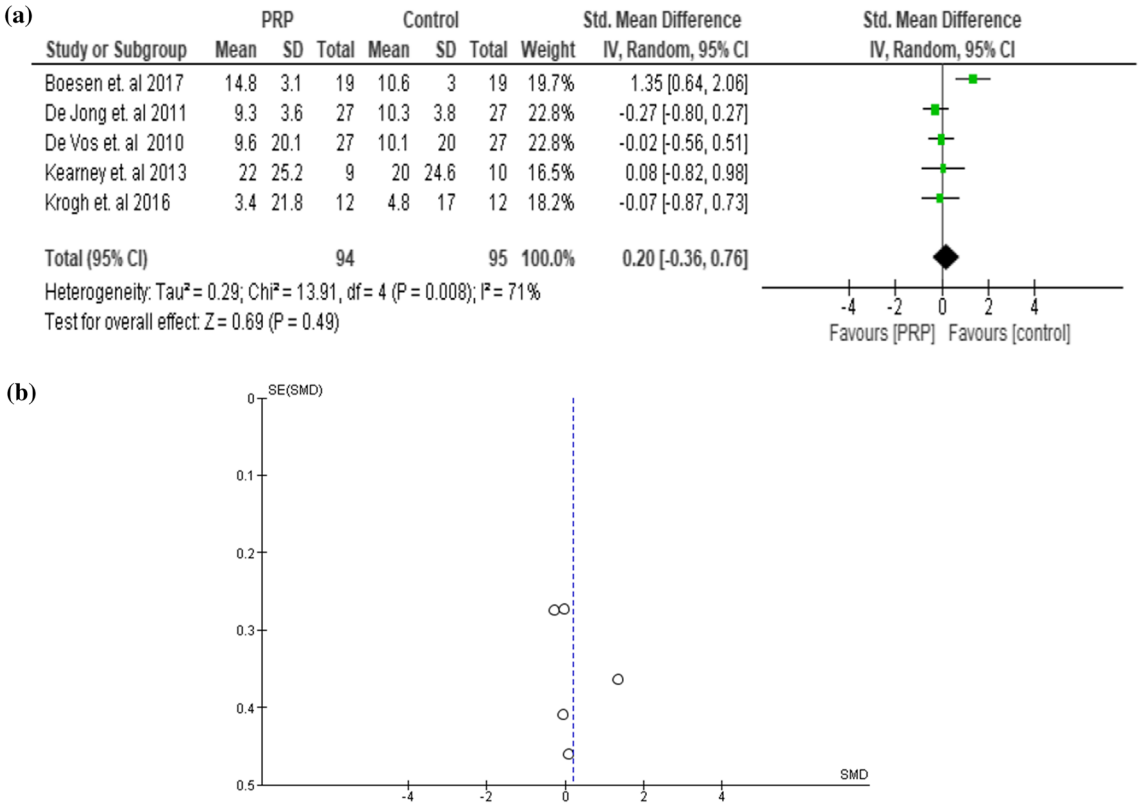

Fig. 3 Forest plot and Funnel plot for VISA-A score between PRP and placebo injections plus eccentric training at 12 weeks after treatment

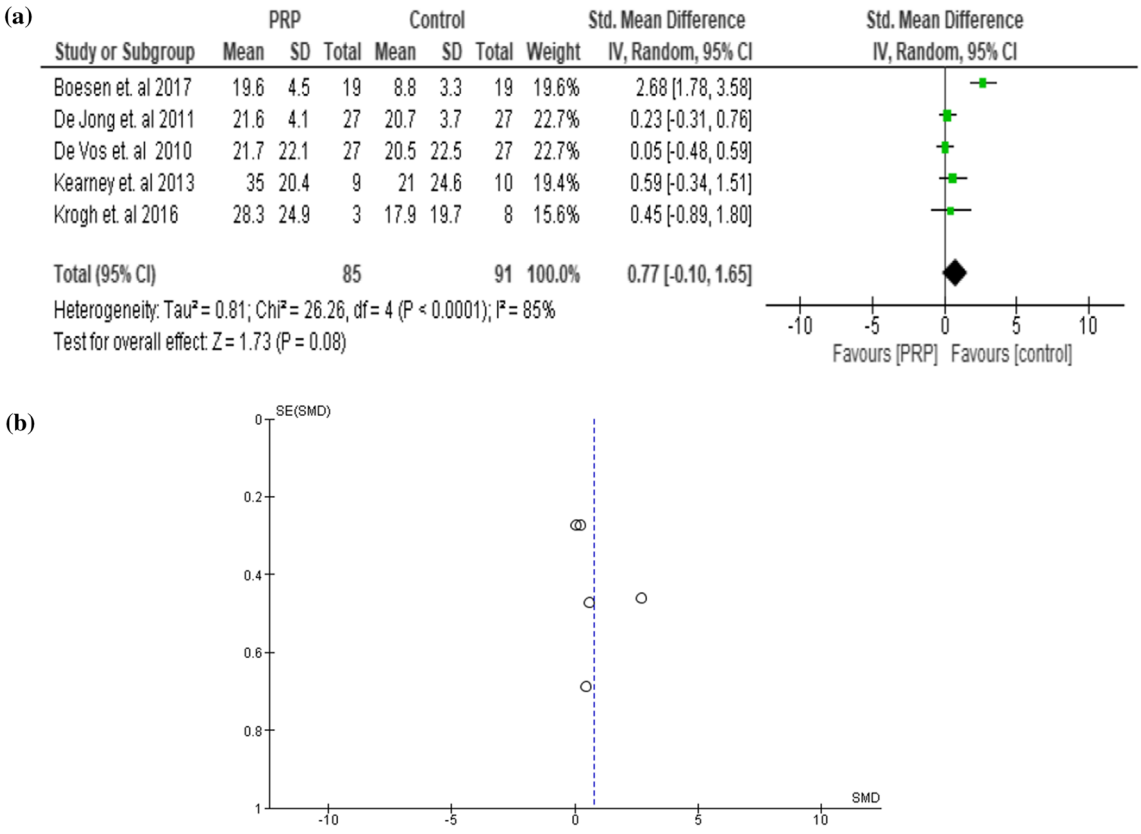

Fig. 4 Forest plot and Funnel plot for VISA-A score between PRP and placebo injections plus eccentric training at 24 weeks after treatment

findings of the random-effect model analysis showed that the cerumen of the PRP group was considerably thinner than that of the control group which was shown on a forest and funnel plot diagram (Fig. 9).

Publication bias and sensitivity analysis

Sensitivity analysis was performed on the entire group or subgroup with significant heterogeneity ($P < 0.10$) to determine the cause of the heterogeneity. The findings showed that the I^2 reduced from 34 to 0% for the VISA-A score six weeks after therapy, and the heterogeneity changed from $P = 0.21$ to $P = 0.55$ after Boesen's study was taken into account. The VISA-A score of the PRP injection group was no longer statistically significant in comparison to the control group. I^2 dropped to 0% for the VISA-A scores from all other time points, but the study's findings remained essentially the same. Sensitivity analysis was conducted in just one study.

Discussion

PRP has been utilised in clinical settings for a long time; however, its effectiveness in treating AT is still up for debate. The efficacy of PRP is comparable to that of the placebo, according to the quantitative analysis of the five items of grade-I clinical evidence in this investigation. The exact aetiology causing AT is uncertain, and several factors influence its onset. The majority of research indicates that inappropriate exercise training, overwork, and anatomic deformities brought on by weakness are the main causes of AT. The initial localised inflammation of the Achilles tendon is caused by several reasons. Degenerative alterations and eventually a partial or total rupture of the Achilles tendon are caused by these effects [21]. The Achilles tendon does not receive any blood supply. Because of this, it heals far more slowly than other

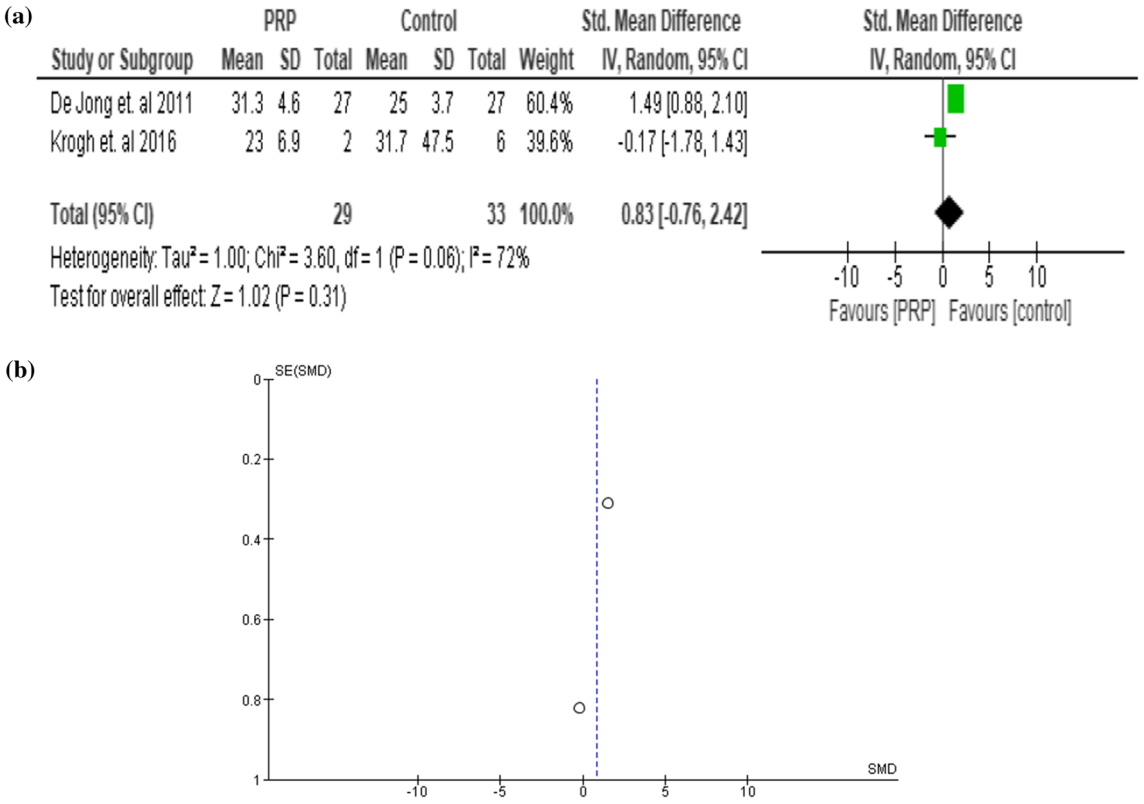

Fig. 5 Forest plot and Funnel plot for VISA-A score between PRP and placebo injections plus eccentric training at 1 year after treatment

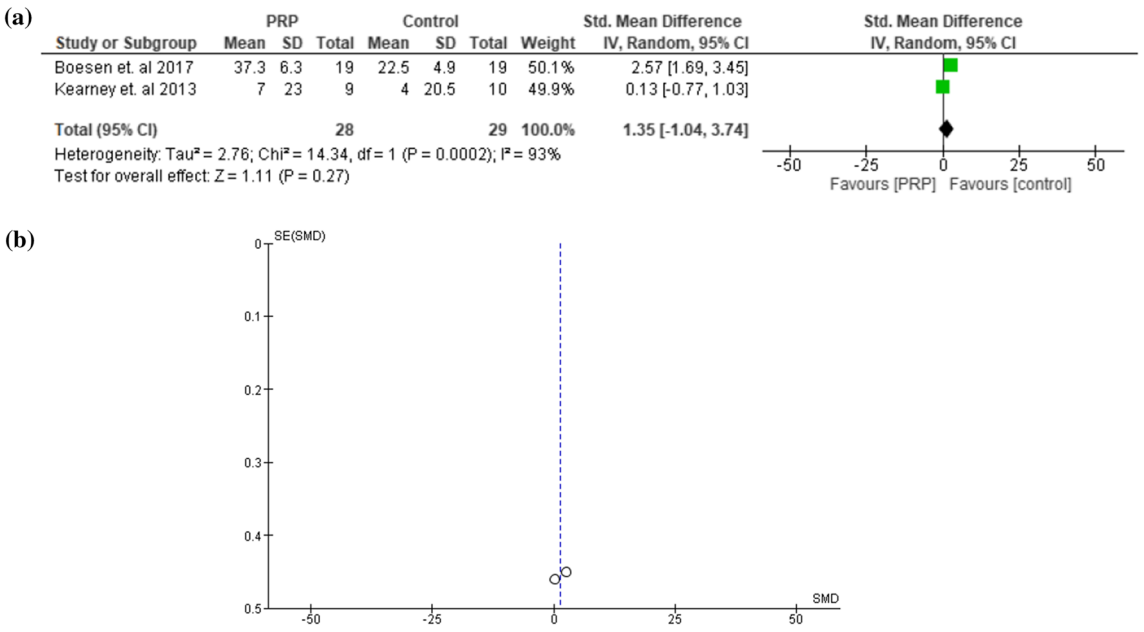

Fig. 6 Forest plot and Funnel plot for VAS score between PRP and placebo injections plus eccentric training at 6 weeks after treatment

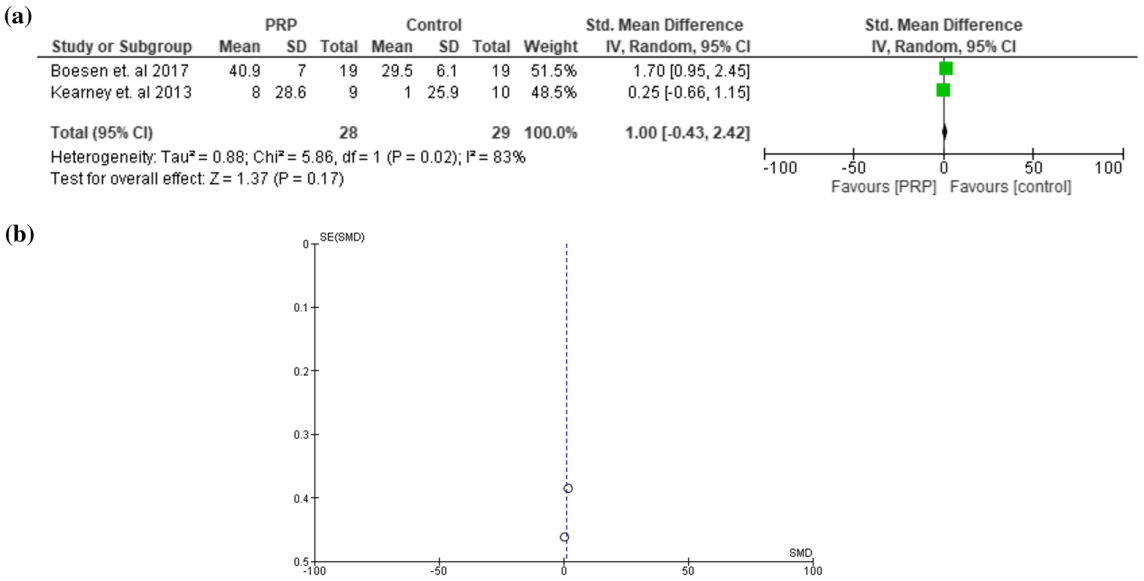

Fig. 7 Forest plot and Funnel plot for VAS score between PRP and placebo injections plus eccentric training at 12 weeks after treatment

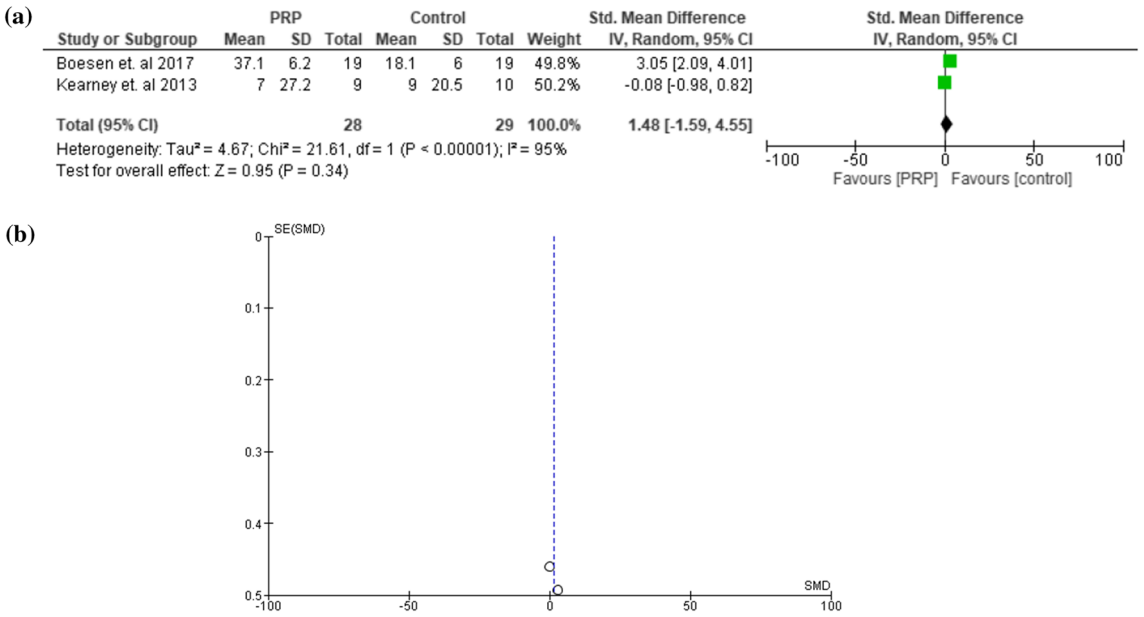

Fig. 8 Forest plot and Funnel plot for VAS score between PRP and placebo injections plus eccentric training at 24 weeks after treatment

connective tissues. As research has advanced, experts have realised that growth factors are crucial to the regeneration of the Achilles tendon and have discussed using PRP to treat AT.

To separate PRP from whole blood, a cell separation method is employed. Growth factors, which are necessary for tissue healing, can be secreted by platelets. These elements promote angiogenesis, collagen synthesis, and tendon cell proliferation, all of which support tendon regeneration. Numerous laboratory-based investigations and a small number of clinical trials have shown that PRP on AT has a positive therapeutic effect; as a result, PRP is frequently utilised in clinical practice to treat AT [22].

PRP offers patients with tendon illnesses effective pain alleviation and patient satisfaction, according to Murawski et.al [23]. However, there are drawbacks to such trials, such as the absence of a control group and efficient disease specificity, blinding and measurement, techniques. De Jonge et.al [16] looked into how well placebo and PRP injections, either alone or in combination with centrifuge training, worked to

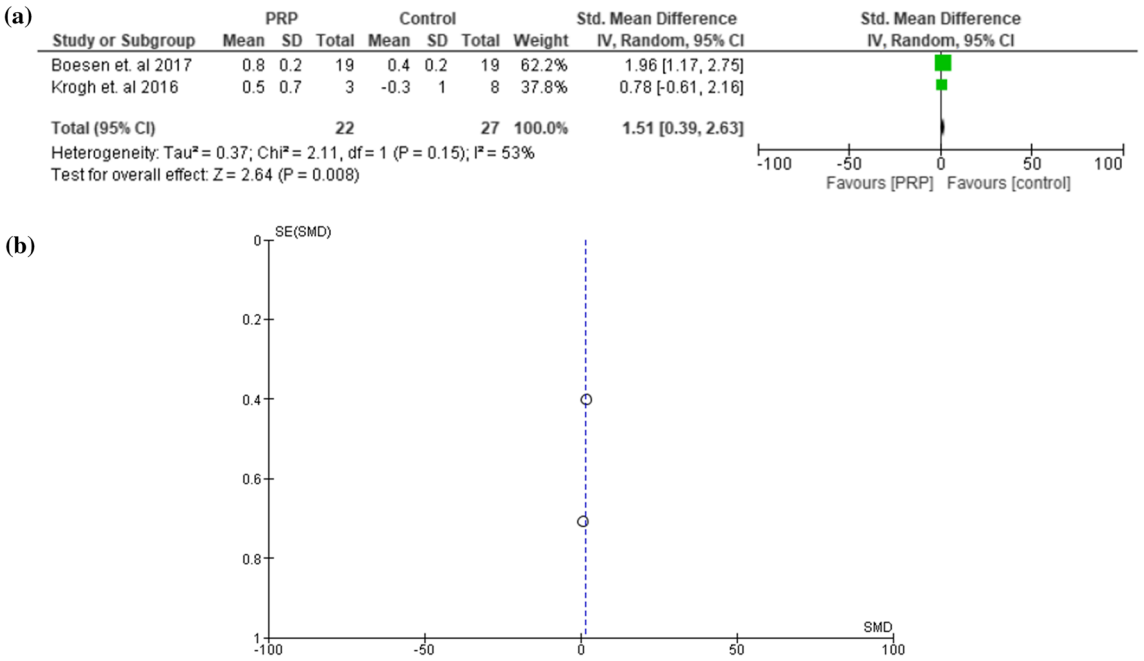

Fig. 9 Forest plot and Funnel plot for Measurement of Achilles tendon thickness between PRP and placebo injections plus eccentric training

reduce pain and increase function in individuals with tendinitis. They found in their study that individuals with tendinitis did not significantly benefit from PRP or a placebo in terms of pain alleviation or function. This study has important therapeutic significance because chronic tendinopathy is increasingly being treated with PRP. These results, however, are restricted to laboratory and clinical studies.

In vitro and animal studies, PRP encourages the synthesis of tendon collagen and neovascularisation. However, instead of using a perfect tendinitis model, these research studies used tendons that were normal or damaged. In a double-blind, randomised controlled experiment, PRP was used to treat 54 individuals with persistent Achilles tendon inflammation. They discovered that PRP injection had no impact on the neovascularisation score or the acoustic echo structure of the Achilles tendon lesion. The clinical use of PRP is not supported by these findings.

Boesen et.al [18] work stood out from the others in this meta-analysis, according to sensitivity analysis. His study was one of the first RCTs to demonstrate that when compared to a placebo, PRP is effective. One explanation for the discrepancy in outcomes could be that Boesen et al. [18] employed four PRP injections spaced two weeks apart, as opposed to just one in earlier RCTs. Patients with chronic gingivitis who received PRP injections had successful clinical results in terms of function and pain relief, according to Abate et al. [24]. PRP has the potential to encourage tendon repair, even though the potential method by which it can treat tendinitis is uncertain. Growth factors including PDGF, EGF, IGF and TGF-1 are all present in PRP and play crucial roles in regulating the repair of damaged tissue. The Achilles tendon is exposed to growth factors for a longer period after repeated injections. This result encourages the healing of Achilles tendon tissue [25].

In contrast to other RCTs, Boesen's study [18] used a different rehabilitation programme. In the RCTs incorporated in this study, eccentric training was given to the experimental and control groups. After 10 days, patients in Boesen's study [18] were permitted to progressively recover. However, all participants in previous research skipped vigorous activity for 4 to 6 weeks. Movement during AT rehabilitation was shown to be comparable to 6 weeks of halting exercise by Verrall et al. [26]. There is inadequate proof to support the idea that rest can enhance prognosis. In a 5-year follow-up research on eccentric training, Van der Plas et al. [27] found that 58 patients with AT improved to 83.6 from 49.2 in a period of 5 years. Additionally, 39.7% of patients reported total pain relief at follow-up, and when measured, it was found that the Achilles tendon's thickness in the sagittal plane dropped from 8.05 to 7.50 mm at baseline. Tendon thickness measurement has its importance because the dimensions correlations in a normal Achilles tendon and tendinopathy tendon differ. The tendinopathy process is complex and represents not only a simple enlargement of the Achilles tendon, but changes the whole tendons' geometry as well [28]. Eccentric training is useful in the treatment of chronic tendinitis because it can reduce pain and fasten the process of tendon remodelling and tissue healing [29].

Our observations with chronic AT are in line with a recent meta-analysis and systematic review carried out by Chen et al. [30], which discovered that PRP therapy did not significantly enhance patient's VAS scores when compared to alternative treatments. Our research showed that the Achilles tendon's thickness dramatically decreased following PRP injection, which is objective proof that Achilles tendinitis symptoms have been relieved. PRP is generated from the patient and given after it underwent the vitro centrifugation process. The PRP itself, therefore, has no danger of disease transmission and does not induce immunological rejection. This discovery is supported in conditions other than AT. The negative effects of PRP are non-specific and resolve quickly without causing lasting harm [31]. The literature used in this study did not mention any negative effects from PRP injections near tendons.

Strength: We had well-defined inclusion and exclusion criteria for the study, and hence, only RCTs with grade-I clinical evidence of effectiveness were included in this meta-analysis.

Weakness: High heterogeneity remains in the quantitative analysis of the included RCT studies. Heterogeneity in these studies can be contributed to various factors which include the extent of tendinitis, PRP production methods, PRP cell component, the mode of activation, the frequency and dose of injection, and the control group. The included studies' scoring standards and methods also differed. Even though analysis of the subgroup at follow-up was performed and the function score of the ankle joint was unified and summed up, heterogeneity was ineffectively reduced.

Opportunity: There is a need for future RCTs, to reduce heterogeneity in the existing research literature.

Threat: The various types of PRP were not differentiated in this investigation. Therefore, it is impossible to overstate the effectiveness and safety of a particular PRP therapy for tendinitis. The heterogeneity in PRP production techniques and the lack of a standardised approach contributed to this limitation. Additionally, the study did not classify the patients' ages and severity of the disease due to limited patient data derived from the included RCTs. Due to this incapacity, it was not possible to determine which patients would respond the best to PRP treatment for AT and who would be most sensitive to its effects.

Conclusion

According to the results of our meta-analysis, PRP injection is an effective treatment for chronic AT. PRP has a unique potential for increasing function and reducing discomfort in AT patients, according to research on its diverse modes of action.

Author contributions All authors have contributed equally to the preparation of the manuscript.

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Data and materials availability This published article contains all the data generated or analysed during this study.

Declarations

Conflict of interest The authors declare that they do not have any conflict of interest.

PRISMA 2020 checklist statement The authors have read the PRISMA 2020 checklist, and the manuscript was prepared and revised according to the PRISMA 2020 checklist.

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