Meta-Analysis

Comparative Effectiveness of Minimally Invasive Nonsurgical Treatments for Plantar Fasciitis: A Network Meta-analysis of 30 Randomized Controlled Trials

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Background: Several minimally invasive nonsurgical treatments have been widely applied for plantar fasciitis (PF). To date, controversy still exists regarding the effectiveness of these approaches for treating PF.

Objective: The purpose of this study was to perform a comprehensive comparison of the currently available invasive nonsurgical treatments for PF regarding short- and mid-term reductions in pain using a network meta-analysis (NMA).

Study Design: NMA of randomized controlled trials (RCTs) for minimally invasive nonsurgical treatments of PF.

Methods: The EMBASE, PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched for eligible studies. Patients were adults age ≥ 18 years with PF. The outcome measures were the visual analog scale (VAS) scores at 3-6 weeks and 4-6 months. Pairwise meta-analysis and NMA based on a Bayesian analysis were performed, and all potential comparisons and rank of probabilities were calculated.

Results: Thirty RCTs were included in the NMA. The trials investigated 20 treatments or combined treatments, including autologous whole blood, botulinum toxin A (BTA), ultrasound-guided gastrocnemius injection of botulinum toxin (BTA in the gastrocnemius), corticosteroid (CS), miniscalpel-needle (MSN), placebo, platelet-rich plasma (PRP), and the ultrasound-guided technique and peppering technique (PEP). The MSN treatment may be the best choice.

Limitations: Some treatments were investigated in only one study or at one follow-up period and were separated from the network at 4-6 months. Other limitations include the inconformity of the treatment schedule and dose.

Conclusions: The MSN treatment should be recommended as the best therapy, followed by BTA in the gastrocnemius and BTA. CS and PRP are common medications that remain valuable in clinical practice. PEP can be performed after the injection of medication.

Key words: Plantar fasciitis, randomized controlled trials, network meta-analysis, Bayesian analysis, visual analog scale, botulinum toxin A

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Plantar fasciitis (PF) (1), as the most common cause of nontraumatic heel pain, is estimated to account for 11-15% of all foot problems in adults worldwide. Riddle and Schappert (2) reported that approximately 100,000 patients have consulted clinics or hospitals for this disorder. The pain radiates from the ventral heel pad or the medial tubercle of the calcaneus or extends along the plantar fascia into the medial longitudinal arch of the foot of patients. Characteristically, the pain is always exacerbated by movement and weight bearing, particularly during the initial steps taken after standing (3).

The interventions for PF consist of noninvasive and invasive treatments. Currently, several noninvasive treatments are available, including rest, oral nonsteroidal anti-inflammatory drugs (NSAIDs), stretching, foot arch supports, heel cups, night splints, and acupuncture. Some therapies with energy resource are also practiced in clinics (3), such as extracorporeal shock wave, ultrasound, low-level laser therapy, noninvasive interactive neurostimulation, and pulsed radiofrequency treatment. Multiple physical therapies have been recommended by physicians and physiotherapists (4,5). Minimally invasive nonsurgical therapies include different kinds of medicine injection. Dry needling, miniscalpel-needle (MSN), peppering technique (PEP), and ultrasound-guided technique (UG) are always combined with injections. These therapies are always employed after the failure of noninvasive therapies.

This review focuses on minimally invasive nonsurgical therapy. We included all potential treatments. Evaluations of the peppering and ultrasound-guided technique combined with treatment were conducted independently. We posed the following questions: What is the ranking of available invasive treatments, and which treatment exerts the best effect on PF? Does an additional technique (PEP and UG) improve the effect or not?

Methods

Inclusion and Exclusion Criteria

Types of Studies

For our analysis, we included properly designed randomized controlled trials (RCTs) evaluating the effects of minimally invasive nonsurgical treatments on PF. We adopted a rigorous standard for the included studies to ensure that this review is high quality. We required that the included studies adequately described the method of randomization. Non-RCTs, abstract-only papers, and RCT protocols were excluded. Self-contrast studies were also excluded.

Types of Patients

We included studies that described adult participants (age ≥ 18 years) with PF. No restrictions on gender or race were established. Patients with plantar fascial fibromatosis, tarsal tunnel syndrome, plantar nerve lesions, Morton neuroma, ormetatarsalgia were excluded. Special populations, such as athletes, patients with systemic diseases, individuals serving in the military, and others were also excluded.

Types of Interventions

Any comparative study investigating minimally invasive non-surgical treatments, including combination techniques such as corticosteroids (CS) under UG or with the peppering technique, were included. We required that each study include at least 2 minimally invasive nonsurgical therapies or compared one treatment with a placebo. Open surgery and other types of surgery, such as endoscopic fasciotomy, were excluded.

Types of Outcomes

The outcome was the visual analog scale (VAS) pain score at 3-6 weeks, 4-6 months and 12 months of follow-up; if the data form was a scale ranging from 0-100 points, we translated it to the 0-10-point scale. Outcomes derived from other pain relief methods, such as the Wong–Baker Faces Pain Score and the Foot Functional Index, were excluded because they would cause bias.

Our study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search Strategy

PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched on Feb 13, 2020. The following keywords were used to specifically search the databases for RCTs: plantar fasciitis, heel spur syndrome, chronic plantar fasciitis, and calcaneodynia (Supp. Table 1). In addition, we also scanned the relevant trials included in previous systematic reviews and meta-analyses of PF to ensure literature saturation. No language limitations were used.

Study Selection

Two independent reviewers (Li and Zhang) inde-

pendently reviewed the titles and abstracts of all studies retrieved by the search. Duplicates were removed. In addition, the full text was obtained and examined if necessary. Then, the reviewers used the eligibility criteria to select the potentially relevant studies. If a disagreement on the inclusion or exclusion of a study occurred, a third reviewer was consulted.

Data Extraction and Quality Assessment

Two reviewers (Li and Zhang) extracted the basic information from the included studies using a predesigned extraction form, consisting of interventions, body mass index (BMI), percentage of women patients, average age, duration of the condition, and outcome measures. Next, the data were integrated. Discrepancies between the results were largely resolved through discussions; however, a third reviewer was consulted if an agreement was unable to be reached. The outcome was the VAS pain score. The values were adjusted to a range of 0-10 points, where 0 indicated no pain and 10 indicated the worst imaginable pain.

If data from more than one follow-up time point were available at 3-6 weeks and/or 4-6 months, the time points nearest to 4 and 20 weeks were used for the 2 different follow-up periods. In addition, several states of pain were described. We used the following priority levels: overall pain, morning pain, active pain, and first-step pain. Interventions that were derived from the same principle but utilized different approaches were assigned the same treatment name. Next, the Cochrane Risk of Bias Tool of RevMan (Review Manager, Version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) was used to evaluate the quality of the included RCTs.

Two reviewers (Li and Zhang) independently evaluated the quality of the trials. The Cochrane Collaboration tool was used to evaluate the risk of bias in the included RCTs, which covers the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias.

Statistical Analysis

First, a pairwise meta-analysis was performed using random effects models. Every pair of studies investigating the same treatments was analysed. Next, the results were reported as the mean difference (MD) with a corresponding 95% confidence interval (CI), in addition to the number of pairs of studies. These statistical analyses were performed using STATA software, Version 14 with the metan package (StataCorp LP, College Station, TX).

Second, random effects network models were developed within a Bayesian framework using the Markov Chain Monte Carlo algorithm in WinBUGS (Bayesian inference Using Gibbs Sampling for Windows, version 1.4.3; Imperial College and MRC, UK) (6). The model was based on 3 Markov chains for 100,000 iterations after a burn-in of 50,000. A thinning interval of 10 was applied, and thus one sample was collected for every 10 iterations. Consequently, 30,000 samples were obtained for each parameter. In this process, the Brooks-Gelman-Rubin method was used to assess the convergence between direct and indirect variances (7). According to the theory proposed by Brooks and Gelman, if the result of the Potential Scale Reduction Factor (PSRF) is approximately one or equal to one, convergence has been reached. This result was also presented by the MD with a 95% CI. If the null value was not included in the 95% CI of the MD, a statistically significant difference was indicated. The rank probability of each treatment was estimated using WinBUGS, and the data were then imported into STATA. Next, plots of the surface under the cumulative ranking (SUCRA) curves were generated (8). The SUCRA value was presented as the percentage of the area under the curve: 100% indicates the best treatment and 0% indicates the worst treatment. Comparisons with VAS recorded before treatment are shown in a Forest plot to assess the absolute therapeutic efficacy of all procedures. The network order in STATA was used to plot the MDs and 95% CIs for the 2 different follow-up durations.

Inconsistency Analysis

If a "loop" (e.g., A-B-C) was identified in the network, each comparison in the loop (e.g., A-B) might have indirectly resulted from the other comparisons (e.g., A-C and C-B); consequently, the direct and indirect result may be different. The inconsistency of the model was assessed using the node-splitting method (9). If the *P*-value was less than 0.05, an inconsistency was detected. The node-splitting models were generated using the gemtc package (version 0.6-1, http://cran.r-project.org/ package=gemtc) in the R statistical software (version 3.2.3, http://www.r-project.org) (10).

Sensitivity Analysis and Meta-regression Analysis

A sensitivity analysis was conducted to assess the effect of low-quality studies after they were excluded. We recalculated the network result with the rank probability.

If no significant difference was observed, the outcome of the network meta-analysis (NMA) was considered valid.

Furthermore, meta-regression analysis was conducted to test the relationship between the sample size and treatment effect. As recommended by the United Kingdom National Institute for Health and Care Excellence, a single interaction term was used as the covariate (11) .The deviance information criterion (DIC) (12) was used as the measurement of model fit. Thus, a lower DIC value suggested a more parsimonious model. If the reduction in the DIC was less than 3, the covariate was not considered associated with the result. Additionally, a regression parameter named the coefficient was calculated. If the null value was included in the 95% CI of the parameter, the association was not supported.

Ethical Approval

This systematic review does not require ethical approval because only data collected indirectly from the literature was included and evaluated.

Results

Eligible Studies

Our search strategy identified 1,695 articles. After reviewing the titles and abstracts, 158 articles were chosen for further analysis. After a careful screening of the full text, 128 articles were discarded for the reasons listed in Fig. 1. Of these 128 articles, 22 articles did not meet the criterion of an intervention, 6 articles did not meet the criterion of an intervention or participant, 58 articles were not RCTs, 20 articles did not report available follow-up outcomes, one article was a protocol for an RCT, and 21 articles did not provide available VAS results. The remaining 30 RCTs were used in the qualitative synthesis procedure (13-42). All interventions were grouped into 23 treatment strategies (Table 1).

For some RCTs, treatments comprised more than 2 interventions. The network included 26 studies reporting outcomes at 3-6 weeks, 19 studies reporting outcomes at 4-6 months, and 6 studies reporting outcomes at 12 months. A meta-analysis cannot be performed due to the outcomes at 12 months could not form a closed loop. The total numbers of patients included in the analyses of outcomes at 3-6 weeks, 4-6 months and 12 months were 1,405, 1,126, and 397 respectively.

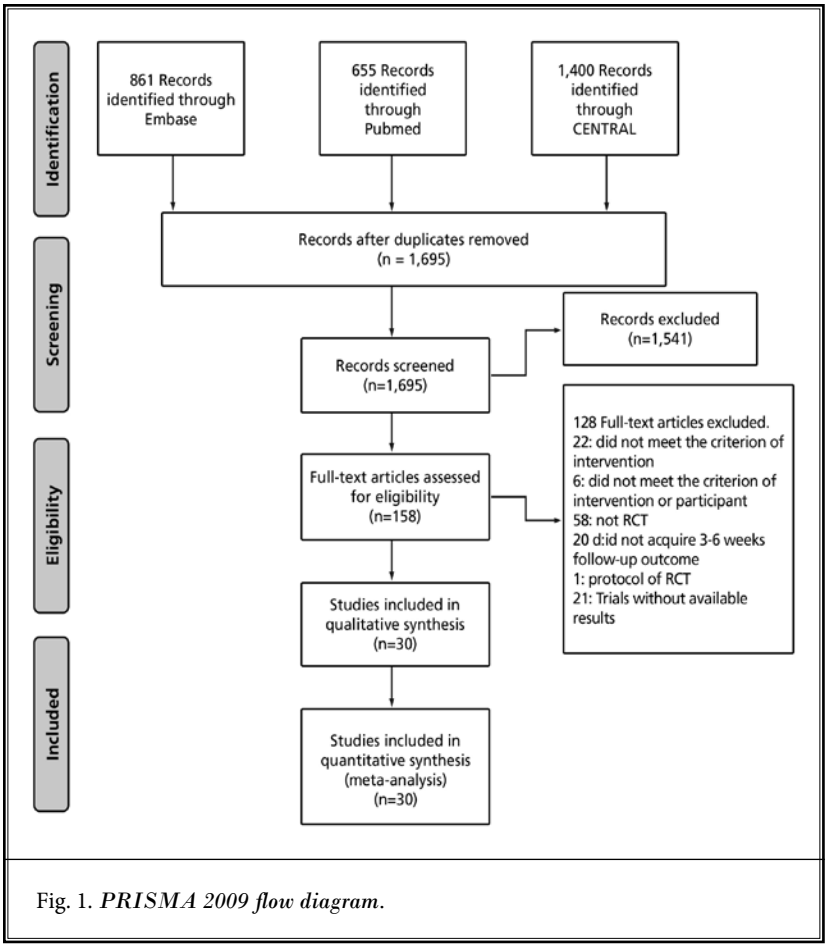

Fig. 1. *PRISMA 2009 flow diagram.*

Multiple headings were extracted, including author, publication year, duration of condition, duration of follow-up, performance time, intervention, sample size, number of total and women patients, average age, BMI, and VAS results (Table 2). Twenty-two studies (13,16-20,22,23,25-29,31-35,37,40-42) have 3-6 months follow-up durations, 6 studies (14,21,30,36,38,39) followed up to 12 months; only one study (38) followed up to 36 months. Among them, 27 studies performed the treatments only once, while 3 studies performed the treatments more than once during the follow-up.

The results of the risk of bias analysis of the included RCTs generated using RevMan software are listed in Fig. 2. Allocation concealment was mentioned in only 10 of the articles. The generation of a ran-

dom sequence was described in detail in 21 reports. In addition, performance bias is the worst, with 10 studies with a high risk and 13 studies with an unclear risk, possibly leading to bias. Blinding of invasive treatments is difficult because these treatments involve several procedures and pieces of equipment.

Publication bias was evaluated by constructing funnel plots; the results revealed a lack of substantial asymmetry, indicating that the small-study effect was not significant (Fig. 3).

Results of the Premarket Approval (PMA)

All direct comparisons were imported into STATA software and analysed using the metan package with a random model. The MDs and 95% CIs were calculated. Regarding the results obtained at 3-6 weeks, 30 pairs of comparisons were performed and the 95% CIs of 20 pairs did not include the null value. Regarding the results obtained at 4-6 months, 10 of the 25 compared pairs showed statistically significant differences in their 95% CIs. The results are listed in the lower-left triangle of Table 3 (A and B, respectively), and statistically significant differences are shaded.

Results of the NMA

Two comprehensive network graphs were built using STATA software (Fig. 4; The size of the circle and numbers beside the treatment names represent the number of patients, and the thickness of the edge represents the number of studies). CS as the main compared treatment has 408 patients in 3-6 weeks and 328 patients in 4-6 months. For the 3-6-week duration, two4-arm and three 3-arm studies were included. For the 4-6-month duration, two 4-arm and one 3-arm studies were included. Four of the 19 treatments, prolotherapy, platelet-rich plasma (PRP), CS, and autologous whole blood (AWB) under ultrasound guidance, which were mentioned in 2 studies (38,42), were not connected with the other 15 treatments. Thus, the results obtained from patients receiving 4 and 15 treatments were calculated separately. All potential comparisons were calculated using WinBUGS and presented as the MDs and 95% CIs. All the PSRF parameters were ultimately close to one, indicating that a strong convergence had been achieved. The results are listed in the upper-right triangle of Table 3, and statistically significant differences are shown in bold.

Statistically significant differences in the 3-6-week results were detected in 24 of 190 comparisons. The most significant differences were observed for comparisons with placebo (PLA), botulinum toxin A (BTA) in the gastrocnemius, MSN, and PEP.

The results obtained at 4-6 months revealed 16 statistically significant differences in 105 comparisons. MSN was significantly more advantageous than PLA, CS, CS+PEP, PEP, AWB, PRP, PRP+PEP, CS+ tibial nerve block (TNBlock), polydeoxyribonucleotide (PDRN), and dry needling. Although there was no statistically significant difference compared to BTA, tenoxicam (TEN)+PEP, TNBlock, or BTA in the gastrocnemius, MSN trends towardbetter efficacy than those.

The absolute therapeutic efficacy of every treatment was calculated using the NMA model and indicated a reduction in the VAS score compared with the score recorded prior to treatment. Because the network of 4-6 months was separated into 2 parts, we present

Table 1. *Interventions were grouped into 23 treatment strategies.*

Treatment	
AWB	Autologous whole blood
AWB+UG	Autologous whole blood under ultrasound guidance
BTA	Botulinum toxin A
BTA+UG	Botulinum toxin A under ultrasound guidance
BTA in the gastrocnemius	Ultrasound-guided gastrocnemius injection of botulinum toxin
CS	Corticosteroid
CS+PEP	Corticosteroid combined with peppering
CS+TNBlock	Corticosteroid with tibial nerve block
CS+UG	Corticosteroid under ultrasound guidance
Dry Needling	Dry needling
MSN	Miniscalpel-needle
PEP	Peppering technique
PDRN	Polydeoxyribonucleotide
PLA	Placebo
PRF	Ultrasound-guided pulsed radio-frequency stimulation of the posterior tibial nerve
PRP	Platelet-rich plasma
PRP+PEP	Platelet-rich plasma combined with peppering
PRP+UG	Platelet-rich plasma under ultrasound guidance
Prolotherapy+UG	Prolotherapy under ultrasound guidance
RFNA	Radio-frequency nerve ablation
TEN	Tenoxicam
TEN+PEP	Tenoxicam combined with peppering
TNBlock	Tibial nerve block

the absolute effect for all treatments in one graph. This approach helped us compare all 19 treatments together. Therefore, the absolute effect on a reduction in the VAS score at the 2 follow-up periods was separately listed in the plot, and any change associated with treatment was compared with the results obtained before the treatment.

PLA, BTA, BTA in the gastrocnemius, CS, CS+PEP, MSN, ultrasound-guided pulsed radiofrequency stimulation of the posterior tibial nerve (PRF), PRP and PRP+PEP produced significantly better outcomes than the scores recorded before treatment at both short-term and mid-term follow-up periods. CS+UG only exerted significant effect at 3-6 weeks. CS+TNBlock, TNBlock, and PRP+UG did not exert significant effects at short-term follow-up, but the efficacy improved over time and these treatments produced significantly better effects at the mid-term follow-up. These results are presented in the plot (Fig.5).

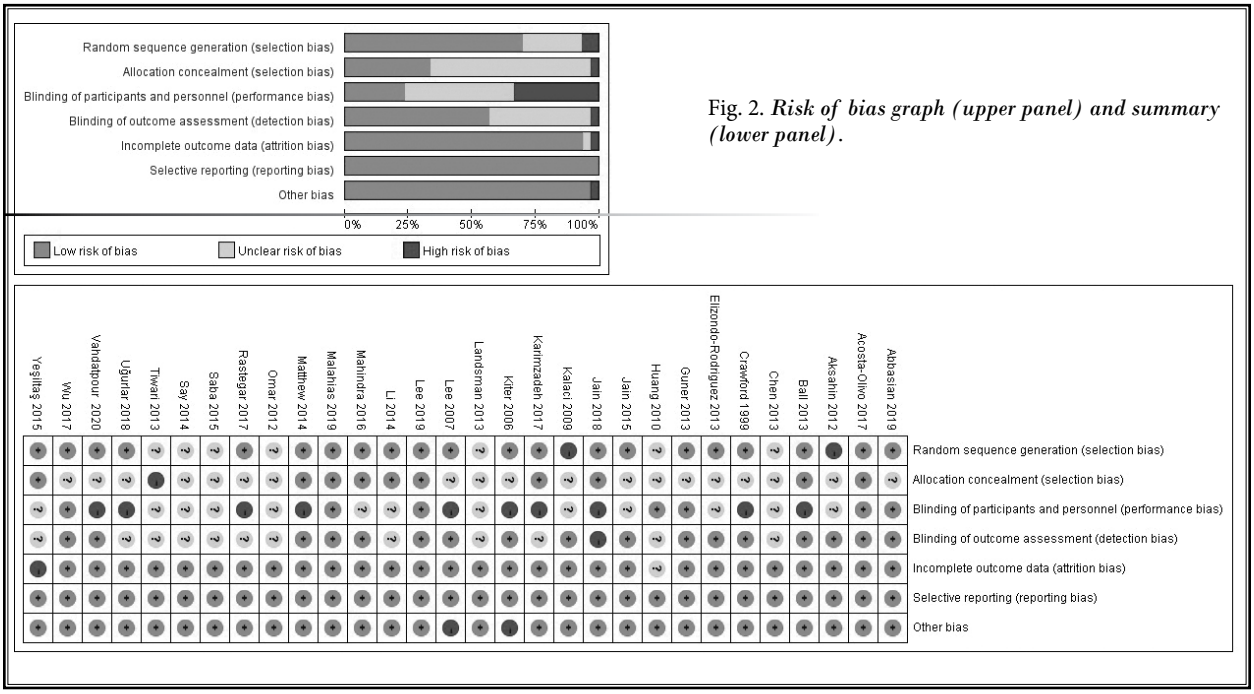

Fig. 2. *Risk of bias graph (upper panel) and summary (lower panel).*

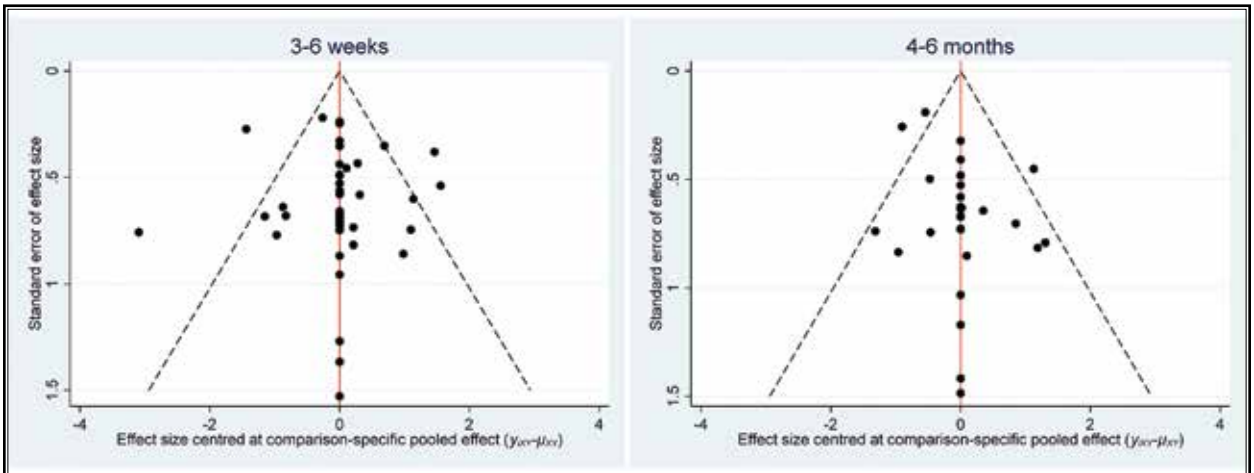

Fig. 3. *Comparison-adjusted funnel plots (left panel: 3-6 weeks;right panel: 4-6 months).*

Table 2. *Characteristics of the included studies.*

Author	Publication year	Duration of condition (months)	Duration of follow-up	Performance time	Intervention	Sample size	Number (%) of female patients	Average age (years)	BMI (Mean ± SD)	Pre-treatment	VAS (Mean ± SD)		
											3-6 weeks	4-6 months	12 months
Kalaci et al. (13)	2009	8.1 ± 12.78 11.9 ± 20.59 9.4 ± 8.38 8.44 ± 7.99	6 months	1	AWB PEP CS CS+PEP	25 25 25 25	19 (76.0%) 18 (72.0)% 17 (68.0%) 16 (64.0%)	NA	27.55 ± 4.86 29.6 ± 4.07 31.92 ± 4.18 32.77 ± 5.02	6.84 ± 2.27 6.72 ± 1.74 6.96 ± 2.71 7.24 ± 2.22	4.32 ± 2.93 4.56 ± 2.45 3.04 ± 2.32 2.20 ± 2.45	3.53 ± 3.06 3.40 ± 2.88 1.52 ± 2.14 0.96 ± 1.24	NA
Jain et al. (14)	2015	> 12 months	12 months	1	CS+PEP PRP+PEP	30 30	14 (63.6%) 16 (66.7%)	55.6	NA	8.27 ± 1.95 8.30 ± 0.88	NA	3.28 ± 3.55 3.70 ± 3.58	5.33 ± 3.47 3.30 ± 3.69
Saba and El-Sherif (15)	2015	25.20± 23.21 24.54 ± 22.24	4 weeks	1	CS+UG CS	10 11	21 (100%)	45.2 46.45	36.37 ± 2.55 36.45 ± 6.05	8.75 ± 1.23 8.64 ± 1.03	0.70 ± 0.67 0.95 ± 1.01	NA	NA
Yesiltas et al. (16)	2015	15.52 ± 11.87 30.21 ± 30.82	6 months	1	CS AWB	21 28	10 (57.6%) 18 (64.3%)	48.28 42.71	31.13 ± 3.56 29.67 ± 3.99	8.38 ± 1.86 8.05 ± 1.71	3.06 ± 3.12 5.31 ± 3.01	3.92 ± 3.33 4.31 ± 3.50	NA
Say (17)	2014	NA	6 months	1	PRP+PEP CS+PEP	25 25	20 (80.0%) 19 (76.0%)	47 48.6	NA	8.8 ± 1.0 8.7 ± 0.9	2.4 ± 0.8 4.0 ± 1.1	1.0 ± 0.8 2.6 ± 0.9	NA
Ball et al. (18)	2013	6 6 7	3 months	1	CS+UG CS PLA	22 22 21	12 (54.5%) 14 (63.6%) 10 (47.6%)	49 49.1 50.1	30.7 ± 5.1 31.8 ± 5.0 32.4 ± 5.7	6.20± 1.92 6.55 ±1.96 5.60± 2.79	3.31 ± 2.84 3.03 ± 2.73 5.09 ± 3.14	2.84 ± 2.49 2.82 ± 2.48 5.38 ± 3.38	NA
Chen et al. (19)	2013	NA	3 months	1	CS+UG CS	16 16	11 (68.8%) 8 (50.0%)	55.69	27.09 ± 2.58 28.27 ± 3.04	7.06 ± 1.12 6.44 ± 1.83	2.38 ± 2.19 3.38 ± 2.09	NA	NA
Elizondo-Rodriguez et al. (20)	2013	NA	6 months	1	BTA CS	19 17	9 (47.4%) 11 (64.7%)	41.6 44.5	NA	7.1 ± 1.75 7.7 ± 1.32	1.9 ± 1.51 3.4 ± 1.24	1.5 ± 2.17 3.8 ± 1.15	NA
Guner et al. (21)	2013	> 3 months	12 months	1	TEN+PEP CS+PEP	32 31	NA	NA	29.91 ± 1.996 30.40 ± 2.884	8.26 ± 1.41 7.97 ± 1.37	NA	3.06 ± 1.91 2.97 ± 2.41	2.94 ± 2.04 3.17 ± 2.31
Tiwari and Bhargava (22)	2013	6+- 20.6	6 months	1	PRP CS	30 30	NA	NA	NA	5.90 ± 0.76 6.03 ± 0.85	2.1 ± 1.0 2.7 ± 0.75	2.0 ± 0.45 2.8 ± 0.76	NA
Akşahin et al. (23)	2012	8.64 ± 5.39 9.4 ± 5.18	6 months	1	CS PRP	30 30	17 (56.7%) 18 (60.0%)	45.67 46.36	29.6 ± 4.07 32.77 ± 5.02	6.2 ± 1.61 7.33 ± 0.62	4.4 ± 2.09 5.6 ± 1.64	3.4 ± 2.32 3.93 ± 2.02	NA
Omar et al. (24)	2012	NA	6 weeks	1	PRP CS	15 15	15 (100%) 15 (100%)	42.5 44.5	NA	8.2± 1.3 8.8 ± 0.9	2.6 ± 2.1 6.5 ± 2.6	NA	NA
Huang et al. (25)	2010	NA	3 months	1	BTA+UG PLA	25 25	19 (76.0%) 19 (76.0%)	54.4 51.5	NA	5.9 ± 0.9 5.4± 0.6	3.4 ± 1.0 5.1 ± 0.8	NA	NA

Table 2 con't. *Characteristics of the included studies.*

Author	Publication year	Duration of condition (months)	Duration of follow-up	Performance time	Intervention	Sample size	Number (%) of female patients	Average age (years)	BMI (Mean ± SD)	Pre-treatment	VAS (Mean ± SD)		
											3-6 weeks	4-6 months	12 months
Lee and Ahmad (26)	2007	7.2 ± 5.6 8.3 ± 7.7	6 months	1 or more re-injection	AWB CS	30 31	28 (93.3%) 29 (93.5%)	48.3 49.2	26.0±4.6 26.1±5.0	7.3 ± 1.8 6.9 ± 1.7	4.6 ± 2.3 2.9 ± 2.8	3.6 ± 2.6 2.4 ± 3.0	NA
Kiter et al. (27)	2006	> 6 months	6 months	1	PEP BTA CS	15 15 14	31 (70.5%)	50.7	NA	6.4 ± 1.1 7.6 ± 1.3 7.28 ± 1.2	NA	2.0 ± 2.2 2.4 ± 1.8 2.57 ± 2.9	NA
Crawford et al. (28)	1999	6±20.6 months	6 months	1	PLA CS+TNblock CS TNblock	27 26 27 26	NA	56.88 53.69 59.41 58.81	NA	5.5±2.1 5.5±2.1 5.6±2.3 5.8±2.8	4.0±2.9 4.5±2.6 2.9±2.5 5.3±2.9	3.3±2.7 2.5±3.2 2.4±2.6 0.6±1.1	NA
Mahindra et al. (29)	2016	NA	3 months	1	PRP+PEP CS+PEP PEP	25 25 25	17 (68%) 13 (52%) 14 (56%)	30.72 33.92 35.48	NA	7.44±1.04 7.72±1.17 7.56±1.15	3.76±1.53 2.84±1.46 7.12±1.12	NA	NA
Li et al. (30)	2014	8.81 ± 2.79 9.80 ± 2.94	12 months	1	MSN CS	31 30	19 (61%) 25 (83%)	54.74 56.93	NA	6.94 ± 1.77 7.33 ± 2.09	1.61 ± 2.14 4.03 ± 2.37	0.90 ± 1.72 6.32 ± 2.64	1.07 ± 1.69 6.48 ± 2.70
Cotchett et al. (31)	2014	13.4±14.1 13.7 ±17.3	3 months	6 times	Dry Needling PLA	39 42	24 (58.6%) 16 (37.2%)	54.4 ±12.4 57.8±12.0	30.3±5.7 28.4±4.4	6.77± 2.09 5.85 ±1.95	3.81± 2.30 4.26± 2.41	NA	NA
Landsman et al. (32)	2013	NA	4 months	1	RFNA PLA	8 9	NA	NA	NA	5.38±2.97 6.78±2.54	4.06 ±2.10* 0.8±1.81*	NA	NA
Karimazadeh et al. (33)	2017	7.8 ± 3.6 11.6	4 months	1	AWB CS	12 12	7 (46.7%) 9 (66.7%)	42.8 ± 11.5 46.8 ± 12.0	30.3±5.7 28.4±4.4	8.5 ± 2.2 7.7 ± 1.4	6.6 ± 1.9 4.4 ± 2.2	NA	NA
Vahdatpour et al. (34)	2020	27.56±30.92 29.84±29.35	6 months	1	PRP CS	16 16	12 (75%) 11 (68.8%)	45.44±7.74 47.12±10.70	NA	8.50±0.97 7.12±1.78	5.50±1.86 3.50± 3.19±1.80	NA	NA
Lee et al. (35)	2019	NA	6 months	"Thrice, normal saline injected on the 2nd and 3rd injection in CS group"	CS PDRN	21 20	17 (77.3%) 12 (54.5%)	50.8±11.5 56.2±12.9	NA	7.4±1.6 7.2±1.7	2.6±2.1 4.2±1.7	3.0±1.9 3.5±2.4	NA
Rastegar et al. (36)	2017	NA	12 months	1	CS Dry Needling	34 32	20 (57.1%) 18 (51.4%)	42.03 ± 10.30 39.84 ± 7.96	NA	6.96 ± 0.87 6.41 ± 0.83	0.32 ± 0.71 3.47 ± 1.32	1.79 ± 1.55 1.28 ± 1.46	2.09 ± 1.58 0.69 ± 0.93
Jain et al. (37)	2018	7.6 ± 2.3 7.3 ± 2.9	6 months	1	CS PRP+PEP	40 40	14 (30%) 20 (50%)	38.9 ± 9.5 37.7 ± 10.3	24.5 ± 3.3 23.7 ± 3.4	8.6 ± 1.1 8.4 ± 1.0	5.7 ± 2.7 6.5 ± 1.7	3.3 ± 2.8 3.0 ± 2.6	NA

Rank Probability

Rank probability indicates the potential efficacy ranking of each treatment. A larger area under the curve in the plot represents a better effect. Figure 6 shows the treatment with the greatest probability of being the most effective based on the area under the SUCRA curve; the inferior treatments are also presented. The percentage of the area under the curve is also listed. Regarding the outcomes assessed at 3-6 weeks, MSN, BTA in the gastrocnemius, BTA, PRF, radio-frequency nerve ablation (RFNA) and CS+UG showed the best treatment effects, while prolotherapy+UG, PRP+UG, PEP, TNBlock ,and PLA produced the worst outcomes. Because prolotherapy+UG, PRP+UG, CS+UG and AWB+UG did not connect with the other 15 options, the SUCRA of 15 options was only calculated at 4-6 months. MSN ranked first, followed by BTA in the gastrocnemius, BTA, TNBlock and PRP+PEP, while PEP, AWB, PLA and polydeoxyribonucleotide (PDRN) resulted in the worst outcomes.

Inconsistency Analysis

At the 2 different durations, 16 comparisons were necessary to detect the inconsistency. All the results are listed in Table 4, with $P > 0.05$ indicating the lack of a significant difference between the direct and indirect results of these comparisons. Inconsistencies were not detected in all the comparisons.

Sensitivity Analysis and Meta-Regression Analysis

Low-quality studies included data from the 3-6-week (26) and 4-6-month (26,27) follow-up periods. The comparison in the study by Lee (26) conducted in 2007 was CS with AWB. The 2006 study by Kiter (27) was a 3-arm trial comparing PEP, BTA, and CS. After excluding these pairs of data, the rank probability of 2 networks was calculated again. PRP and PRP+PEP were from 66.6% and 66.7% at 3-6 weeks to 66.8% and 65.9% at 4-6 months respectively. Despite there being small changes in SUCRA values, they still showed a position swap in rank. No other changes in rank were observed for the results obtained at 3-6 weeks and 4-6 months. Based on these data, the results of the NMA are robust.

Table 2 con't. *Characteristics of the included studies.*

Author	Publication year	Duration of condition (months)	Duration of follow-up	Performance time	Intervention	Sample size	Number (%) of female patients	Average age (years)	BMI (Mean ± SD)	Pre-treatment	VAS (Mean ± SD)		
											3-6 weeks	4-6 months	12 months
Uğurlar et al. (38)	2018	13.2 13.9 14.5	36 months	3	Prolotherapy + UG PRP + UG CS+UG	40 39 40	19 (47.5%) 20 (51.3%) 23 (57.5%)	37.5 38.4 40.1	26.7 26.6 27.3	7.0 ± 6.4 7.9 ± 7.6 7.4 ± 5.5	6.9 ± 6.5 7.8 ± 6.5 3.2 ± 2.4	3.0 ± 2.4 2.6 ± 0.3 5.2 ± 3.6	6.5 ± 6.4 5.6 ± 4.4 6.8 ± 4.4
Abbasian et al. (39)	2019	10.6 ± 1.4 10.1 ± 1.3	12 months	1	BTA in the Gastrocnemius PLA	15 13	6 (40%) 4 (30.8%)	47.3 ± 6.1 45.6 ± 9.7	24.8 ± 1.9 29.3 ± 1.3	8.0 ± 0.8 7.8 ± 0.8	2.2 ± 0.6 6.5 ± 1.1	0.87 ± 0.7 5.0 ± 1.5	7.7 ± 0.8* 3.8 ± 1.9*
Wu et al. (40)	2017	9.60±5.26 10.00±4.93	3 months	1	PRF PLA	20 20	12 (67.7%) 9 (50%)	49.45±9.90 44.75±13.89	NA	6.03±1.82 6.06±1.79	2.39±1.16 5.87±1.69	NA	NA
Acosta-Olivo et al. (41)	2017	NA	4 months	1	CS PRP	14 14	22 (78.6%)	44.8	NA	5.67±1.54 4.53±1.12	2.21±1.69 2.42±1.45	0.47±1.34 0.33±0.72	NA
Malahias et al. (42)	2018	NA	6 months	1	PRP+UG AWB+UG	18 18	NA	NA	NA	7.4± 1.79 6.9 ±1.97	NA	2.9± 3.44 4.3± 3.7	NA

Abbreviations: AWB - autologous whole blood; AWB+UG - autologous whole blood under ultrasound guidance; BTA - botulinum toxin A; BTA+UG - botulinum toxin A under ultrasound guidance; BTA in the gastrocnemius - ultrasound-guided gastrocnemius injection of botulinum toxin; CS - corticosteroid; CS+PEP - corticosteroid combined with peppering; CS+TNBlock - corticosteroid with tibial nerve block; CS+UG - corticosteroid under ultrasound guidance; dry needling - dry needling; MSN - miniscalpel-needle; PEP - peppering technique; PDRN - polydeoxyribonucleotide; PLA - placebo; PRF - ultrasound-guided pulsed radio-frequency stimulation at the posterior tibial nerve; PRP - platelet-rich plasma; PRP+PEP - platelet-rich plasma combined with peppering; PRP+UG - platelet-rich plasma under ultrasound guidance; prolotherapy+UG - prolotherapy under ultrasound guidance; RFNA - radio-frequency nerve ablation; TEN - tenoxicam; TEN+PEP - tenoxicam combined with peppering; TNBlock - tibial nerve block

*The change between pre-treatment and post-treatment.

Table 3. *Results (MDs with 95% CIs) of the PMA and NMA a. The upper-right triangle presents the findings (MDs with 95% CIs) of the NMA conducted using WinBUGS software version 1.4.3. b. The lower-left triangle presents the findings (MDs with 95% CIs) of the PMA conducted using STATA software version 14, and n refers to the numbers of RCTs that directly compared the 2 interventions. A positive MD favor the lower-right intervention, a negative MD favours the upper-left intervention. Statistically significant findings are shown in bold.*

A. Results (MDs with 95% CIs) of the PMA and NMA of VAS scores at 3-6 weeks.

PLA	3.46 (-0.35,7.23)	2.21 (-0.86,5.33)	**4.51 (1.36,7.59)**	**2.56 (0.50,4.58)**	2.92 (-0.17,6.02)	0.20 (-2.86,3.2)	**3.00 (0.52,5.47)**	0.06 (-2.41,2.55)	**4.58 (0.65,8.46)**	0.75 (-3.10,4.54)	-0.29 (-3.47,2.90)	0.72 (-1.95,3.36)	**3.44 (0.22,6.64)**	-1.10 (-5.78,3.54)	**2.79 (0.27,5.29)**	2.82 (-0.26,5.89)	3.27 (-0.35,6.85)	-0.31 (-3.45,2.77)	-1.10 (-5.88,3.68)
	BTA	-1.26 (-6.13,3.67)	1.04 (-3.88,6.00)	-0.90 (-4.07,2.30)	-0.54 (-4.49,3.47)	-3.26 (-7.63,1.15)	-0.46 (-4.16,3.28)	-3.40 (-7.41,0.66)	1.12 (-3.42,5.73)	-2.71 (-7.23,1.83)	-3.75 (-7.74,0.36)	-2.74 (-6.33,0.86)	-0.02 (-4.95,4.99)	-4.57 (-9.50,0.82)	-0.68 (-4.19,2.89)	-0.64 (-4.61,3.35)	-0.19 (-5.31,5.02)	-3.77 (-8.21,0.68)	-4.56 (-10.00,0.91)
n = 1, 2.20 (1.73, 2.67)		BTA+UG	2.30 (-2.12,6.71)	0.35 (-3.37,4.06)	0.71 (-3.67,5.11)	-2.01 (-6.35,2.31)	'0.79 (-3.14,4.72)	-2.14 (-6.13,1.81)	2.38 (-2.63,7.31)	-1.46 (-6.43,3.38)	-2.50 (-6.95,1.98)	-1.49 (-5.58,2.56)	1.23 (-3.25,5.69)	-3.31 (-8.50,2.27)	0.58 (-3.39,4.55)	0.62 (-3.73,4.94)	1.06 (-3.69,5.83)	-2.52 (-6.87,1.84)	-3.30 (-8.95,2.35)
n = 1, 4.50 (3.86, 5.15)			BTA in Gastrocnemius	-1.95 (-5.66,1.75)	-1.59 (-5.95,2.81)	-4.31 (-8.71,0.03)	-1.51 (-5.47,2.43)	**-4.44 (-8.4,-0.49)**	0.08 (-4.91,5.01)	-3.76 (-8.71,1.14)	**-4.80 (-9.21,-0.33)**	-3.79 (-7.88,0.31)	-1.07 (-5.54,3.37)	**-5.61 (-11.14,-0.03)**	-1.72 (-5.72,2.26)	-1.68 (-6.05,2.65)	-1.24 (-5.95,3.51)	**-4.82 (-9.22,-0.43)**	-5.60 (-11.2,0.04)
n = 2, 2.03 (0.26, 3.80)	n = 1, -0.90 (-1.86, 0.06)			CS	0.36 (-1.92,2.71)	-2.36 (-5.42,0.66)	0.44 (-1.44,2.32)	**-2.5 (-4.93,-0.04)**	2.02 (-1.25,5.32)	-1.81 (-5.12,1.43)	**-2.85 (-5.25,-0.39)**	**-1.84 (-3.51,-0.18)**	0.88 (-2.91,4.68)	-3.66 (-8.05,0.70)	0.23 (-1.21,1.70)	0.27 (-1.99,2.55)	0.71 (-3.36,4.88)	-2.87 (-5.97,0.25)	-3.66 (-8.15,0.88)
				n = 1, 1.12 (-0.23, 2.47)	CS+PEP	-2.72 (-6.57,1.09)	0.08 (-2.90,3.03)	-2.86 (-6.24,0.46)	1.66 (-2.35,5.69)	-2.17 (-6.22,1.78)	**-3.21 (-5.39,-1.00)**	-2.20 (-4.73,0.29)	0.52 (-3.97,4.93)	-4.02 (-8.99,0.90)	-0.13 (-2.90,2.59)	-0.09 (-2.08,1.85)	0.35 (-4.35,5.09)	-3.23 (-7.11,0.65)	-4.01 (-9.08,1.07)
n = 1, -0.50 (-1.84, 0.84)				**n = 1, -1.70 (-2.99, -0.41)**		CS+Tnblock	2.80 (-0.71,6.28)	-0.14 (-3.73,3.54)	4.38 (-0.08,8.85)	0.55 (-3.95,5.02)	-0.49 (-4.38,3.43)	0.52 (-2.92,4.01)	3.24 (-1.14,7.70)	-1.30 (-6.52,3.94)	2.59 (-0.79,6.00)	2.63 (-1.17,6.47)	3.07 (-1.62,7.76)	-0.51 (-3.93,2.88)	-1.29 (-6.64,4.18)
n = 1, 2.38 (0.68, 4.08)				n = 3, 0.47 (-0.65, 1.59)			CS+UG	-2.94 (-5.87,0.04)	1.58 (-2.20,5.36)	-2.25 (-6.05,1.51)	**-3.29 (-6.35,-0.18)**	-2.28 (-4.78,0.23)	0.44 (-3.60,4.48)	**-4.10 (-8.10,-0.17)**	-0.22 (-2.59,2.19)	-0.18 (-3.11,2.73)	0.27 (-4.06,4.69)	-3.31 (-6.84,0.20)	-4.10 (-8.19,0.03)
n = 1, 1.37 (0.41, 2.33)				**n = 1, -3.70 (-4.18, -3.21)**				Dry Needling	**4.52 (0.39,8.59)**	0.68 (-3.39,4.76)	-0.35 (-3.82,3.14)	0.66 (-2.28,3.60)	3.37 (-0.71,7.38)	-1.17 (-6.15,3.73)	2.72 (-0.12,5.57)	2.76 (-0.58,6.11)	3.21 (-1.12,7.55)	-0.37 (-4.11,3.29)	-1.16 (-6.20,3.86)
				n = 1, 2.03 (0.89, 3.17)					MSN	-3.84 (-8.47,0.83)	**-4.87 (-8.91,-0.78)**	**-3.86 (-7.54,-0.18)**	-1.15 (-6.19,3.92)	**-5.69 (-11.13,-0.18)**	-1.80 (-5.43,1.80)	-1.76 (-5.75,2.29)	-1.31 (-6.56,4.00)	**-4.89 (-9.40,-0.37)**	**-5.68 (-11.18,-0.03)**
				n = 1, -1.80 (-2.90, -0.70)						PDRN	-1.04 (-5.05,3.05)	-0.03 (-3.68,3.67)	2.69 (-2.23,7.70)	-1.85 (-7.28,3.62)	2.04 (-1.49,5.71)	2.08 (-1.86,6.11)	2.52 (-2.73,7.79)	-1.06 (-5.49,3.48)	-1.84 (-7.28,3.82)
				n = 1, -1.76 (-3.07, -0.45)	**n = 2, -3.75 (-5.27, -2.23)**						PEP	1.01 (-1.62,3.55)	3.73 (-0.84,8.23)	-0.81 (-5.88,4.21)	**3.08 (0.24,5.87)**	**3.11 (0.77,5.43)**	3.56 (-1.23,8.34)	-0.02 (-3.96,3.93)	-0.81 (-5.93,4.28)
				n = 4, -1.61 (-2.31, -0.92)	**n = 1, -2.52 (-3.91, -1.13)**						n = 1, 0.36 (-0.98, 1.71)	AWB	2.72 (-1.44,6.86)	-1.82 (-6.48,2.81)	2.06 (-0.16,4.27)	2.1 (-0.44,4.66)	2.55 (-1.91,7.06)	-1.03 (-4.51,2.49)	-1.82 (-6.55,2.96)
n = 1, 3.45 (2.41, 4.49)													PRF	-4.54 (-10.19,1.08)	-0.65 (-4.71,3.42)	-0.61 (-5.02,3.83)	-0.17 (-5.01,4.64)	-3.75 (-8.19,0.72)	-4.53 (-10.38,1.27)
							n = 1, -4.10 (-6.59, -1.61)							Prolotherapy+UG	3.89 (-0.66,8.52)	3.93 (-0.97,8.89)	4.37 (-1.40,10.24)	0.79 (-4.45,6.04)	0.01 (-4.29,4.34)
				n = 5,0.21 (-0.90,1.32)											PRP	0.04 (-2.63,2.72)	0.48 (-3.86,4.9)	-3.09 (-6.52,0.33)	-3.88 (-8.61,0.86)
				n = 1, -1.00 (-1.86, -0.14)	n = 2, 0.26 (-2.58, 3.10)						**n = 1, 3.24 (2.55, 3.93)**					PRP+PEP	0.44 (-4.27,5.16)	-3.13 (-7.00,0.72)	-3.92 (-9.00,1.12)
n = 1, 3.26 (1.39, 5.14)																	RFNA	-3.58 (-8.34,1.09)	-4.37 (-10.38,1.60)
n = 1, -1.00 (-2.47, 0.47)				**n = 1, -2.20 (-3.62, -0.787)**		n = 1, -0.50 (-1.93, 0.93)												TNBlock	-0.79 (-6.10,4.56)
							n = 1, -4.10 (-6.78, -1.42)							n = 1, 0.00 (-3.00, 3.00)					PRP+UG

Table 3 con't. *Results (MDs with 95% CIs) of the PMA and NMA a. The upper-right triangle presents the findings (MDs with 95% CIs) of the NMA conducted using WinBUGS software version 1.4.3. b. The lower-left triangle presents the findings (MDs with 95% CIs) of the PMA conducted using STATA software version 14, and n refers to the numbers of RCTs that directly compared the 2 interventions. A positive MD favor the lower-right intervention, a negative MD favours the upper-left intervention. Statistically significant findings are shown in bold.*

B. Results (MDs with 95% CIs) of the PMA and NMA of the VAS scores at 4-6 months.

PLA	1.01 (-1.81,3.86)	1.71 (-1.73,5.23)	-0.5 (-3.91,2.95)	0.04 (-3.11,3.27)	1.12 (-2.12,4.34)	2.11 (-1.42,5.57)	3.11 (-0.90,7.00)	1.90 (-2.39,6.35)	0.81 (-2.07,3.68)	**3.01 (0.17,5.88)**	**6.02 (2.05,9.96)**	0.32 (-3.67,4.39)	0.97 (-2.90,4.78)	**4.33 (1.67,6.96)**				
n = 1, 1.00 (-0.31, 2.31)	CS	0.70 (-1.24,2.77)	-1.51 (-3.40,0.44)	-0.97 (-2.37,0.48)	0.11 (-1.45,1.66)	1.11 (-0.99,3.17)	2.10 (-0.64,4.84)	0.90 (-2.43,4.35)	-0.19 (-3.11,2.71)	2.01 (-0.86,4.90)	**5.02 (2.27,7.75)**	-0.68 (-3.47,2.16)	-0.03 (-2.62,2.57)	3.33 (-0.59,7.21)				
	n = 1, 0.84 (-0.39, 2.07)	CS+PEP	-2.21 (-4.63,0.14)	-1.67 (-3.88,0.45)	-0.59 (-3.2,1.89)	0.40 (-1.43,2.09)	1.40 (-2.07,4.77)	0.19 (-2.52,2.91)	-0.89 (-4.49,2.60)	1.31 (-2.19,4.76)	**4.32 (0.85,7.69)**	-1.39 (-4.90,2.05)	-0.74 (-4.09,2.51)	2.63 (-1.78,6.94)				
	n = 2, -1.27 (-3.04, 0.50)	**n = 1, -2.96 (-4.20, -1.72)**	PEP	0.54 (-1.41,2.40)	1.62 (-0.93,4.00)	2.62 (-0.01,5.12)	**3.61 (0.21,6.90)**	2.40 (-1.20,6.05)	1.32 (-2.21,4.78)	**3.52 (0.04,6.97)**	**6.53 (3.14,9.87)**	0.82 (-2.59,4.15)	1.47 (-1.81,4.64)	**4.84 (0.46,9.17)**				
	n = 4, -0.82 (-1.84, 0.21)	**n = 1, -2.97 (-4.29, -1.65)**	n = 2, 0.45 (-0.50, 1.41)	AWB	1.08 (-1.05,3.16)	2.07 (-0.29,4.36)	3.07 (-0.04,6.13)	1.86 (-1.57,5.37)	0.77 (-2.48,4.02)	2.98 (-0.24,6.16)	**5.99 (2.87,9.05)**	0.28 (-2.94,3.43)	0.93 (-2.09,3.88)	**4.30 (0.07,8.39)**				
	n = 3, 0.13 (-0.90, 1.15)				PRP	0.99 (-1.64,3.57)	1.99 (-1.14,5.11)	0.78 (-2.90,4.61)	-0.30 (-3.59,2.96)	1.90 (-1.33,5.16)	**4.91 (1.71,8.07)**	-0.80 (-4.01,2.45)	-0.15 (-3.16,2.90)	3.22 (-0.99,7.41)				
	n = 1, 0.10 (-0.93, 1.13)	**n = 2, 0.80 (-1.23, 2.83)**				PRP+PEP	1.00 (-2.38,4.47)	-0.21 (-3.33,3.11)	-1.30 (-4.78,2.32)	0.90 (-2.61,4.47)	**3.91 (0.49,7.36)**	-1.79 (-5.34,1.79)	-1.14 (-4.48,2.26)	2.22 (-2.16,6.64)				
	n = 1, 2.10 (1.16, 3.04)						BTA	-1.21 (-5.55,3.24)	-2.29 (-6.26,1.73)	-0.09 (-4.07,3.96)	2.92 (-1.03,6.75)	-2.79 (-6.70,1.17)	-2.14 (-5.89,1.64)	1.23 (-3.47,5.99)				
		n = 1, 0.20 (-0.75, 1.15)						TEN+PEP	-1.09 (-5.59,3.23)	1.11 (-3.32,5.48)	4.12 (-0.29,8.41)	-1.58 (-6.04,2.81)	-0.93 (-5.24,3.24)	2.43 (-2.75,7.49)				
n = 1, 0.80 (-0.63, 2.23)	n = 1, -0.20 (-1.63, 1.23)								CS+TNblock	2.20 (-0.67,5.11)	**5.21 (1.22,9.22)**	-0.49 (-4.58,3.59)	0.16 (-3.74,4.04)	3.52 (-0.42,7.45)				
n = 1, 3.00 (1.68, 4.32)	**n = 1, 2.00 (0.68, 3.32)**								**n = 1, 2.20 (0.77, 3.63)**	TNblock	3.01 (-1.01,6.95)	-2.69 (-6.68,1.42)	-2.04 (-5.92,1.83)	1.32 (-2.59,5.20)				
	n = 1, 5.03 (3.89, 6.17)										MSN	**-5.70 (-9.60,-1.72)**	**-5.06 (-8.82,-1.29)**	-1.69 (-6.45,3.15)				
	n = 1, -0.70 (-1.95, 0.55)											PDRN	0.65 (-3.21,4.47)	4.01 (-0.87,8.82)				
	n = 1, -0.04 (-0.67, 0.59)												DryNeedling	3.36 (-1.29,8.06)				
n = 1, 4.33 (3.53, 5.13)														BTA+UG_in_G				
															PRP+UG	-1.88 (-8.30,4.69)	-1.29 (-8.07,5.42)	-3.09 (-9.82,3.70)
															n = 1,-1.90 (-3.92,0.12)	AWB+UG	0.59 (-8.76,9.91)	-1.21 (-10.64,8.01)
															n = 1, -1.30 (-4.21, 1.61)		Prolotherapy +UG	-1.80 (-8.34,4.75)
															n = 1, -3.10 (-5.88, -0.32)		n = 1, -1.80 (-4.09, 0.49)	CS+UG

AWB, autologous whole blood; AWB+UG, autologous whole blood under ultrasound guidance; BTA, botulinum toxin A; BTA+UG, botulinum toxin A under ultrasound guidance; BTA in the gastrocnemius, ultrasound-guided gastrocnemius injection of botulinum toxin; CS, corticosteroid; CS+PEP, corticosteroid combined with peppering; CS+TNBlock, corticosteroid with tibial nerve block; CS+UG, corticosteroid under ultrasound guidance; MSN, miniscalpel-needle; PEP, peppering technique; PDRN, polydeoxyribonucleotide; PLA, placebo; PRF, ultrasound-guided pulsed radiofrequency stimulation at the posterior tibial nerve; PRP, platelet-rich plasma; PRP+PEP, platelet-rich plasma combined with peppering; PRP+UG, platelet-rich plasma under ultrasound guidance; prolotherapy+UG, prolotherapy under ultrasound guidance; RFNA, radio-frequency nerve ablation; TEN, tenoxicam; TEN+PEP, tenoxicam combined with peppering; TNBlock, tibial nerve block

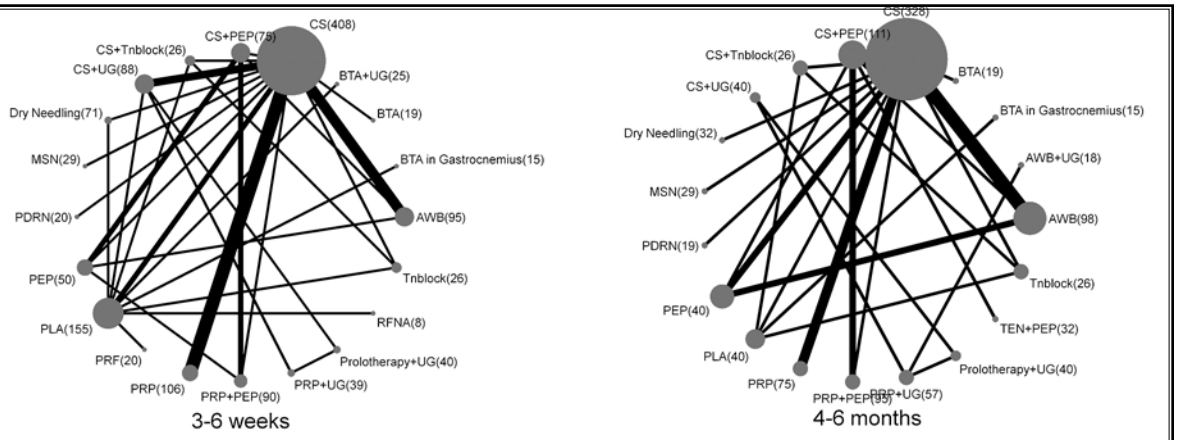

Fig. 4. *Network of comparisons of minimally invasive nonsurgical treatments for PF (left panel: 3-6 weeks; right panel: 4-6 months).*

Note: The size of the circle and numbers beside the treatment names represents the number of patients and the thickness of the edge represents the number of studies.

Abbreviations: AWB - autologous whole blood; AWB+UG - autologous whole blood under ultrasound guidance; BTA - botulinum toxin A; BTA+UG - botulinum toxin A under ultrasound guidance; BTA in the gastrocnemius - ultrasound-guided gastrocnemius injection of botulinum toxin; CS - corticosteroid; CS+PEP - corticosteroid combined with peppering; CS+TNBlock - corticosteroid with tibial nerve block; CS+UG - corticosteroid under ultrasound guidance; dry needling - dry needling; MSN - miniscalpel-needle; PEP - peppering technique; PDRN - polydeoxyribonucleotide; PLA - placebo; PRF - ultrasound-guided pulsed radio-frequency stimulation of the posterior tibial nerve; PRP - platelet-rich plasma; PRP+PEP - platelet-rich plasma combined with peppering; PRP+UG - platelet-rich plasma under ultrasound guidance; prolotherapy+UG - prolotherapy under ultrasound guidance; RFNA - radio-frequency nerve ablation; TEN - tenoxicam; TEN+PEP - tenoxicam combined with peppering; TNBlock - tibial nerve block.

A meta-regression analysis was performed using the 2 follow-up period networks; no significant change in the DIC was observed (Table 4). Thus, the covariate (the sample size of the study) was not associated with the treatment effects.

Discussion

Summary of Findings

The results of the pairwise analysis and NMA showed good concordance, which has been presented in the matrix table. The results of NMA usually had wider 95% CIs than the pairwise analysis. In other words, the NMA is more stringent and less likely to yield positive results than the PMA.

The effects of most treatments were measured at both follow-up periods, except for AWB+UG, BTA+UG, PRF, RFNA, and TEN+PEP based on the absolute therapeutic efficacy (Fig. 5). All treatment outcomes were increased at the follow-up period, except for CS+UG and PRP, which decreased at 4-6 months.

Although the majority of the MDs had a wide CI (Table 3), including the null value and increasing the difficulty of deriving a certain conclusion, some treatments produced a positive result.

MSN

MSN resulted in the best therapeutic effect compared with other options at both 3-6 weeks and 4-6 months or the measurements recorded before treatment. It also exhibited the highest probability (86.4%, 96.9%) of being the most effective treatment in SUCRA curves for the 2 follow-up periods. The absolute effects were -5.46 (-9.35, -1.53) and -8.53 (-12.49, -4.51), which were very significant at both follow-up periods compared with the pretreatment value. The side effects of MSN reported in a previous study (31) were mild distending pain and subcutaneous bleeding at the treatment site that resolvedwithin 2 days.

BTA in the Gastrocnemius

BTA in the gastrocnemius (39) is a novel technique in which 70 IU of BTA are injected in the medial head of the gastrocnemius muscle under ultrasound guidance. It showed 85.5% and 85.9% cumulative probabilities of effectiveness at 3-6 weeks and 4-6 months, and was second behind MSN.

BTA

The cumulative probabilities of the effectiveness of the BTA injection in foot fascia were 74.3% and

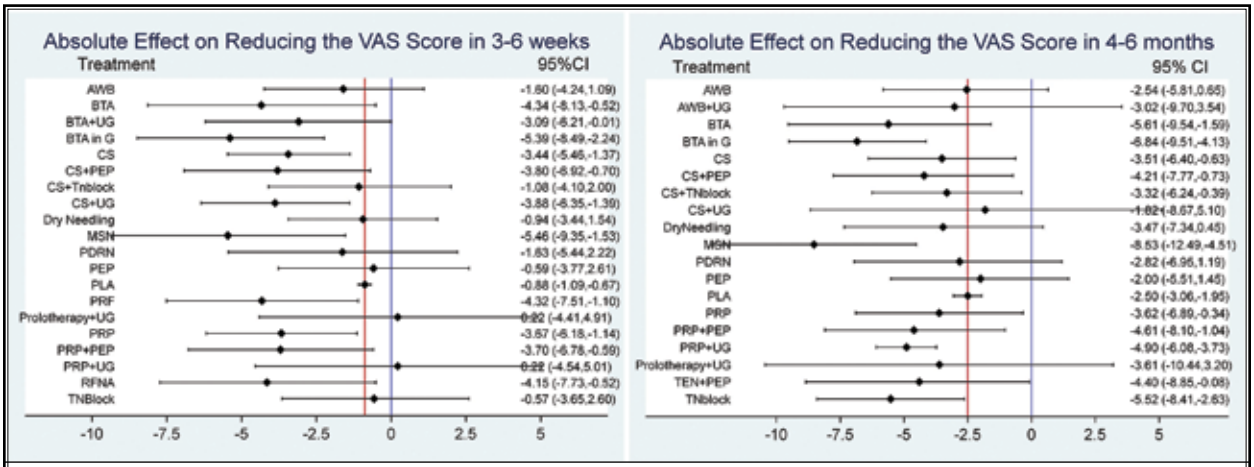

Fig. 5. *Absolute effect on reducing the VAS score (left panel: 3-6 weeks; right panel: 4-6 months).*
Abbreviations: AWB - autologous whole blood; AWB+UG - autologous whole blood under ultrasound guidance; BTA - botulinum toxin A; BTA+UG - botulinum toxin A under ultrasound guidance; BTA in the gastrocnemius - ultrasound-guided gastrocnemius injection of botulinum toxin; CS - corticosteroid; CS+PEP - corticosteroid combined with peppering; CS+TNBlock - corticosteroid with tibial nerve block; CS+UG - corticosteroid under ultrasound guidance; dry needling - dry needling; MSN - miniscalpel-needle; PEP - peppering technique; PDRN - polydeoxyribonucleotide; PLA - Placebo; PRF - ultrasound-guided pulsed radio-frequency stimulation of the posterior tibial nerve; PRP - platelet-rich plasma; PRP+PEP - platelet-rich plasma combined with peppering; PRP+UG - platelet-rich plasma under ultrasound guidance; prolotherapy+UG - prolotherapy under ultrasound guidance; RFNA - radio-frequency nerve ablation; TEN - tenoxicam; TEN+PEP - tenoxicam combined with peppering; TNBlock - tibial nerve block.

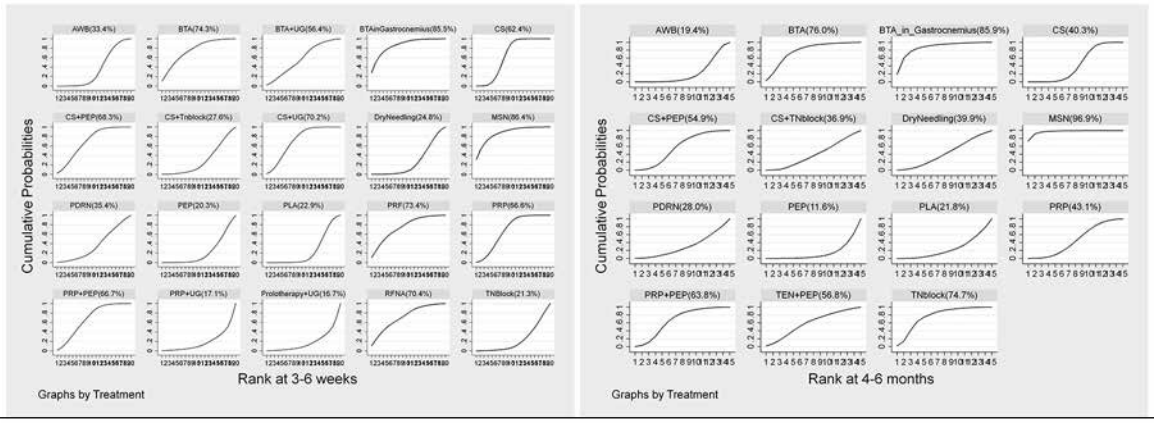

Fig. 6. *SUCRA values of comparisons of minimally invasive non-surgical treatments for PF (left panel: 3-6 weeks; right panel: 4-6 months).*
Abbreviations: AWB - autologous whole blood; AWB+UG - autologous whole blood under ultrasound guidance; BTA - botulinum toxin A; BTA+UG - botulinum toxin A under ultrasound guidance; BTA in the gastrocnemius - ultrasound-guided gastrocnemius injection of botulinum toxin; CS - corticosteroid; CS+PEP - corticosteroid combined with peppering; CS+TNBlock - corticosteroid with tibial nerve block; CS+UG - corticosteroid under ultrasound guidance; dry needling - dry needling; MSN - miniscalpel-needle; PEP - peppering technique; PDRN - polydeoxyribonucleotide; PLA - placebo; PRF - ultrasound-guided pulsed radio-frequency stimulation of the posterior tibial nerve; PRP - platelet-rich plasma; PRP+PEP - platelet-rich plasma combined with peppering; PRP+UG - platelet-rich plasma under ultrasound guidance; prolotherapy+UG - prolotherapy under ultrasound guidance; RFNA - radio-frequency nerve ablation; TEN - tenoxicam; TEN+PEP - tenoxicam combined with peppering; TNBlock - tibial nerve block.

76.0% at the 2 follow-up periods after MSN and BTA in the gastrocnemius. The absolute effects recorded in the 2 follow-up periods (-4.34 [-8.13, -0.52] and -5.61 [-9.54, -1.59], respectively) were significant compared with the pretreatment period. BTA+UG also exerted a positive effect, but, unfortunately, the

Table 4. *Results of the inconsistency and meta-regression analyses.*

	3-6 weeks		4-6 months	
	Comparison	***P* value**	**Comparison**	***P* value**
Inconsistency	PLA vs CS	0.210550	CS vsCS+PEP	0.332325
	PLA vs CS+UG	0.632450	CS vs PRP+PEP	0.191975
	PLA vs Dry Needling	0.169875	CS+PEP vs PEP	0.272425
	CS vs CS+PEP	0.564700	CS+PEPvs AWB	0.130250
	CS vs Dry Needling	0.171150	CS+PEPvs PRP+PEP	0.199150
	CS vs PEP	0.334275		
	CS vs PRP+PEP	0.224300		
	CS+PEP vs AWB	0.789175		
	CS+PEP vs PRP+PEP	0.345650		
	PEP vs AWB	0.518750		
	PEP vs PRP+PEP	0.790250		
DIC	without the covariate 110.551	with the covariate 110.853	without the covariate 70.44	with the covariate 70.51
Regression coefficient	0.03069 (-0.07386, 0.03056)		-0.1755 (-1.412, 0.8997)	

results for BTA+UG were unavailable at 4-6 months of follow-up.

CS, CS+UG and CS+PEP

CS is a widely used therapy. Twenty-four of 30 studies mentioned a single application of CS alone or in combination with an ultrasound-guided or peppering technique. The absolute therapeutic effects of CS and CS+PEP at 3-6 weeks were significant (-3.44 [-5.46, -1.37] and -3.80 [-6.92, -0.70], respectively). But the effects of the 2 treatments were improved slightly at 4-6 months (-3.51 [-6.40, -0.63] and -4.21 [-7.77, -0.73], respectively). The SUCRA values of CS decreased from 62.4% to 40.3%, and the SUCRA value of CS+PEP decreased from 68.3% to 54.9% in the comparison of the 2 follow-up periods. The effect of CS+UG reduced from -3.88 (-6.35, -1.39) at 3-6 weeks to -1.82 (-8.67, 5.10) at 4-6 months.

PRP, PRP+UG, and PRP+PEP

PRP is a new and developing treatment that has been applied to treat several forms of tendinitis (43). PRP has also been combined with ultrasound-guided and peppering techniques. The absolute effects of PRP+PEP and PRP+UG improved from 3-6 weeks to 4-6 months of follow-up (-3.70 [6.18, -1.14] to -4.61 [-8.10, -1.04] and 0.22 [-4.54, 5.01] to -4.90 [-6.08, -3.73], respectively). Meanwhile, the absolute effect of PRP decreased slightly over time from -3.67 (-6.18, -1.14) to -3.62 (-6.89, -0.34). The cumulative probabilities of the effectiveness of PRP and PRP + PEP were 43.1% and 63.8%.

PEP

Treatment with peppering alone was worse than PLA at both short- and mid-term follow-up periods.

The peppering technique has also been widely used after an injection of medication. In our meta-analysis, CS+PEP and PRP+PEP were better than CS and PRP alone at both short- and mid-term follow-up periods (CS vs CS+PEP, 1.12 [-0.23, 2.47] and 0.84 [-0.39, 2.07] in the pair-wise analysis; 0.36 [-1.92, 2.71] and 0.70 [-1.24, 2.77] in the NMA at 3-6 weeks and 4-6 months of follow-up; PRP vs PRP+PEP, 0.40 [-2.63, 2.72] and 0.99 [-1.64, 3.57] in the NMA at 3-6 weeks and 4-6 months of follow-up, Table 3). Treatment with PEP also resulted in a higher cumulative probability, as shown in Fig. 6 (CS [62.4%]: CS+PEP [68.3%], PRP [66.6%], and PRP+PEP [66.7%] at 3-6 weeks of follow-up; CS [40.3%], CS+PEP [54.9%], PRP [43.1%], and PRP+PEP [63.8%] at 4-6 months of follow-up). Therefore, PEP is recommended for application after an injection.

UG

UG is a noninvasive technique that allows the operator to determine a better injection site in the foot fascia. Several treatments have been applied with or without ultrasound guidance, such as AWB, BTA, CS, and PRP. We did not identify a significant advantage of medication injection under ultrasound guidance as shown in Table 3 and Fig. 6. The SUCRAvalues for the comparisons at 3-6 weeks of follow-up were BTA (74.3%), BTA+UG (56.4%), CS (62.4%), CS+UG (70.2%), PRP (66.6%), and PRP+UG (17.1%). At 4-6 months,

because PRP+UG, AWB+UG and CS+UG were not connected with the other treatments, we were unable to conclusively determine whether UG helps promote the therapeutic effect.

Other Treatments

PRF, prolotherapy+UG, RFNA, TEN, and TNBlock displayed ordinary treatment effects compared with MSN, BTA and BTA in the gastrocnemius. As medicine injections, AWB and PDRN exerted the worst mid-term effects (19.4% and 28.0%, Fig. 6).

Findings of Previous Reviews and Other RCTs

A systematic review of the minimally invasive nonsurgical management of PF discussed 6 treatments. BTA, PRP and intratissue percutaneous electrolysis dry needling produced similar or better effects than CS in the mid-term follow-up (44).

Ten common options, including extracorporeal shockwave therapy, NSAID injection, oral NSAID, CS, and orthoses, were compared and calculated in a network meta-analysis (45). Due to equivocal evidence, the authors were unable to determine which treatment is the most effective for PF.

The review by Ang (46) included 10 RCTs examining CS injection therapies. Significant differences in VAS scores were not observed between the ultrasound- and palpation-guided corticosteroid injection groups. Regarding the peppering technique, 3 RCTs (14,28,30) obtained a coincidence outcome. We obtained some insights from our meta-analysis.

Recently, Tsikopoulos et al (47) conducted a comprehensive study of injection therapies for PF and found that the micronized dehydrated human amniotic/chorionic membrane was the best treatment in the short term. In addition, BTA, which was the best single medicine therapy in our study, was potentially the best therapy because it produced significant pain relief at 6 months. Additionally, PRP showed a good pooled result at 0-6 months. The effect of PRP also improved over time in the present study.

Hsiao et al (48) conducted a network meta-analysis of blood-derived products, extracorporeal shockwave therapy and CS. The results obtained at 6 months showed that PRP performed better than CS. The conclusion is consistent with our findings. Li et al (49) conducted a meta-analysis comparing corticosteroid and placebo injections and found that CS is better than PLA in the early follow-up period.

Li et al (50) conducted a meta-analysis of 5 RCTs comparing ultrasound- and palpation-guided injections of corticosteroid in terms of their effects on VAS scores and plantar fascia thickness. CS with UG produced superior effects, inconsistent with our results. Dry needling has been studied as an alternative treatment in a systematic review (51) that included only 3 non-RCTs; a conclusion is difficult to draw based on this limited sample. In our network analysis, dry needling resulted in a mediocre outcome.

Limitations

Our study has some limitations. First, some treatments were investigated in only one study or at one follow-up period. For the treatments with ample evidence, further studies examining these treatments will increase the power of these results.

Second, all treatments analyzed at 4-6 months were not connected in one network, and thus some comparisons between treatments were not calculated. The 4 treatments that did not connect with the other treatments were 4 medication injections under ultrasound guidance at 4-6 months.

Third, the treatment schedule and dose varied, e.g., the patients in some studies were administered a second injection and other studies included additional therapies, e.g., exercise.

Fourth, because of the insufficient blinding in some studies, potential bias in the assessment of treatment effects may occur.

Fifth, because there are few reported outcomes at 12 months, we cannot perform a meta-analysis, and therefore cannot give a conclusion based on long-term follow-up.

At last, conceptual and statistical heterogeneity and incoherence were inevitable in our meta-analysis.

Advantages and Strengths

To the authors' knowledge, the minimally invasive nonsurgical therapies for PF have been compared with all potential treatments analyzed in RCTs. The quantified results were obtained from a PMA and NMA.

We calculated the indirect comparisons using the Bayesian model, and the inconsistency, sensitivity, and meta-regression analyses were also performed using the Bayesian model.

The problems of conventional meta-analyses, such as selection bias and recall bias, are best avoided with a prospective design.

Our research only included the RCTs with a prospective design. The sensitivity analysis did not show a

significant change in the cumulative probability ranks, and no significant change in the DIC was observed in the results of the meta-regression analysis. All P-values in the inconsistency analysis were less than 0.05. Therefore, the outcome of this meta-analysis is valid and reliable.

We performed 2 different follow-up periods for the analysis, which provided us some insights into changes over time.

Conclusions

MSN produces the best effect; it is a type of minimally invasive surgery that is easy to administer and thus is well recommended for practitioners. However, it requires a special miniscalpel-needle, which may restrict the application. BTA in the gastrocnemius is not injected into the foot fascia and is listed as the second best effect. CS combined with ultrasound guidance and the peppering technique produces a limited effect, but is economical for patients and accepted by clinicians—still providing value in practice. Although UG is a noninvasive technique, we do not find evidence confirming that it promotes the treatment effect. PEP exerts a positive effect when it is combined with other medications. It is easy to handle and should be added to the injection.

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Clinical Trials: CRD42020168308

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Supplemental Table 1. *Search strategy for PubMed*.

No.	Query
#27	#11 and #26
#26	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
#25	Search plantar fasciosis[Title/Abstract]
#24	Search painful heel[Title/Abstract]
#23	Search heel spur[Title/Abstract]
#22	Search plantar fasciopathy[Title/Abstract]
#21	Search plantar heel pain[Title/Abstract]
#20	Search calcaneodynia[Title/Abstract]
#19	Search heel pain[Title/Abstract]
#18	Search Plantar Fasciitis, Chronic[Title/Abstract]
#17	Search Fasciitis,Chronic Plantar[Title/Abstract]
#16	Search Chronic Plantar Fasciitis[Title/Abstract]
#15	Search Fasciitis, Plantar, Chronic[Title/Abstract]
#14	Search Heel Spur Syndrome[Title/Abstract]
#13	Search Plantar Fasciitis[Title/Abstract]
#12	Search fasciitis, plantar[MeSH Terms]
#11	#9 not #10
#10	Search (animals[MeSH Terms] NOT humans[MeSH Terms])
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#8	Search groups[Title/Abstract]
#7	Search trial[Title/Abstract]
#6	Search randomly[Title/Abstract]
#5	Search drug therapy[MeSH Subheading]
#4	Search placebo[Title/Abstract]
#3	Search randomized[Title/Abstract]
#2	Search controlled clinical trial[Publication Type]
#1	Search randomized controlled trial[Publication Type]