Systematic Review and Meta-Analysis

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The effectiveness of dextrose prolotherapy in plantar fasciitis

A systemic review and meta-analysis

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Abstract

Background: Dextrose prolotherapy (DPT) is considered to be a type of regenerative therapy and is widely used in various musculoskeletal disorders. Plantar fasciitis is a common cause of heel pain that affects the quality of life of many people. We aimed to evaluate the effectiveness and safety of DPT for plantar fasciitis.

Methods: PubMed, Embase, and the Cochrane Library were searched from their respective inception dates to June 2021. Only randomized controlled trials comparing DPT and other interventions for plantar fasciitis were included in this review. Standardized mean differences (SMDs) with 95% confidence intervals were calculated for comparison. The outcome measurements included visual analog score, numeric rating scale, Foot Function index, Revised Foot Function index, American Orthopedic Foot and Ankle Score, and plantar fascia thickness. Post-treatment duration was classified as short-term (1–2 months), medium-term (3 months), or long-term (6 months).

Results: Six studies with 388 adult patients diagnosed with plantar fasciitis were included for the meta-analysis. In terms of pain scores improvement, DPT was superior to placebo or exercise in the short-term (SMD: −1.163, 95%CI: −2.17 to −0.156) and the medium-term (SMD: −1.394, 95%CI: −2.702 to −0.085). DPT was inferior to corticosteroid injection in the short-term (SMD: 0.781, 95%CI: 0.41 to 1.152). For functional improvement, DPT was superior to placebo or exercise in the short-term (SMD: −1.51, 95%CI: −2.96 to −0.059), but inferior to corticosteroid injection (SMD: 0.526, 95%CI: 0.161 to 0.89) and extracorporeal shock wave therapy in the short-term (SMD: 0.484, 95%CI: 0.145 to 0.822). Randomized controlled trials showed a better pain improvement in the long-term for patients treated with DPT compared to corticosteroid ($P = .002$) and exercise control ($P < .05$). No significant differences were found between patients treated with DPT and patients treated with platelet-rich plasma.

Conclusion: Dextrose prolotherapy was a safe and effective treatment option for plantar fasciitis that may have long-term benefits for patients. The effects were comparable to extracorporeal shock wave therapy or platelet-rich plasma injection. Further studies with standardized protocols and long-term follow-up are needed to address potential biases.

Abbreviations: AOFAS = American Orthopedic Foot and Ankle Score, DPT = dextrose prolotherapy, ESWT = extracorporeal shock wave therapy, FAAM = Foot and Ankle Ability Measure, FFI = Foot Function index, FFI-R = Revised Foot Function index, NRS = numeric rating scale, PF = plantar fascia, PRP = platelet-rich plasma, RCT = randomized controlled trials, SMD = standardized mean differences, VAS = visual analog score.

Keywords: dextrose injection, meta-analysis, plantar fasciitis, prolotherapy

Editor: Walid Kamal Abdelbasset.

Supplementary: Detailed descriptions of database search algorithms, quality assessment details, and critical appraisal checklist were included in the Supplementary Materials.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the present study are publicly available.

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How to cite this article: Lai WF, Yoon CH, Chiang MT, Hong YH, Chen HC, Song W, Chin YP. The effectiveness of dextrose prolotherapy in plantar fasciitis: a systemic review and meta-analysis. Medicine 2021;100:51(e28216).

Received: 24 July 2021 / Received in final form: 26 October 2021 / Accepted: 22 November 2021

http://dx.doi.org/10.1097/MD.0000000000028216

1. Introduction

Plantar fasciitis is the most frequent cause of heel pain that is associated with walking disabilities, and can significantly affect the quality of life of affected adults.[1,2] One review article reported incidence rates ranging from 4.5% to 10.0% among runners.[3] Although the etiopathogenesis of plantar fasciitis is still unclear, the degeneration of plantar fascia (PF) is considered an important mechanism.[4] One recent meta-analysis[5] found increased ankle dorsiflexion, high body mass index, and high body mass as the most significant risk factors.

The diagnosis of plantar fasciitis is mainly based on history-taking and physical examination. Evaluation of PF thickness by ultrasonography can help both the diagnosis of plantar fasciitis and the monitoring of therapeutic response.[6] Non-surgical treatments, including activity modification, physical therapy, oral medications, extracorporeal shockwave therapy, and injectional therapies, are recommended as first-line treatment options for plantar fasciitis, with around 70% to 80% of patients experiencing subsequent pain relief.[7]

Corticosteroid is one of the most widely used injectant for plantar fasciitis, providing rapid relief of heel pain with its strong anti-inflammatory effects. However, results from a Cochrane review[8] showed only short-term (1 month) benefit of corticosteroid injections along with several reports of serious complications (post-injection flare, soft tissue infection, and plantar fascial rupture).

Therefore, other injectants targeting the restoration of degenerated PF have been explored in pursuit of better long-term outcomes.[9] Dextrose prolotherapy involves injecting hypertonic dextrose solution to the local lesion, and may facilitate the recovery of connective tissue injury.[10] Despite inconsistent results found between reviews of dextrose prolotherapy in the treatment of various musculoskeletal disorders,[11,12] 1 pilot study[13] found a promising outcome of dextrose injection for plantar fasciitis.

Recently, several randomized control trials have investigated the efficacy and superiority of dextrose prolotherapy compared to other therapies in the treatment of plantar fasciitis, but the evidence is still not well established. Therefore, we conducted a systematic review and meta-analysis to analyze the effectiveness of dextrose prolotherapy for plantar fasciitis.

2. Method

2.1. Search strategy

Electronic databases, including the Cochrane Library, PubMed, and Embase, were searched from their respective inception dates to June 2021 by 2 of the authors (WFL and MTC) for articles related to the research question. The research question based on patient-intervention-comparison-outcome principles was: Population: adults patients diagnosed with plantar fasciitis; Intervention: dextrose prolotherapy; Comparison: placebo or any other treatments; and Outcomes: any outcome measurements related to pain and functional evaluation of foot. The following keywords were used in different combinations, including their synonyms: "prolotherapy," "dextrose," "glucose," and "plantar fasciitis." The Medical Subject Heading terms of keywords were also used. The detailed search keywords and strategies are shown in Table 1, Supplemental Digital Content, http://links.lww.com/MD2/A749. Bibliographies of included trials and relevant systematic reviews were also screened for related studies. There were no language restrictions on our searches. The review is registered with the Research Registry (http://www.researchregistry.com/) as "reviewregistry1178." Given we only analyzed publicly available articles in the current study, ethical approval from an institutional review board was not required.

2.2. Eligibility criteria

We included articles investigating the efficacy of dextrose prolotherapy in adults diagnosed with plantar fasciitis. Included studies had at least 1 control group that received no therapy or therapies other than dextrose prolotherapy. The included studies must have pain or functional outcome measurements. Only published randomized controlled trials (RCTs) with full-text availability were included. Case series, abstracts alone, and conference papers were excluded. Studies without extractable outcome data for analysis were also excluded.

2.3. Quality assessment

The quality of included RCTs was assessed using the Jadad scale,[14] which consists of 3 aspects with a total score ranging from 0 to 5. The methodological quality is evaluated with regard to 3 aspects: randomization, blinding, and withdrawals and dropouts of participants. Higher scores represent higher methodological quality. The quality of articles was considered as "high" if it scored more than 3 points. Cochrane risk-of-bias tool for randomized trials Version 2 (RoB 2) was used for risk of bias assessment. The tool assessed bias of 5 domains for RCTs and stratified into "low" or "high" risk of bias, or "some concerns." Two authors evaluated the quality of included studies independently. Discrepancies between the 2 authors were solved by a discussion with a third author.

2.4. Outcome selection

The primary outcome was plantar fasciitis-associated pain as evaluated by any continuous numerical outcome measurement (ie, visual analog scale, numeric rating scale, or other scales). The secondary outcome was foot function assessed by any index or scales. Outcomes for different treatment groups were compared at different follow-up timepoints categorized as short-term (1–2 months after treatment), medium-term (3 months after treatment), and long-term (6 months after treatment).

2.5. Data extraction

The relevant data of the included studies were reviewed and extracted by 2 of the authors using a pre-designed data form. The recorded information included sample size, first author, year of publication, country, demographic data of participants, injection protocol of dextrose prolotherapy, regimens of comparative arms, follow-up, and treatment outcomes. The agreement between the 2 authors who extracted the data was assessed via Cohen kappa coefficient. The kappa coefficient between 0.8 to 0.99 was interpreted as almost perfect agreement, 0.61 to 0.80 as substantial agreement, 0.41 to 0.60 as moderate agreement, 0.21 to 0.40 as fair agreement, and 0 to 0.20 as slight agreement. Disagreement between 2 of the authors was resolved through discussion with a third author. If the extractable data in studies were inadequate for analysis, we contacted the respective corresponding author via e-mail for further information.

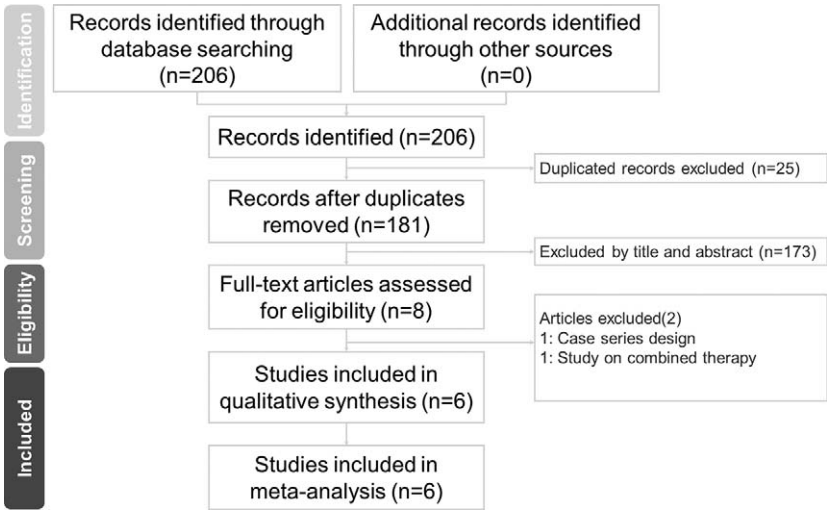

Figure 1. Preferred reporting items for systematic reviews and meta-analyses.

2.6. Data synthesis and analysis

All analyses were performed using the Comprehensive Meta-Analysis program version 3 (Biostat, Englewood, NJ 07631, USA). We compared the primary and secondary outcomes between dextrose prolotherapy and comparator patient groups. If data were available, the treatment effects among treatment groups were compared at different follow-up time points: short-, medium-, and long-term outcomes as defined in "Outcome selection" above. The results were presented with standardized mean differences (SMDs) and corresponding 95% confidence intervals (CI). A random-effects model was used for a meta-analysis. Statistical significance was defined as P-values $< .05$. The evaluation of publication bias would not be conducted if the number of included articles was less than 10 according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Heterogeneity was assessed by the I^2 test. $I^2 > 50\%$ was considered as a significant heterogeneity.

3. Result

A total of 203 articles were identified from the first screening, from which 25 duplicates were removed, and 170 articles were further excluded after screening titles and abstracts. Eight studies were then assessed for eligibility. One study was excluded due to its case-series study design[13] and 1 study was excluded because it evaluated the effect of combined corticosteroid and dextrose injection.[16] Ultimately, 6 RCTs were included for the meta-analysis. The details of study inclusion and exclusion are displayed in Figure 1.

The sample size of included studies ranged from 21[17] to 158.[18] The mean age of participants ranged from 36.2[17] to 50.3[19] years. The shortest symptom duration across studies was at least 8 weeks.[19] The duration of follow-up ranged from 12 weeks[19–21] to 36 months.[18] Regarding dextrose prolotherapy (DPT) protocols, the concentrations of the injected dextrose solution ranged from 1.5%[18] to 20%,[19,21] and only in 2 studies,[19,21] injected dextrose solution did not add any local anesthetics (lidocaine or bupivacaine). Various injection regimens were adopted: 2 studies[18,20] had 3 prolotherapy sessions; 3 studies[17,21,22] had 2 sessions; and 1 study involved 1 session.[19] The comparative arms included 1 or more of normal saline injection, extracorporeal shock wave therapy (ESWT), exercise control, platelet-rich plasma (PRP), and corticosteroid injection. The ultrasound-guided injection was used in 5 studies. No serious adverse events after dextrose prolotherapy were reported. The agreement between the 2 reviewers who extracted data was almost perfect (kappa coefficient = 0.91).

Several outcome measurements were used in the included studies. For the evaluation of pain, the included studies employed the visual analog score (VAS), the numeric rating scale, or the pain subscale of the Foot Function index (FFI-pain). Other outcome measurements included the American Orthopedic Foot and Ankle Score, Foot and Ankle Ability Measure, Revised FFI, FFI, and PF thickness measured by ultrasonography. The summary of characteristics of included studies is shown in Table 1.

With regard to methodological quality assessment, the Jadad scores of included studies ranged from 3 to 5. All included studies scored at least 3 points. In 4 studies, blinding was inadequate or not described.[17,18,20,21] The scores of each study are shown in Table 2, Supplemental Digital Content, http://links.lww.com/MD2/A750. Four studies[17,18,20,21] showed some concerns over deviation from the intended interventions domain according to the risk of bias assessment; 2 studies[17,21] had some concerns over the measurement of outcome. Generally, the included studies had low to some concerns of risk of bias. Figure 1A.1B, Supplemental Digital Content, http://links.lww.com/MD2/A752.

3.1. Dextrose prolotherapy vs placebo or exercise

Data from 2 studies[20,22] were pooled and analyzed. The DPT group had significantly lower pain scores both in the short-term (SMD: −1.163, 95%CI: −2.17 to −0.156, $I^2 = 83.5\%$) and medium-term (SMD: −1.394, 95%CI: −2.702 to −0.085, $I^2 = 89.5\%$). DPT produced better functional outcomes than the placebo or exercise control group in the short-term (SMD: −1.51, 95%CI: −2.96 to −0.059, $I^2 = 91\%$), although no significant

Table 1

Characteristics of included studies.

Study	Country	Age (years), Mean	Mean symptom duration	Intervention (N)	Follow-up	Outcome measures	Adverse event	Jadad scores
Kim, 2014[17]	Korea	DPT: 37.8 PRP: 36.2	DPT: 2.9 yrs PRP: 2.8 yrs	DPT(11): 1.5 mL 20% dextrose + 0.5 mL 0.5% lidocaine. PRP(10): Huons HC-1000 System, 2 mL All USG injection at 0, 2 wks.	28 wks	VAS, FFI	No	3
Ersen, 2017[20]	Turkey	DPT: 45 Control: 46.3	DPT: 32.8 mos Control: 34.3 mos	DPT(26): 3.6 mL 15% dextrose + 0.4 mL lidocaine. USG injection at 0, 3, 6 wks. Control(24): stretching exercise 3 times per week for 3 mos.	12 mos	VAS, AOFAS, FFI	No	3
Uğurlar, 2018[18]	Turkey	ESWT: 39.2 DPT: 37.5 PRP: 38.4 CS: 40.1	ESWT:15.7 mos DPT: 13.2 mos PRP: 13.9 mos CS: 14.5 mos	ESWT(39): 6 Hz, 2000 pulse, 4 bars. DPT(40): 1 mL 0.5% bupivacaine + 3 mL 5% dextrose + 6 mL NS. PRP(39): Arthrex ACP Double Syringe System, 2 mL. CS(40): 1 mL betamethasone(40 mg/mL) All USG at 0, 1, 2 wks.	36 mos	VAS, FFI-R	No	3
Mansiz-Kaplan, 2019[22]	Turkey	DPT: 46.7 NS: 46.2	>6 mos	DPT(30): 5 mL 30% dextrose + 4 mL NS + 1 mL 2% lidocaine, inject 5 mL. NS(30): 9 mL NS + 1 mL 2% lidocaine, inject 5 mL. All palpation guided injection(0, 3 wks)	15 wks	VAS, FFI, PF thickness	No	5
Asheghan, 2020[21]	Iran	DPT: 46.5 ESWT: 43.7	4.6 mos	DPT(29): 2 mL 20% dextrose. USG injection(0, 1 wk) ESWT (30): radial, 2000 shocks, 2 Bars,10 Hz(0, 1, 2 wks)	12 wks	VAS, FAAM, PF thickness	No	3
Raissi, 2021[19]	Iran	DPT: 50.3 CS: 42.15	>8 wks	DPT(20): 2 mL 20% dextrose. CS (20): 1 mL methylprednisolone (40 mg/mL) + 1 mL NS. All USG injection at 0 wk	12 wks	NRS, FAAM, PF thickness	No	5

AOFAS = American Orthopedic Foot and Ankle Score, CS = corticosteroid, DPT = dextrose prolotherapy, ESWT = extracorporeal shock wave therapy, FAAM = Foot and Ankle Ability Measure, FFI = Foot Function index, FFI-R = Revised Foot Function index, mo = month, NRS = numeric rating scale, NS = normal saline, PF = plantar fascia. N = sample size, PRP = platelet-rich plasma, USG = ultrasound-guided, VAS = visual analog score.

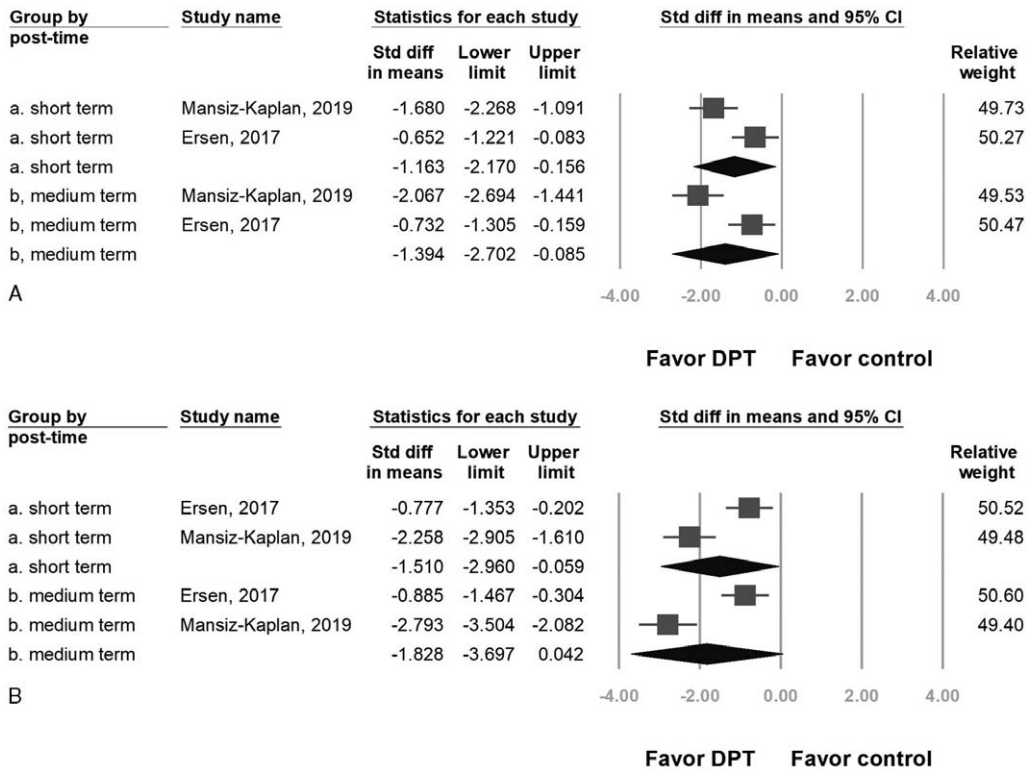

Figure 2. Forest plot comparing DPT with control (placebo or exercise), post-intervention. (A) Pain scores, outcome measure: VAS. I^2: short-term = 83.5% and medium-term = 89.5%. (B) Functional scores, outcome measure: FFI. I^2: short-term = 91% and medium-term = 94%. DPT = dextrose prolotherapy, FFI = Foot Function index, VAS = visual analog score.

difference was seen in the medium-term (SMD: −1.828, 95%CI: −3.697 to 0.042, $I^2 = 94\%$) (Fig. 2A.2B).

Only 1 study[20] had long-term follow-up and showed a significant improvement in the VAS score with DPT compared to the exercise control group($P < .05$). No significant difference was seen for functional outcomes with long-term follow-up ($P = .113$).

3.2. Dextrose prolotherapy vs platelet-rich plasma injection

Data from 2 RCTs[17,18] were pooled and analyzed. No significant difference was seen between DPT and platelet-rich plasma injection with respect to pain scores following treatment in the short-term (SMD: −0.127, 95%CI: −0.519 to 0.266, $I^2 = 0\%$), medium-term (SMD: 0.014, 95%CI: −0.378 to 0.406, $I^2 = 0\%$) and long-term (SMD: 0.103, 95%CI: −0.29 to 0.495, $I^2 = 0\%$). No significant difference in functional outcome post-intervention was observed in the short-term (SMD: −0.144, 95%CI: −0.538 to 0.249, $I^2 = 0\%$), medium-term (SMD: 0.006, 95%CI: −0.386 to 0.398, $I^2 = 0\%$), and long-term (SMD: 0.073, 95%CI: −0.32 to 0.465, $I^2 = 0\%$) (Fig. 3A and B). In addition, 1 study[22] found significantly decreased PF thickness over short-term ($P < .001$) and medium-term follow-up ($P < .001$) in the DPT group as compared with the group that received normal saline injections.

3.3. Dextrose prolotherapy vs corticosteroid injection

Two RCTs[18,19] were included in this subgroup analysis. In the short-term, lower pain scores after treatment were observed in the corticosteroid injection group than in the DPT group (SMD: 0.781, 95%CI: 0.41 to 1.152, $I^2 = 0\%$), but no significant difference was seen between these 2 groups in the medium-term (SMD: −0.303, 95%CI: −0.846 to 0.24, $I^2 = 51.7\%$). Significantly better functional outcomes were seen in the corticosteroid injection group in the short-term (SMD: 0.526, 95%CI: 0.161 to 0.89, $I^2 = 0\%$), but no significant difference was observed in the medium-term (SMD: −0.11, 95%CI: −0.587 to 0.367, $I^2 = 38.8\%$) (Fig. 4A and B). One study[19] compared PF thickness between the DPT and corticosteroid injection groups, showing significantly decreased plantar fascia thickness in the DPT group compared with the corticosteroid injection group in the short-term ($P = .004$)

3.4. Dextrose prolotherapy vs extracorporeal shock wave therapy

Data from 2 studies[18,21] were analyzed. No significant difference in pain scores was found between DPT and ESWT in the short-term (SMD: 0.249, 95%CI: −0.782 to 1.28, $I^2 = 88.9\%$) and the medium-term (SMD: 0.211, 95%CI: −0.123 to 0.546, $I^2 = 0\%$). In terms of functional improvement, better outcomes were observed for the ESWT group (vs DPT) in the short-term (SMD: 0.484, 95% CI: 0.145 to 0.822, $I^2 = 0\%$); however, no significant difference in functional improvement was found in the medium-term (SMD: 0.297, 95%CI: −0.394 to 0.989, $I^2 = 75.5\%$) (Fig. 5A and B). One study[21] found significant reductions in PF thickness compared with baseline in DPT and ESWT groups in short-term ($P < .0001$) and medium-term ($P < .0001$), but no significant difference between 2 groups was found.

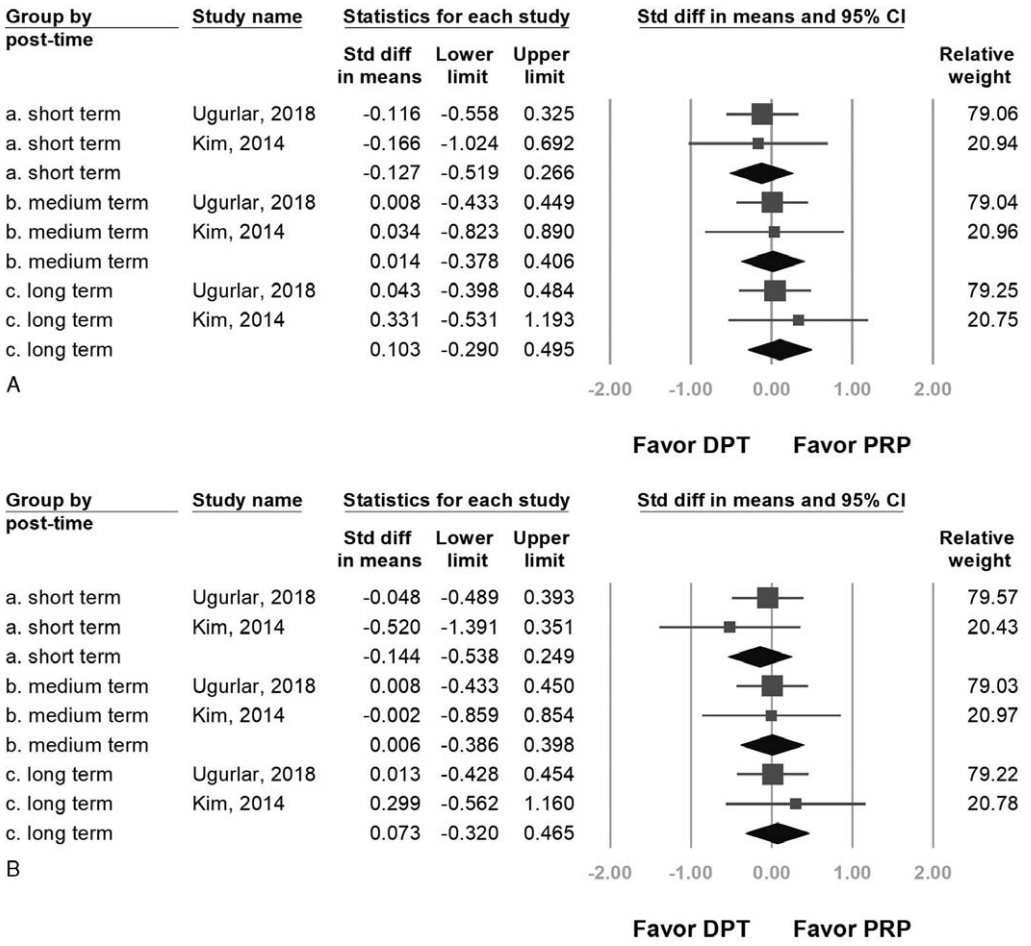

Figure 3. Forest plot comparing DPT with PRP, post-intervention. (A) Pain scores, outcome measure: pain subscale of FFI or FFI-R. I^2: short-term = 0%, medium-term = 0%, and long-term = 0%. (B) Functional scores, outcome measure: FFI, FFI-R. I^2: short-term = 0%, medium-term = 0%, and long-term = 0%. DPT = dextrose prolotherapy, FFI = Foot Function index, FFI-R = Revised Foot Function index, PRP = platelet-rich plasma.

Only 1 study[18] compared the long-term outcomes between the DPT, ESWT, and corticosteroid injection groups. Patients who received DPT had lower post-treatment VAS scores (long-term follow-up) compared with patients treated with corticosteroid injection ($P = .002$). Treatment effect of DPT and ESWT for pain scores and functional outcomes showed no significant difference in the long-term.

4. Discussion

The goal of this study was to assess the efficacy of DPT in the treatment of adult patients with plantar fasciitis. Our analysis found superiority of DPT over placebo or exercise in improving pain in both the short-term and medium-term. DPT also improved pain in the long-term compared to exercise; better short-term functional improvements in the DPT group were also noted. Compared with other therapies (PRP, ESWT, or corticosteroid injection) that had been proven to be effective in pain improvement for plantar fasciitis,[9,23,24] DPT was only inferior to corticosteroid injection in the short-term, and was shown to be to be more effective than corticosteroid injection in improving plantar fasciitis-related pain in the long-term. We also found the effect of DPT was comparable to PRP injection in the short-, medium- and long-term. To the best of our knowledge, this is one of the first meta-analyses investigating the impact of the DPT effect on plantar fasciitis based on RCTs.

Dextrose prolotherapy is considered to be a type of regenerative injection therapy aimed at soft tissue repair and strengthening.[25] Different from platelet-rich plasma, dextrose solution does not contain biologic agents but could still help in the soft tissue injury recovery process. Although the underlying mechanism of dextrose solution over soft tissue was still under investigation, hypertonic dextrose solution can be proved to cause localized trauma at the injection site as well as initiate an inflammatory process which was related to the soft tissue healing reactivation.[26] Based on animal studies, researchers had found connective tissue proliferation (cartilage, ligament, and tendon) after dextrose injection at the injured site.[27–29] Topol et al[30] also observed greater knee cartilage re-growth and improvements in pain following dextrose injection via arthroscopy in severe knee osteoarthritis patients. Johnston et al[31] found that hypertonic dextrose solution could stimulate chondrocytes to increase collagen deposition and proliferate. The study conducted by Maniquis-Smigel et al[32] had demonstrated a 48-hour analgesic effect of 5% dextrose solution via epidural injection in patients with lower back pain. Moshrif and Elwan[16] also

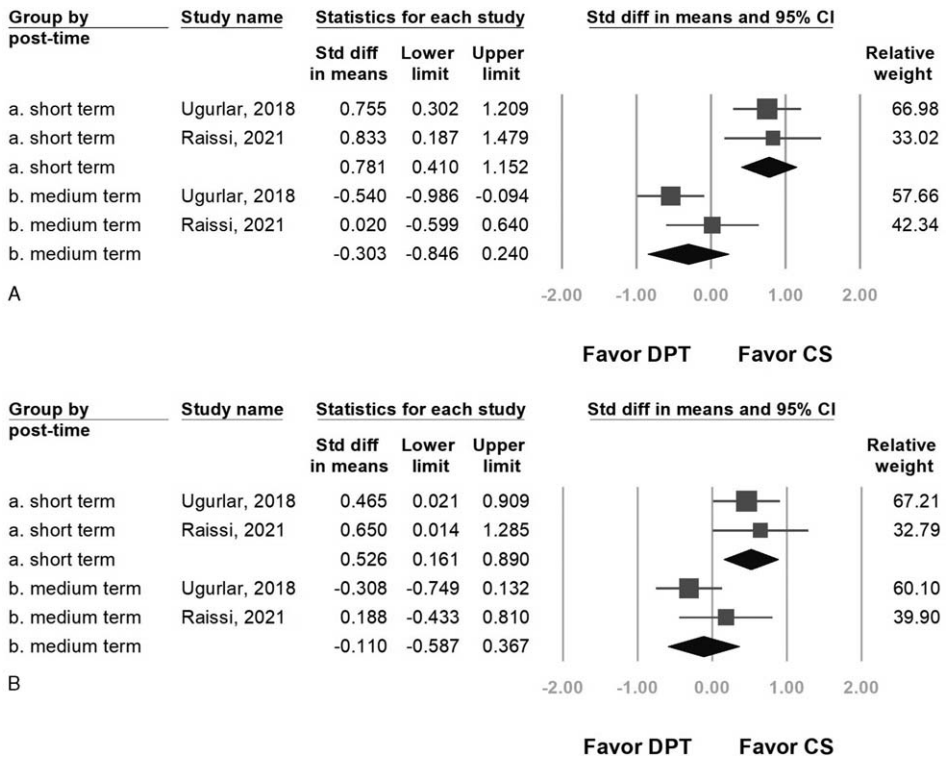

Figure 4. Forest plot comparing DPT with CS, post-intervention. (A) Pain scores, outcome measure: VAS, NRS. I^2: short-term = 0% and medium-term = 51.7%. (B) Functional scores, outcome measure: FFI, FAAM. I^2: short-term = 0% and medium-term = 38.8%. CS = corticosteroid injection, DPT = dextrose prolotherapy, NRS = numeric rating scale, VAS = visual analog score.

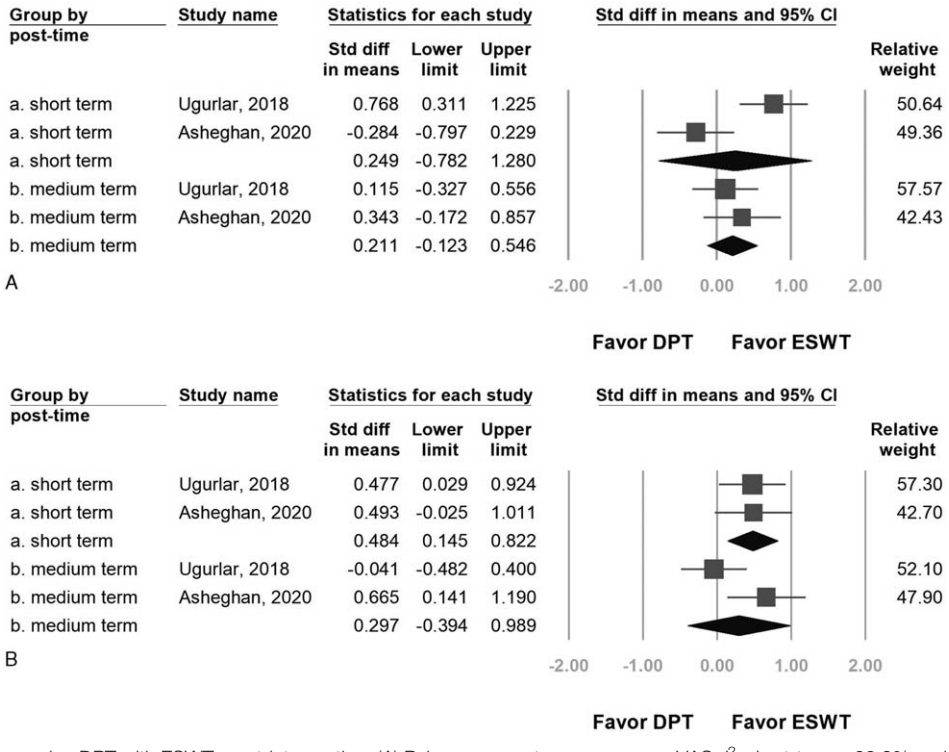

Figure 5. Forest plot comparing DPT with ESWT, post-intervention. (A) Pain scores, outcome measure: VAS. I^2: short-term = 88.9% and medium-term = 0%. (B) Functional scores, outcome measure: FFI, FAAM. I^2: short-term = 0% and medium-term = 75.5%. DPT = dextrose prolotherapy, ESWT = extracorporeal shock wave therapy, FFI = Foot Function index, FAAM = Foot and Ankle Ability Measure.

found that corticosteroid injections with an additional 0.5 mL of 5% dextrose solution had better analgesic effects for patients with plantar fasciitis at the 2-week follow-up. Han et al[33] investigated the mechanism of analgesic effects of dextrose in a mouse model of fibromyalgia and found that the effect was associated with activation of acid-sensing ion channel 1a and substance P release. However, Rabago et al[34] and Bertrand et al[35] reported symptom improvement without accompanying connective tissue change on imaging (ultrasonography or magnetic resonance imaging) studied in patients receiving DPT, which cannot be explained by the analgesic effect of dextrose alone. In this review, 3 included studies[19,21,22] found that DPT was able to decrease abnormal swelling of PF in patients and reduce pain intensity. Other related physiological changes following injection of local dextrose injection as well as their correlation to clinical symptoms require further research.

Corticosteroid injections are commonly used to achieve short-term pain relief for a variety of different musculoskeletal diseases.[23,36,37] However, corticosteroid injections may potentially cause serious complications, for example, soft tissue atrophy, infection, decreased tendon and ligament strength, and rupture of PF.[23,38–41] DPT has been shown to be related to fewer complications, the majority of which have been related to the process of the injection itself.[10] Moreover, DPT demonstrated better long-term therapeutic effects for musculoskeletal diseases than corticosteroid injection did in several studies.[42–45] Though DPT was inferior to corticosteroid injection for improving pain in the short-term in our meta-analysis, the 2 therapies had similar impacts on improving plantar fasciitis-related pain in the medium-term, and 1 RCT done by Uğurlar et al[18] even showed a better long-term prognosis for DPT than with corticosteroid injection. Furthermore, no adverse events were reported for DPT among the studies included in this meta-analysis. Although more evidence is required, the research to date supports the use of DPT as a preliminary treatment for plantar fasciitis.

Plantar fasciitis is a multifactorial disease, the etiopathogenesis of which remains unclear. Risk factors for developing plantar fasciitis include obesity, overuse, and biomechanical factors.[5,46] Although traditionally thought to be an inflammatory process involving the PF,[1] Lemont et al discovered that the histopathology of plantar fasciitis is more related to a degenerative process, that is, a form of "fasciosis."[4] Consequently, regenerative therapies like PRP injection, ESWT, and DPT have been used in the treatment of plantar fasciitis.[24,47,48] In our meta-analysis, DPT demonstrated comparable efficacy to ESWT and PRP injection. Although no analysis of cost-effectiveness was done for the 3 therapies, DPT has some obvious cost-effective advantages over other treatment approaches, such as the use of an inexpensive solution and a simple preparation process overall, which may make it an attractive treatment option for both physicians and patients in different countries.[49] The relative simplicity of DPT may also mean that standardization of DPT treatment will not be so difficult to achieve in future clinical studies.

Several systematic reviews have evaluated the efficacy of DPT in the treatment of various musculoskeletal disorders, including plantar fasciitis.[9,11,12,50] Tsikopoulos et al[9] concluded that PRP and DPT had similar effects in the treatment of plantar fasciitis at 28 weeks post-treatment, but noted that more high-quality head-to-head comparisons were needed. Sanderson et al[50] similarly concluded that DPT was effective for plantar fasciitis, based on the findings of 1 RCT and 1 case-series study. While Bae et al[11] found long-term positive effects on pain control of DPT for osteoarthritis, tendinopathy, and fasciitis, Chung et al[12] did not observe statistically significant effects of DPT compared to placebo on pain control for connective tissue injury, including plantar fasciitis; both studies pooled data for various musculoskeletal diseases, which may have led to potential biases and inconsistent results. The present study included more RCTs related to plantar fasciitis than previous reviews and specifically compared the treatment results between DPT and other therapies in plantar fasciitis patients.

Our study has several limitations. First, the overall size of included patients was relatively small (N = 388). Moreover, only 3 out of the 6 included studies involved long-term follow-up (6 months). These factors may lead to potential unseen biases and affect the validity of our conclusions. Therefore, more studies with long-term follow-up are needed. Second, substantial heterogeneity was found in some of our results. Since different patient-inclusion criteria, patient demographics, and intervention protocols were observed, it was difficult to eliminate the heterogeneity in this review. Third, there was insufficient data to compare the differential treatment effects of various DPT protocols (in relation to dextrose concentration, injection technique, number of injections, and the time interval between injections). While Tsai et al[51] found better efficacy of pain control of ultrasound-guided corticosteroid injection for plantar fasciitis than with palpation-guided corticosteroid injection, no such comparison has yet to be conducted for DPT. The optimal method and protocol for administering DPT in patients with plantar fasciitis remains unknown and requires further investigation. Nonetheless, our study demonstrated more evidence supporting the use of DPT in plantar fasciitis and efficacy comparison of DPT to other treatments for clinicians and patients. Moreover, our review provided several research directions for future studies.

In conclusion, dextrose prolotherapy appears to be an inexpensive, safe, and effective approach to treat plantar fasciitis, the benefits of which may last for at least 6 months post-treatment. Comparable efficacy in improving pain was observed among dextrose prolotherapy, extracorporeal shock wave therapy, and platelet-rich plasma injection. Although dextrose prolotherapy was inferior to corticosteroid injection in the short-term, dextrose prolotherapy had the potential to outperform corticosteroid injections in the long-term. More studies with longer follow-up and larger sample sizes, also standardization and optimization of intervention protocols, and cost-effectiveness analysis should be undertaken to confirm our findings (Table 3, Supplemental Digital Content, http://links.lww.com/MD2/A751.).

Acknowledgment

We would like to thank Fang-Yu Liang for her administrative support.

Author contributions

Wei-Fu, Hui-Chuan, and Ying-Han did the conceptualization; Wei-Fu and Meng Ting did the search algorithm formulation and complete the quality assessment and data extraction process; Wei-Fu and Meng Ting did the formal analysis; Wei-Fu and Ying-Han wrote the original draft preparation; Wei-Fu, Chang Ho,

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