Comparative effectiveness of autologous blood-derived products, shock-wave therapy and corticosteroids for treatment of plantar fasciitis: a network meta-analysis

Ming-Yen Hsiao¹, Chen-Yu Hung², Ke-Vin Chang¹,³, Kuo-Liong Chien³,⁴, Yu-Kang Tu³ and Tyng-Guey Wang⁵

Abstract

Objective. To compare the efficacy of autologous blood-derived products (ABPs), CSs and shock-wave (SW) therapy in the treatment of plantar fasciitis.

Methods. Electronic databases were searched for studies that compared ABPs, CSs and SW therapy for the treatment of plantar fasciitis, published up to June 2014. The primary and secondary outcomes were reduction in visual analogue scale (VAS) score at 3 and 6 months and odds ratio of treatment success, respectively. Groups were compared by traditional pair-wise meta-analysis and by network meta-analysis.

Results. Seven randomized controlled trials and three quasi-experimental studies that included 604 patients were enrolled. Pair-wise meta-analysis indicated a trend favouring ABPs over CSs regarding VAS reduction at 3 months; this benefit was significant in a subgroup analysis of platelet-rich plasma (PRP) vs CSs. There were no significant between-group differences in VAS reduction at 6 months and in treatment success. Network meta-analysis showed that ABPs had the highest probability of being the best treatment at 3 months, but ABPs were slightly inferior to SW for VAS reduction at 6 months. Although SW therapy had the highest likelihood of treatment success, the between-group differences in probabilities were less remarkable than those for pain reduction at 3 and 6 months.

Conclusion. ABPs, followed by CSs, were best in providing relief from pain at 3 months. SW therapy and ABPs had similar probabilities of providing pain relief at 6 months, and were better than CSs at that time. Subgroup analysis indicated that an ABP regimen consisting of platelet-rich plasma improves treatment efficacy.

Key words: autologous blood-derived products, platelet-rich plasma, shock-wave therapy, corticosteroid, plantar fasciitis.

Rheumatology key messages

- Autologous blood-derived products, followed by CSs, were best in providing early pain relief in plantar fasciitis.
- Shock therapy and autologous blood-derived products provided better pain reduction in plantar fasciitis than CSs at 6 months.
- The type of autologous blood-derived products affects treatment outcome, and platelet-rich plasma appears to increase treatment efficacy in plantar fasciitis.

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Submitted 3 July 2014; revised version accepted 20 January 2015

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Introduction

Plantar fasciitis is a major cause of heel pain and corticosteroid (CS) injection is the most common treatment for this disorder. Several randomized controlled trials (RCTs) have demonstrated the efficacy of CS injections in providing immediate pain relief and normalization of plantar fascia thickness [1, 2]; however, there are limitations with this treatment. In particular, some studies have reported different durations of pain relief, presumably due to the use of different injection regimens and needle-guiding techniques; and there can be complications, such as heel pad atrophy and rupture of the plantar fascia [3, 4].

Shock-wave (SW) therapy is another common non-invasive method for treatment of recalcitrant plantar fasciitis, and several meta-analyses have documented its advantages over placebo treatments [5, 6]. However, the therapeutic response to SW therapy depends on the intensity, pulse cycle and SW modality (focused or radial) [5]. Injection of autologous blood-derived products (ABPs) that contain bioactive growth factors appears to be a promising treatment for chronic tendon disorders. Lee and Ahmad [7] first investigated this method for treatment of plantar fasciitis in 2007. Plantar fasciitis is considered a degenerative process rather than an inflammatory process, so ABPs are theoretically superior to CSs because they have the potential to stimulate tissue regeneration. Nevertheless, clinical trials that compared ABPs and CSs for treatment of plantar fasciitis have produced conflicting results. Although all three treatment options appear to be more effective than placebos in alleviating plantar heel pain, the most effective treatment is currently uncertain. Therefore, the present study aimed to undertake a network meta-analysis that compared the therapeutic efficacy of ABPs, CSs and SW therapy for the treatment of plantar fasciitis.

Methods

Trial selection

We identified eligible trials by an electronic search of PubMed and Scopus, from the earliest records to June 2014. We used PubMed because of its open access and comprehensive coverage of biomedical literature, and Scopus to confirm that all relevant articles had been retrieved [8–10]. The Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, ClinicalTrials.gov, bibliographies of included trials, and related meta-analyses and reviews were manually reviewed to search for additional references. Embase was not used because of unavailability in our hospital medical library, and we speculated that the influence on the search result was minor, due to similar index rates for Pubmed and Embase regarding orthopaedic medicine [11]. We included all published RCTs and quasi-experimental studies that compared the efficacy of ABPs, CSs and SW therapy for the treatment of plantar fasciitis. The key terms [plantar fasciitis, autologous blood, platelet-rich plasma (PRP), corticosteroid and SW] were entered as medical subject headings and text words for all searches.

Case reports, case series and single-arm, longitudinal follow-up studies were excluded. We focused on adults with recalcitrant plantar fasciitis with no history of antecedent trauma. Recalcitrant plantar fasciitis was defined as chronic plantar fasciitis for >3 months or plantar fasciitis failing to respond to conservative treatments. The diagnosis of plantar fasciitis was based on a history of plantar heel pain and tenderness over the medial calcaneus tubercle [5]. Each included multiple-arm trial was required to examine at least two arms of the three treatments (SW therapies, CSs or ABPs), and the data from groups given other treatments were not included for analysis. For example, in a three-arm trial using SW therapy, CSs and saline injections, we only extracted the outcome in the SW therapy and CS groups and did not include the saline group in the network comparisons.

Radial and focused SW therapies were placed in the same category, and trials were included even if they used different imaging modalities to guide treatment. Reduction in pain [based on visual analogue scale (VAS) score] and treatment success were treated as the primary and secondary outcome measurements. In the 10-cm VAS, the score was 0 if there was no pain and 10 if it was the worst imaginable pain [12]. The included trials differed in their definitions of treatment success, but most used a decrease in VAS score or in heel tenderness of >50% from baseline. The treatment success was reported at the last follow-up point in each trial, in spite of variations in the follow-up duration. Since the functional scales used in each trial were substantially different, treatment success turned out to be the most important surrogate marker for evaluating patient satisfaction and functional improvement.

Data extraction and quality assessment

After duplicates were removed, two authors independently reviewed all the articles and assessed whether an article was eligible for inclusion. Disagreement was solved by discussion and any controversy was resolved by the corresponding author. The extracted data included patient characteristics, treatment regimens, timing of treatment administration and details of outcome measurements. The quality of each RCT was evaluated by the Jadad scale, in which the aggregate score ranged from 0 to 5 points, and trials with scores <3 were classified as low quality [8–10]. The Newcastle–Ottawa scale was used to assess quasi-experimental studies by evaluation of the quality of selection, comparability, exposure and outcome. The maximum score was 9 points, and studies with total scores <4 points were classified as low quality [8–10]. Discrepancies between the two independent evaluations were resolved through discussion and consensus. Table 1 shows the results of the quality assessments.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Group</th>
<th>Enrolled, n. (M/F)</th>
<th>Average age, years</th>
<th>Average BMI, kg/m²</th>
<th>Average disease duration, months</th>
<th>Treatment cycles</th>
<th>Interval of treatment</th>
<th>Total dose or volume</th>
<th>Details of interventions</th>
<th>Outcome measure</th>
<th>Follow-up, months</th>
<th>Adverse Event</th>
<th>Quality assessment, points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPs vs CS</td>
<td>Quasi-experimental study</td>
<td>PRP</td>
<td>30 (11/19)</td>
<td>34.0</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>At least 3</td>
<td>1</td>
<td>NA</td>
<td>8 ml</td>
<td>54 ml blood centrifuged, 14 min</td>
<td>VAS, FADI, AFAS</td>
<td>3</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Shetty et al. [28]</td>
<td>CS</td>
<td>30 (13/17)</td>
<td>39.2</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>At least 3</td>
<td>1</td>
<td>NA</td>
<td>40 mg</td>
<td>40 mg triamcinolone acetonide + 3 ml 2% lignocaine</td>
<td>30-50 ml blood, centrifuged 3200 r.p.m., 15 min</td>
<td>Not mentioned</td>
<td>1, 3, 6</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Mukesh and Tiwari [28]</td>
<td>RCT</td>
<td>PRP</td>
<td>30</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>1</td>
<td>NA</td>
<td>5 ml</td>
<td>40 mg (1 ml) methylprednisolone</td>
<td>25 ml blood centrifuged, 1800 r.p.m., 15 min</td>
<td>Not mentioned</td>
<td>3 (weeks), 6</td>
<td>NA</td>
</tr>
<tr>
<td>Aksahin, 2012</td>
<td>Quasi-experimental study</td>
<td>PRP</td>
<td>30 (12/18)</td>
<td>46.36</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>8.64</td>
<td>1</td>
<td>NA</td>
<td>40 mg</td>
<td>5 ml</td>
<td>PRP + 2 ml 2% prilocaine</td>
<td>VAS, MRMS</td>
<td>3 (weeks), 6</td>
</tr>
<tr>
<td>Omar et al. [27]</td>
<td>RCT</td>
<td>PRP</td>
<td>15 (0/15)</td>
<td>42.5</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>1</td>
<td>NA</td>
<td>Not mentioned</td>
<td>150 ml blood centrifuged 320 g, 15 min, then 2000 g, 15 min</td>
<td>VAS, FHSQ</td>
<td>6 (weeks)</td>
<td>Not mentioned</td>
<td>2</td>
</tr>
<tr>
<td>Kalaci et al. [30]</td>
<td>Quasi-experimental study</td>
<td>CS</td>
<td>15 (0/15)</td>
<td>46.5</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>1</td>
<td>NA</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>2 ml triamcinolone</td>
<td>VAS, MRMS</td>
<td>3 (weeks), 6</td>
<td>NA</td>
</tr>
<tr>
<td>Lee et al. [7]</td>
<td>RCT</td>
<td>ABPs</td>
<td>31 (4/28)</td>
<td>48.3</td>
<td>26</td>
<td>7.2</td>
<td>1</td>
<td>NA</td>
<td>1.5 ml</td>
<td>1.5 ml autologous blood + 1 ml 2% lignocaine</td>
<td>VAS, TT</td>
<td>6 (weeks), 3, 6</td>
<td>Pain (n = 4), no infection or rupture</td>
<td>3</td>
</tr>
<tr>
<td>ABPs vs SW</td>
<td>RCT</td>
<td>PRP</td>
<td>19 (10/9)</td>
<td>46</td>
<td>23.4</td>
<td>12</td>
<td>1</td>
<td>NA</td>
<td>3 ml</td>
<td>US-guided, 10 ml blood centrifuged, 1500 r.p.m., 5 min</td>
<td>VAS, AOFAS, AHS PFT</td>
<td>1, 3, 6</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>Chew et al. [34]</td>
<td>SW</td>
<td>19 (11/8)</td>
<td>45</td>
<td>25.3</td>
<td>18</td>
<td>2</td>
<td>1 week</td>
<td>4000 pulses</td>
<td>EFD 0.02-0.42 mJ/mm², 2000 pulses, 10 min</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS vs SW</td>
<td>RCT</td>
<td>CS</td>
<td>30 (14/16)</td>
<td>34.2</td>
<td>28.8</td>
<td>NA</td>
<td>2</td>
<td>2 weeks</td>
<td>8 mg (4 ml)</td>
<td>US-guided, betamethasone dipropionate + betamethasone sodium phosphate, total 4 mg (2 ml + 0.5% Xylocaine)</td>
<td>Mayo CSS, PFT</td>
<td>3</td>
<td>nil</td>
<td>2</td>
</tr>
<tr>
<td>Sabers et al. [32]</td>
<td>CS</td>
<td>30 (14/16)</td>
<td>34.2</td>
<td>28.8</td>
<td>NA</td>
<td>2</td>
<td>2 weeks</td>
<td>8 mg (4 ml)</td>
<td>US-guided, betamethasone dipropionate + betamethasone sodium phosphate, total 4 mg (2 ml + 0.5% Xylocaine)</td>
<td>Mayo CSS, PFT</td>
<td>3</td>
<td>nil</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>CS vs SW</td>
<td>RCT</td>
<td>SW</td>
<td>30 (13/17)</td>
<td>34.3</td>
<td>29.2</td>
<td>NA</td>
<td>2</td>
<td>2 weeks</td>
<td>2000-3000 pulses</td>
<td>EFD 0.28 mJ/mm², 1000-1500 *2 s</td>
<td>VAS, HTI</td>
<td>3</td>
<td>Pain (n = 4), no infection</td>
<td>2</td>
</tr>
<tr>
<td>Yuvel et al. [33]</td>
<td>RCT</td>
<td>CS</td>
<td>33 (5/29)</td>
<td>44.7</td>
<td>NA</td>
<td>39.4 (weeks)</td>
<td>1</td>
<td>NA</td>
<td>45.3 mg</td>
<td>Betamethasone dipropionate (6.43 mg/ml) + Betamethasone sodium phosphate (2.63 mg/ml) + 0.5 ml 2% lignocaine</td>
<td>With nerve block (post tibial, superficial/deep peroneal, sural, saphenous), 20 ml 2% Prilocaine</td>
<td>Mild erythema (n = 2), Throbbing sensation (n = 2)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Porter and Shadbolt [31]</td>
<td>CS</td>
<td>64 (20/44)</td>
<td>39.9</td>
<td>NA</td>
<td>14.6 (weeks)</td>
<td>1</td>
<td>NA</td>
<td>5.7 mg (1 ml)</td>
<td>5.7 mg (1 ml) betamethasone + 2 ml 1% lignocaine</td>
<td>VAS, TT</td>
<td>3, 12</td>
<td>Pain (n = 6), no infection or rupture</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SW</td>
<td>61 (22/39)</td>
<td>38.6</td>
<td>NA</td>
<td>12.7 (weeks)</td>
<td>3</td>
<td>NA</td>
<td>3000 pulses</td>
<td>EFD 0.08 mJ/mm², 1000 pulses *3 s</td>
<td>VAS, AOFAS, AHS PFT</td>
<td>1, 3, 6</td>
<td>NA</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*Indicates the follow-up time points that were used for the meta-analysis of successful treatment rates. bIndicates that quality scores were from the Jadad scale. cIndicates that quality scores were from the Newcastle-Ottawa scale. ABPs: autologous blood-derived products; AFAS: American Foot and Ankle Score; AHS: Ankle-Hindfoot Scale; AOFAS: American Orthopaedic Foot and Ankle Society; EFD: energy flux density; F: female; FADI: Foot and Ankle Disability Index; FHSQ: foot health status questionnaire; HTI: Heel Tenderness Index; M: male; Mayo CSS: Mayo Clinic Scoring system; MRMS: Modified Roles and Maudsley scores; NA: not applicable; PFT: plantar fascia thickness; PRP: platelet-rich plasma; RCT: randomized controlled trial; SW: shock wave; TT: tenderness threshold; US: ultrasound; VAS: Visual Analogue Scale. The follow-up time points that were used for the meta-analysis of VAS reduction at 3 or 6 months are shown in bold.
Data synthesis and analysis

Data were extracted from baseline measurements and at (or as close as possible to) 3 and 6 months after the initial treatment. A deviation of <6 weeks from the predefined 3 and 6 months was allowed. The mean change in VAS score ($\Delta_{\text{VAS}}$) from baseline is the primary outcome, and its standard deviation (SD$_{\text{VAS}}$) was estimated as previously described [8–10]: 

$$\frac{(n_{\text{CG}} - 1) \times (\text{SD of } \Delta_{\text{VAS,CG}})^2 + (n_{\text{RG}} - 1) \times (\text{SD of } \Delta_{\text{VAS,RG}})^2}{(n_{\text{CG}} - 1) + (n_{\text{RG}} - 1)}$$

where CG and RG represent the comparator and reference groups, and $n_{\text{CG}}$ and $n_{\text{RG}}$ represent the number of patients in the comparator group and reference group.

The secondary outcome was the odds ratio (OR) of treatment success: the odds of satisfying results in the comparative group divided by the odds in the reference group [5]. Values exceeding 1 indicated better therapeutic responses. The rule of intention-to-treat was applied on the calculation of the s.d. of the change in VAS score. In the formula, the number of patients in the control group and the reference group is equal to the number on the initial treatment assignment and not on the treatment eventually completed.

Traditional pair-wise comparisons (ABPs vs CSs, CSs vs SW therapy, ABPs vs SW therapy) were conducted using Stata 12.0 (STATA Corporation, College Station, TX, USA) and a random effects model to account for between-study heterogeneity. The subgroup analyses were predefined, based on the study design (RCT vs quasi-experimental studies) and regimens of ABPs. Since the concentration of growth factors and cytokines is the major determinant of treatment efficacy of ABPs, data from the subgroup using PRP, a more potent concentrate of autologous growth factors, was extracted for analysis. Statistical heterogeneity across studies was quantified using the chi-square test (or the Cochran Q-test) and calculation of inconsistency.
(I²), with a P > 0.10 considered to be statistically significant [13]. Begg’s test was used to estimate publication bias, defined as the tendency for positive trials to be published and for negative and null trials to remain unpublished [14].

Network meta-analysis was conducted by using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo techniques [5, 15]. The first 1000 simulations were discarded, and the posterior probabilities were estimated by implementing 200,000 simulations. Convergence of iterations was evaluated using the Gelman–Rubin–Brooks statistic. The mixed-treatment comparisons were used to investigate the reductions in VAS score and the ORs of the treatment success by a random effects model. This analysis provided probabilities of being the best treatment based on direct and indirect comparisons of ABPs, CS injections and SW therapy. All P-values were two-sided, and P < 0.05 was considered statistically significant, except for testing of between-study heterogeneity.

Results

Characteristics of included studies

We identified 180 citations in the literature from electronic databases. Two additional articles were found through manual searches for references from Cochrane Systematic Reviews [16] and a narrative review of the related topic [17]. After removal of duplicates, the 110 citations were screened by title and abstract, and we assessed 18 of these for eligibility (Fig. 1). The excluded studies were four single-arm trials that evaluated pain before and after PRP injection [18–21], one RCT that did not measure pain by VAS score or therapeutic response rate [22], one two-arm trial that compared PRP injections and dextrose prolotherapy [23], one commentary of a published article [24] and one proposed study protocol that did not report outcomes [25]. The final meta-analysis included seven RCTs and three quasi-experimental studies. Four of the included studies compared PRP and CSs [26–29], two compared ABPs and CSs [7, 30], three compared SW therapy and CSs [31–33], and one compared PRP and SW therapy [34]. Most of the enrolled studies employed head-to-head comparisons. In one four-arm RCT, we used data from two arms (in which patients were treated with ABPs or CSs), and excluded the remaining groups that received peppered injections [30]. In one three-arm RCT, we excluded the results from one group that was given conventional physical therapy [34]. The 10 enrolled studies had a total of 604 patients, 184 of whom were men (Table 1). The average age ranged from 34 to 53 years. The follow-up period ranged from 3 weeks to 12 months, and the final assessment in most trials was at 6 months after the initial treatment. The most common CSs were triamcinolone and betamethasone, followed by methylprednisolone. ABPs and CSs were each administered as single injections in all trials. In studies of SW therapy, there were two or three treatment sessions, and the energy efflux intensity ranged from 0.02 to 0.42 mJ/mm².

Pair-wise meta-analysis

Fig. 2 shows the between-group differences in pain reduction at 3 and 6 months, and the OR of treatment success comparing autologous blood-derived products (ABPs), CSs and shock-wave therapy.

(A) Pain reduction at 3 months, (B) pain reduction at 6 months and (C) the OR of treatment success comparing autologous blood-derived products (ABPs), CSs and shock-wave therapy.

Subgroup analysis of the seven RCTs did not contradict the results from analysis of all 10 studies (Table 2). Due to
Table 2: Summary of direct and mixed comparisons of treatment effectiveness

<table>
<thead>
<tr>
<th>Direct comparison</th>
<th>Direct comparison (RCT only)</th>
<th>Direct comparison (quasi-experimental studies only)</th>
<th>Mixed comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized mean difference of VAS reductions at 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABPs vs CS (reference)</td>
<td>1.20 (–0.33 to 2.74)</td>
<td>0.97 (–1.03 to 2.97)</td>
<td>1.44 (–2.44 to 5.24)</td>
</tr>
<tr>
<td>SW vs CS (reference)</td>
<td>–0.87 (–4.15 to 2.40)</td>
<td>–0.87 (–4.15 to 2.40)</td>
<td>–</td>
</tr>
<tr>
<td>ABPs vs SW (reference)</td>
<td>0.00 (–2.55 to 2.55)</td>
<td>0.00 (–2.55 to 2.55)</td>
<td>–</td>
</tr>
<tr>
<td>Standardized mean difference of VAS reductions at 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABPs vs CS (reference)</td>
<td>0.41 (–0.77 to 1.59)</td>
<td>0.55 (–0.75 to 1.85)</td>
<td>–0.27 (–3.10 to 2.56)</td>
</tr>
<tr>
<td>SW vs CS (reference)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ABPs vs SW (reference)</td>
<td>1.00 (–2.10 to 4.10)</td>
<td>–</td>
<td>1.00 (–2.10 to 4.10)</td>
</tr>
<tr>
<td>OR of treatment success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABPs vs CS (reference)</td>
<td>0.97 (0.55 to 1.73)</td>
<td>1.38 (1.08 to 1.76)</td>
<td>0.67 (0.36 to 1.25)</td>
</tr>
<tr>
<td>SW vs CS (reference)</td>
<td>1.34 (0.62 to 2.88)</td>
<td>1.34 (0.62 to 2.88)</td>
<td>–</td>
</tr>
<tr>
<td>ABPs vs SW (reference)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

All values are expressed by point estimates with 95% confidence intervals (pair-wise meta-analysis) or credible intervals (network meta-analysis). *Although the confidence interval of the OR of treatment success of autologous blood-derived products versus CS did not cross the value of 1, only one randomized controlled trial was included in the pair-wise comparison. ABPs: autologous blood-derived products; RCT: randomized controlled trial; SW: shock wave; VAS: visual analogue scale.

Discussion

The present meta-analysis compared the efficacy of ABPs, CSs and SW therapy in the treatment of plantar fasciitis. The pair-wise comparisons indicated a trend favouring ABPs over CSs for pain reduction at 3 months, and a statistically significant difference in a subgroup comparison of PRP over CSs. Pair-wise comparisons indicated no significant differences in the three treatments in terms of pain reduction at 6 months and treatment success. Network meta-analysis indicated that ABPs had the highest probability of being the best treatment at 3 months. At 6 months, SW therapy was the best treatment, but was only slightly better than ABPs at that time. Notably, the difference in treatment success for ABPs and CSs was less than the difference in pain reduction for ABPs and CSs at 3 and 6 months.

The results of the network meta-analysis indicated that ABPs were likely to be the best treatment for pain reduction at 3 months. Among the between-group comparisons in pair-wise meta-analyses, only the point estimate of VAS score difference of ABPs vs CS exceeded 1.1 cm, the minimal clinically significant change on a 10-cm scale [12]. Thus, the findings of both analyses favour ABPs as the most effective regimen for pain relief from plantar fasciitis at 3 months. In addition, previous studies indicated a positive association between the biological benefits of ABPs and the amount of intra-serum growth factors, which are abundant in platelets [35, 36]. Therefore, we separately analysed patients receiving PRP injections. This subgroup analysis indicated statistically significant superiority of PRP over CSs, and confirmed that different ABP regimens have different efficacy in pain reduction. The network meta-analysis indicated that SW therapy had the lowest probability of being the best treatment for pain reduction at 3 months. However, this analysis might underestimate the true capability of SW therapy for initial symptom relief because the magnitude of pain reduction following SW therapy is proportional to the substantial heterogeneity in therapeutic protocols and relatively smaller numbers of included trials, the subgroup analyses were not conducted in the groups receiving SW therapy or CSs. Separate analysis of studies that used PRP (Fig. 3) indicated that the standardized mean differences in VAS score reduction for PRP vs CS (reference) was 1.81 (95% CI 0.02, 3.60) at 3 months, 0.66 (95% CI –0.60, 1.92) at 6 months (Fig. 3), and the OR of treatment success was 1.21 (95% CI 0.74, 1.98). All P-values (determined by Begg’s test) were >0.05, and there was no obvious funnel plot asymmetry, suggesting no significant publication bias.

Network meta-analysis

Convergence of the network model was achieved by use of 200 000 iterations. Table 2 shows the standardized mean difference in VAS score reduction and OR of the treatment success. In agreement with the results of the pair-wise meta-analysis, the three treatments had no significant differences in either outcome measure. An advantage of network meta-analysis is that it allows estimation of the distribution of probabilities for each treatment upon each outcome measure. Thus, the probability of being the best treatment for pain relief at 3 months was 16.8% for CSs, 78.3% for ABPs and 4.8% for SW therapy. For pain reduction at 6 months, the probability of being the best treatment was 9.3% for CSs, 41.0% for ABPs and 49.6% for SW therapy. Analysis of successful treatment rate indicated that the probability of being the best treatment was 27.3% for CSs, 19.6% for ABPs and 53.0% for SW therapy (Fig. 4).
energy efflux density [5], and most of the included trials used low-intensity SWs.

The network meta-analysis showed that SW therapy and ABPs had similar probabilities of being the best treatment at 6 months (49.6% vs 41.0%), but the probability that CSs were the best treatment at that time was only 9.3%. The pair-wise meta-analysis also indicated a small but non-significant advantage of ABPs over CSs at 6 months. Thus, both analyses indicate that CSs provide a less sustained benefit against plantar fasciitis, which is primarily a degenerative process. In contrast, SW therapy was least effective for pain reduction at 3 months, but most effective at 6 months. SW therapy is believed to relieve the pain associated with plantar fasciitis by destruction of sensory unmyelinated nerve fibres and elicitation of neovascularization in degenerative tissues [35, 37]. The small effect of SW therapy in pain reduction at 3 months might be due to incomplete sensory nerve denervation due to the use of low-energy SW therapy; the greater effect at 6 months may be due to the initiation of regenerative processes by neovascularization. ABPs and CSs also appeared to be less effective at 6 months than at 3 months, although SW therapy was more effective at 6 months than at 3 months. Previous research indicated that the injection dose of ABPs was positively related to therapeutic efficacy [10]. Thus, the use of single injections in most of the included studies may explain the reduced efficacy of ABPs at 6 months.

Analysis of the ORs of treatment success indicated smaller differences between the three therapies than the differences in VAS score at 3 months and 6 months (Fig. 4). The discrepancy between treatment success and VAS changes may be because the data used for calculation of treatment success were from the last follow-up points, and this ranged from 3 to 6 months among the included studies. Although separating the endpoints of treatment success according to different timing is a preferable approach, the network analysis could not be performed because only two arms of treatments were available at each endpoint (Table 1). Nonetheless, our analysis of VAS changes clearly indicated that the efficacy of the three treatments changed over time, and the data for treatment success further strengthened our points that therapeutic effectiveness was time dependent. In addition, there was significant variation in the different trials regarding the definition of satisfactory therapeutic response. Therefore, due to the considerable heterogeneity in assessment times and definitions of outcome variables among the included studies, we did not interpret the effects of the three treatments based on the ORs of treatment success.

**Fig. 3** Forest plots of between-group comparisons of treatment effects

(A) Pain reduction at 3 months, (B) pain reduction at 6 months and (C) the OR of treatment success comparing platelet-rich plasma (PRP), CSs and shock-wave therapy.

**Fig. 4** Probabilities of being the best treatment calculated from the network meta-analysis

The probabilities that autologous blood-derived products (ABPs), CSs and shock-wave therapy were the best treatment for visual analogue scale (VAS) reduction at 3 and 6 months, and treatment success.
The present meta-analysis has two major clinical implications. First, injections of ABPs (especially the PRP regimen) can be considered the best choice, and CSs can be considered the second-best option, for early pain relief in patients with chronic plantar fasciitis. If SW therapy is to be used, we suggest adjustment of the intensity to a higher level to provide better initial pain reduction. Second, SW therapy and ABPs provide better pain relief at 6 months, although multiple injections of ABPs may provide even better long-term pain relief.

Study limitations

There are some limitations in our meta-analysis. First, foot function is considered a crucial outcome variable, but some studies did not report this outcome, and the trials that did report functional assessments used different metrics. Although transformation of the different functional scales into effect sizes might allow head-to-head comparisons, we chose the mean VAS score difference and successful treatment rate, which are relatively standardized measurements, for our outcome analysis. Second, some of the included studies used quasi-experimental designs, which were of lower quality than RCTs. However, the inclusion of quasi-experimental research apparently did not distort our conclusions, because the results of subgroup analysis of the seven RCTs were compatible with the results from all 10 studies. Third, although the point estimates of pooled effect sizes show some discrepancy between direct and mixed treatment comparisons in ABPs vs SW therapies, a substantial part of their 95% CIs overlapped (Table 2). Therefore, no significant difference can be identified between results from direct and mixed treatment comparisons. In addition, the result of direct comparison of ABPs vs SW therapies was derived from only one study [33], leading to an increase in difference of point estimate between direct and mixed-treatment comparisons. Fourth, we did not enrol trials that merely used one of the three treatments (SW, CSs or ABPs) in comparison with placebos. The main reason was notable discrepancy in placebo treatments according to different therapeutic options, which made indirect comparisons through the connection of the placebo treatment less feasible.

Finally, the included studies had remarkable variation in injection regimens, therapeutic cycles, SW intensity and needle-guidance techniques, and this may explain why most of our comparisons were statistically insignificant. However, we identified some significant between-treatment differences following subgrouping, highlighting the importance of selecting a specific regimen for ABPs, such as PRP.

Conclusion

The present meta-analysis compared the efficacy of ABPs, CSs and SW therapy in the treatment of plantar fasciitis. The results demonstrated that ABPs, followed by CSs, were best in providing early pain relief. However, SW therapy and ABPs provided better pain reduction than CSs at 6 months. The type of ABP regimen seems to affect treatment outcome, and PRP appears to increase treatment efficacy.

Acknowledgements

We would like to express special thanks to all the investigators conducting the trials included in the present meta-analysis.

Funding: This research was supported by grants from the National Science Council (NSC 101-2314-B-002-MY3).

Disclosure statement: The authors have declared no conflicts of interest.

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