The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy

A Meta-analysis of Randomized Controlled Clinical Trials

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Background: Tendinopathy is very common in the general population. There are increasing numbers of clinical studies referring to platelet-rich plasma (PRP) and platelet-poor plasma (PPP) as treatments for tendinopathy.

Purpose: To perform a meta-analysis of the outcomes of the PRP groups by preparation method and injection technique in tendinopathy. To determine the clinical effectiveness of the preparations and to evaluate the effect of controls used in the studies reviewed.

Study Design: Systematic review and meta-analysis.

Methods: The PubMed, EMBASE, CINAHL, and Medline databases were searched in March 2012, April 2014, and August 2015, and randomized controlled trials using autologous blood, PRP, PPP, or autologous conditioned plasma in tendinopathy with outcome measures of pain and follow-up time of 3 months were included in this review. Trials including surgery, tendon tears, and muscle or ligament injuries were excluded. Study quality was assessed using the Cochrane Collaboration risk-of-bias tool by 2 reviewers. Data were pooled using random-effects meta-analysis. The primary outcome measure was a change in pain intensity. Where more than 1 pain scale was included, a functional score was selected ahead of a visual analog scale score.

Results: A total of 18 studies (1066 participants) were included. Eight studies were deemed to be at low risk of bias. The most significant outcomes in the PRP groups were seen in those treated with highly cellular leukocyte-rich PRP (LR-PRP) preparations: GPS kit (standardized mean difference [SMD], 35.75; 95% CI, 28.40-43.10), MyCells kit (SMD, 31.84; 95% CI, 17.56-46.13), Prosys kit (SMD, 42.99; 95% CI, 37.73-48.25), and unspecified LR-PRP (SMD, 34.62; 95% CI, 31.69-37.55). When the LR-PRP system types were grouped, there was a strongly positive effect (SMD, 36.38; 95% CI, 34.00-38.77) when compared with leukocyte-poor PRP (SMD, 26.77; 95% CI, 18.31-35.22). In assessing the control groups, there was no clear difference between different types of control injections: saline (SMD, 14.62; 95% CI, 10.74-18.50), local anesthetic (SMD, 15.00; 95% CI, 7.66-22.34), corticosteroid (SMD, 23.82; 95% CI, 10.74-18.50), or dry needling (SMD, 25.22; 95% CI, 21.27-29.16).

Conclusion: There is good evidence to support the use of a single injection of LR-PRP under ultrasound guidance in tendinopathy. Both the preparation and intratendinous injection technique of PRP appear to be of great clinical significance.

Keywords: platelet-rich plasma; tendinitis; tendinopathy; platelet separation system; meta-analysis; injection therapy

Tendinopathy is one of the most common reasons for presentation to a medical practitioner, representing 30% of all presentations for musculoskeletal complaints.26 The most frequently discussed sites include the elbow (both tennis and golfer’s elbow), rotator cuff, Achilles tendon, patellar tendon, and gluteal tendons. There are multiple treatments described in the literature including physical therapy; shock wave treatment; nonsteroidal anti-inflammatory drugs; and injections of glucocorticoid, prolotherapy, autologous blood, polidocanol, botulinum toxin, and platelet-rich plasma (PRP).30 Despite the pathophysiological role of inflammation being debated, the most commonly used treatment for chronic tendinopathy is glucocorticoid injections. These offer good short-term improvement, less than 3 months, but do not confer a benefit in the longer term.PRP is one treatment that has been embraced in recent years as a potentially safe, effective treatment for tendinopathy.17 PRP is defined as platelet-rich concentrate with platelet levels greater than baseline when compared with whole blood. The potential uses of PRP extend from skin and wound healing to the treatment of tendinopathy and...
osteoarthritis. There is widespread interest in the use of PRP in the treatment of tendinopathy as well as an increasing number of randomized controlled trials (RCTs) studying the effectiveness of PRP in tendinopathy, particularly in tennis elbow. There is still no consensus as to whether PRP confers a beneficial effect, as not all trials have failed to demonstrate a positive benefit.

We found 6 systematic reviews published between 2010 and 2014 assessing the effectiveness of PRP in tendinopathy. Despite analyzing the same data, they reported contrasting conclusions, from concluding that PRP is efficacious to finding that there is strong evidence against the type of pain score used and its maximum score; and peritendinous or intratendinous injections. Controls were accepted as other active injections, placebo, or conservative management.

According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the PRISMA-IPD Statement (see Appendix 1, available online at http://ajsm.sagepub.com/supplemental).

Eligibility Criteria, Patients, and Interventions

RCTs using injections of PRP or autologous blood products in the treatment of tendinopathy (of any type) were included if they treated adults (aged 18 years). Trials that included patients undergoing surgery or treatment of nontendon soft tissue injuries (e.g., muscle, ligament, or fascia) were not eligible. Eligible interventions included injections of any autologous blood product including whole blood, PRP or platelet-poor plasma (PPP), or autologous conditioned plasma (ACP). We allowed any dosage, volume, number of injections, and peritendinous or intratendinous injections. Controls were accepted as other active injections, placebo, or conservative management.

Outcomes

We considered the most important primary outcome measure as a change in pain intensity or function. Previous meta-analyses have demonstrated that the “benefit from PRP” is most evident at longer time points or “have a significant impact on improving pain and/or function over time.” Therefore, a minimum acceptable follow-up of 12 weeks for studies was included, and data from 6- and 12-month follow-up were included where available. In the event that more than 1 pain scale was included in the study, we selected the Patient-Rated Tennis Elbow Evaluation (or equivalent for other tendons) ahead of a visual analog scale or verbal rating scales. Only 1 pain score measure was used for each study.

Data Sources and Search Strategy

A search strategy for RCTs investigating the treatment of tendinopathy with autologous blood products was carried out. The full search strategy is contained in Appendix 2 (available online); key search terms included “platelet-rich plasma,” “autologous conditioned serum,” “autologous blood and tendinitis,” “tendinopathy,” and the terms for all common tendinopathy such as “tennis elbow,” “Achilles tendinitis/tendinopathy,” “patellar tendinitis,” “hamstring,” “rotator cuff,” and “gluteal tendinopathy.” The PubMed, EMBASE, CINAHL, and Medline databases were searched for 5 years up to March 2012. A repeat search was performed in April 2014 and August 2015. The language was restricted to English.

Study Selection

Initial screening and study selection were performed by 2 authors (J.F. and M.B.). Any disagreement was discussed between these 2 authors, and a third author (M.Z.) was available to determine a consensus. A total of 72 records were identified through database searching (Figure 1). An additional 3 studies were obtained from review articles. After duplicates were removed, 65 records were screened. Twenty-one records were excluded on review of the abstract, as they were protocol registrations, not RCTs, related to surgical procedures or conditions other than tendinopathy. The number of full-text articles assessed for eligibility was 44. Of these, 22 studies were excluded: 5 related to rotator cuff tears, 2 related to muscle injuries, 13 related to surgical interventions, and 2 were non-PRP studies. Of the 22 articles available for analysis, 2 sets of articles were combined after discussion, as they related to the same data sets. Two articles were excluded: Kazemi et al had data only available to 8 weeks, which did not meet the minimum criteria for analysis, and Mishra and Pavelko had no analyzable data available in the published form, and despite personal contact with the authors, it was not possible to obtain data for analysis for this work. This meant that there were 18 articles available for full analysis (Table 1).

Data Collection Process

Data from the included trials were extracted by one reviewer (J.F.) and checked by a second reviewer (M.B.). The extracted data were included in an Excel spreadsheet (Microsoft Corp) and included the title of the article and authors; the kit or product type and technique; the region being treated; the number of participants in the trial enrolled and completed; whether the trial was an RCT; the type of pain score used and its maximum score; and...
the 2-, 3-, 6-, and 12-month scores and their SDs. Where
the SDs were not reported, they were calculated from the
95% CIs. Where neither of these was available, the authors
were approached directly using the email address on their
publication to obtain the raw data. One study, Mishra
et al, 36 had no published SDs or 95% CIs, but these were pro-
vided after personal contact with the authors. The technique
used in all PRP groups was described as single/multiple injec-
tions, intratendinous (peppering), with or without local anes-
thetic. One study’s authors were approached to confirm their
technique, as it was not clear from the publication whether
local anesthetic was used. 49

Assessment of Risk of Bias

Because it is accepted that the inclusion of trials with
a high risk of bias may distort the results of a meta-
alysis, 23,32 the Cochrane Collaboration tool for assessing
the risk of bias was used. The following factors were
assessed: randomization sequence generation; allocation
concealment; blinding of patients, investigator, and asses-
sor; attrition rates; and financial interest by companies.
These were given a rating of low, unclear, or high risk of
bias. An RCT was ranked as having low, medium, or
high risk overall based on the key areas of allocation con-
cealment, reporting of attrition rates, and patient and
assessor blinding (low = all key areas rated low, medium
= 2 or 3 factors rated high or uncertain, and high = all 4
factors rated high).

Measures of Treatment Effect

The weighted mean difference with the 95% CI was calculated
when continuous outcomes were measured on standard scales. Where continuous outcomes were reported on nonstan-
donard scales, the standardized mean difference (SMD) was cal-
culated. All analyses were performed on an intention-to-treat
basis. As changes from baseline scores were analyzed, we
imputed a change-from-baseline SD using a correlation coeffi-
cient based on the Cochrane guidelines. 24

Assessment of Heterogeneity

Heterogeneity among trials was assessed using the $I^2$
statistic (>50% is considered as having substantial hetero-
genity). We used a random-effects meta-analysis as an
overall summary when appropriate.

Statistical Analysis

We used the scores for the change in pain intensity at base-
line and at 3, 6, and 12 months where available. These
were SMDs for each study and each control/treatment
group. There were a variety of pain scales used across
the studies. Thus, the application of an individual arm-
based approach to the meta-analysis was used so each
blood product type and each control type were evaluated
separately within each study trial. Data appear as the
change in pain from baseline with SDs and 95% CIs for
each time point. A fixed-effects model was used if no signif-
icant heterogeneity existed between studies.

All statistical analyses were performed using STATA
version 13 (StataCorp LP). Forest plots were utilized to
assess statistical heterogeneity.

RESULTS

Of the 75 studies identified by the search, a total of 18 studies
were included in the qualitative synthesis. As outlined in Fig-
ure 1, studies were excluded if they related to rotator cuff
tears rather than tendinopathy, assessed muscle injuries,
were duplicates, related to ligament injuries, had surgical
interventions, or did not use an autologous blood or PRP
product.

Studies were analyzed for type of control and type and
technique of treatment. All treatments consisted of intraten-
dinous injections with a prior administration of 1 to 2 mL of
local anesthetic unless specified otherwise, as follows:

1. Autologous blood injection (ABI): 7 studies
2. Leukocyte-rich PRP (LR-PRP) produced from the
   buffy coat layer:
   a. GPS kit (Biomet Biologistics): 6 studies
   b. MyCells kit (Kaylight Ltd): 1 study
   c. Prosys kit (Tozai Holdings Inc): 1 study
   d. Unspecified kit as LR-PRP: 2 studies

Records identified through database searching
(N = 72)
Records after duplicates removed
(n = 65)
Records screened
(n = 65)
Records excluded
(n = 21)
Full-text articles assessed for eligibility
(n = 44)
Full-text articles excluded: cuff tear 5,
muscle 2, ACL/surgical 13, not PRP 2
(n = 22)
Studies included in qualitative synthesis
(n = 22)
Studies included in quantitative synthesis
(meta-analysis) (n = 18)

Figure 1. Flow of information through a systematic review
for platelet-rich plasma in tendinopathy.
3. LR-PRP produced from the buffy coat layer with 10 to 15 mL injected prior (GPS kit and high volume of local anesthetic): 1 study

4. Leukocyte-poor PRP (LP-PRP): 1 study

5. ACP (leukocyte-poor PPP): 1 study

Nine studies used a single injection, and 4 used 2 injections. All except for 2 studies used ultrasound guidance. All studies used 1 to 3 mL of local anesthetic injected superficially, except for 1 study that injected the local anesthetic with PRP and 1 study that used 10 to 15 mL of local anesthetic superficially. Only 1 study activated PRP before the injection: Behera et al, who also used LP-PRP.

Four studies buffered PRP before use with sodium bicarbonate.

Controls were divided into

1. Injections:
   a. Corticosteroid: 6 studies
   b. Saline: 4 studies
   c. Local anesthetic: 2 studies
   d. Dry needling: 4 studies

2. Noninjections:
   a. Eccentric training: 1 study
   b. Shock wave treatment: 2 studies

Two studies used 2 control arms: Wolf et al used corticosteroid and saline as controls against autologous blood, and Krogh et al also used corticosteroid and saline as controls against the GPS kit. No differentiation was made for differing tendon sites.

Risk-of-Bias Assessment

No studies were eliminated on bias risk alone. Table 2 shows the 8 studies deemed to have a low risk of bias based on the 4 key areas of allocation concealment, patient and assessor blinding, and attrition.

Network Meta-analysis

A total of 18 studies (1066 participants) were included. Seventeen studies were deemed to be at low or medium risk of bias. The changes in pain scores for treatments and controls presented by treatment type are shown in Appendix Figure A1 (available online).

The most significant outcome in the PRP groups was observed in those treated with highly cellular LR-PRP preparations: GPS kit (SMD, 35.75; 95% CI, 28.40-43.10), MyCells kit (SMD, 31.84; 95% CI, 17.56-46.13), Prosys kit (SMD, 42.99; 95% CI, 37.73-48.25), and unspecified LR-PRP (SMD, 34.62; 95% CI, 31.69-37.55).

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**TABLE 1**

*Articles Available for Quantitative Analysis*

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Tendon</th>
<th>No. of Patients</th>
<th>Therapy</th>
<th>Outcome</th>
<th>Time, mo</th>
<th>Comment</th>
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<td>Bell et al5 (2013)</td>
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<td>53</td>
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<td>VISA-A</td>
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<td>Thanasas et al6 (2011)</td>
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<td>27</td>
<td>GPS/ABI</td>
<td>VAS</td>
<td>3, 6</td>
<td>Included</td>
</tr>
<tr>
<td>Creaney et al5 (2011)</td>
<td>TE</td>
<td>130</td>
<td>LR-PRP/ABI</td>
<td>PRTEE</td>
<td>3, 6</td>
<td>Included</td>
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<td>Wolf et al3 (2011)</td>
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<td>ABI/CSI/saline</td>
<td>DASH</td>
<td>2, 6</td>
<td>Included</td>
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<td>100</td>
<td>GPS/CSI</td>
<td>DASH</td>
<td>3, 6, 12</td>
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<td>60</td>
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<td>Not included</td>
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<td>57</td>
<td>ABI/CSI/SWT</td>
<td>VAS</td>
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<td>GPS-HLA/CSI/saline</td>
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<td>3, 12</td>
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<td>20</td>
<td>GPS/LA</td>
<td>VAS</td>
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<td>MCCPI</td>
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<tr>
<td>Gautam et al15 (2015)</td>
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<td>DASH</td>
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<td>RC</td>
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<td>GPS/saline</td>
<td>WORC</td>
<td>3, 6</td>
<td>Included</td>
</tr>
</tbody>
</table>

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*ABI, autologous blood injection; ACP, autologous conditioned plasma; CSI, corticosteroid injection; DASH, Disabilities of the Arm, Shoulder and Hand; DN, dry needling; Ecc, eccentric training; GPS, GPS kit; GPS-HLA, GPS kit and 10 mL of local anesthetic; LA, local anesthetic injection; LP-PRP, leukocyte-poor platelet-rich plasma, no kit specified; LR-PRP, leukocyte-rich platelet-rich plasma, no kit specified; MC, MyCells kit; MCCPI, modified Mayo Clinic Performance Index for the Elbow; Nirschl, Nirschl Score for elbow; Prosys, Prosys kit; PRTEE, Patient-Rated Tennis Elbow Evaluation; PT, patellar tendinitis (jumper’s knee); RC, rotator cuff; Saline, saline injection; SPDI, Shoulder Pain and Disability Index; SWT, shock wave treatment; TE, tennis elbow (lateral epicondylitis); VAS, visual analog scale for pain; VISA-A, Victorian Institute of Sport Assessment–Achilles; VISA-P, Victorian Institute of Sport Assessment–Patella; WORC, Western Ontario Rotator Cuff Index.


d0 There were 60 patients at the beginning of the study; the final number of study patients was 17.

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3. References 4, 14, 16, 19, 28, 31, 36, 40, 49.
The ACP group also had a positive response (SMD, 32.67; 95% CI, 1.42-63.93). LP-PRP did not appear to be as effective (SMD, 26.77; 95% CI, 18.31-35.22).

Because it appeared that LR-PRP preparations produced a more positive outcome than LP-PRP preparations, this was compared in a forest plot grouped analysis (see Appendix Figure A2, available online). Results showed a strongly positive effect of LR-PRP (SMD, 36.38; 95% CI, 34.00-38.77) when compared with LP-PRP (SMD, 26.77; 95% CI, 18.31-35.22).

One study using LR-PRP with the administration of 10 to 15 mL of local anesthetic did not obtain positive results31 (SMD, 14.83; 95% CI, 11.11-18.55). While there was no local anesthetic administered at the time of the PRP injection, the volume injected prior was more than 10 times the amount used by other studies. Given the potential negative effect of local anesthetic on PRP, this may be the reason that this group performed poorly.7

In assessing the control groups, there was no clear difference between different types of control injections: saline (SMD, 14.62; 95% CI, 10.74-18.50), local anesthetic (SMD, 15.00; 95% CI, 7.66-22.34), corticosteroid (SMD, 23.82; 95% CI, 10.74-18.50), or dry needling (SMD, 25.22; 95% CI, 21.27-29.16). None of these controls was truly a placebo, as all these injections produce a measurable effect on the outcome, but they did produce effective controls for this type of clinical trial.

DISCUSSION

Essentially, there are 2 main types of PRP produced. The first is from the plasma layer. It aims to exclude red and white cells from the preparation and to collect as many platelets from the remaining “plasma” layer as possible. The resultant product is low in red and white cells and has a low level of platelets (1.5 to 3 times baseline levels). The ACP kit works in this way and has been shown to have 1.36 to 2.634 times the baseline platelet concentrations with low white cell counts. Thus, the ACP kit was classified as PPP, being lower in platelet count but also low in white cell count. The second type of product is made from the buffy coat layer. It aims to take platelets from both the plasma and the cellular layer and thus is generally much higher in platelet count, yielding 32.67 to 2.634 times the baseline level of platelets.3,12,29 It does, however, concentrate the white cells in equal amounts and is thus high in both leukocytes and platelets (LR-PRP). It is possible to produce LP-PRP by filtering out the white cells after preparation, as was conducted by Behera et al.4 A recent laboratory study by these authors (unpublished data) showed that the difference between PRP kit preparations is quite profound in terms of the total white cell count, ranging from 35.8 × 10⁶/L in LR-PRP to 1.3 × 10⁹/L in LP-PRP.

This study shows that the outcome of PRP is different depending on the method of preparation of PRP and the injection technique. There were 4 different types of PRP preparations and techniques studied. Highly cellular LR-PRP shows strongly positive outcomes in treating tendinopathy when assessed in the network meta-analysis.

For LP-PRP, the type of PRP and the usually single-injection technique using small volumes of superficial local anesthetic with a 5- to 6-pass peppering technique, generally under ultrasound guidance, are consistent across the studies. Tendons included in this analysis included 5

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Treatment</th>
<th>No. of Patients</th>
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<th>Doctor Blinding</th>
<th>Allocation Concealment</th>
<th>Patient Blinding</th>
<th>Assessor Blinding</th>
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<td>Arik et al (2014)</td>
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</table>

*The 8 bolded studies were assessed as having a low risk of bias based on the key areas (allocation concealment, patient and assessor blinding, and attrition). ABI, autologous blood injection; HRB, high risk bias; LRB, low risk bias; MRB, medium risk bias; PRP, platelet-rich plasma; URB, uncertain risk bias.*
studies on tennis elbow, 2 studies on the rotator cuff, 2 studies on the patellar tendon, and 1 on the Achilles tendon. Only 1 trial was included using LP-PRP; hence, the data are too limited to draw conclusions at this stage. There is some evidence that the use of local anesthetic reduces the effectiveness of PRP in vitro. This meta-analysis demonstrates that LR-PRP is effective, but it is important to note that all groups used local anesthetic injected prior to and superficial to the tendon.

We have not presented the data in contrast to placebos/controls in part as many studies have active controls, for example, Creaney et al. who compared ABIs with PRP, and because our secondary goal was to determine whether the choice of control made a difference to the outcomes. Several reviewers have suggested that glucocorticoid injections should not be used as a control as they confer a negative outcome and therefore make the difference in the active (PRP) treatment look greater. We would contest that all injections are clinically active treatments whether this is dry needling, saline, or local anesthetic administration. Thus, the data have been presented as changes in pain scores from baseline for all modalities, be they controls or active treatments.

We also wished to identify whether the type of control may affect the results of trials, particularly the use of corticosteroid. It has been argued by de Vos et al. that corticosteroid has a negative effect on tendinopathy, and thus when used as a control, it will make the mean difference greater than it would if it were compared with other types of injectable controls. Corticosteroid injections show an improvement up to 3 months and then a decline in effectiveness, as shown in the most recent Cochrane review by Dean et al. Our network meta-analysis found that corticosteroid, dry needling, and saline injections did not have a positive outcome in the treatment of tendinopathy: saline (SMD, 14.62; 95% CI, 10.74-18.50), local anesthetic (SMD, 15.00; 95% CI, 7.66-22.34), corticosteroid (SMD, 23.82; 95% CI, 10.74-18.50), and dry needling (SMD, 25.22; 95% CI, 21.27-29.16). In fact, corticosteroid and dry needling both have a greater change from baseline than saline or local anesthetic and would thus show a less positive outcome when compared with active treatment groups, the opposite effect to that postulated by de Vos et al. It is therefore considered that any corticosteroid, dry needling, or saline injections are good controls for clinical trials assessing tendinopathy, and consequently, trials using corticosteroid, saline, local anesthetic, or dry needling as a control would be valid when used in a meta-analysis. Taking into account the recommendations of the World Medical Association’s Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, which states, “the benefits, risks, burdens and effectiveness of a new intervention must be tested against the best current proven intervention, except in the following circumstances: The use of a placebo, or no treatment, is acceptable in studies where no current proven treatment exists,” our network meta-analysis would support the inclusion of data where corticosteroid, local anesthetic, saline, or dry needling are used as a control in the treatment of tendinopathy.

The strength of this meta-analysis is that we have shown a difference in outcomes in treating tendinopathy directly related to the type of PRP produced. All previous meta-analyses have grouped PRP types together. The weakness of this meta-analysis is that it has not been possible to separate the results into grouping by tendon, as there are insufficient trials in each area at present. However, as the number of trials increases, it will be possible to determine whether there are differences across tendon locations with different PRP preparations. Nevertheless, the causes of tendinopathy are similar, and conclusions can be drawn for tendinopathy as a group.

CONCLUSION

This network meta-analysis has identified that the type of PRP and the techniques used affect the outcomes and should always be included in any meta-analysis in the future, as predicted by Moraes et al. and recommended by Gosens and Mishra. Our systematic review and network meta-analysis found strong evidence that LR-PRP improves outcomes in tendinopathy and confirms the results published by Baksh et al. The technique for the injection of LR-PRP includes the use of 1 to 2 mL of local anesthetic injected prior to LR-PRP superficial to the tendon. A single LR-PRP is injected using a peppering technique intratendinously into the affected area, generally under ultrasound guidance.

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