The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Clinical Trials

Jane Fitzpatrick, Max Bulsara and Ming H. Zheng

Am J Sports Med published online June 6, 2016
DOI: 10.1177/0363546516643716

AJSM PreView, published on June 6, 2016 as doi:10.1177/0363546516643716

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

A Meta-analysis of Randomized Controlled Clinical Trials

Jane Fitzpatrick,*† MBBS, FACSP, Max Bulsara,‡ BSc(Hons), MSc, PhD, and Ming H. Zheng,† MD, PhD, FRCPath, FRCPA
Investigation performed at the University of Western Australia, Perth, Australia

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,[18] 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.[8] 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

*Address correspondence to Jane Fitzpatrick, MBBS, FACSP, University of Western Australia, 35 Stirling Highway, M508 Crawley, WA, 6009 Australia (email: jane.fitzpatrick@research.uwa.edu.au).
†University of Western Australia, Perth, Australia.
‡University of Notre Dame Australia, Freemantle, Australia.

The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

The American Journal of Sports Medicine, Vol. XX, No. X
DOI: 10.1177/0363546516643716

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.[11,14,22,31,40,49,50] There is still no consensus as to whether PRP confers a beneficial effect, as not all trials have failed to demonstrate a positive benefit.[14,31]

We found 6 systematic reviews published between 2010 and 2014 assessing the effectiveness of PRP in tendinopathy.[1,3,13,15,30,37] Despite analyzing the same data, they reported contrasting conclusions, from concluding that PRP is efficacious[1] to finding that there is "strong evidence against platelet-rich plasma."[15] The majority of comments stated that there is great difficulty reaching a conclusion because of the variance of the type of PRP produced. In a Cochrane review of PRP in soft tissue injuries, Moraes et al[37] indicated that "there is need for standardization of PRP preparation methods." In their editorial review, Gosens and Mishra[21] commented on the systematic review performed by de Vos et al,[15] concluding that "it would be better to break out the results by specific study design and PRP type."

Thus, we conducted a meta-analysis to assess the comparative effectiveness of PRP types in tendinopathy. We also assessed the effectiveness of different controls used in RCTs.

METHODS

Our review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the PRISMA-IPD Statement[32,48] (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 (eg 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"[1] or "have a significant impact on improving pain and/or function over time."[13] 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.[11,14,22,40] Two articles were excluded: Kazemi et al[27] had data only available to 8 weeks, which did not meet the minimum criteria for analysis, and Mishra and Pavelko[35] 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

[§]References 3, 8, 14, 20, 22, 36, 40, 43, 46.

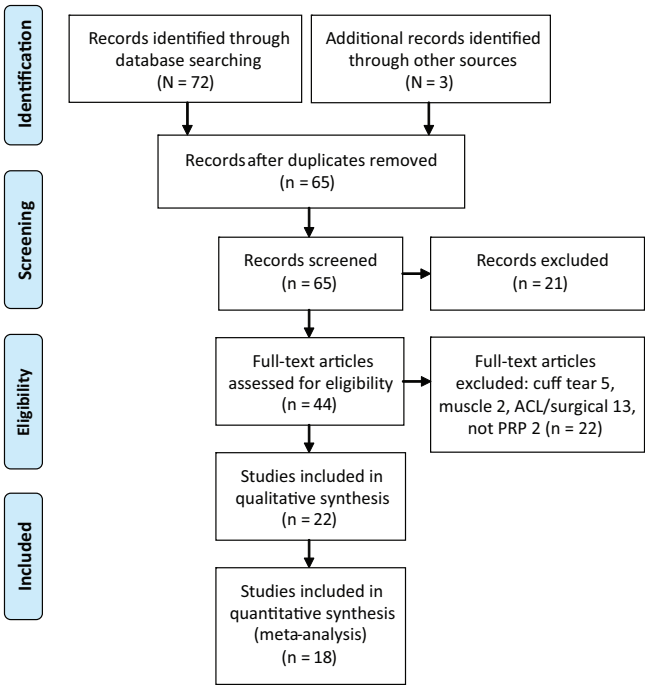

Figure 1. Flow of information through a systematic review for platelet-rich plasma in tendinopathy.

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 provided after personal contact with the authors. The technique used in all PRP groups was described as single/multiple injections, intratendinous (peppering), with or without local anesthetic. 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-analysis,[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 assessor; 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 concealment, 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 nonstandard scales, the standardized mean difference (SMD) was calculated. 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 coefficient based on the Cochrane guidelines.[24]

Assessment of Heterogeneity

Heterogeneity among trials was assessed using the I^2 test statistic (>50% is considered as having substantial heterogeneity). 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 baseline 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 significant 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 Figure 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 intratendinous 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[2,5,9,38,39,49,51]
2. Leukocyte-rich PRP (LR-PRP) produced from the buffy coat layer:
   a. GPS kit (Biomet Biologistics): 6 studies[14,16,28,36,40,49]
   b. MyCells kit (Kaylight Ltd): 1 study[50]
   c. Prosys kit (Tozai Holdings Inc): 1 study[41]
   d. Unspecified kit as LR-PRP: 2 studies[9,19]

TABLE 1
Articles Available for Quantitative Analysis[a]

Author (Year)	Tendon	No. of Patients	Therapy	Outcome	Time, mo	Comment
Bell et al[5] (2013)	Achilles	53	ABI/DN	VISA-A	6	Included
Pearson et al[39] (2012)	Achilles	28	ABI/Ecc	VISA-A	3	Included
Thanasas et al[49] (2011)	TE	27	GPS/ABI	VAS	3, 6	Included
Creaney et al[9] (2011)	TE	130	LR-PRP/ABI	PRTEE	3, 6	Included
Wolf et al[51] (2011)	TE	28	ABI/CSI/saline	DASH	2, 6	Included
de Vos et al[14] (2010), de Jonge et al[11] (2011)	Achilles	54	GPS/saline	VISA-A	3, 12	Included
Peerbooms et al[40] (2010), Gosens et al[22] (2011)	TE	100	GPS/CSI	DASH	3, 6, 12	Included
Kazemi et al[27] (2010)	TE	60	ABI/CSI	DASH	2	Not included
Ozturan et al[38] (2010)	TE	57	ABI/CSI/SWT	VAS	3, 6, 12	Included
Krogh et al[31] (2013)	TE	60/17[b]	GPS-HLA/CSI/saline	PRTEE	3, 12	Included
Mishra and Pavelko[35] (2006)	TE	20	GPS/LA	VAS	2, 6	Not included
Vetrano et al[50] (2013)	PT	46	MC/SWT	VISA-P	2, 6, 12	Included
Mishra et al[36] (2014)	TE	225	GPS/LA	PRTEE	3, 6	Included
Behera et al[4] (2015)	TE	25	LP-PRP/LA	MMCPI	3, 6, 12	Included
Arik et al[2] (2014)	TE	80	ABI/CSI	PRTEE	3	Included
Dragoo et al[16] (2014)	PT	25	GPS/DN	VISA-P	3, 6	Included
Rha et al[41] (2013)	RC	30	Prosys/DN	SPDI	3, 6	Included
Stenhouse et al[47] (2013)	TE	28	ACP/DN	Nirschl	2, 6	Included
Gautam et al[19] (2015)	TE	30	LR-PRP/CSI	DASH	3, 6	Included
Kesikburun et al[28] (2013)	RC	40	GPS/saline	WORC	3, 6	Included

[a]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 10-15 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; MMCPI, 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.
[b]There were 60 patients at the beginning of the study; the final number of study patients was 17.

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[31]
4. Leukocyte-poor PRP (LP-PRP): 1 study[4]
5. ACP (leukocyte-poor PPP): 1 study[47]

Nine studies used a single injection,[‖] and 4 used 2 injections.[9,41,47,50] All except for 2 studies used ultrasound guidance.[36,40] All studies used 1 to 3 mL of local anesthetic injected superficially, except for 1 study that injected the local anesthetic with PRP[40] and 1 study that used 10 to 15 mL of local anesthetic superficially.[31] Only 1 study activated PRP before the injection: Behera et al,[4] who also used LP-PRP. Four studies buffered PRP before use with sodium bicarbonate.[14,31,36,40]

Controls were divided into

1. Injections:
   a. Corticosteroid: 6 studies[2,19,31,38,40,51]
   b. Saline: 4 studies[14,28,31,51]
   c. Local anesthetic: 2 studies[4,36]
   d. Dry needling: 4 studies[5,16,41,47]
2. Noninjections:
   a. Eccentric training: 1 study[39]
   b. Shock wave treatment: 2 studies[38,50]

[‖]References 4, 14, 16, 19, 28, 31, 36, 40, 49.

Two studies used 2 control arms: Wolf et al[51] used corticosteroid and saline as controls against autologous blood, and Krogh et al[31] 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).

TABLE 2
Risk-of-Bias Assessment for the Included Studies[a]

Author (Year)	Treatment	No. of Patients	Bias Risk Factor							Overall Risk of Bias
			Company Interest	Sequence Generation	Doctor Blinding	Allocation Concealment	Patient Blinding	Assessor Blinding	Attrition	
Bell et al[5] (2013)	ABI	53	LRB	LRB	HRB	LRB	LRB	LRB	LRB	LRB
Pearson et al[39] (2012)	ABI	28	LRB	LRB	HRB	HRB	HRB	HRB	LRB	MRB
Thanasas et al[49] (2011)	PRP	27	LRB	LRB	HRB	HRB	HRB	LRB	LRB	MRB
Creaney et al[9] (2011)	PRP	130	LRB	URB	HRB	LRB	LRB	HRB	LRB	MRB
Wolf et al[51] (2011)	ABI	28	LRB	LRB	HRB	LRB	LRB	HRB	HRB	MRB
de Vos et al[14] (2010)	PRP	54	LRB	LRB	LRB	LRB	LRB	LRB	LRB	LRB
Gosens et al[22] (2011)	PRP	100	LRB	LRB	LRB	LRB	LRB	LRB	LRB	LRB
Ozturan et al[38] (2010)	ABI	57	LRB	URB	HRB	URB	HRB	HRB	LRB	MRB
Krogh et al[31] (2013)	PRP	60	LRB	LRB	HRB	LRB	LRB	LRB	LRB	LRB
Vetrano et al[50] (2013)	PRP	46	LRB	LRB	HRB	LRB	HRB	LRB	LRB	MRB
Mishra et al[36] (2014)	PRP	225	HRB	LRB	LRB	LRB	LRB	LRB	LRB	LRB
Behera et al[4] (2015)	PRP	25	LRB	URB	HRB	URB	URB	URB	LRB	MRB
Arik et al[2] (2014)	ABI	80	LRB	URB	HRB	HRB	HRB	HRB	LRB	MRB
Dragoo et al[16] (2014)	PRP	25	LRB	LRB	LRB	LRB	LRB	LRB	LRB	LRB
Rha et al[41] (2013)	PRP	30	LRB	LRB	HRB	LRB	LRB	LRB	LRB	LRB
Stenhouse et al[47] (2013)	PRP	28	LRB	LRB	HRB	LRB	HRB	HRB	LRB	MRB
Gautam et al[19] (2015)	PRP	30	LRB	URB	HRB	HRB	HRB	HRB	HRB	HRB
Kesikburun et al[28] (2013)	PRP	40	LRB	LRB	LRB	LRB	LRB	LRB	LRB	LRB

[a]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.

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 results[31] (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 1.3[6] to 2.6[34] 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 approximately 3 to 8 times the baseline level of platelets.[6,12,29] 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 35.8×10^9/L in LR-PRP to 1.3×10^9/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

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.[7] 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,[9] 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.[25,44,47] 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[15] 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.[10] 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.[15] 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[52] 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.[33,42,45]

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[37] and recommended by Gosens and Mishra.[21] 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.[3] 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.

ACKNOWLEDGMENT

The authors acknowledge Susie Morton of the Epworth Healthcare Library, Richmond, Australia.

REFERENCES

1. Ahmad Z, Brooks R, Kang SN, et al. The effect of platelet-rich plasma on clinical outcomes in lateral epicondylitis. *Arthroscopy*. 2013; 29(11):1851-1862.
2. Arik HO, Kose O, Guler F, Deniz G, Egerci OF, Ucar M. Injection of autologous blood versus corticosteroid for lateral epicondylitis: a randomised controlled study. *J Orthop Surg (Hong Kong)*. 2014; 22(3):333-337.
3. Baksh N, Hannon CP, Murawski CD, Smyth NA, Kennedy JG. Platelet-rich plasma in tendon models: a systematic review of basic science literature. *Arthroscopy*. 2013;29(3):596-607.
4. Behera P, Dhillon M, Aggarwal S, Marwaha N, Prakash M. Leukocyte-poor platelet-rich plasma versus bupivacaine for recalcitrant lateral epicondylar tendinopathy. *J Orthop Surg (Hong Kong)*. 2015;23(1):6-10.
5. Bell KJ, Fulcher ML, Rowlands DS, Kerse N. Impact of autologous blood injections in treatment of mid-portion Achilles tendinopathy: double blind randomised controlled trial. *BMJ*. 2013;346:f2310.
6. Carmona JU, López C, Sandoval JA. Review of the currently available systems to obtain platelet related products to treat equine musculoskeletal injuries. *Recent Pat Regen Med*. 2013;3(2):148-159.
7. Carofino B, Chowaniec DM, McCarthy MB, et al. Corticosteroids and local anesthetics decrease positive effects of platelet-rich plasma: an in vitro study on human tendon cells. *Arthroscopy*. 2012;28(5):711-719.
8. Coombes BK, Bisset L, Vincenzo B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. *Lancet*. 2010;376(9754):1751-1767.
9. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in

resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. *Br J Sports Med*. 2011;45(12):966-971.
10. Dean BJ, Lostis E, Oakley T, Rombach I, Morrey ME, Carr AJ. The risks and benefits of glucocorticoid treatment for tendinopathy: a systematic review of the effects of local glucocorticoid on tendon. *Semin Arthritis Rheum*. 2014;43(4):570-576.
11. de Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med*. 2011;39(8):1623-1629.
12. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. *Arthroscopy*. 2012;28(7):998-1009.
13. de Vos RJ, van Veldhoven PL, Moen MH, Weir A, Tol JL, Maffulli N. Autologous growth factor injections in chronic tendinopathy: a systematic review. *Br Med Bull*. 2010;95:63-77.
14. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA*. 2010;303(2):144-149.
15. de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. *Br J Sports Med*. 2014;48(12):952-956.
16. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. *Am J Sports Med*. 2014;42(3):610-618.
17. Engebretsen L, Steffen K, Alsousou J, et al. IOC consensus paper on the use of platelet-rich plasma in sports medicine. *Br J Sports Med*. 2010;44(15):1072-1081.
18. Fredberg U, Stengaard-Pedersen K. Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation. *Scand J Med Sci Sports*. 2008;18(1):3-15.
19. Gautam VK, Verma S, Batra S, Bhatnagar N, Arora S. Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: clinical and ultrasonographic evaluation. *J Orthop Surg (Hong Kong)*. 2015;23(1):1-5.
20. Gosens T, Den Oudsten BL, Fievez E, van 't Spijker P, Fievez A. Pain and activity levels before and after platelet-rich plasma injection treatment of patellar tendinopathy: a prospective cohort study and the influence of previous treatments. *Int Orthop*. 2012;36(9):1941-1946.
21. Gosens T, Mishra AK. Editorial in response to the systematic review by de Vos et al: 'Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review'. *Br J Sports Med*. 2014;48(12):945-946.
22. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med*. 2011;39(6):1200-1208.
23. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
24. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. London: The Cochrane Collaboration; 2011.
25. Inoue M, Hojo T, Nakajima M, Kitakoji H, Itoi M. Comparison of the effectiveness of acupuncture treatment and local anaesthetic injection for low back pain: a randomised controlled clinical trial. *Acupunct Med*. 2009;27(4):174-177.
26. Kaux JF, Forthomme B, Goff CL, Crielaard JM, Croisier JL. Current opinions on tendinopathy. *J Sports Sci Med*. 2011;10(2):238-253.
27. Kazemi M, Azma K, Tavana B, Rezaiee Moghaddam F, Panahi A. Autologous blood versus corticosteroid local injection in the short-term treatment of lateral elbow tendinopathy: a randomized clinical trial of efficacy. *Am J Phys Med Rehabil*. 2010;89(8):660-667.
28. Kesikburun S, Tan AK, Yilmaz B, Yasar E, Yazicioglu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: a randomized controlled trial with 1-year follow-up. *Am J Sports Med*. 2013;41(11):2609-2616.
29. Kevy SV, Jacobson MS. Comparison of methods for point of care preparation of autologous platelet gel. *J Extra Corpor Technol*. 2004;36(1):28-35.
30. Krogh TP, Bartels EM, Ellingsen T, et al. Comparative effectiveness of injection therapies in lateral epicondylitis: a systematic review and network meta-analysis of randomized controlled trials. *Am J Sports Med*. 2013;41(6):1435-1446.
31. Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. *Am J Sports Med*. 2013;41(3):625-635.
32. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
33. Lui PP, Maffulli N, Rolf C, Smith RK. What are the validated animal models for tendinopathy? *Scand J Med Sci Sports*. 2011;21(1):3-17.
34. Mazzocca AD, McCarthy MB, Chowaniec DM, et al. Platelet-rich plasma differs according to preparation method and human variability. *J Bone Joint Surg Am*. 2012;94(4):308-316.
35. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med*. 2006;34(11):1774-1778.
36. Mishra AK, Skrepnik NV, Edwards SG, et al. Platelet-rich plasma significantly improves clinical outcomes in patients with chronic tennis elbow: a double-blind, prospective, multicenter, controlled trial of 230 patients. *Am J Sports Med*. 2014;42(2):463-471.
37. Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. *Cochrane Database Syst Rev*. 2014;4:CD010071.
38. Ozturan KE, Yucel I, Cakici H, Guven M, Sungur I. Autologous blood and corticosteroid injection and extracoporeal shock wave therapy in the treatment of lateral epicondylitis. *Orthopedics*. 2010;33(2):84-91.
39. Pearson J, Rowlands D, Highet R. Autologous blood injection to treat Achilles tendinopathy? A randomized controlled trial. *J Sport Rehabil*. 2012;21(3):218-224.
40. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med*. 2010;38(2):255-262.
41. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. *Clin Rehabil*. 2013;27(2):113-122.
42. Riley G. The pathogenesis of tendinopathy: a molecular perspective. *Rheumatology (Oxford)*. 2004;43(2):131-142.
43. Schnabel LJ, Jacobson MS, Miller BJ, McDermott WG, Fortier LA. Platelet rich plasma (PRP) treatment for tendinitis. *Trans Orthop Res Soc*. 2006;52:1054.
44. Sconfienza LM, Bandirali M, Serafini G, et al. Rotator cuff calcific tendinitis: does warm saline solution improve the short-term outcome of double-needle US-guided treatment? *Radiology*. 2012;262(2):560-566.
45. Scott A, Docking S, Vicenzino B, et al. Sports and exercise-related tendinopathies: a review of selected topical issues by participants of the second International Scientific Tendinopathy Symposium (ISTS) Vancouver 2012. *Br J Sports Med*. 2013;47(9):536-544.
46. Seijas R, Ares O, Alvarez P, Cusco X, Garcia-Balletbo M, Cugat R. Platelet-rich plasma for calcific tendinitis of the shoulder: a case report. *J Orthop Surg (Hong Kong)*. 2012;20(1):126-130.
47. Stenhouse G, Sookur P, Watson M. Do blood growth factors offer additional benefit in refractory lateral epicondylitis? A prospective, randomized pilot trial of dry needling as a stand-alone procedure versus dry needling and autologous conditioned plasma. *Skeletal Radiol*. 2013;42(11):1515-1520.
48. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA*. 2015;313(16):1657-1665.

49. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. *Am J Sports Med*. 2011;39(10):2130-2134.
50. Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A. Platelet-rich plasma versus focused shock waves in the treatment of jumper's knee in athletes. *Am J Sports Med*. 2013;41(4):795-803.
51. Wolf JM, Ozer K, Scott F, Gordon MJ, Williams AE. Comparison of autologous blood, corticosteroid, and saline injection in the treatment of lateral epicondylitis: a prospective, randomized, controlled multicenter study. *J Hand Surg Am*. 2011;36(8):1269-1272.
52. World Medical Association. Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. October 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed September 22, 2015.