Efficacy of platelet-rich plasma as conservative treatment in orthopaedics: a systematic review and meta-analysis

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Background. The aim of this systematic review and meta-analysis was to evaluate the benefit of platelet-rich plasma (PRP) in non-surgical orthopaedic procedures.

Material and methods. We searched the Cochrane Wounds Specialized Register, CENTRAL, MEDLINE (through PUBMED), Embase, and SCOPUS. We also searched clinical trials registries for ongoing and unpublished studies and checked reference lists to identify additional studies.

Results. We found 36 randomised controlled trials (2,073 patients) that met our inclusion criteria. The included studies mostly had small numbers of participants (from 20 to 225). Twenty-eight studies included patients with lateral epicondylitis or plantar fasciitis. PRP was compared to local steroids injection (19 studies), saline injection (6 studies), autologous whole blood (4 studies), local anaesthetic injection (3 studies), dry needling injection (3 studies), and to other comparators (4 studies). Primary outcomes were pain and function scores, and adverse events. On average, it is unclear whether or not use of PRP compared to controls reduces pain scores and functional score at short- (up to 3 months) and medium- (4-6 months) term follow-up. The available evidence for all the comparisons was rated as very low quality due to inconsistency, imprecision, and risk of bias in most of the selected studies. There were no serious adverse events related to PRP injection or control treatments.

Conclusions. The results of this meta-analysis, which documents the very marginal effectiveness of PRP compared to controls, does not support the use of PRP as conservative treatment in orthopaedics.

Keywords: platelet-rich plasma, PRP, orthopaedics, treatment.

Introduction

Platelet-rich plasma (PRP) is a mixture of highly concentrated platelets and associated growth factors. It is obtained from whole blood through a 2-phase centrifugation process: the first for the separation of blood components, and the second for the final PRP production. There are currently over 40 commercial systems that have been developed to concentrate autologous whole blood into a platelet-rich substance[1]. Besides platelets, PRP contains some inflammatory cells (i.e. monocytes and polymorphonuclear neutrophils) and large amounts of proteins, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), and adhesion molecules (i.e. fibrin, fibronectin and vitronectin)[2-4]. Such growth factors and cells have been shown to promote cell recruitment, proliferation and angiogenesis, which may be implicated in tissue regeneration and healing[5-8]. Thanks to these biological regenerative properties, a number of investigators have studied the potential clinical benefit of PRP, also from human umbilical cord blood[7,8], in a wide array of conditions ranging from dermatological disorders to oromaxillofacial surgery[9-11]

In addition, a number of randomised controlled clinical trials (RCTs) have evaluated PRP use in the orthopaedic setting, particularly for tendon and ligament injuries, and several systematic reviews and meta-analysis have been subsequently published, although with contrasting results[12-20]. With the aim of elucidating this controversial issue, we have performed a systematic review and meta-analysis on the efficacy of PRP as conservative treatment in orthopaedics.

Material and methods

This systematic review was conducted according to the recommended PRISMA checklist guidelines[21].

Search strategy

A computer-assisted literature search of the MEDLINE (through PUBMED), EMBASE, SCOPUS, OVID and Cochrane Library electronic databases was

performed (last search April 30, 2018) to identify RCTs on the conservative non-surgical use of PRP in orthopaedics. A combination of the following text words was used to maximise search specificity and sensitivity: "platelet rich plasma", "conservative", "orthopaedics", "tendon", "tendinopathy", "tendinitis", "ligament", "randomized clinical controlled trials", "Achilles tendinopathy", "plantar fasciitis", "lateral epicondylitis", "tennis elbow", "patellar tendinopathy" and "rotator cuff tendinopathy". In addition, we checked the reference lists of the most relevant items (original studies and reviews) in order to identify potentially eligible studies not captured by the initial literature search.

Study selection and inclusion criteria

Study selection was performed independently by two reviewers (MF and MC), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (CM). Eligibility assessment was based on the title or abstract and on the full text if required. Articles were eligible if they reported either in the title or in the abstract the use of PRP in orthopaedics. Only RCTs published in full in English were included in this systematic review and meta-analysis. Studies enrolling less than 10 patients were excluded, along with RCTs evaluating platelet-poor plasma and autologous conditioned plasma.

For the purpose of this systematic review, trials evaluating the role of PRP in surgical orthopaedic procedures were excluded. We selected five groups of disorders:

- lateral epicondylitis;
- Achilles tendinopathy;
- plantar fasciitis;
- patellar tendinopathy;
- rotator cuff tendinopathy.

Types of interventions

Trials evaluating platelet-poor plasma and autologous conditioned plasma were excluded. We compared intralesional, injected PRP preparation with:

- local steroids injection;
- placebo injection;
- whole blood injection;
- local anaesthetic injection;
- exercise and other physical therapies (e.g. low-dose radiation therapy, eccentric loading programme);
- any other medications given locally or systemically aimed at treating pain; and
- combinations of the active interventions listed above.

Outcomes

Primary outcomes included pain as measured by standard validated pain scale, e.g. Visual Analogue Score (VAS) is a continuous scale comprised of a horizontal (HVAS) or vertical (VVAS) line, usually 10 centimetres (100 millimetres, mm) in length, anchored by 2 verbal descriptors, one for each symptom extreme (higher scores = worse pain). In order to compare the results of the studies, the different scales used were converted into mm. Functional measurement by any standard validated scale, such as the American Orthopedic Foot and Ankle Society Score (AOFAS), and Disabilities of the Arm, Shoulder and Hand (DASH) score were also included. With functional scale, a higher scale indicated better function. Serious adverse events (e.g. infection at the injection site, heel fat pad atrophy, and plantar fascia rupture) were also evaluated. Secondary outcomes included tendon thickness in mm evaluated by ultrasounds.

The outcome measures were sub-grouped into two-time periods: short-term (within 3 months from the intervention) and medium-term (from 4 to 6 months). A long-term period (12 months) was not evaluated because few studies reported it and a pooled analysis of data was not possible. If multiple time points were reported within our time frames, we extracted the latest time point (e.g. if data were reported at four weeks, five weeks, three months and six months, we extracted outcomes at three and six months).

Data collection and analysis

For each RCT included in the systematic review, the following data were extracted by two reviewers (MF and MC) independently: first author, year of publication, orthopaedic disease, details of intervention in study and control group, sample size, mean age and male:female ratio (PRP and control groups), outcome measurements, follow-up period, and main results. Measures of treatment effect were mean differences (MD) together with 95% confidence intervals (CI) for continuous outcome measures (e.g. pain scores and functional improvement). For this measure, the score had to be reported as mean and standard deviation (SD); when studies reported other dispersion measures such as standard error (SE) of the mean or 95% Confidence Interval (CI) of the mean, we calculated the SD in order to perform the relevant meta-analytical pooling. We used final scores in preference to change in scores or cumulative incidence such as reduction of pain score reaching a predetermined size (for example ≥25% or ≥50%, indicated as "success"). Disagreement was resolved by consensus and by the opinion of a third reviewer (CM), if necessary.

The study weight was calculated using the Mantel-Haenszel method. We assessed statistical heterogeneity using t^2, Cochran's Q and I^2 statistics. The I^2 statistic describes the percentage of total variation across trials

that is due to heterogeneity rather than sampling error. In the case of no heterogeneity (I^2=0), studies were pooled using a fixed-effects model. Where values of I^2 were >0, a random-effects analysis was undertaken. All calculations were made using Stata 15.1, R version 3.4.3, and REVMAN 5[22].

We undertook subgroup analysis for duration of follow-up (short-term and medium-term, as defined above) and, where appropriate, for type of control intervention (e.g. PRP *vs* local steroids injection).

Assessment of risk of bias in included studies

Two review Authors (MF, MC) independently assessed the risk of bias of each included study following the domain-based evaluation described in the *Cochrane Handbook for Systematic Reviews of Interventions*[23]. They discussed any discrepancies and achieved consensus on the final assessment. The Cochrane "Risk of bias" tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other issues relating to bias. For the selective reporting domain, we added an item for the outcome "adverse events" because reporting was inadequate only for this outcome. We have presented our assessment of risk of bias using two "Risk of bias" summary figures: 1) a summary of bias for each item across all studies; and 2) a cross-tabulation of each trial by all of the "Risk of bias" items.

Summary of findings tables

We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes and constructed a summary of findings table using REVMAN 5[24]. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of available data for the main outcomes[25]. The summary of findings tables also includes an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias[27].

When evaluating the "Risk of bias" domain, we down-graded the GRADE assessment when we classified a study as being at high risk of bias for one or more of the following domains: selection, attrition, performance, detection, reporting, and other bias; or when the "Risk of bias" assessment for selection bias was unclear (this was classified as unclear for either the generation of the randomisation sequence or the allocation concealment domain). For the outcomes VAS, AOFAS and DASH, we down-graded for high risk of bias in performance and detection domains, since we judged that these outcomes, self-reported by patients or collected by physicians to help standardise the assessments of patients with these disorders, are likely to be influenced by lack of blinding. The following outcomes have been presented in the summary of findings table: i) pain outcomes: VAS at 3 and 6 months of follow-up; ii) functional outcome: AOFAS at 3 and 6 months of follow-up; iii) serious adverse events (0-24 months).

Results

A total of 5,577 articles were identified after the initial electronic and manual search (Figure 1). Of these, 5,402 were excluded because they focused on other topics. Thus, 175 potentially relevant articles were selected and the next screening led to the exclusion of 139 additional studies (reviews, protocols of RCTs, non-randomised studies, duplicates, studies containing no informative data). Among RCTs reporting different follow-up of the same trial[27-30], we included only the last published update[28,30]. Thirty-six randomised studies[28,30-64] were included in the systematic review (see Table I for main characteristics and results of the included studies). Overall, 2,337 patients were enrolled in the 36 RCTs selected for the review. Of the 36 studies included in the systematic review, 11 were conducted in patients with lateral epicondylitis[28,31,32,37,40,41,45,47-49,51], 14 in patients with plantar fasciitis[38,43,44 46,50,52-55,58,60,62-64], 4 in patients with Achilles tendinopathy[30,36,56,61], 3 in patients with

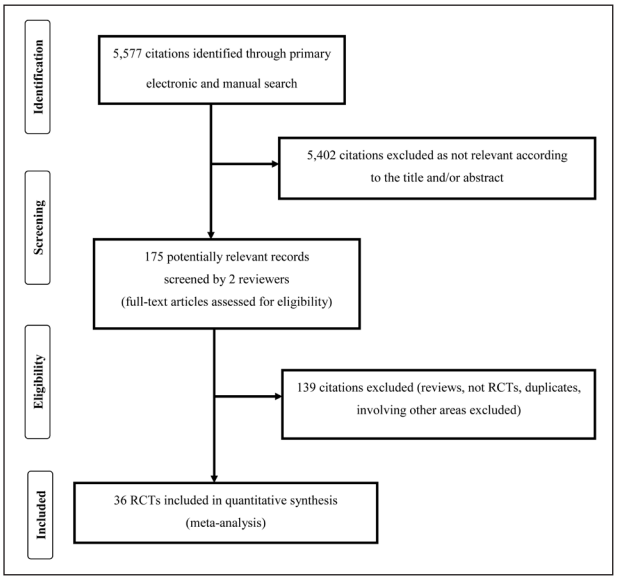

Figure 1 - Flow chart of the inclusion of the studies. RCT: randomised controlled clinical trials.

Table I - Characteristics and main results of the included studies on the non-surgical use of platelet-rich plasma (PRP) in orthopaedics.

Study (year)[ref]	Disease	Intervention		Cases/ controls (number)	Cases/ controls (mean age)	Cases/ controls (M:F ratio)	Outcome measurement	Follow-up (months)	Results
		PRP	*Control*						
De Jonge *et al.* (2011)[30]	Achilles tendinopathy	Single injection 4 mL	Saline single injection 4 mL	27/27	49/50	13:14/13:14	VISA-A score, US	12	No superiority of PRP *vs.* placebo
Thanasas *et al.* (2011)[31]	Lateral epicondylitis	Single injection 3 mL	AWB single injection 3 mL	14/14	36.6/35.9	4:10/3:11	VAS, Liverpool Elbow score	6	Significant VAS improvement in PRP group at 6 weeks
Gosens *et al.* (2011)[28]	Lateral epicondylitis	Single injection 3 mL	Corticosteroid single injection 3 mL	51/49	46.8/47.3	23:24/23:24	VAS, DASH	24	Significant pain reduction and function improvement in PRP group at 2 years
Creaney *et al.* (2011)[32]	Lateral epicondylitis	Two injections 1.5 mL	AWB two injections 1.5 mL	80/70	48/53	46:34/39:31	PRTEE	6	PRP was not superior to AWB
Omar *et al.* (2012)[33]	Lateral epicondylitis	Single injection	Single steroid injection	15/15	40.5/37.5	6:9/5:10	VAS, DASH	1.5	No significant differences between groups
	Plantar fasciitis	Single injection	Single steroid injection	15/15	42.5/44.5	0:15/0:15	VAS, FHSQ	1.5	PRP was superior to steroid injection
Kesikburun *et al.* (2013)[34]	Rotator cuff tendinopathy	Single injection 5 mL	Saline single injection 4 mL	20/20	45.5/51.4	7:13/6:14	VAS, WORC, SPADI score	12	No superiority of PRP *vs.* placebo
Vetrano et al (2013)[35]	Patellar tendinopathy	Two injections 2 mL	ESWT three sessions	23/23	26.9/26.8	20:3/17:6	VAS, VISA-P, Blazina scale	12	PRP was superior to ESWT at 12 months
Kearney *et al.* (2013)[36]	Achilles tendinopathy	Single injection 3-5 mL	Eccentric loading programme	10/10	47.8/49.9	4:6/3:7	VISA-A, EQ-5D	6	No statistically significant difference between groups
Krogh *et al.* (2013)[37]	Lateral epicondylitis	Single injection 3-3.5 mL	Single injection 3 mL steroid or saline	20/40	47.6/43.9	9:11/11:9	PRTEE	3	No differences between groups at 3 months
Tiwari and Barghava (2013)[38]	Plantar fasciitis	Single injection 5 mL	Single injection 40 mg/mL steroid	30/30	NR	NR	VAS	6	PRP was superior to steroid at 6 months
Rha *et al.* (2013)[39]	Rotator cuff tendinopathy	Single injection 3 mL	Single dry needling injection	20/19	52.2/53.9	9:11/8:11	SPADI score, US	6	PRP was superior to dry needling at 6 months
Raeissadat *et al.* (2014)[40]	Lateral epicondylitis	Single injection 2 mL	AWB single injection 2 mL	31/30	47.2/45.3	8:23/6:24	VAS, Mayo score, PTT	2	PRP was not superior to AWB
Mishra *et al.* (2014)[41]	Lateral epicondylitis	Single injection 2-3 mL	Single injection 2-3 mL bupivacaine	112/113	48.4/47.4	NR	VAS	6	Significant VAS improvement in PRP group at 6 months
Dragoo *et al.* (2014)[42]	Patellar tendinopathy	Single injection 6 mL	Single dry needling injection	9/12	28/40	8:1/12:0	VAS, VISA-P, Tegner activity scale, Lysholm knee scale, SF-12	6	PRP was not superior to dry needling at 6 months
Kim and Lee (2014)[43]	Plantar fasciitis	Two injections 2 mL	Two injections 2 mL dextrose/ lidocaine	10/11	36.2/37.8	4:6/7:4	FFI	6	No statistically significant difference between groups
Monto (2014)[44]	Plantar fasciitis	Single injection 3 mL	Single injection 40 mg steroid	20/20	51/59	8:12/9:11	AOFAS score	24	PRP was more effective and durable than steroid
Behera *et al.* (2015)[45]	Lateral epicondylitis	Single injection 3.5 mL	Single injection 3.5 mL bupivacaine	15/10	38/37	3:12/5:4	VAS, MMCPIE, Nirschl score	12	PRP was superior to bupivacaine

PRP: platelet-rich plasma; AWB: autologous whole blood; M: male; F: female; VAS: visual analog scale; PTT: pressure pain threshold; VISA-A: Victorian Institute of Sport Assessment-Achilles; VISA-P: Victorian Institute of Sport Assessment-Patella; US: ultrasound; NR: not reported; WORC: Western Ontario Rotator Cuff Index; SPADI: Shoulder PAIN And Disability Index; DASH: Disability of the Arm, Shoulder and Hand score; PRTEE: Patient-Related Tennis Elbow Evaluation; SF-12: 12 Item Short Form Health Survey; ESWT: Extracorporeal Shock Wave Therapy; FHSQ: Foot Health Status Questionnaire; ROM: range of motion; FFI: Foot Function Index; AOFAS: American Orthopedic Foot and Ankle Society; RM: Roles-Maudsley; EQ-5D: EuroQuol 5-Dimension questionnaire; FADI: Fot and Ankle Disability Index; RMS: Roles and Maudsley score; FAAM: Foot and Ankle Ability Measurement; ADL: activity of daily living; IHOT-33: International Hip Outcome Tool-33; MHHS: Modified Harris Hip Score; ASES: American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form; CMS: Constant-Murley Score; SST: Simple Shoulder Test.

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Table I - Characteristics and main results of the included studies on the non-surgical use of platelet-rich plasma (PRP) in orthopaedics. *(continued from previous page)*

Study (year)[ref]	Disease	Intervention		Cases/ controls (number)	Cases/ controls (mean age)	Cases/ controls (M:F ratio)	Outcome measurement	Follow-up (months)	Results
		PRP	*Control*						
Jain *et al* (2015)[46]	Plantar fasciitis	Single injection 2.5 mL	Single injection 40 mg steroid	24/22	56	8:16/8:14	VAS, AOFAS, RM score	12	PRP was significantly more effective than steroid
Yadav et al (2015)[47]	Lateral epicondylitis	Single injection 1 mL	Single injection 40 mg (1 mL) steroid	30/30	36.6/36.7	10:20/7:23	VAS, DASH	3	All parameters improved more significantly in PRP group at 3 months
Khaliq *et al.* (2015)[48]	Lateral epicondylitis	Single injection 3 mL	Single injection 3 mL steroid	51/51	33.6/34.2	21:30/24:27	VAS	3 weeks	PRP was more effective than steroid
Gautam *et al.* (2015)[49]	Lateral epicondylitis	Single injection 2 mL	Single injection 2 mL (40 mg/mL) steroid	15/15	NR	NR	VAS, DASH	6	PRP was superior to steroid at 6 months
Sherpy *et al.* (2016)[50]	Plantar fasciitis	Single injection 3 mL	Single injection 2 mL (40 mg/mL) steroid	25/25	37.5/38.5	2:23/0:25	VAS, FHSQ, US	3	No significant difference between groups
Palacio *et al.* (2016)[51]	Lateral epicondylitis	Single injection 3 mL	Single injection 3 mL steroid	20/20	46.6/46.2	NR	DASH, PRTEE	6	No significant difference between groups
Mahindra *et al.* (2016)[52]	Plantar fasciitis	Single injection 2.5-3 mL	Single injection 2 mL (40 mg) steroid	25/25	30.7/33.9	8:17/12:13	VAS, AOFAS	3	Better AOFAS outcome in PRP group at 3 months
Vahdatpour *et al.* (2016)[53]	Plantar fasciitis	Single injection 3 mL	Single injection 2 mL steroid	16/16	45.4/47.12	4:12/5:11	VAS, RMS	6	Significant improvement with PRP
Homayouni et al (2016)[54]	Plantar fasciitis	Single injection 2 mL	Single injection 2 mL steroid	15/15	44.7/43.6	7:8/6:9	VAS, FAAM	2	No significant differences between groups at 2 months
Gogna *et al.* (2016)[55]	Plantar fasciitis	Single injection 3 mL	Low-dose radiation (total 3.0 Gy)	20/20	28.6/26.5	14:6/12:8	VAS, AOFAS, US	6	No significant differences between groups
Krogh *et al.* (2016)[56]	Achilles tendinopathy	Single injection 6 mL	Single injection 6 mL saline	12/12	46.7/51.8	7:5/6:6	VISA-A	3	PRP was not superior to placebo
Shams *et al.* (2016)[57]	Rotator cuff tendinopathy	Single injection 2-2.5 mL	Single injection 5 mL (40 mg) steroid	20/20	52/50	10:10/11:9	ASES, VAS, CMS, SST	6	No significant difference between groups at 6 months
Vahdatpour *et al.* (2016)[58]	Plantar fasciitis	Single injection 3 mL	AWB single injection	17/17	45.5/47.5	4:13/5:12	RMS, US	3	No significant differences between groups
Nejati *et al.* (2017)[59]	Shoulder impingement syndrome	Single injection 6 mL	Exercise therapy	22/20	52.5/54	9:13/6:14	VAS, ROM, DASH, WORC	6	PRP was not superior to exercise therapy
Acosta-Olivo *et al.* (2017)[60]	Plantar fasciitis	Single injection 3 mL	Single injection steroid	16/16	NR	NR	VAS, FADI, AOFAS	4	No significant difference between groups
Boesen *et al.* (2017)[61]	Achilles tendinopathy	Four injections	Single injection steroid or saline	19/38	43.1/40.9	NR	VISA-A, VAS	6	Steroid was more effective than PRP at 6 months
Shekhar *et al.* (2017)[62]	Plantar fasciitis	Single injection 4 mL	Single injection 4 mL saline	60/60	42.0/46.8	24:36/27:33	VAS, AOFAS Foot Scale, US	6	PRP was superior to placebo at 6 months
El Mallah *et al.* (2017)[63]	Plantar fasciitis	Single injection 3 mL	Dry needling protocol	15/15	43.0/45.0	5:10/4:11	FFI, US	3	PRP was more effective than dry needling at 3 months
Tank *et al.* (2017)[64]	Plantar fasciitis	Single injection 3 mL	Single injection steroid	30/50	40.9/37.8	11:19/19:31	VISA, FAAM, US	6	PRP was more effective than steroid at 6 months

PRP: platelet-rich plasma; AWB: autologous whole blood; M: male; F: female; VAS: visual analog scale; PTT: pressure pain threshold; VISA-A: Victorian Institute of Sport Assessment-Achilles; VISA-P: Victorian Institute of Sport Assessment-Patella; US: ultrasound; NR: not reported; WORC: Western Ontario Rotator Cuff Index; SPADI: Shoulder PAIN And Disability Index; DASH: Disability of the Arm, Shoulder and Hand score; PRTEE: Patient-Related Tennis Elbow Evaluation; SF-12: 12 Item Short Form Health Survey; ESWT: Extracorporeal Shock Wave Therapy; FHSQ: Foot Health Status Questionnaire; ROM: range of motion; FFI: Foot Function Index; AOFAS: American Orthopedic Foot and Ankle Society; RM: Roles-Maudsley; EQ-5D: EuroQuol 5-Dimension questionnaire; FADI: Fot and Ankle Disability Index; RMS: Roles and Maudsley score; FAAM: Foot and Ankle Ability Measurement; ADL: activity of daily living; IHOT-33: International Hip Outcome Tool-33; MHHS: Modified Harris Hip Score; ASES: American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form; CMS: Constant-Murley Score; SST: Simple Shoulder Test.

rotator cuff tendinopathy[34,39,57], 2 in patients with patellar tendinopathy[35,42], and one[58] in patients with shoulder impingement syndrome; one of these studies[33] included both elbow tendinopathy and plantar fasciitis patients. In the 36 studies, PRP was compared to local steroids injection (19 studies)[28,33,37,38,44,46-54,57,60,61,64], to saline injection (6 studies)[30,34,37,56,61,62], to autologous whole blood (4 studies)[31,32,40,58], to local anaesthetic injection (3 studies)[41,43,45], to dry needling injection (3 studies)[39,42,63], and others comparators (4 studies)[35,36,55,59] (Table I). The outcomes more commonly reported were: VAS, AOFAS, DASH, a miscellanea of other scores (see Table I).

Risk of bias in included studies

Thirty-four studies (94%) were at high risk of bias for one or more domains, and 28 studies (77%) were at unclear risk of bias for one or more domains; 2 studies[34,39] were judged at low risk of bias in all the domains (Figure 2A and B).

Allocation

We assessed 3 studies as being at high risk of selection bias, as randomisation was by alternating the 2 treatments, so the intervention allocations could have been foreseen in advance[31,43,50]. The reports of another 22 studies were unclear as far as random sequence generation and/or allocation concealment were concerned, while 11 studies were at low risk of selection biases.

Blinding

Twenty-one studies (58%) reported as open label, and these were graded as high risk of performance bias (blinding of participants and personnel). Five studies were graded at unclear risk of detection bias due to the fact that they did not provide information to permit judgement about "high" or "low" risk of bias related to the blinding of participants and personnel[31,36,42,43,55]. Ten studies were reported as double blind[28,30,34 39,41,42,51,52,60,61]. Nineteen studies were graded at low risk of detection bias due to the fact that the assessor was blinded to treatment allocation; 16 studies were graded at unclear risk of detection bias due to the fact that they did not provide information to permit judgement about "high" or "low" risk of bias related to the blinding of outcome assessors; one study[65] was graded at "high risk" of bias.

Incomplete outcome data

Three studies[36,55,64] were judged at high risk of attrition bias because there was a high proportion of enrolled subjects who left the study due to unsatisfactory effect of the initial treatment. Another 3 studies[43,47,51] were judged at unclear risk of bias. The remaining studies were judged at low risk of bias.

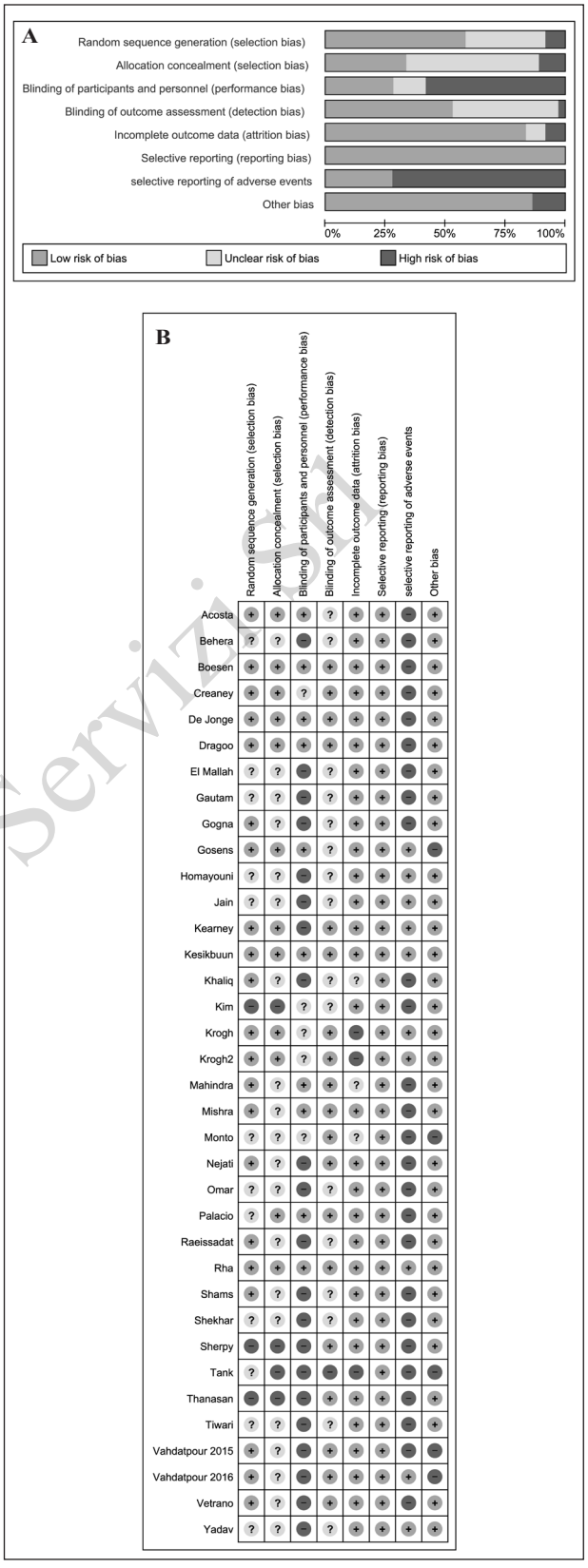

Figure 2 - A) Risk of bias graph and (B) summary.
PRP: Platelet-rich plasma; SD: standard deviation; IV: intravenous; CI: Confidence Interval.

Selective reporting

Selective reporting was low in all included studies for all the outcomes except adverse events. For the outcome adverse events, 26 out of 36 trials (72%) were judged at high risk of bias. The reporting of adverse events was generally inadequate, and 14 trials did not mention complications of treatment at all. Where adverse events were reported, these often consisted of short statements of the absence of adverse events in the study results or discussion without any indication of systematic recording.

Other potential sources of bias

We judged five studies to be at high risk for other sources of bias: four because of unbalance at baseline[28,44,53,54] and one[64] because it did not provide information on the randomisation process despite enrolling 30 patients in the experimental group and 50 in the control group.

Effects of interventions

For the summary of findings for the main comparison, see Table II, Figures 3 and 4, and *Online supplementary content (Figures S1-S10)*.

Lateral epicondylitis

Data from seven studies investigating PRP for lateral epicondylitis reported mean and SD for pain and/or functional measure scales[28,31,33,40,48,49,51]. The results for VAS at 3 and 6 months in PRP and any control groups are presented in Figures 3 and 4. At 3 months, pooled data from 6 trials (328 patients) showed no clear between group differences in VAS (MD −2.86; 95% CI: −8.57/2.85; I^2=80%); very low-quality evidence down-graded for serious risk of bias (particularly selection and performance bias), for inconsistency (due to substantial heterogeneity), and for imprecision (95% CIs include line of no effect). (See summary of findings in Table II). At 6 months, pooled data from 3 trials (158 patients) showed slightly better pain scores of PRP compared to control (MD −12.97; 95% CI: −20.61/−5.34; I^2=78%); very low-quality evidence, down-graded twice for serious risk of bias (selection, performance and other bias), once for inconsistency. The results were much the same in subgroup analyses of studies with steroids as control (*Online supplementary content, Figures S1 and S2*). At 3 months, pooled data from four trials (260 patients) showed no clear between-group differences in VAS (MD 0.67; 95% CI: −2.61/3.95; I^2=0%); very low-quality evidence, down-graded for serious risk of biases and serious imprecision. At 6 months, pooled data from 2 trials (130 patients) showed slightly better pain scores of PRP compared to control (MD −16.98; 95% CI: −26.50/−7.47; I^2=57%); very low-quality evidence was down-graded (for serious risk of biases and for inconsistency).

Elbow pain was also reported as DASH score in 4 studies (200 patients)[28,33,49,51]. At 3 months, DASH did not change significantly between groups (*Online supplementary content, Figures S3 and S4*). At 6 months, PRP showed slightly better pain scores compared to any control (MD −7.53; 95% CI: −9.11/−5.95) and in the subgroup analysis *versus* steroids (MD −8.17; 95% CI: −10.03/−6.31) (*Online supplementary content, Figures S5 and S6*). All these comparisons were graded as very low-quality evidence due to serious risk of bias (selection, performance and other bias), imprecision (at 3 months), and inconsistency.

Plantar fasciitis

Data from 15 studies investigating PRP for plantar fasciitis reported mean and SD for pain and/or functional measure scales[33,38,43,44,46,50,52-55,58,60,62-64]. The results for VAS at 3 months (8 studies, 420 patients) and 6 months (6 studies, 300 patients) in PRP and any control groups are presented in Figures 3 and 4. Pooled data showed slightly better pain scores in PRP treated group at 6 months (MD −7.87; 95% CI: −14.90/−0.85; I^2=89%), but not at 3 months (MD −8.25; 95% CI: −17.70/1.20; I^2=94%); very low-quality evidence down-graded for serious risk of biases, inconsistency and serious imprecision at 3 months (Table II). Likewise, in subgroup analyses of studies with steroids as control (*Online supplementary content, Figures S1 and 2S*), pooled data showed slightly better pain scores in PRP treated group both at 6 months (5 trials, 260 patients; MD −9.47; 95% CI: −17.98/−0.97; I^2=92%;) but not at 3 months (8 studies, 420 patients; MD −8.95; 95% CI: −17.70/1.20; I^2=94%); very low-quality evidence, down-graded for serious risk of biases, inconsistency and serious imprecision at 3 months.

The most commonly reported function measure was AOFAS; all these studies were conducted in plantar fasciitis patients and had local steroids injection as control group. Both at 3 months (4 studies, 178 patients)[44,46,52,60] and at 6 months (5 studies, 218 patients)[44,46,52,55,60], AOFAS did not change significantly between the PRP and steroids group (MD, 4.26; 95% CI: −5.96/12.47; and 4.25; 95% CI: −5.92/14.42, respectively) (*Online supplementary content, Figures S7 and S8*). All these comparisons were graded as very low-quality evidence due to risk of bias, imprecision and inconsistency. As shown in Table I, there were other functional measurements included as outcome measures reported in the included studies, e.g. Foot Health Status Questionnaire (FHSQ), Mayo clinic performance index for elbow (MCPIE), maximum grip strength (MGS), and others, but because few (1 or 2) studies reported them, we decided not to conduct a quantitative synthesis for these outcomes. Four studies reported plantar fascia thickness measured by ultrasounds[50,55,58,63]. The results at 3 months (3 studies, 112

Table II - Platelet rich plasma (PRP) compared with control intervention for tendinopathies: summary of findings[§].

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	N. of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk	*Corresponding risk*				
	Control	*PRP*				
PAIN score: Visual Analogue Score (VAS)	Various controls, including local steroids injection					VAS 0-100 (higher scores = worse pain)
VAS - short-term follow-up (1-3 months) - Elbow tendinopathy	Mean VAS score across control groups ranged from 17 to 45.5 in control groups	Mean VAS score in the intervention groups was 2.86 lower (8.57 lower to 2.85 higher)	MD −2.86 (95% CI: −8.57 to 2.85)	6 studies (328 participants)	⊕⊖⊖⊖ very low[1, 2, 3]	On average, it is unclear whether or not use of PRP compared to controls reduces pain score at short-term follow up. The between group differences were small and unlikely to be clinically important
VAS - medium-term follow up (4-6 months). - Elbow tendinopathy	Mean VAS score across control groups ranged from 25 to 55.8 in control groups	Mean VAS score in the intervention groups was 12.97 lower (5.34 to 20.61 lower)	MD −12.97 (95% CI: −20.61 to −5.34)	3 studies (158 participants)	⊕⊖⊖⊖ very low[1,2]	Marginal clinical benefit of PRP at medium-term follow up. The between group differences were small and unlikely to be clinically important
VAS - short-term follow up (1-3 months) - Plantar fasciitis	Mean VAS score ranged across control groups from 5 to 65 in controls groups	Mean VAS score in the intervention groups was 2.86 lower (8.57 lower to 2.85 higher)	MD −2.86 (95% CI: −8.57 to 2.85)	8 studies (420 participants)	⊕⊖⊖⊖ very low [1,2, 3]	On average, it is unclear whether or not use of PRP compared to controls reduces pain score at short-term follow up. The between group differences were small and unlikely to be clinically important
VAS - medium-term follow up (4-6 months) -Plantar fasciitis	Mean VAS score across control groups ranged from 5 to 48 in controls groups	Mean VAS score in the intervention groups was 7.87 lower (14.9 lower to 0.85 lower)	MD −7.87 (95% CI: −14.9 to −0.85)	6 studies (300 participants)	⊕⊖⊖⊖ very low[1, 2]	Marginal clinical benefit of PRP at medium-term follow up. The between group differences were small and unlikely to be clinically important
Serious adverse events (0-6 months) - Elbow tendinopathy, plantar fasciitis, Achilles tendinopathy, rotator cuff tendinopathy	0 events	0 events	Not estimable	22 studies (1,265 participants)	⊕⊖⊖⊖ very low[1, 2, 3]	There were no reports of serious adverse events (e.g. injection site infection, plantar fascia rupture) during the follow-up period (1.5-24 months) of 22 trials
Function score: American Orthopedic Foot and Ankle Society Score (AOFAS)	Controls were represented only by local steroids injection					AOFAS 0-100 (higher score=better function)
AOFAS - short-term follow up (1-3 months) - Plantar fasciitis	Mean AOFAS score across control groups ranged from 81 to 96.8 in control groups (steroids)	Mean AOFAS score in the steroids groups was 4.26 higher (3.96 lower to 12.47 higher) than in intervention group	MD 4.26 (95% CI: −3.96 to 12.47)	4 studies (188 participants)	⊕⊖⊖⊖ very low[1, 2, 3]	On average, it seems that the use of PRP compared to local steroids injection does not increase function score at short-term follow-up
AOFAS - medium-term follow up (4-6 months) - Plantar fasciitis	Mean VAS score across control groups ranged from 74 to 97.2 in controls groups (steroids)	Mean AOFAS score in the steroids groups was 4.25 higher (5.92 lower to 14.42 higher) than in intervention group	MD 4.25 (95% CI: −5.92 to 14.42)	5 studies (218 participants)	⊕⊖⊖⊖ very low[1,2, 3]	On average, it seems that the use of PRP compared to local steroids injection does not increase function score at medium-term follow-up

[§]Patient/population: adults with elbow tendinopathy or plantar fasciitis; Settings: outpatient; Intervention: PRP; Comparison: various controls, including local steroids injection, placebo, autologous whole blood, anaesthetic.

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). GRADE: Working Group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate. [1]Down-graded once for inconsistency, due to substantial heterogeneity (I2>80%). [2]Down-graded twice because of high risk of bias or unclear risk of selection bias, and at high risk of other bias (unbalance at baseline between groups) in several of the selected studies. [3]Down-graded once for imprecision (95%CI includes line of no effect). [4]Down-graded once due to serious risk of bias (especially reporting bias) and twice for very serious imprecision (no events). CI: confidence interval; MD: mean difference.

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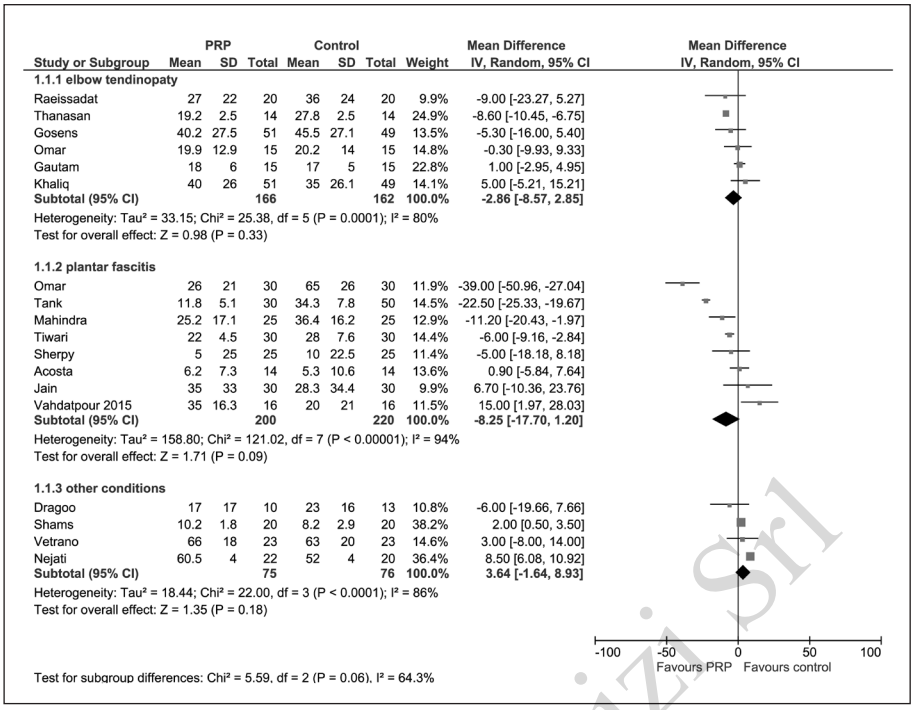

Figure 3 - Forest plot of Visual Analogue Score (VAS) at 3 months..

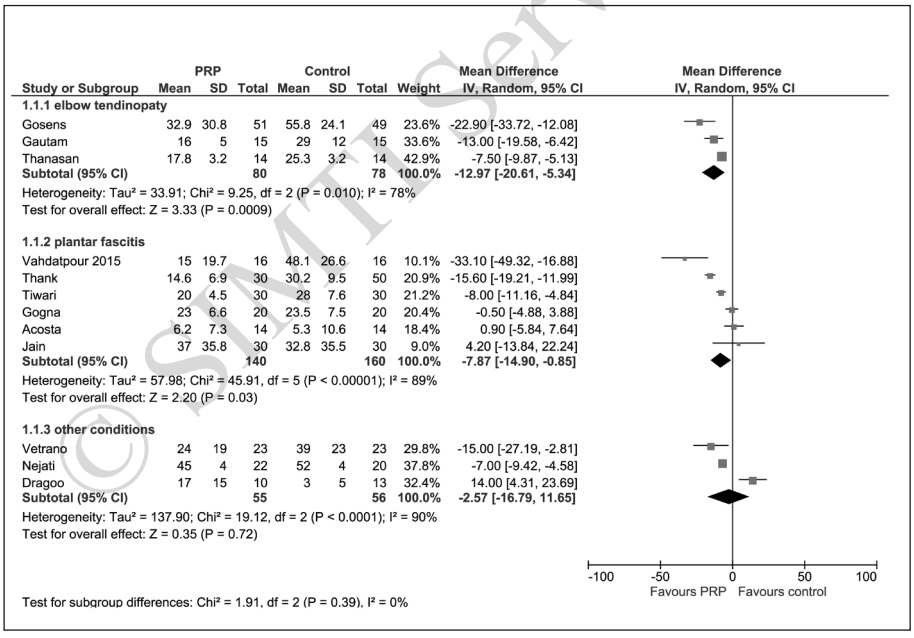

Figure 4 - Forest plot of Visual Analogue Score (VAS) at 6 months.

patients) and 6 months (4 studies, 152 patients) showed no clear between-group differences (*Online supplementary content, Figures S9 and S10*). All these comparisons were graded as very low-quality evidence due to risk of bias and serious imprecision (112 patients from 3 trials).

Other tendinopathies

Data from 4 studies (151 patients) investigating PRP for a variety of tendinopathies (patellar tendinopathy[42], jumper's knee[35], subacromial impingement syndrome[59], and rotator cuff tears[57]) reported mean and SD for pain measure scales. The results at 3 and 6 months showed no clear between-group differences in VAS in the cumulative analysis (Figures 3 and 4).

Adverse events

In 22 studies (1,265 participants), no participant was reported to have developed any serious events (e.g.

application site infections, heel fat pad atrophy, and plantar fascia rupture) in the follow-up period (from 1.5 to 24 months) in either PRP or control groups. Most trials did not describe monitoring processes for identifying or recording complications; and usually limited the reporting to a single statement regarding their absence. This comparison was graded as very low-quality evidence, and was down-graded once due to serious risk of bias (especially reporting bias) and twice for very serious imprecision (no events), reflecting the fact that numbers were not sufficient to detect rare events.

Other less serious, short-term adverse events, mostly post-injection pain, were reported in 6 trials. In one study, comparing PRP to dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis[44], it was reported that most patients in both groups reported local pain or discomfort that started on the day of injection and subsided gradually afterwards. Likewise, an initial worsening of pain because of the activation of the inflammation cycle was observed in patients with lateral epicondylitis receiving PRP[28]; this usually lasted 1-2 weeks. Local pain or discomfort were also reported from another trial in most of the patients receiving PRP for lateral epicondylitis[31]. Pain at the site of injection was also reported in a small proportion of patients receiving PRP or controls in 3 studies[35,37,41].

Discussion

Since its first development in the 1980s, PRP therapy has been gaining popularity, and orthopaedics immediately seemed to be the ideal sector in which to test the regenerative potential of this technology[3]. Since then, PRP has been used in the clinic to promote healing in a wide array of musculoskeletal disorders[18]. However, in spite of this extensive experience, relatively few studies have been conducted on the use of PRP as conservative treatment in orthopaedics. A recently published meta-analysis which evaluated the clinical impact of PRP on tendinopathy compared to placebo or dry needling injections did not demonstrate a significantly greater clinical benefit for PRP at a 6-month follow-up[65]. In addition, a 2014 meta-analysis found no evidence that PRP was effective in chronic lateral epicondylitis[66].

In the present meta-analysis, the largest published so far on this issue, we found a very low quality of evidence that PRP injection may not result in lower pain and function scores in the short- (1-3 months) and medium- (4-6 months) term follow-up, although a marginal benefit at medium-term follow-up (4-6 months) for the VAS outcome was observed. In most of the comparisons, the 95% CI crossed the line of no benefit, and at best indicates the possibility of a very marginal clinical benefit. Difference in pain is a measure often derived from a 100 mm VAS. The minimal clinically important difference (MCID) between pre- and post-intervention is taken as 8 mm for average pain and 19 mm for first step pain[67]. Our findings show that the mean VAS score in the PRP group was 2.86 mm lower than in the control group on short-term follow-up, and 12.97 mm lower at medium-term follow-up in lateral epicondylitis, and 8.25 mm lower at short-term follow-up, and 7.87 mm lower at medium-term follow-up in plantar fasciitis; these are differences that can be regarded as clinically marginal.

The quantitative analysis conducted in this systematic review has, however, several limitations which do not allow us to draw definite conclusions on the PRP efficacy in this setting. The first limitation is certainly the heterogeneity of the studies evaluated, particularly in the efficacy outcomes. Another important limitation of this meta-analysis is that we were not able to determine the long-term (>12 months) effect of PRP due to the lack of enough time points in the studies evaluated. It is indeed possible, as claimed by some investigators[68], that the best clinical benefit of PRP application in orthopaedics can occur in the long-term period. Finally, we would like to outline the lack of standardisation for PRP production among the different studies, which makes the PRP products heterogeneous and qualitatively very different from each other, and this limits the validity of an inter-studies comparison.

Further, adequately powered, randomised trials are needed to better define potential indications, long-term benefit, and optimal treatment protocols of PRP as conservative treatment in orthopaedics. These studies should also perform an adequate cost-benefit analysis of PRP therapy compared with other standard, less expensive, treatments.

Disclosure of conflicts of interest

GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result. The other Authors declare no conflicts of interest.

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