Platelet-Rich Plasma in the treatment of patellar tendinopathy: a systematic review

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Final accepted manuscript

Abstract

Background

Patellar tendinopathy (PT) is a major cause of morbidity in both high-level and recreational athletes. Whilst there is good evidence for the effectiveness of eccentric exercise regimens in its treatment, a large proportion of patients have disease which is refractory to such treatments. This has led to the development of novel techniques including platelet-rich plasma (PRP) injection, which aims to stimulate a normal healing response within the abnormal patellar tendon. However, little evidence exists at present to support its use.

Purpose

The aim of this systematic review was to determine the safety and effectiveness of PRP in the treatment of PT, and to quantify its effectiveness relative to other therapies for PT.

Study design

Systematic review.

Methods

A systematic review was conducted in accordance with the PRISMA guidelines. A literature review was conducted of the Medline, EMBASE and Cochrane databases, as well as trial registries. Both single-arm and comparative studies were included. The outcomes of interest were pain (as measured by visual-analogue or other, comparable scoring systems), functional scores and return to sport. Study quality and risk of bias were assessed using the MINORS score (for non-randomised studies) and the Cochrane risk of bias tool.

Results

Eleven studies fitted the inclusion criteria. Of these, two were randomised, controlled trials (RCTs), and one was a prospective, non-randomised cohort study. The remainder were single-arm case series. All non-comparative studies demonstrated a significant improvement in pain and function following PRP injection. Complications and adverse outcomes were rare. The results of the comparative studies were inconsistent and superiority of PRP over control treatments could not be conclusively demonstrated.

Conclusions

PRP is a safe and promising therapy in the treatment of recalcitrant PT. However, its superiority over other treatments such as physiotherapy remains unproven. Further RCTs are required to determine the relative effectiveness of the many available treatments for PT, and to determine the subgroups of patients who stand to gain the most from the use of these therapies.

Introduction

Patellar tendinopathy (PT, also known as Jumper's Knee or Patellar Tendinitis) is a major cause of morbidity in both recreational and elite athletes, and is a leading factor contributing to the decision to retire from high-level sport[32]. The prevalence of symptomatic PT in high-risk sports such as volleyball may be as high as 45%[23]. Ultrasound may reveal sub-clinical disease in a further proportion of asymptomatic athletes[6]. The mainstay of treatment is rest with physiotherapy in the form of eccentric exercises; corticosteroid injections and surgical debridement are reserved for recalcitrant cases[25]. In recent years, newer treatments such as ultrasound, extra-corporeal shockwave therapy (ESWT) and novel injectables such as platelet-rich plasma (PRP) have become widespread[26].

Platelet-rich plasma (PRP) is a concentrate of platelets and growth factors produced by centrifugation from a sample of autologous blood. The use of PRP was popularised in the 1990s in plastic and maxillofacial surgery[28], but its use has grown markedly in the field of orthopaedics in the last ten years (**Error! Reference source not found.**). Current applications of PRP in orthopaedics include the treatment of muscle or ligament injuries, tendinopathies and enthesiopathies, osteoarthritis, and as an adjunct to operative treatments[10]. The use of PRP is intended to enhance the native ability of tissues to repair themselves by the presence of high concentrations of growth factors[31]. Given that PT is believed to be a disorder of tendon repair, the use of PRP holds great promise in this context[25]. This is supported by the results of preclinical studies which have demonstrated increased levels of macrophages and Type I and III collagen in tendons treated with PRP[10]. However, whilst PRP has become increasingly widely-used for PT, high-quality randomised studies examining its use have only recently started reporting[5, 31].

The aim of this systematic review is to assess the state of the evidence for the use of PRP for the treatment of PT. Specifically, we aimed to determine the safety of PRP in the context of PT, the effect of PRP on knee pain, function, and return to sports, and the relative effectiveness of PRP compared to current gold-standard treatments for PT.

Methods

Systematic review was performed according to the PRISMA guidelines[24]. The review was registered prospectively in the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD**********).

A search was conducted of studies contained within the Medline, EMBASE and Cochrane databases between 1st January 1974 and 13th February 2014. The search terms were the same for each: "(patellar or patella) AND (platelet OR PRP)". Inclusion criteria were: all studies examining the effect of platelet-rich plasma on adults with non-surgically treated patellar tendinopathy, published in English, Spanish or French, in the time-period of the search. Studies were excluded if a more recent report of the same cohort of patients were available, or if patients had undergone, or were undergoing surgery at the same time as receiving PRP. Studies examining multiple tendinopathies were excluded if data were not presented separately for PT. Eligible studies included randomised controlled trials (RCTs), cohort or case-control studies, and case series. Case reports pertaining to complications are also reported. Titles of identified studies were screened to identify those related to the subject of interest; the abstracts of these studies were then screened and the full-text manuscripts of relevant studies were retrieved for inclusion in the review. Finally, three clinical trial databases (clinicaltrials.gov, the EU clinical trials register, and the ISRCTN register) were searched using the same search string to identify unreported trials or those that are in progress.

Studies that met the inclusion criteria were read and data were extracted. The two authors extracted the data independently from each study using the same forms. For comparative studies, Forest plots were produced to visualise the outcome of multiple studies. Risk of bias in retrieved RCTs was assessed using the Cochrane Collaboration tool[14]; for non-randomised and non-comparative studies the Methodological Index for Non-Randomised Studies (MINORS) was used[27]. Inadequate numbers of comparative studies were identified to justify meta-analysis; as a result, a descriptive systematic review was undertaken with no attempt at statistical data synthesis.

Results

Results of literature search

The PubMed search returned 86 citations, and the EMBASE search returned an additional 138. The search of the Cochrane library revealed one systematic review (of PRP for any tendinopathy) which contained 19 studies, of which one concerned PT. The protocol for screening and exclusion of studies is given in the flow-chart in **Error! Reference source not found.**. Ultimately, 11 studies were included in the final review. Of the 11 studies, three compared PRP to a control intervention (two randomised, controlled trials and one prospective cohort study)[5, 8, 31]. Of the remaining seven studies, one was a cohort study comparing two groups of patients

receiving PRP (the groups were defined on the basis of previous interventions and for the purposes of this review this study is treated as a case series)[12]; six were case series[3, 7, 9, 20, 34]; and one was a report of three cases[2]. Details of the included studies are given in **Error! Reference source not found.**.

Non-comparative studies

This review contains eight non-comparative studies, with a combined total of 181 patients. All are consecutive case series, except for one cohort study comparing two groups of patients receiving PRP, and one report of three cases in which symptoms deteriorated after PRP treatment.

The protocol for PRP use varies between studies, with 1-3 injections being given at varying intervals. Most use ultrasound to locate the point of maximal tendinopathy, but the studies of Gosens[12], Filardo[9] and Kon[20] did not use ultrasound guidance and the study of Wilson[34] does not specify. Similarly, the use of local anaesthetic (LA) varies, with one study (Gosens *et al*[12]) specifying that bupivacaine and adrenaline were injected with the PRP; all other studies specify that LA was not used, that it was only used subcuataneously, or did not specify (**Error! Reference source not found.**).

Pain and functional outcomes and return to sport

All of the case series report improvements in pain and functional outcomes at between six months and two years following PRP injection (Table 2), although to varying degrees. Four studies report on return to sport. Charrouset *et al*[3] report that 75% of patients returned to their pre-injection activity by the three month mark, and that this was sustained to two years; similar findings were reported by Filardo *et al* (81% return to sport)[9], and Kon *et al* reports that most patients were able to return to their pre-symptom level of sporting activity[20]. However, the study of Gosens *et al* reports that only 22% of their patients were able to exercise without pain at six months[12].

Adverse outcomes

Three studies report on patients who were deemed to have failed treatment and who went on to surgery (total of 11 tendons). Bowman[2] reports on three treatment failures where pain worsened following PRP injection with a commensurate change in USS/MRI findings. All improved following a prolonged period of physiotherapy (with ESWT in one patient). Ferrero *et al*[7] report three cases of severe post-procedure pain, which they attribute to inflammatory response. Kon et *al* report one similar case[20]; in all four cases, symptoms resolved with conservative treatment. Several studies make the link between compliance with the rehabilitation regimen and ultimate success following injection.

Comparative studies

Three studies compare PRP to control interventions. Of these, two are RCTs. Dragoo *et al* randomised 23 patients with MRI-confirmed chronic PT to receive a single injection of PRP, dry-needlng and an exercise regimen (n=10) or dry needling and exercise alone (n=13)[5]. They report improvement in both groups, but a significantly superior VISA-P score for the PRP group at 12 weeks (improvement of 25.4 points ±23.3 in the PRP group, compared to 5.2 ±12.5 in controls, p=0.02). However, no difference is seen in terms of pain, and the effect on VISA-P was lost by six months. Lysholm score was significantly better in the control group than the PRP group at six months (improvement by 14.7 ±19.1 in the PRP group compared to 45.4 ±18.8 in the controls, p=0.006).

Vetrano *et al* randomised 46 patients with USS-confirmed chronic PT to receive either two injections of PRP, two weeks apart, and an exercise programme (n=23), or three sessions of ESWT (over one week) with the same exercise programme[31]. They report improvement in both groups, but greater improvements in VISA-P score and pain in the PRP group at two, six and twelve months, and greater satisfaction in the PRP group. Neither this study nor the study of Dragoo *et al*[5], report any clinically relevant side-effects in any patient.

The third comparative study was the prospective cohort study of Filardo *et al*. 15 patients who had failed conservative (10 patients) or surgical (5 patients) treatment underwent three PRP injections, at 15-day intervals and a physiotherapy regimen[9]. The control group had not had any previous treatment; they received the physiotherapy regimen alone. The control group was comparable in terms of age and pre-operative symptoms, but had had symptoms for a significantly shorter period of time (mean of 8.4 months, compared to 24.1 months in the PRP group, p=0.004). No significant differences were determined between the groups in either pain or VISA-P at six months following the intervention. The results of the comparative studies in terms of VISA-P and pain are given in Figures 3 and 4.

Unpublished and ongoing studies

Only one study was returned from the search of clinical trial registries. Trial number NCT01843504, registered on ClinicalTrials.gov, is a single-blind randomised trial of (n=44) comparing PRP to placebo in patients with established PT (for more than three months) refractory to physiotherapy and other non-surgical treatments. The PRP group will receive a single injection of 5mL PRP under ultrasound-guidance. The control group will receive the same volume of normal saline. It is listed as being in the recruitment phase with an estimated completion date of March 2014. In common with the other RCTs reported above, the primary outcome

measure is the VISA-P score, along with the IKDC score and an ultrasound assessment of the tendon. Outcomes will be reported at intervals up to 32 weeks post-injection.

Methodological quality and bias assessment

The two randomised trials were assessed using the Cochrane tool. This tool was developed as a qualitative measure and does not produce a score, but rather presents the assessed risk of bias in seven domains. Both trials presented a low risk of bias overall; results of the assessments are presented in **Error! Reference source not found.**. The non-comparative studies were assessed using the MINORS score. There was substantial variation in the methodological scores between studies. Most studies were reported to be prospective, and both choice of outcome measure and follow-up interval were appropriate in all studies. However, most studies failed to report whether the patients were recruited consecutively or whether the assessors were blinded, and four of the seven studies failed to report the level of loss to follow-up.

Discussion

This systematic review has identified a growing number of comparative and non-comparative studies assessing the effectiveness of PRP in the treatment of PT. Amongst those studies were two recent, high-quality RCTs. In the published literature, PRP appears to be safe, with few reports of complications associated with its use in PT. In case series of PRP for PT, statistically significant improvements have been demonstrated in both pain and functional scores, at follow-up intervals up to two years. However, the comparative studies have not demonstrated conclusively that PRP is superior to existing treatments, either in terms of pain or functional outcomes.

The conclusions that can be drawn from this review are limited by the paucity of available, comparative, studies. Meaningful meta-analysis was not possible due to the small numbers of RCTs in this area and lack of standardisation of the interventions used in the control groups. However, the fact that there are two recent, high-quality randomised studies, with a third in progress, reflects the increasingly high standard of studies being published in the orthopaedic and sports medicine literature[4, 13]. Further encouragement can be drawn from the apparent consensus over outcome measures, with the VISA-P score (for function) and visual analogue pain scores being used in the majority of the included studies. PRP has been demonstrated to be safe and effective in the studies reported here; further appropriately-powered RCTs are required to demonstrate its superiority over existing treatments.

PT is believed to be a degenerative condition related to failure of the repair mechanisms of tendon. Repeated minor traumas overwhelm the tendon's capacity to repair itself, and an area of abnormal tissue (tendinosis) develops, characterised by disorganisation of collagen fibres, calcification, proliferation of fibroblasts and neovascularisation, all of which are thought to be indicative of attempts at healing[29, 32]. As such, most novel therapies aim to disrupt the area of tendinosis and to allow ingress of interlukins and growth factors such as VEGF, stimulating the production of more ordered collagen bundles as part of a more normal healing response[21]. Such treatments include ESWT, low-intensity pulsed ultrasound, and injection therapies such as sclerosants, dry-needling and injections of autologous blood. PRP works by the same rationale, directly introducing these factors into the area of abnormal tendon, stimulating increased macrophage activity and resulting in increased levels of Type I and III collagen *in vitro*[10].

The theoretical effectiveness of each of these novel therapies is yet to be proven[11]. As is the case with PRP, the majority of studies examining each of these therapies are single-arm, retrospective case series[11]. Like PRP, ESWT appears to be safe and single-arm studies report promising improvements in pain and function following its administration[30]. However, a single high-quality RCT (n=62) has been published which demonstrated no difference between athletes treated with active ESWT and those treated with placebo ESWT[35]. Low-intensity pulsed ultrasound has been demonstrated to accelerate healing of PT in animal models, but has not been demonstrated to be effective in clinical studies[11]. Injection therapies have shown promise, but there are few studies to support their widespread use. A series of 120 tendons treated with ultrasound-guided sclerosant therapy produced moderate improvements overall and a smaller RCT (n=43) by the same group demonstrated a statistically significant benefit of sclerosant therapy when compared to those receiving placebo injections of LA alone[15, 16]. A single series of 44 patients receiving dry-needling and whole blood injection in addition to a structured rehabilitation programme has demonstrated a significant improvement in VISA-P scores at a mean of 14.8 months (range, 6-22 months)[17]. However, this study is limited by the lack of a control group.

As such, the current mainstay of treatment for PT remains physiotherapy, with good evidence of effectiveness when programmes of eccentric training and decline squats are used[22, 25]. Various surgical treatments, both arthroscopic and open, have been described, and there is little evidence to suggest which is most effective[25]. Whilst there is a single RCT demonstrating superiority of arthroscopic patellar tendon shaving over sclerosant injection, a further RCT of 40 patients has demonstrated no advantage of open surgery over eccentric exercises alone[1, 33]. Studies of surgical management for PT are hampered by the difficulty with conducting

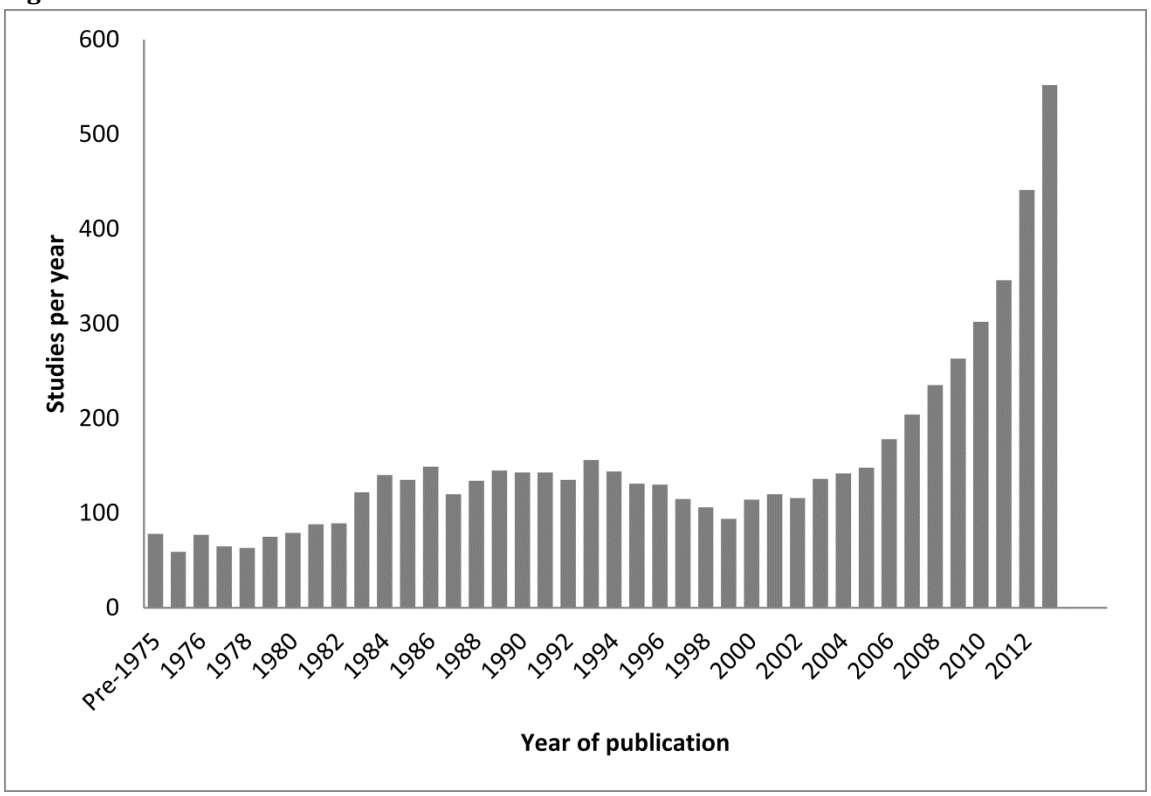
placebo-controlled trials in surgery, and by the fact that many other non-surgical treatments will generally have been attempted before surgery is offered.

Even with access to the variety of therapies available, a complete cure for PT is rare: in one study of 991 male former elite athletes from a variety of sports, 20% reported that patellar tendinopathy was the main reason for retiring from elite sport, and many report mild ongoing symptoms following retirement[18, 19].

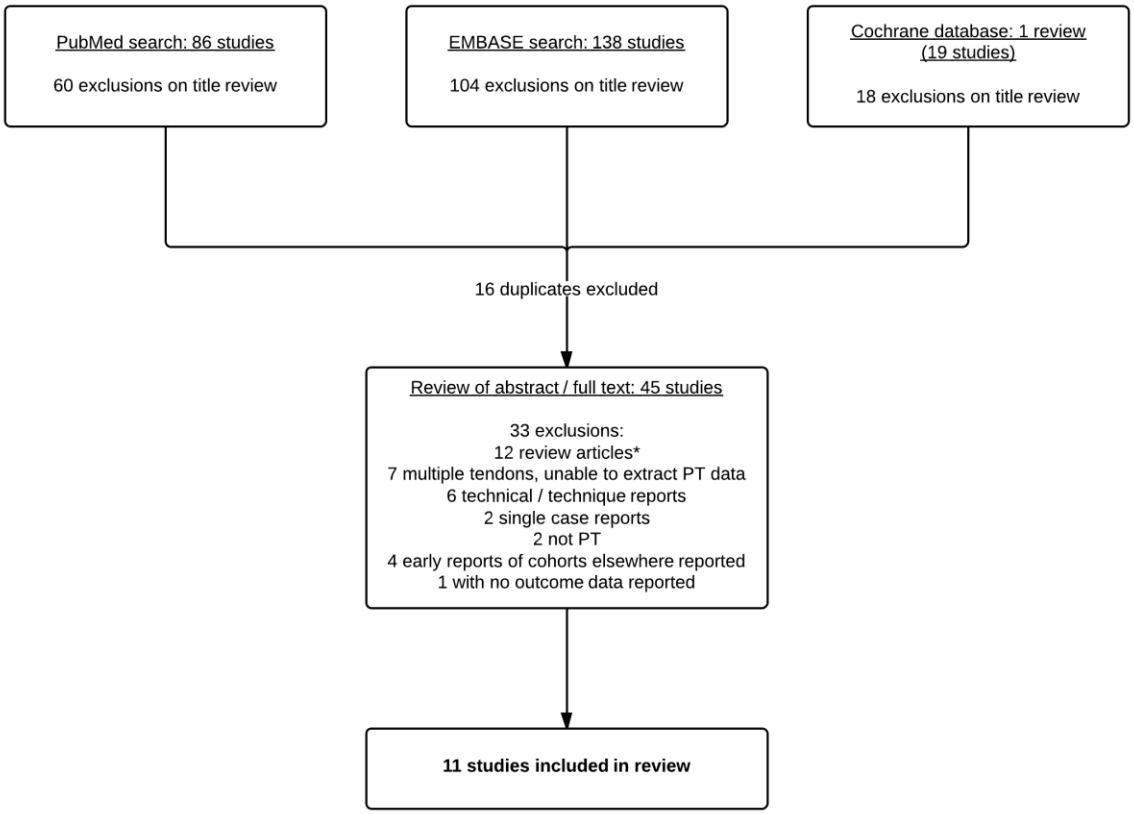
The results of this review raise the hope that PRP could be an effective treatment for PT. PRP has been demonstrated to be safe and effective in single-arm studies of patients with recalcitrant PT. However, there is currently insufficient evidence for the superiority of PRP over other treatments, and further high-quality randomised studies are required before PRP can be recommended as the gold-standard treatment for the large group of patients who suffer significant morbidity and activity restriction as a result of PT.

Legends for Figures and Tables

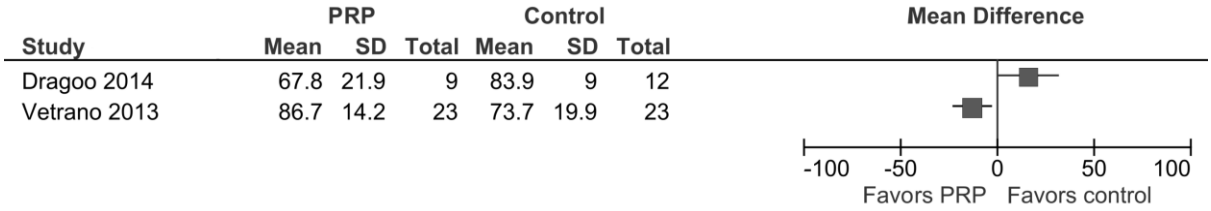
Figures



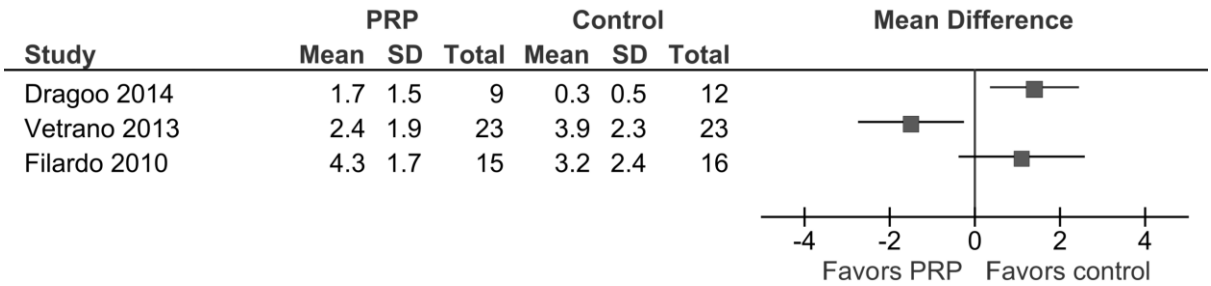
1. Number of publications per year featuring the term 'Platelet-rich plasma' (figures taken from the PubMed database)



2. Flow chart of study protocol
   *review articles include narrative and systematic reviews of PRP in mixed populations but none examining PRP for patellar tendinopathy exclusively



3. Forest plot – comparative studies of six month VISA-P



4. Forest plot – comparative studies of six-month Visual Analogue Score for pain.

Tables

1. Characteristics of included studies. RCT – Randomised Controlled Trial; MRI – magnetic resonance imaging; PT – patellar tendinopathy; PRP – platelet-rich plasma; VISA-P – Victoria Institute of Sport Assessment questionnaire (Patella); TAS – Tegner Activity Scale; VAS – Visual Analogue Scale; USS – Ultrasound Scan; ESWT – Extracorporeal Shock Wave Therapy; EQ-VAS – EuroQol general quality of life Visual Analogue Scale; IKDC – International Knee Documentation Committee score; SANE – Single Assessment Numeric Evaluation; Dx –diagnosis; ADLs – Activities of Daily Living; NSAIDs – Non-Steroidal Anti-Inflammatory Drugs; SF-36 – Short Form (36) health survey.

2. Outcomes of case series and methodological quality assessment (MINORS score)

3. Risk of bias assessment for the two randomised studies

Table 1

1st author	Year	Design	Prospective	N	Inclusion criteria	PRP protocol	Comparator group	Follow-up	Outcome scores
Charousset[1]	2014	Case series	Yes	28	USS / MRI –confirmed PT for ≥4 months. Failed injections, ESWT, physiotherapy or laser therapy.	PRP extracted with ACP kit (Arthrex). 3 x weekly injections under USS guidance. 1-2 extra injections given if clinically indicated. No LA used. Eccentric exercise programme.	None	4 weeks, 3, 6, 12, 18 and 24 months.	VISA-P; Lysholm score; Pain VAS.MRI assessment of tendon.
Dragoo[2]	2014	RCT	Yes	23	MRI-confirmed PT refractory to 6 weeks physiotherapy. No previous surgery	PRP extracted with GPSIII kit (Biomet). LA only subcutaneously. 10x needle penetration of sheath. PRP group received 6mL leukocyte-rich PRP. Eccentric exercise programme (both groups).	Dry needling x 10; same eccentric exercise programme as PRP group	3, 6, 9, 12 weeks and ≥6 months	VISA-P; TAS; Lysholm score; Pain VAS; SF-12
Vetrano[3]	2013	RCT	Yes	46	USS-confirmed PT for ≥6 months. Elite/non-elite athletes. Unilateral. No previous surgery or steroids.	PRP extracted with Recover kit (Kaylight). 2 x 2mL PRP in 2 weeks at hypoechogenic portion of tendon under USS guidance. No LA used. Eccentric exercises (2 week course, both groups).	ESWT; 3 sessions at 48-72hr intervals. 2,400 impulses; EFD 0.17-0.25mJ/mm^2.	2, 6, and 12 months	VISA-P; Pain VAS; modified Blazina scale
Filardo[4]	2013	Case series	Yes	43	MRI / USS-confirmed PT for ≥3 months. Failed injections, ESWT, or surgical management	3 sessions of PRP at fortnightly intervals. In each, multiple injections into USS-identified site Eccentric exercise programme (12 weeks). LA not specified	None	2 and 6 months and 'latest', min 36 months, (mean 48.6)	VISA-P, TAS, EQ-VAS, Blazina scale, satisfaction, return to sports. USS in 26 pts
Bowman[5]	2013	Case reports	-	-	-	-	-	-	-
Wilson[6]	2012	Case series	Yes	8	USS-confirmed chronic PT. Failed conservative therapy for ≥12 months	Unspecified	None	48 weeks	IKDC, Knee SANE, USS-measured tendon thickness
Gosens[7]	2012	Cohort	Yes	36	Chronic PT refractory to physiotherapy (clinical Dx; MRI in 21). Group 1 (n=14) previous injections / surgery. Group 2 (n=22) no previous injections / surgery.	PRP extracted with Recover kit (Biomet). 3mL PRP with bupivacaine/adrenaline. 1mL injected into point of maximal tenderness. Remainder injected into tendon / patella junction (5 penetrations). Eccentric exercises.	Comparison on basis of previous treatment. All patients received PRP	Latest follow-up, mean 18.4 months.	VISA-P, VAS (x 3) for pain during ADLs, work, and sport.
Ferrero[8]	2012	Case Series	Yes	28	MRI / USS-confirmed PT for ≥3 months. Failed ESWT, US therapy or corticosteroid injection. No systemic disease or recent NSAIDs.	2 sessions, three weeks apart. In each, dry needling then injection of PRP into degenerate area of tendon under USS-guidance. LA only used subcutaneously.	None	20 days and six months.	VISA-P, USS-measured tendon thickness.
Filardo[9]	2010	Cohort	Yes	31	MRI / USS-confirmed PT for >3 months. PRP group: failed injections / surgery. Controls: no prior treatment. No systemic disease / recent NSAIDs.	3 sessions, each 15 days apart. Non USS-guided multiple injections into tender area (4-6 penetrations). 24 hours of rest with cryotherapy then one month strengthening programme. LA not specified.	Physiotherapy – same regimen as PRP group.	Six months	TAS, EQ-VAS, Pain VAS.
Kon[9]	2009	Case series	Yes	27	MRI / USS-confirmed PT for >3 months. Failed injections / surgery.	3 sessions, each 15 days apart. Non USS-guided multiple injections into tender area (4-6 penetrations). 24 hours of rest with cryotherapy then one month strengthening programme. LA not specified.	None	Six months	TAS, EQ-VAS, SF-36. Patient-reported functional recovery and satisfaction.
Volpi[10]	2007	Case series	No	10	MRI – confirmed Chronic PT <1 year history. Failed physiotherapy, NSAIDs, ESWT.	PRP extracted with GPSII kit (Biomet). Subcutaneous LA only. USS-guided injection (5-8 penetrations). Eccentric exercises from 5 weeks.	None	Latest follow-up, mean 120 days.	VISA-P MRI appearences

Table 2

Study	MINORS score (out of 14)	Principal follow-up interval	N	Primary pain outcome				Primary functional outcome				Other outcomes			
				Score used	Baseline	Follow-up	P Value	Score used	Baseline	Follow-up	P value	Outcome	Baseline	Follow-up	P Value
Charousset 2014	12	2 years	28	VAS	7 (4-8)	0.8 (0-3)	<0.001	VISA-P	39 (28-60)	94 (60-100)	<0.001	Lysholm	60 (40-70)	96 (70-100)	<0.001
Filardo 2013	8	6 months	43	Blazina	3a (16 pts) 3b (27 pts)	0-2 (32 pts) 3a-b (11 pts)	<0.001	VISA-P	44.1 ±15.6	76.6 ± 25	<0.001	Quality of life (EQ-VAS)	67.8 ±14.7	83.5 ±15.2	<0.001
Wilson 2012	10	48 weeks	8	-	-	-	-	IKDC	52.3 ±8.6	83.0 ±11.1	0.01	USS tendon thickness (mm)	10.4 ±1.8	9.1 ±0.9	0.02
Gosens 2012	7	18.4 months (mean)	14 (gp 1)	VAS (during sport)	8.6 ±0.9	3.8 ±2.9	0.003	VISA-P	41.8 ±14.3	56.3 ±26.2	0.093	VAS (during ADLs)	6.5 ±2.3	2.8 ±2.2	0.005
			22 (gp 2)		8.5 ±1.1	5.1 ±3.2	<0.001		39.1 ±16.6	58.6 ±25.4	0.003		5.6 ±2.9	2.6 ±27	0.001
Ferrero 2012	7	6 months	28	-	-	-	-	VISA-P	56 ±18	74 ±14	0.044	USS tendon thickness (mm)	17 ±8	11 ±5	0.031
Kon 2009	10	6 months	27	SF-36 pain	35.7	71.6	<0.001	-	-	-	-	Satisfaction	-	80%	-
Volpi 2007	5	120 days (mean)	11	-	-	-	-	VISA-P	39.3 (24-64)	75.0 (58-92)	<0.001	MRI			

Table 3

Study	MINORS score (out of 14)	Principal follow-up interval	N	Primary pain outcome				Primary functional outcome				Other outcomes			
				Score used	Baseline	Follow-up	P Value	Score used	Baseline	Follow-up	P value	Outcome	Baseline	Follow-up	P Value
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Volpi 2007	5	120 days (mean)	11	-	-	-	-	VISA-P	39.3 (24-64)	75.0 (58-92)	<0.001	MRI			

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