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Platelet Rich Plasma In Musculoskeletal Pathologies

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Abstract

Purpose: To evaluate the effectiveness of platelet rich plasma (PRP) in musculoskeletal pathologies.

Methods*:* We completed a review of the literature on the use of PRP in tendon, muscle, bone, and intra-articular pathologies (Chapter 2). We completed a systematic review and meta-analysis on the effectiveness of PRP in ultrasound guided versus palpation guided injections of PRP in non-operative treatment of tendon and muscle pathologies using an indirect analysis method (Chapter 3). We conducted a randomized controlled trial to determine the effectiveness of PRP versus corticosteroid (CS) injections in patients with plantar fasciitis (Chapter 4).

Results*:* Most studies evaluating the effectiveness of PRP in musculoskeletal pathologies are for the treatment of tendon and intra-articular pathologies, with fewer studies assessing its effectiveness in muscle and bone healing. The published studies included in the review had a heterogenous summation of results that could not be used to conclusively determine the superiority of PRP over other treatments for musculoskeletal pathologies. We included 26 studies in our systematic review to compare ultrasound versus palpation guided injections of PRP. We found no statistically significant difference between ultrasound versus palpation guided injections for failure rates and pain outcomes at two months, two to three months, and six months following injection ($p > 0.05$). The comparison of functional outcomes at six months showed a significant effect in favor of palpation guided injections ($p = 0.01$), but heterogeneity of the analysis was high ($I^2 = 83.5\%$) and we were unable to make any definitive conclusions on the results. In our RCT, we found no statistically significant difference between PRP versus CS injections for our primary outcome of pain and function using the American Orthopaedic Foot and Ankle Society Ankle-hindfoot scale, at six months or one year. We also found no statistically significant difference for all other outcomes at six months and one year.

Conclusion*:* The results in all three of our studies do not provide supporting evidence for the superior effectiveness of PRP injections in musculoskeletal pathologies. There are currently no

clear indications for the clinical use of PRP injections in musculoskeletal pathologies and further research is needed in this area.

Keywords: Platelet rich plasma, musculoskeletal pathologies, ultrasound guided injections, palpation guided injections, tendon, muscle, bone, intra-articular, ligament, plantar fasciitis, corticosteroid injections

Co-Authorship Statement

With the assistance of my supervisors (Dr Dianne Bryant and Dr Kevin Willits) and the guidance of my committee (Dr Dianne Bryant, Dr Kevin Willits, and Dr Al Getgood) we designed three separate studies to address each of the research questions. I was solely responsible for the literature search and writing of the review paper. I was solely responsible for the organization and planning of the systematic review and meta-analysis. I was assisted in the literature search, accumulation of studies, and extraction of data for the systematic review and meta-analysis by a second and third independent reviewer (Laura Churchill and Alliya Remtulla). The ethics submission and initial recruitment of patients for the Plantar Fasciitis RCT was done by Lyndsay O'Brecht, but I recruited and completed follow up visits for the majority of the patients included in the study and was solely responsible for the final data analysis and manuscript writing. All supervisors and committee members reviewed each manuscript and provided their suggestions and feedback.

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Preface

Conception of the research questions came from collaboration with my supervisors Dr Kevin Willits, through his clinical practice as a fellowship trained orthopaedic surgeon, and Dr Dianne Bryant, who is a health research methodologist. I was solely responsible for the literature search and structuring of the first draft of the review paper which was then edited by my supervisors prior to submission for publication. Under the guidance of Dr Bryant, I created the protocol for the systematic review and meta-analysis. I enlisted the assistance of my colleagues Laura Churchill (PhD student) and Alliya Remtulla (PhD student) to serve as independent reviewers in the literature search, study quality rating, and data extraction. I was solely responsible for the statistical data analysis and writing of the first draft of the manuscript. The manuscript was circulated for feedback between the independent reviewers and my supervisors prior to submission. The randomized controlled trial was designed by my supervisors and Lyndsay O'Brecht, a master's student under the supervision of my current supervisors. Lyndsay recruited the first 26 patients and I recruited an additional 88 patients. I was responsible for data collection, data analysis, and the first draft of the manuscript which was circulated for feedback to my supervisors prior to submission.

Chapter 1 Introduction

The overall purpose of this thesis was to evaluate the effectiveness of platelet rich plasma (PRP) as a treatment for musculoskeletal pathologies. PRP was introduced in the late 1990's in the oral and maxillofacial field but the demand for PRP in sports medicine took off in 2009, largely fueled by the media when Hines Ward and Troy Polamalu of the Pittsburgh Stealers used PRP for their sports pathologies prior to the team winning the NFL Superbowl. Since then the number of published studies has grown.

PRP is a concentrated volume of human platelets suspended in plasma[66]. PRP is obtained when whole blood from an individual is spun in a centrifuge to separate the blood into its components (plasma, leukocytes, platelets and red blood cells) before drawing the plasma, platelets (and potentially leukocytes) from the solution and injecting it into the injury site. The theory behind the effectiveness of PRP is that the elevated concentration of growth-factor-releasing platelets will improve tissue healing.

Platelets release growth factors that are responsible for the anabolic (tissue building) processes involved in tissue healing. The most common growth factors found in PRP include platelet-derived epidermal growth factor (PD-EGF), platelet-derived growth factor (PDGF) A and B, transforming growth factor (TGF-β1), insulin-like growth factor (IGF-I, II), vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF), and basic fibroblast growth factor (bFGF)[28].

The concentration of platelets found in PRP compared to whole blood varies between each system and by individual; from being similar to the concentration found at time of blood draw to up to 8 times the concentration. With differences in platelet concentration it makes sense that there is also a variation in the concentration of growth factors and other bioactive components responsible for tissue healing. It is important to note however, that a positive association between increased platelet count and the concentration of growth factors present in a PRP solution remains unproven as does the association between concentration and healing.

Platelets are activated and begin secretion of the growth factors when the clotting mechanism of blood begins. The secretion of the growth factors naturally begins within 10 minutes of clotting, and 95% of the growth factors are released within 1 hour of activation[67]. Some systems

encourage the use of activators such as thrombin, to activate the platelets and begin the secretion of growth factors upon application of the PRP solution to the injured area. Others rely on the natural clotting mechanism for the activation process of the platelets[13,24,69,109]. Most systems also promote the addition of an anticoagulant, preferably anticoagulant citrate dextrose solution A (ACD-A) or sodium citrate[13], to prevent early clotting and enhance growth factor function.

The consensus of the ideal speed, force, and spin procedure (i.e. single versus double spin) for centrifugation continues to be debated and more research is needed to compare the clinical effectiveness of the solutions produced by each to conclusively determine superior effectiveness amongst preparation systems.

In summary, the volume of good quality evidence in support of PRP is small and diluted by the heterogeneity amongst studies caused by differences in the composition of PRP. Specifically, there are a number of commercial systems available from industry and each system has a unique protocol for the preparation and administration of the PRP solution to the injured tissue (Appendix 1). Variations include the amount of blood drawn, whether to add an anticoagulant, the spin time and speed of the centrifuge, whether to add an activator, and whether the resultant PRP solution should include leukocytes

The thesis consists of three chapters. Our first chapter is a published systematized review of the literature[37] evaluating the effectiveness of PRP in muscle, tendon, cartilage, bone and intra-articular applications for musculoskeletal pathologies in humans (permission in Appendix 2) . We also summarized the results of systematic reviews comparing studies that evaluate the use of PRP in orthopaedic bone and soft tissue pathologies, and in arthroscopic rotator cuff repair.

Next, because some have argued that the effectiveness of PRP in musculoskeletal pathologies may be hindered by the inaccurate injection of the treatment into the target tissue[31,110], our second chapter is a systematic review and meta-analysis to compare the effectiveness of ultrasound-guided versus palpation alone when performing PRP injections in tendon and muscle pathologies.

Finally, because the methodological strength of the published literature is weak, we designed and implemented a methodologically rigorous randomized controlled trial (RCT) to compare the

effectiveness of PRP versus corticosteroid injections in patients with plantar fasciitis. Specifically, we built in methods to increase our certainty about our conclusions and reduce the potential for bias including increasing the sample size, randomization, blinding of patients and outcome assessors, stratification by symptom duration, and performing an adjusted analysis to control for differences in pre-intervention health status and characteristics.

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Chapter 2 The Use of Platelet-rich Plasma in Orthopedic Pathologies

2.1   Abstract

Platelet-rich plasma (PRP) is an autologous concentration of blood-derived human platelets in a small volume of plasma. The types of PRP vary according to the commercial preparation system used, the platelet concentration, or the anticoagulant or activator used. Autologous conditioned plasma is an autologous concentration of human platelets in plasma 2 to 4 times greater than that which is found in blood at baseline. Platelets are important to the normal healing response of tissue by the local secretion of growth factors and recruitment of reparative cells in an area of injury. PRP is theorized to create an optimal healing environment in a region of tissue injury. This was a literature review of currently published studies using PRP in orthopedic pathologies. We performed a literature search in PubMed and Medline in April 2013. We concluded that given the number of variations of PRP available and the lack of high-level published studies, there was insufficient evidence to conclusively support its clinical use.

Key Words: autologous conditioned plasma, platelet-rich plasma, orthopedic pathologies, sports medicine, growth factors, tissue healing.

2.2   Introduction

Platelet-rich plasma (PRP) is an autologous concentration of blood-derived human platelets in a small volume of plasma. Platelets are recognized as the major sources of growth factors and proteins associated with tissue healing within blood clots and are involved in tissue regeneration through the recruitment, proliferation, and differentiation of cells. The theoretical concept that concentrating platelets at the injured site could accelerate and optimize the healing mechanisms set the rationale for the development and continued research into the use of PRP in the clinical application for orthopedic pathologies. PRP is a general term for this type of solution and includes autologous conditioned plasma, platelet-enriched plasma, platelet-rich concentrate, autogenous platelet gel, platelet releasate, platelet rich in growth factors, and others[1–3]. These vary depending on the commercial preparation system, the platelet concentration, the anticoagulant or activator used, or whether the resultant PRP contains leukocytes[4,5]. The most

commonly used term in the literature is PRP. For this reason (and for simplicity) we will use the term PRP throughout this review to refer to the general category of solutions that result in an elevated concentration of platelets within a sample of plasma.

2.3   What are Platelets?

Platelets are a type of white blood cell derived from the fragmentation of precursor megakarocytes and formed in the marrow[3,6,7]. They are the smallest of the blood cells, measuring approximately 2 μm in diameter. Platelets contain more than 30 bioactive proteins including some of the key growth factors, many of which have a fundamental role in the early stages of tissue healing[3,4]. Commonly found elements which are crucial to the role of tissue healing include platelet-derived growth factor AB, transforming growth factor b-1, and vascular endothelial growth factor. Plasma is the fluid content of blood and contains clotting factors and other proteins and ions[8]. The effect of PRP on tissue healing is a function of many variables, including platelet concentration, the volume of PRP delivered, the extent and type of pathology, and the overall medical condition of the patient[4,9,10]. Debate continues regarding the optimal quantity of platelets and growth factors required for soft tissue and bone healing[11-16]. A concentration 4 or more times that of whole blood has also been proposed[11] but lower concentrations of 2 to 3 times that of baseline blood has also been shown to be effective in cell culture studies [12,13]. Since the 1990s, PRP has been used in an array of fields including maxilla-facial surgery[11,14] and plastic surgery[15,16]. A growing body of laboratory evidence supports the use of PRP injections for the treatment of muscle and tendon pathologies and degeneration[17–20]. In vitro and in vivo studies suggest that growth factors released by platelets recruit reparative cells and may augment soft-tissue repair[20,21]. Another advantage of platelet-rich therapies is the antibactericidal effects of the antibacterial and fungicidal proteins stored in platelets, which may help to prevent infection[22,23].

2.4   Preparation and Delivery of PRP

There is considerable variation in the preparation of PRP. However, most processes include taking a sample of autologous blood and adding a form of citrate as an anticoagulant which is added before centrifugation of the blood[6]. The anticoagulants most commonly used are

anticoagulant citrate dextrose-A and citrate phosphate dextrose. These anticoagulants support the metabolic needs of platelets and the viable separation of platelets in an undamaged manner[3,24,25]. Some systems do not require the use of an anticoagulant especially if the PRP is administered before clotting has been initiated[26]. The autologous blood is spun using a centrifuge, filter, or separation system to separate the red blood cells from the leukocytes and platelets[27]. The resultant is a visibly layered solution of red blood cells on the bottom, a thin milky-white layer of leukocytes in the middle, and a yellow-tinged upper portion of PRP. The efficiency of red blood cell separation and platelet concentration is dependent on the preparation system used, but all PRP preparations contain the non-cellular components of plasma, including clotting factors[27]. PRP can be administered with or without an activating agent, such as bovine thrombin, at the time of delivery into the area of injury[28]. Both leukocyte-poor and leukocyte-rich preparations have been used[29–31].

2.5   Review of the Literature

Animal studies have been used to show the effectiveness of PRP on soft-tissue and bone healing as the physiology is generally known to be comparative with that of humans[20,32–35]. In the clinical setting however, results are often not as readily transferable possibly because the physical structure or more specifically the biomechanics and or load dispersion through soft tissues, joints, and bone differs between humans and animals. We conducted a search using PubMed and Medline in April 2013 with combinations of the following key words: platelet rich plasma, platelet-rich plasma, growth factors, orthopaedic pathologies, sports medicine, muscle, tendon, bone, and ligament. Studies were eligible for review if they explored the effectiveness of PRP in muscle, tendon, bone, or ligaments in humans. We further reduced this volume of literature by selecting those studies with the highest levels of evidence[36]. Each relevant study is presented in brief summary showing all significant findings for consideration of implications of PRP in orthopedic pathologies. Study details are summarized in Tables 1 and 2.

Study	Study Design	Control Groups	Blinded	Sample size	Outcome Measures	Validated Outcome measures	Length of Follow-up (months)
Everts et al (2008)	RCT	Yes	Yes (Patients, Assessor)	40 (20/20)	VAS, ASES, SIS, ROM	Yes	3
Randelli et al. (2008)	RCT	Yes	Yes (Patients, Assessor)	53 (26/27)	Constant score, VAS, SER, UCLA, SST, MRI, Ultrasound	Yes	24
Devos et al. (2010)	RCT	Yes	Yes (Patients, Assessor)	54 (27/27)	VISA-A, return to sports, patient satisfaction,	Yes	6
Creaney et al. (2011)	RCT	Yes	Yes (Patients, Assessor)	150 (80/70)	PRTEE	Yes	6
Castricini et al. (2011)	RCT	Yes	Yes (Patients)	80 (43/45)	Constant score, MRI	Yes	(+/-) 20.2
Gosens et al. (2011)	RCT	Yes	Yes (Patients, Assessor)	100 (51/49)	VAS, DASH	Yes	24
Cervellin et al. (2012)	RCT	Yes	Yes (Patient)	40 (20/20)	VAS, VISA, MRI	Yes	12
Rha et al. (2012)	RCT	Yes	Yes (Patient, Assessor)	39 (20/19)	SPADI	Yes	6
Weber et al. (2012)	RCT	Yes	Yes (Patient, Assessor)	60 (30/30)	ROM, UCLA, SST, ASES, MRI	Yes	12
Krogh et al. (2013)	RCT	Yes	Yes (Patient, Assessor)	60 (20/20/20)	PRTEE, Ultrasound	Yes	12
Klaasen et al. (2011)	Retrospective Cohort	Yes	No	161 (76/91)	Radiographs (Brooker Grading)	Yes	12

Wei et al. (2012)	Prospective cohort	Yes	Yes (Patient, Assessor)	254 (85/101/90)	AOFAS, Radiographs, CT Scan	Yes	72
Wright-Carpenter et al. (2004)	Pilot study	Yes	No	29 (18/11)	Return to sport, MRI	No	(+/-) 17.7
Wetzel et al. (2013)	Retrospective Cohort	Yes	No (Not mentioned)	15 (10/5)	VAS, Return to work, Return to sport, Patient-reported satisfaction, NPRS	No	4.5 (treatment), 2 (control)
Orrego et al. (2008)	RCT	Yes	Yes (Patient, Assessor)	108 (26/27/28/27)	MRI, Lysholm Score, IKDC	Yes	6
Nin et al. (2009)	RCT	Yes	Yes (Patient, Assessor)	100 (50/50)	VAS, Anterior laxity, IKDC, Inflammatory parameters, Radiographs, MRI	Yes	24
Patel et al. (2013)	RCT	Yes	Yes (Patient, Assessor)	78 (27/25/26)	WOMAC, VAS, Patient satisfaction	Yes	6

Table 1 Summary of Studies

Abbreviations: RCT, randomized controlled trial; ASES, American Should and Elbow Surgeons; SIS, Shoulder Index Score; VAS, visual analog scale; SER, strength in external rotation; SST, simple shoulder test; UCLA, University of California; VISA-A, Victorian Institute of Sports Assessment – Achilles; DASH, Disabilities of the Arm, Shoulder, and Hand; PRTEE, Patient-Related Tennis Elbow Evaluation; NPRS, Nirschl Phase Rating Scale; IKDC, International Knee Documentation Committee score; WOMAC, Western Ontario and McMaster Universities Arthritis Index questionnaire; AOFAS, American Orthopaedic Foot and Ankle Society; SPADI, Shoulder Pain And Disability Index; MRI, Magnetic Resonance Imaging

Study	Study Design	No. Of Studies	Included study designs
Sheth et al. (2012)	Systematic Review and Meta-analysis	33	RCT (n = 23), Prospective cohort (n = 10)
Chahal et al. (2012)	Systematic Review and Meta-analysis	5	RCT (n = 2), Prospective cohort (n = 3)

Table 2 Systematic Reviews and Meta-analyses

2.5.1   PRP in Tendon Healing

Everts et al[37] published results of a randomized controlled trial (RCT) that evaluated the use of platelet-leukocyte gel (PLG) in open subacromial decompression surgery for 40 patients (treatment=20, control=20) with chronic impingement syndrome of the shoulder. At 6 weeks the PLG group showed significant improvement in visual analog scale (VAS) pain scores that were part of the American Shoulder and Elbow Surgeons tool ($P<0.05$). Patients with PLG also used significantly less pain medication ($P<0.05$) and scored significantly better on the shoulder index score postoperatively ($P<0.05$). Patients with PLG had significantly improved scores on the activities of daily living questionnaire 2 weeks postoperatively ($P<0.05$) and demonstrated greater range of motion (ROM) improvement at 2 weeks ($P<0.05$).

Randelli et al[38] published results of a RCT for the effectiveness of PRP in tendon healing in patients undergoing arthroscopic repair of a complete rotator cuff tear. Patients received either an intraoperative application of PRP with an autologous thrombin component (n=26) or no treatment in the control group (n=27), and were followed up for over 2 years. Outcome measures were VAS for pain, Constant score, strength in external rotation (SER), Simple Shoulder Test (SST), University of California-Los Angeles (UCLA), and tendon integrity assessed using magnetic resonance imaging (MRI). The pain score in the treatment group was lower than the control group at 3, 7, 14, and 30 days after surgery ($P<0.05$). Scores on the SST, UCLA, Constant scores, and SER were significantly better in the treatment group than the control group at 3 months after surgery ($P<0.05$). There was no difference between the groups at 6, 12, and 24 months. The follow-up MRI showed no significant difference in the healing rate of the rotator cuff tear. In the subgroup of grade 1 and 2 tears, with less retraction, SER in the PRP group was significantly higher at 3, 6, 12, and 24 months postoperative ($P<0.05$).

De Vos et al[39] performed a RCT of 54 patients with chronic Achilles tendinopathy. Patients were randomized to receive a PRP injection (n=27) or placebo (n=27). The validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which evaluated pain score and activity level, was completed at baseline and 6, 12, and 24 weeks. Secondary outcomes included subjective patient satisfaction, return to sports, and adherence to eccentric exercises. Authors

found no statistically significant differences between treatment groups for any of their outcomes (P>0.05).

Creaney et al[40] conducted a RCT comparing autologous blood injection (n=70) and PRP (n=80) in patients with elbow tendinopathy who had failed conservative physical therapy. Each patient received 2 injections: 1 at baseline and 1 a month later. Patient-related tennis elbow evaluation was the primary outcome measure which patients completed at baseline, 1, 3, and 6 months. Authors found no statistically significant differences in the improvement of scores between groups (P<0.05).

Castricini et al[41] completed a RCT that included 88 patients with a rotator cuff tear who received arthroscopic rotator cuff repair with (n=43) or without (n=45) augmentation with autologous platelet-rich fibrin matrix. The primary outcome was the postoperative difference in the Constant score between the 2 groups, and the secondary outcome was the integrity of the repaired rotator cuff, as evaluated by MRI. The authors found no statistically significant differences between groups for either of the outcome measures (P<0.05).

Gosens et al[42] published the 2-year results for an ongoing study comparing PRP and corticosteroid injection for the treatment of chronic lateral epicondylitis. One hundred patients were randomized to a leukocyte-enriched PRP group (n=51) or the corticosteroid group (n=49). The primary outcomes were the pain VAS scores and the DASH outcome scores. The PRP group had a statistically significant reduction of 25% on pain and DASH scores (P<0.05) without a reintervention after 2 years. When baseline pain and DASH scores were compared with the scores at 2-year follow-up, both groups significantly improved across time (intention-to-treat principle). However, the DASH scores of the corticosteroid group returned to baseline levels, whereas those of the PRP group significantly improved (as-treated principle; P<0.05).

In a RCT, Cervellin et al[43] evaluated the effectiveness of PRP in 40 young athletes following bone-patellar tendon-bone technique for anterior cruciate ligament (ACL) pathologies. Patients were randomized to undergo ACL reconstruction with patellar tendon grafts and bone-patellar tendon-bone technique with (n=20) or without (n=20) PRP gel applied to the donor site. Outcome measures included reduction in anterior knee pain, kneeling pain, and donor-site morbidity as evidenced by evaluation of VISA and VAS scoring scales and MRI analysis of the

tendon and bone defect. At 12-month follow-up, VISA scores were significantly higher in the patients treated with PRP (P<0.05). No other outcomes were found to be statistically different.

Rha et al[44] compared the effects of 2 PRP injections (n=20) with those of 2 dry needling injections (n=19) in patients with a supraspinatus tendon lesion (tendinosis or a partial tear <1cm). The outcomes included the Shoulder Pain and Disability Index, passive ROM, a physician global rating scale at the 6-month follow-up, and an ultrasound measurement. There was a statistically significant improvement in clinical outcomes in the PRP group (P<0.05) from 6 weeks to 6 months. At 6 months the mean Shoulder Pain and Disability Index also showed a statistically significant difference between groups in favor of the PRP treatment (P<0.05).

Weber et al[45] conducted a RCT to compare the effectiveness of platelet-rich fibrin matrix (n=30) to a control group with no injection (n=30), in the treatment of arthroscopic rotator cuff repair. Outcome measures collected over 1 year included pain VAS, ROM, UCLA, and SST scores, and recorded narcotic consumption. Mean UCLA shoulder scores were significantly better for the PRP group at 1 year (P<0.05). There were no statistically significant differences found for the other outcomes.

Krogh et al[46] compared a single injection of PRP (n=20) to a glucocorticoid injection (n=20) and a placebo (saline; n=20) in a RCT for patients with chronic lateral elbow epicondylitis. The primary outcome was reduction in pain after 3 months using the PRETEE questionnaire, and secondary outcomes were ultrasonographic changes in tendon thickness and color Doppler activity. Glucocorticoid reduced pain more effectively than did both saline and PRP at 1 month (P<0.05). Glucocorticoid also showed statistically significant reduction of color Doppler activity and reduced tendon thickness (P<0.05) compared with both PRP and saline.

2.5.2   PRP in Bone Healing

Klaassen and Pietrzak[47] completed a retrospective, controlled clinical study that examined the effect of PRP application during closure after total hip arthroplasty on heterotopic ossification. The PRP group consisted of 76 patients with 85 hips evaluated and the control group consisted of 91 patients with 94 hips evaluated. The primary outcome was the unwanted presence of heterotopic ossification evaluated using radiographs and the Brooker classification immediate

postoperative, 6 weeks, 3 months, and 1 year. No significant differences were found between groups.

Wei et al[48] conducted a prospective cohort study to compare the effectiveness of PRP in the treatment of displaced intra-articular calcaneal fractures. Patients received one of 3 treatments: autograft alone (n=101), allograft combined with PRP (n=85), or allograft alone (n=90). Outcome measures included radiographic imaging and 3-dimensional computed tomography to assess the thalamic portion, Bohler angle, the crucial angle of Gissane, and the height, width and length of the calcaneum. The American Orthopedic Foot and Ankle Society ankle-hind-foot scoring system was used to evaluate the hindfoot function at intervals over a period of 6 years. There were statistically significant improvements for patients in the autograft and allograft with PRP treatment groups at 2 and 6 years compared with the allograft alone group (P<0.05) in radiographic assessments.

2.5.3 PRP in Muscle Healing

Wright-Carpenter et al[49] conducted a pilot study on the effects of autologous conditioned serum (n=18) compared with a control group using a combination of deproteinized dialysate from bovine blood and a homeopathic anti-inflammatory drug (Actovigan/Traumeel; n=11). Patients were professional sportsmen with a variety of lower limb muscle strains. Primary outcomes included time to return to sport and MRI. The autologous conditioned serum group returned to full sport participation statistically sooner than the control group (P<0.05).

Wetzel et al[50] compared the effectiveness of PRP in proximal hamstring pathologies in a retrospective cohort of patients. The authors included patients in an analysis who had failed traditional conservative treatment and had received a PRP injection (n=15) and compared them to a cohort who received no treatment (n=5). Outcomes included pretreatment and posttreatment VAS pain scores, Nirschl Phase Rating Scale scores, and return to sport. Both groups showed significant improvements from baseline scores, but there were no significant differences found between groups (P>0.05).

2.5.4   Intra-articular Application of PRP

Orrego et al[51] completed a RCT to determine whether the use of platelet concentrate (PC) and bone plug (BP) accelerates healing in ACL reconstruction. Patients were randomized to PC (n=26), BP (n=28), combination of PC and BP (n=27), and a control group (n=27). Maturation of the graft was evaluated at the femoral tunnel using MRI maturation criteria defined by a low-intensity signal, absence of osteoligamentous interface, and no widening of the femoral tunnel. Subjective and objective evaluations using the Lysholm and International Knee Documentation Committee scores were performed preoperatively and 6 months after surgery. The only significant difference was found at 6 months in the presence of low-intensity mature graft signal at the femoral tunnel in 78% of the BP group and in 100% of the PC group (P<0.05). Tunnel widening (negative result) was seen in 11% of the patients in the BP group versus 41% of the patients in the control group (P<0.05).

Nin et al[52] evaluated the use of platelet-derived growth factor in primary ACL reconstruction with bone-patellar tendon-bone allograft in a RCT of 100 patients. Patients received either platelet-enriched gel (n=50) or a nongel (n=50). Patients were followed at intervals for a period of 24 months and outcome measures were the pain VAS, anterior laxity assessed using an arthrometer, the International Knee Documentation Committee scores, C-reactive protein levels, knee circumference, MRI and radiographic measures. The results did not show any statistically significant differences between the groups for inflammatory parameters, MRI appearance of the graft, and clinical evaluation scores (P>0.05).

Patel et al[53] assessed the use of PRP in a RCT of 78 patients (156 knees) with bilateral osteoarthritis of the knee. Patients were divided into 3 treatment groups: group A (52 knees) received a single injection of PRP, group B (50 knees) received 2 injections of PRP 3 weeks apart, and group C (46 knees) received a single injection of normal saline. Outcome measures included the Western Ontario and McMaster (WOMAC) Universities Arthritis Index questionnaire and pain VAS. Patients were assessed at baseline, 6 weeks, 3 months, and 6 months after treatment. Groups A and B showed significant improvements in all WOMAC parameters and pain VASs at all time points when compared with group C (P<0.05), but no difference observed when comparing groups A and B (P>0.05).

2.5.5 Systematic Reviews

In a systematic review and meta-analysis conducted by Sheth et al[54] that included most studies already described, pain and improved healing and function was evaluated in patients with orthopedic pathologies after the use of PRP. Twenty-three randomized trials and 10 prospective cohort studies met the eligibility criteria. However, the authors concluded that among the identified studies, the PRP products utilized were too dissimilar from each other to justify making a broad statement about the effectiveness of all PRP products and that more studies need to be conducted so that future reviews could present independent analyses by PRP product.

Chahal et al[55] completed a systematic review of the literature and subsequent meta-analysis on the clinical efficacy of PRP in arthroscopic rotator cuff repair of patients with full-thickness rotator cuff tears. Five studies (2 randomized and 3 nonrandomized with comparative control groups) met the inclusion criteria, with a total of 261 patients. Quantitative synthesis of all 5 studies using a random effects model showed that there was no statistically significant difference in the overall rate of rotator cuff retears between patients treated with PRP and those treated without PRP (risk ratio, 0.77; 95% confidence interval, 0.48-1.23). There were also no statistically significant differences in the pooled Constant score, SST, American Shoulder and Elbow Surgeons, UCLA, or SANE score.

2.6 Conclusion

There are currently no clear indications for the use of PRP in orthopedic pathologies. There is a lack of homogenous, high level studies evaluating the effect of PRP in orthopedic pathologies, thus precluding attempts to pool results across studies and preventing us from making conclusions with any degree of certainty.

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Chapter 3 Ultrasound versus palpation guided PRP injections in tendon and muscle pathologies: A systematic review and meta-analysis of randomized and non-randomized trials

3.1 Abstract

Background: There is controversy as to whether the effectiveness of platelet rich plasma (PRP) injections for non-operative treatment of muscle and tendon pathologies is affected by the method of administration. Compared to palpation alone, ultrasound guided injections may offer improved accuracy and subsequent greater effectiveness of PRP for tendon and muscle pathologies.

Objectives: The purpose of this systematic review and meta-analysis was to evaluate the effectiveness of ultrasound guided versus palpation guided PRP injections for the treatment of tendon and muscle pathologies.

Search methods: We searched Pubmed, Medline Ovid, CINAHL, Scopus, SportDiscus, EMBASE, and Cochrane Library from inception to December 2014. We also searched references of recently published review papers and systematic reviews.

Selection criteria: We included Level I, II, and III comparative studies evaluating PRP injection versus a non-PRP control for the non-operative treatment of muscle and/or tendon injury.

Data collection and analysis: Two independent reviewers assessed the titles and abstracts of 5178 studies. Seventy-one studies were identified for full text review, and 26 studies were included in the final analysis. We used a modified version of the Cochrane Collaboration tool to assess risk of bias of included studies. We included 18 studies in our meta-analysis. There were no studies directly comparing ultrasound versus palpation guided injections of PRP, thus we used an indirect comparison using random-effects with associated P values and 95% confidence intervals (CI). We assessed heterogeneity of studies using an I^2 and Tau^2 statistic and Chi^2 test. Specifically, we expected larger effects in studies sponsored by an interested party versus not, and in those studies with a high risk of bias versus not. We also thought heterogeneity may be explained by creating subgroups and therefore explored whether heterogeneity was decreased if

we separated studies that evaluated outcomes in tendon versus muscle, acute (<3 months symptom duration) versus chronic (>3 months symptom duration) pathologies, active control versus sham or placebo, platelet concentration (≤3 versus >3 times baseline blood),and intra-articular injection versus not.

Main results: We found no statistically significant difference in failure rates between patients whose PRP injection was ultrasound-guided or not. There was also no significant difference in pain at less than two months, two to three months, and six months following PRP injection. Disability and functional outcomes at six months had high heterogeneity which could not be explained by our *a priori* expectations. Therefore, we were unable to make any definitive conclusions about the difference in disability and functional outcomes between ultrasound versus palpation guided injections.

Conclusion: There is no evidence to date that ultrasound-guided injection of PRP offers better outcomes than palpation alone.

3.2   Introduction

Over the past decade, the body of literature evaluating the effectiveness of platelet rich plasma (PRP) for the treatment of musculoskeletal pathologies has increased. Its purported regenerative properties drive its continued use as a treatment for tendon, muscle, bone and cartilage, while the autologous nature of PRP and relative ease of preparation, and contribute to its appeal.

Platelets are discoid cells that contain over 30 bioactive proteins in the form of growth factors[1]. At the time of injury, platelets are activated in the presence of damaged tissue and aggregate together to release the growth factors which stimulate the inflammatory response and initial healing process[2]. PRP is a concentrated solution of blood platelets suspended in plasma. By injecting PRP in the injured area, the localized concentration of these growth factors may accelerate tissue and wound healing[3,4].

PRP is obtained from the venous blood of the patient. The process of centrifugation separates the blood into a distinctly layered solution of red blood cells and concentrated platelets in plasma. The PRP is then extracted and injected into the area of injury. Variability in the process depends on the system used and may include variations in time and speed of centrifugation, as well as the addition of an anticoagulant prior to centrifugation and/or an activator shortly before the injection[5].

A number of studies have investigated the effectiveness of PRP injections for the non-operative treatment of tendon pathologies[6–9], and a limited few in muscle pathologies[10–12]. The results, however, remain inconclusive with a continued need for higher powered randomized controlled trials with standardized procedures including preparation methods, administration techniques, and evaluation of outcomes[13,14,15].

One area of considerable debate is whether patient outcomes are more favourable when clinicians use ultrasound to guide the placement of the injection versus relying on palpation alone. Critics argue that neglecting to use ultrasound to guide PRP injections may decrease the accuracy of the placement of the solution, in turn decreasing the effectiveness of PRP[16,17].

Hall et al.[18] defined accuracy of an injection treatment as the placement of the needle tip in the target area of the joint or tissue. The accuracy of an injection may be highly dependent on the target structure (i.e. joint, tendon, or muscle) and expertise of the clinician. Specifically, injured tendon and muscle structures are easier to locate via palpation compared to intra-articular structures. The gap in an Achilles tendon rupture, for example, is easier to locate via palpation than an intra-articular injection for rotator cuff tendinosis. For this reason, most published studies evaluating the effectiveness of ultrasound guided versus palpation guided injections have focused on intra-articular pathologies, and less on tendon, with even fewer focusing on muscle.

For example, in 80 cadavers, Patel et al (2012)[19] compared the effectiveness of ultrasound guided versus palpation guided injections in the glenohumeral joint and found significantly greater accuracy for the ultrasound guided approach (92.5%) over the palpation guided injections (72.5%). Similarly, Peck et al (2010)[20] compared the accuracy of ultrasound (n=10) versus palpation (n=10) guided injections in the acromioclavicular joint of unembalmed cadavers and found significantly greater accuracy in the ultrasound (100%) compared to the palpation guided application (40%) ($p < 0.05$).

Conversely, in living humans with complaints about an intra-articular structure, Rutten et al.[21] reported 100% accuracy for both ultrasound (n = 10) and palpation guided (n = 10) injections of the subacromial-subdeltoid bursa in a RCT of patients with shoulder impingement syndrome ($p > 0.05$). In a study evaluating shoulder pain following intra-articular injection for soft tissue and joint pathologies of the shoulder, Uncuncu et al.[22] found a significant improvement ($p < 0.05$) in the VAS pain scores and Constant scores in patients who received ultrasound guided injections (n = 30) versus anatomical landmark-guided injections (n = 30) of corticosteroids. Similarly, in a RCT by Zufferey et al.[23], the authors found a statistically significant improvement ($p < 0.05$) in pain at rest and percentage of good responders (defined as greater than 50% reduction in pain) at two and six weeks follow up in patients who received ultrasound guided (n = 27) versus those who received palpation guided (n = 29) injections of corticosteroids for the treatment of shoulder pain. Naredo et al.[24] also found a statistically significant improvement ($p < 0.05$) of VAS pain scores and shoulder function assessment (SFA) scores at six weeks, in patients randomized to receive ultrasound guided injections (n = 21) versus palpation guided injections (n = 20) of corticosteroids for painful shoulder pathology.

Conversely, Hashiuchi et al.[25] published the results of a randomized controlled trial comparing the accuracy of ultrasound (n=15) versus palpation guided injections (n=15) of the biceps tendon sheath (tendon versus intra-articular pathology), a palpable tendon. A blinded assessor judged the presence of a contrast agent within the tendon sheath using a CT scan and found that the ultrasound guided injections had significantly greater accuracy (86.7% versus 26.7%) in the injection reaching the target area within the tendon sheath ($p < 0.05$). Regarding patient outcomes, in 2011, Zhang et al.[26] found a statistically significant improvement of VAS pain scores and Constant-Murley scores ($p < 0.05$) for ultrasound guided injections in patients with biceps brachii tendinitis at an average follow up of 31 weeks in a RCT comparing ultrasound (n = 53) versus palpation (n = 45) guided corticosteroid injections.

Li et al. [27] published a systematic review in 2014 comparing the effectiveness of ultrasound versus palpation guided corticosteroid injections in 149 patients with plantar fasciitis. The authors found a statistically significant greater improvement in the ultrasound-guided group for tenderness threshold, plantar fascia thickness, and hypoechogenicity ($p < 0.05$). However, there was no significant difference between treatments for VAS pain, Heel Tenderness Index (HTI), and response rate defined as complete relief of symptoms after one injection ($p > 0.05$). In summary, ultrasound guided injections may be more accurate especially for intra-articular injections, but whether or not this translates to better outcomes seems more likely for intra-articular pathology than tendon or muscle pathology.

To date, there are no published studies directly comparing ultrasound versus palpation guided injections for PRP in musculoskeletal pathologies. Therefore, we conducted a systematic review and meta-analysis to evaluate the effectiveness of ultrasound versus palpation guided injections of PRP to reduce pain and improve function for patients with tendon and muscle pathologies.

3.3   Methods

3.3.1 Protocol

We followed the PRISMA guidelines for reporting a systematic review and meta-analysis[28].

3.3.2 Eligibility Criteria

We included studies that compared the effectiveness of PRP injections versus a non-PRP control group. Inclusion criteria consisted of human studies evaluating treatment of muscle and/or tendon pathologies using a non-surgical approach, with an evidence level of I, II, or III comparative design. We excluded animal, cadaveric, and lab studies; and studies evaluating bone, ligament, cartilage, and wound care pathologies.

3.3.3 Information sources and searches

We consulted with a university librarian to aid with our search of Pubmed, Medline Ovid, CINAHL, Scopus, SportDiscus, EMBASE, and Cochrane Library from inception to December 2014 (Appendix 3). We also searched the references of recently published reviews and systematic reviews evaluating the effectiveness of PRP in musculoskeletal pathologies[29–34]. Our keyword search included "muscle or tendon" combined with variations of the terms "platelet rich plasma" and "injection".

3.3.4 Study Selection

Two reviewers (N.K. and L.C.) independently read the titles and abstracts to determine study eligibility. We reviewed the full text of any study classified by either reviewer as eligible or uncertain. The same independent reviewers screened the full text articles using the same eligibility criteria. Any disagreement was resolved by an independent third party (A.R.). We completed an inter-rater agreement assessment for categorical data for the full text review using a Kappa statistic.

3.3.5 Data collection process

Two reviewers (N.K. and A.R.) independently extracted data from eligible studies. Disagreements between reviewers were resolved by discussion and remaining disagreements were adjudicated by an arbitrator (D.B.).

3.3.6 Data items

We extracted patient population information, treatment and control used, and outcome measures.
Additionally, we included details of the diagnosis, symptom duration, and the addition of
anticoagulants and/or activators to the injection procedure. We contacted the authors of seven
studies to obtain additional information or data. We received additional data from five authors[35–
38], and no response from two authors of three studies[39–41].

3.3.7 Risk of bias in individual studies

Two independent reviewers (N.K. and L.C.) assessed the risk of bias for each study using a
modified version of the Cochrane Collaboration's tool for assessing risk of bias in randomized
trials[42]. Disagreements between reviewers were resolved by discussion and remaining issues
were adjudicated by one of two arbitrators (A.R. and D.B.).We rated the domains for each study
as "high risk" of bias, "low risk" of bias, or "unclear risk". A study was classified as "high risk"
if the particular criteria that posed a threat to the internal validity was not adequately prevented.
A "low risk" of bias meant that the study took all possible precautions to protect the internal
validity. We labelled the study as having an "unclear risk" of bias when there was limited
information from which to assess bias. Risk of bias guidelines are described in Table 3.

Risk of bias guidelines	
RCT's	
Domain	**Description**
Sequence generation	Judged on the likelihood of the method to generate a randomization sequence (e.g. random computer generated ("low") versus odd or even date of birth ("high")) that will result in balanced treatment groups
Allocation concealment	Judged on the effectiveness of the study protocol to reduce the predictability of group allocation (e.g. open list ("high") versus sequentially numbered, opaque, sealed envelopes ("moderate") versus list of managed independently or by computer with checks for duplicate or withdrawn patients ("low")).
Blinding	Judged on the ability of the protocol to blind the patient, caregiver, and/or outcomes assessor where possible, so as not to influence the outcomes

Domain	Description
Attrition	Judged on how likely missing data was related to the treatment or outcome; the balance of missing data between treatment groups; and how likely missing data would influence the results (tolerance).
Reporting	Judged on the study results being reported as specified in the study protocol (i.e. all primary and secondary outcomes were reported using the pre-specified measurements and analyses of all data in its entirety).
Other	Judged on the presence of the occurrence of another factor that may have influenced the study results (e.g. study stopped early or fraudulent claims).
Cohort studies	
Domain	**Description**
Selection bias	Judged on the population sampling method and the unbiased allocation of participants to the treatment groups.
Balance of prognostic factors	Determined by the balance of participant baseline characteristics between treatment groups.
Unbiased outcome assessment	Judged on the ability of the protocol to blind the patient, caregiver, and/or outcomes assessor where possible, so as not to influence the outcomes
Attrition	Judged on how likely missing data was related to the treatment or outcome; the balance of missing data between treatment groups; and how likely missing data would influence the results (tolerance).
Reporting	Judged on the study results being reported as specified in the study protocol (i.e. all primary and secondary outcomes were reported using the pre-specified measurements and analyses of all data in its entirety).
Other	Judged on the presence of the occurrence of another factor that may have influenced the study results (e.g. study stopped early or fraudulent claims).

Table 3 Risk of bias assessment tool used for RCT's and Cohort studies

3.3.8 Summary measures

We analysed pooled data using standard meta-analysis methods with Review Manager (version 5.3)[43]. We consulted with an orthopaedic surgeon (K.W.) to establish common follow up times and outcome measures amongst the studies. We calculated differences between treatment groups using odds ratios with 95% CI for dichotomous data. For continuous data we used standardized mean differences (SMD) with 95% CI for comparisons measuring the same outcome using different scales[44] (Cochrane handbook).

3.3.9 Synthesis of results

We extracted data from studies to compare failure rates as defined by the individual study. If more than one time point was provided in studies, we used the final follow up scores in the analysis. For the continuous outcome measure (pain and patient-reported disability and function) we conducted two analyses at each follow up time point; a change score (final outcome – baseline) and a raw score (final outcome only). For analyses evaluating a pain VAS some studies reported a score from a 10 cm line ranging from 0-10 while others reported a score from 0-100. We converted scores on a scale of 0-100 to a standardized scale of 0-10 prior to pooling the results. We extracted scores of VAS pain scales at three different time intervals: 1) less than two months, 2) two to three months, and 3) six months post-injection.

We compared change in disability and functional outcome scores for ultrasound versus palpation studies at six months follow up. We standardized scores to a scale where a lower score represents worse ability or function.

If not already provided, we converted scores for each study to a mean and standard deviation of the change in score from baseline. When a mean and range were provided, we calculated an estimated standard deviation as follows:

$$(\text{upper limit} - \text{lower limit})/4$$

When a mean and confidence intervals were provided, we calculated the standard deviation as follows (Cochrane handbook 7.7.3.2).

$$SD = \sqrt{n} \text{ x } (\text{Upper limit} - \text{Lower limit})/3.92$$

We found no studies that directly compared ultrasound guided PRP injections versus palpation guided PRP injections. For this reason we completed an indirect comparison of treatment effects as suggested by Bucher et al.[45]. For each follow up period of each outcome measure, we completed subgroup analyses comparing (1) ultrasound guided PRP injections versus control groups; and (2) palpation guided PRP injections versus control groups. We completed a comparison of subgroups in RevMan 5.3 which calculated the between subgroup differences with an associated Chi^2, degrees of freedom, p value, and measure of heterogeneity (I^2). This test

takes into consideration the overlap of confidence intervals of the summary estimates in the two subgroups. If the confidence intervals overlap, there is no difference between the treatments. If the confidence intervals do not crossover, there is a significant difference in effect of treatment.

We did not perform analyses if there were less than two studies in a subgroup comparison. We used inverse variance and a random-effects approach for our meta-analyses. We assessed heterogeneity using a Chi^2 test and I^2 and Tau^2 statistic[46], where an I^2 greater than or equal to 60% was considered the maximum threshold for total heterogeneity[44]. For any comparison with heterogeneity greater than the threshold, we performed additional heterogeneity analyses guided by our *a priori* hypotheses. Specifically, we expected larger effects in studies sponsored by an interested party versus not, and in those studies with a high risk of bias versus not. We also hypothesized that heterogeneity may be explained by creating subgroups and therefore explored whether heterogeneity was decreased if we separated studies that evaluated outcomes in tendon versus muscle, acute (<3 months symptom duration) versus chronic (>3 months symptom duration) pathologies, active control versus sham or placebo, platelet concentration ($\leq$3 versus >3 times baseline blood), and intrarticular versus palpable structures.

3.4   Results

3.4.1 Study selection

Our search yielded 8601 studies (Fig. 1). We identified ten additional studies from the reference lists of review papers. After removal of duplicates, 5179 titles and abstracts remained; 5108 studies were excluded and 71 studies underwent full text review. Following full text review, 26 studies were determined eligible. Inter-rater agreement was excellent (κ=0.88).

3.4.2 Study characteristics

Table 4 and Table 5 describe the included studies. Fourteen studies used ultrasound guided injections during PRP administration, and 12 used palpation alone. Eighteen of the included studies were randomized controlled trials, four were prospective comparative studies and four were retrospective comparative studies.
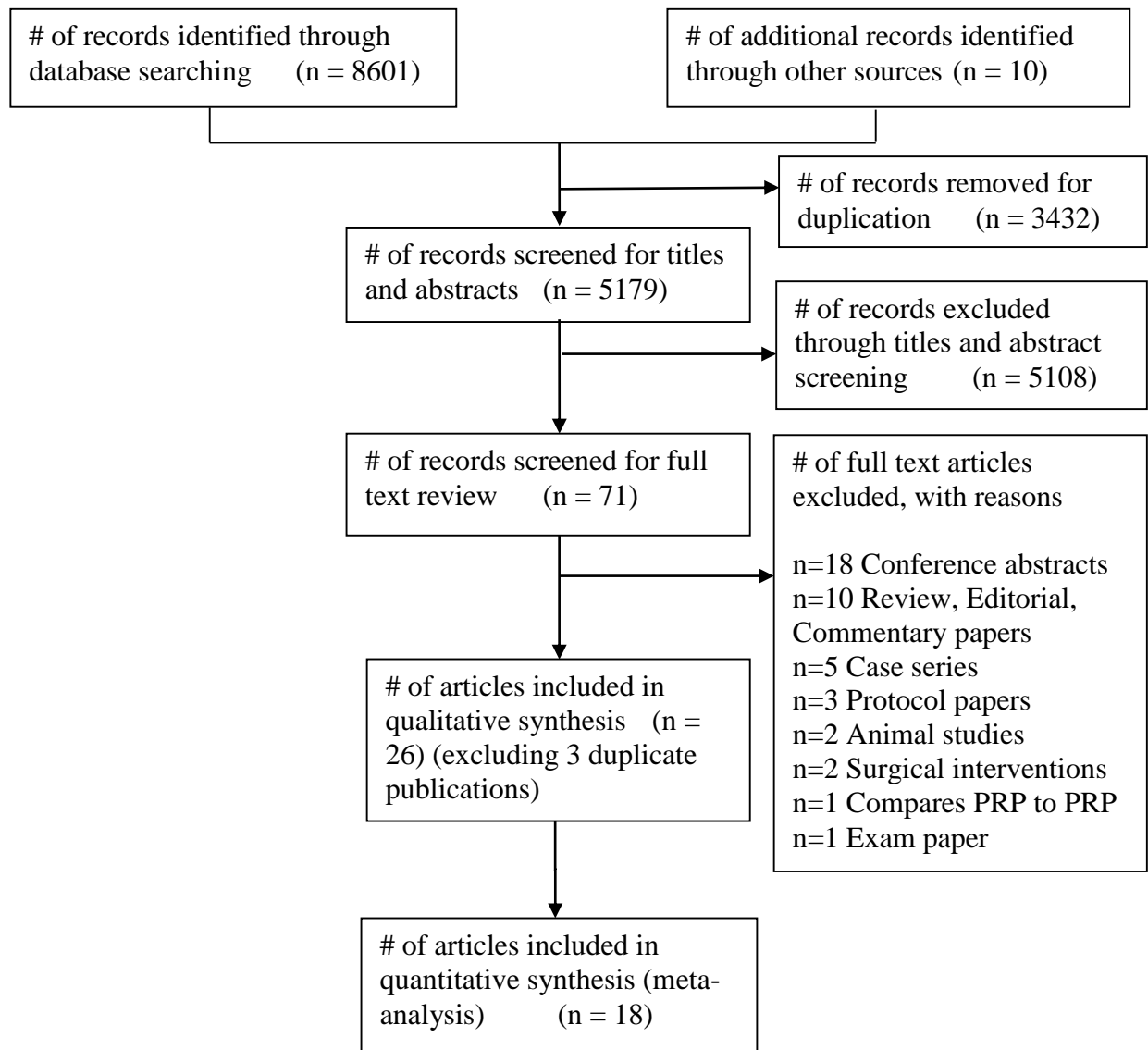
Figure 1 Flow diagram of search process of studies

Study	Design	Pathology	¶PRP treatment (Preparation System and other)	Control	N size	Outcomes	Follow ups	Additives	Results
de Vos 2010[47]/ de Jonge 2011[38]/ de Vos 2011[15]	RCT	Achilles tendionpathy	Recover™ Kit, Biomet	Saline	27/27	VISA-A, Patient satisfaction, Return to Sports, Adherence to eccentric exercise, Ultrasound measures	6 wks; 3, 6 mos; 1 yr	Citrate	No difference
Creaney 2011[36]	RCT	Elbow tendinopathy	Unspecified	Autologous blood	80/70	PRTEE	1, 3, 6 mos	Citrate anticoagulation	Favoured control
Thanasas 2011[48]	RCT	Chronic Lateral Epicondylitis	Recover™ Kit, Biomet	Autologous blood	14/14	VAS pain, Liverpool elbow score	6 wks; 3, 6 mos	Anticoagulant (unspecified)	No difference
Rha 2012[49]	RCT	Rotator cuff (tendinosis or partial tear)	Prosys PRP Kit	Dry needling	20/19	SPADI, ROM, Adverse effects, Ultrasound	3, 6 mos	ACD-A	Favoured PRP
Bubnov 2013[37]	RCT	Muscle injury	Unspecified and Conservative therapy	Conservative therapy	15/15	VAS pain, Strength, ROM, Resistance assessment, Global function score	1, 7, 14, 21 days; 1 mos	Trisodium citrate buffer	No difference
Chew 2013[50]	RCT	Plantar fasciitis	ACP® Double Syringe, Arthrex and Conservative	1) Extracorporeal shock wave therapy and Conservative; 2)	19/19/16	VAS pain, AOFAS ankle-hindfoot scale	1, 3, 6 mos	None	No difference

				Conservative alone					
Kesikbur un 2013[35]	RCT	Chronic rotator cuff tendinopathy	Recover Kit, Biomet (GPS III System)	Saline	20/20	WORC, SPADI, VAS pain with Neer Impingement Sign, ROM	3, 6 wks; 3, 6 mos; 1 yr	None	No differen ce
Krogh 2013[40]	RCT	Lateral Epicondylitis	Recover Kit, Biomet (GPS III System)	1) Saline;2) Glucocorticoi d	20/20/20	PRTEE, Ultrsound measures, pain score.adverse events	1, 3, 6 mos; 1 yr	Sodium citrate	No differen ce
Rettig 2013[51]	Retrospe ctive comparat ive study	Hamstring pathologies	Recover Kit, Biomet (GPS III System) and Physiotherapy	Physiotherap y	5/5	Return to sport	6 mos	ACD-A, sodium bicarbonat e	No differen ce
Tiwari 2013[52]	RCT	Plantar fasciitis	Unspecified	Methyl prednisolone acetate (steroid)	30/30	VAS pain	1, 3, 6 mos	None	No differen ce
Vetrano 2013[6]	RCT	Jumper's knee	MyCells® Autologous Platelet Preparation System	Extracorpore al shock wave therapy	23/23	VISA-P, VAS pain, modified Blazina	2, 6, 12 mos	ACD-A	Favour ed PRP
Dragoo 2014[53]	RCT	Patellar tendinopathy	Recover Kit, Biomet (GPS III System)	Dry needling	10/13	VISA, Tegner, Lysholm, VAS pain, SF-12	3, 6 wks; 2, 3, 6 mos	None	No differen ce
Hamid 2014[11]	RCT	Grade 2 Hamstring muscle pathologies	Recover Kit, Biomet (GPS III System)and Physiotherapy	Physiotherap y	14/14	Return to sport, BPI-SF pain scores	2.5 mos	None	Favour ed PRP
Reurink 2014[54]	RCT	Hamstring pathologies	ACP® Double Syringe, Arthrex	Saline	41/39	Return to sport, Rate of reinjury	2, 6 mos	None	No differen ce

Table 4 Ultrasound guided study details

RCT = randomized controlled trial, PRTEE = patient-rated tennis elbow evaluation, VISA-A = Victorian institute of sport assessment scale Achilles, VAS = visual analogue scale, SF-12 = short form 12, SPADI = shoulder pain and disability index, ROM = range of motion, ACD-A = anticoagulant citrate dextrose solution A, BPI-SF = brief pain inventory short form, WORC = Western Ontario rotator cuff index, wks = weeks, mos = months, yr = year. ¶See Appendix 1 for system details

Study	Design	Pathology	¶PRP treatment (Preparation System and other)	Control	N size	Outcomes	Follow up	Additives	Results
Wright-Carpenter 2004[12]	Retrospective comparative study	Muscle pathologies (variety)	Orthokine®, Autologous Conditioned Serum	Actovegin/ Traumeel	18/11	Return to sport, MRI analysis	16 days	None	Favoured PRP
Mishra 2006[41]	Prospective comparative study	Chronic elbow tendinosis	Recover Kit, Biomet (GPS III System)	Bupivacaine with epinepherine	15/5	VAS pain, Modified Mayo score	4wks; 2, 6 mos	Sodium citrate + Sodium bicarbonate buffer	Favoured PRP
Filardo 2010[55]	Prospective comparative study	Chronic refractory patellar tendinopathy	Not mentioned and Physiotherapy	Physiotherapy	15/16	Tegner, EQ VAS, pain scale, complications, return to sport, patient satisfaction	1, 6 mos	Calcium cholride	No difference
Peerbooms	RCT	Lateral Epicondylitis	Recover Kit, Biomet (GPS III System)	Corticosteroids	51/49	VAS pain scale, Disabilities of	1, 2, 3, 6, 12, 24 mos	Sodium citrate + Sodium	Favoured PRP

2010[56]/ Gosens 2011[57]						the Arm, Shoulder and Hand (DASH)		bicarbonate buffer	
Aksahin 2012[58]	Prospective comparative study	Plantar Fasciitis	Not mentioned	Metilpredniza lone	30/30	VAS pain scale, Roles and Maudsley score	3 wk, 6mos	Calcium	No difference
Omar 2012[59]	RCT	Plantar Fasciitis & Tennis Elbow	Not mentioned	Corticosteroi ds	(15/15)/(15/15)	VAS, DASH (elbow), FHSQ (foot)	6 wks	Citrate phosphate dextrose	No difference (TE) Favoured PRP (PF)
Kearney 2013[60]	RCT	Achilles tendinopathy	GenisisCS Component Concentrating System	Eccentric loading programme	10/10	VISA-A, EQ-5D	6wks; 3, 6 mos	Citrate anticoagulant	No difference
Wetzel 2013[61]	Retrospective comparative study	Hamstring pathologies	Recover Kit, Biomet (GPS III System)	None	10/5	VAS pain, Nirschl Phase Rating Scale Score, Return to Sport	4.5/2 mos	None	No difference
Kaniki 2014[7]	Retrospective comparative study	Achilles tendon	ACP® Double Syringe, Arthrex and Accelerated Rehabilitation	Accelerated Rehabilitation	72/73	Strength, ROM, Calf circumference, Leppilahti scale, AOFAS (PRP only)	6 wks; 3, 6, 12, 18, 24 mos	None	No difference
Mishra 2014[39]	RCT	Tennis Elbow	Recover Kit, Biomet (GPS III System)	Bupivacaine	112/113	Safety, VAS with resisted wrist extension, PRTEE,	1, 2, 3, 6 mos	ACD-A + sodium bicarbonate	Favoured PRP

						extended wrist exam, success rate			
Raeissad at 2014[62]	RCT	Lateral Epicondylitis	Rooyagen Kit Leukocyte-enriched PRP	Autologous Blood	23/22	VAS, modified Mayo Clinic performance index for the elbow, and pressure pain threshold (PPT)	4, 8 wks	ACD-A	Favoured PRP
Say 2014[63]	Prospective comparative study	Plantar fasciitis	Not mentioned	Methylprednisolone (steroid)	25/25	VAS, AFAS	6wks, 6 mos	Sodium citrate + calcium chloride	Favoured PRP

Table 5 Palpation alone study details

VAS = visual analogue scale, DASH = disabilities of the arm, shoulder and hand, MRI = magnetic resonance imaging, EQ VAS = Euroqol visual analogue scale, FHSQ = foot health status questionnaire, PPT = pressure pain threshold, ACD-A = anticoagulant citrate dextrose solution A, ROM = range of motion, AOFAS AHS = American orthopedic foot and ankle society ankle-hindfoot scale, AFAS = American foot and ankle score, wks = weeks, mos = months, yr = year. ¶See Appendix 1 for system details

3.4.3 Risk of Bias within studies

A summary of the risk of bias assessments for RCT's and cohorts can be found in Table 6 and Table 7. Most of the RCT's maintained an overall low risk of bias due to their randomized design which accounts for sequence generation and allocation concealment when performed adequately. The majority of cohort studies had an overall risk of bias that was either low or unclear. The absence of randomization introduces a greater risk of selection bias. However, we also assessed the demographics table of the included studies to determine if known prognostic factors were balanced between groups and better understand the likelihood that a selection bias was present.

Author	Year	Sequence generation	Allocation concealment	Blinding	Attrition	Reporting	Other
Creaney	2011	Unclear	Low	Low	Low	Low	Low
de Jonge/de Vos	2011	Low	Low	Low	Low	Low	Low
Gosens/Peerbooms	2011	Low	Low	Low	Low	Low	Low
Thanasas	2011	Low	Low	Low	Low	Low	Low
Omar	2012	Unclear	Unclear	High	Low	Low	Low
Rha	2012	Low	Low	Low	Low	Low	Low
Bubnov	2013	Unclear	Unclear	High	Low	Low	Low
Chew	2013	Low	Low	Low	Low	Low	Low
Kearney	2013	Low	Low	Low	Low	Low	Low
Kesikburun	2013	Low	Low	Low	Low	Low	Low
Krogh	2013	Low	Low	Low	High	High	Low
Tiwari	2013	Unclear	Unclear	Unclear	Low	Low	Low
Vetrano	2013	Low	Unclear	Low	Low	Low	Low
Dragoo	2014	Low	Low	Low	Low	High	High
Hamid	2014	Low	Low	Low	Low	Low	Low
Mishra	2014	Low	Low	Low	High	High	Low
Raeissadat	2014	Low	Unclear	Low	Low	Low	Low
Reurink	2014	Low	Low	Low	Low	Low	High

Table 6 Risk of bias assessment for RCT's

Author	Year	Selection Bias	Balance of prognostic factors	Unbiased outcome assessment	Attrition	Reporting	Other
Wright-Carpenter	2004	Unclear	High	Unclear	Low	Low	Low
Mishra	2006	Unclear	High	Low	High	High	Low
Aksahin	2010	Low	Low	Low	Low	Low	Low
Filardo	2010	High	High	Low	Low	Low	Low
Wetzel	2013	Low	High	Unclear	Low	High	Low
Rettig	2013	Unclear	Low	Low	Low	Low	Low
Kaniki	2014	Low	Low	High	High	Low	Low
Say	2014	High	Low	Low	Low	Low	Low

Table 7 Risk of bias assessment of cohort studies

3.5   Summary results

3.5.1   Failure rates

Failure rates were reported in five studies. Two studies defined failure as less than 25% improvement of VAS scores from baseline at six months and one year respectively. Two studies reported patient dissatisfaction as failure at one year, and one study defined less than 25% improvement of scores from baseline to six months on the PRTEE questionnaire as failure.

We found no statistically significant differences between the treatment effects of ultrasound versus palpation guided studies for the comparison of failure rates ($p = 0.17$) (Figure 2). Heterogeneity of the group differences was moderately low with $I^2 = 46.5\%$. The overall heterogeneity of studies included in the analysis for both treatments was high ($I^2 = 70\%$).
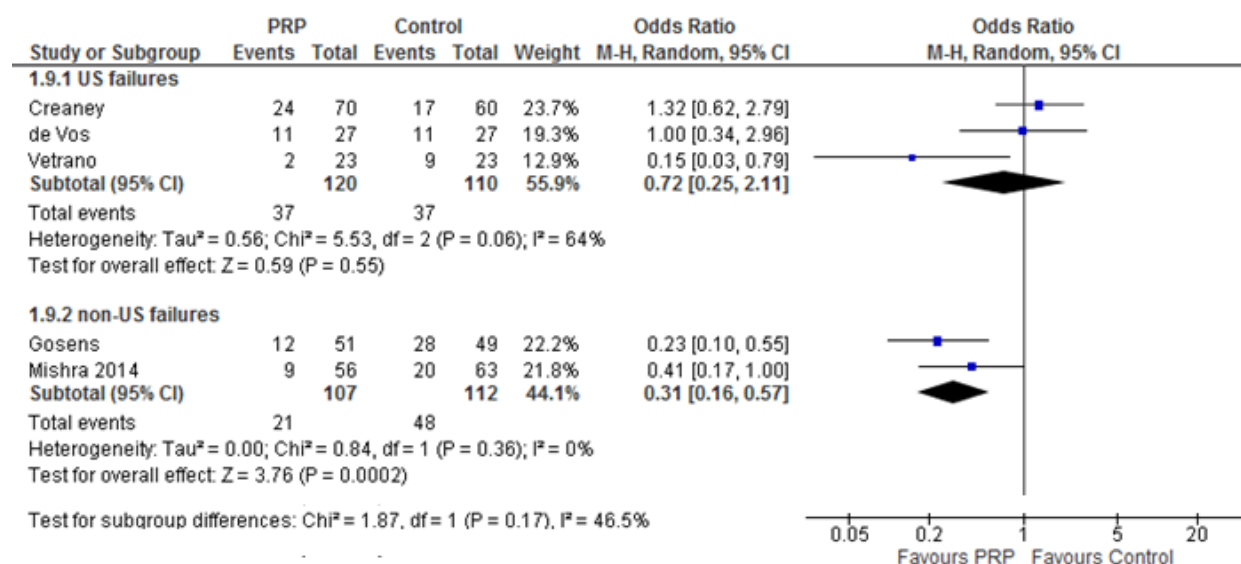
Figure 2 Comparison of failure rates in ultrasound (US) versus palpation (non-US) guided injections of PRP.

3.5.2 VAS Pain scale outcomes

Pain as measured with the visual analogue scale (VAS) was assessed in 13 of the included studies. One study measured pain using the BPI-SF pain scores[64] which measured pain intensity as an average of five VAS pain scales with a total score out of 10. Because the metric differed between studies, we used the standardized mean difference to pool the results.

We found no statistically significant differences between the treatment effects of ultrasound versus palpation guided injections at less than two months for the change in VAS pain scores from baseline ($p = 0.60$) (Fig. 3). Heterogeneity of the group differences was low with $I^2 = 0\%$. In addition, we compared raw scores between treatment groups at less than two months and found no significant difference in treatment effect between groups ($p = 0.37$).

Study or Subgroup	PRP Mean	PRP SD	PRP Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 VAS <2 months US change scores								
Bubnov	7.6	0.83	15	6.8	0.93	15	7.2%	0.88 [0.13, 1.64]
Chew	2.3	2.7	19	1.65	2.4	33	8.9%	0.25 [-0.31, 0.82]
Kesikburun	3.78	3.01	20	4.28	3.31	20	8.4%	-0.15 [-0.78, 0.47]
Thanasas	3.75	1.72	14	2.5	1.93	14	7.1%	0.66 [-0.10, 1.43]
Tiwari	3.8	1.29	30	3.33	1.15	30	9.4%	0.38 [-0.13, 0.89]
Subtotal (95% CI)			98			112	41.0%	0.36 [0.04, 0.68]
Heterogeneity: Tau² = 0.03; Chi² = 5.23, df = 4 (P = 0.26); I² = 23%								
Test for overall effect: Z = 2.19 (P = 0.03)								
1.1.2 VAS <2 months non-US change scores								
Akasahin	1.73	1.9	30	1.8	2.68	30	9.5%	-0.03 [-0.54, 0.48]
Filardo	2.3	2.29	15	3.5	2.96	16	7.5%	-0.44 [-1.15, 0.27]
Gosens	1.33	2.92	51	2.19	3	49	10.6%	-0.29 [-0.68, 0.11]
Omar (PF)	5.6	2.59	15	2.3	2.89	15	7.0%	1.17 [0.39, 1.95]
Omar (TE)	4.2	2.47	15	4.3	2.77	15	7.5%	-0.04 [-0.75, 0.68]
Raeissadat	3.2	2.72	20	3.2	2.94	20	8.4%	0.00 [-0.62, 0.62]
Say	6.4	1.3	25	4.7	1.45	25	8.5%	1.22 [0.61, 1.82]
Subtotal (95% CI)			171			170	59.0%	0.21 [-0.27, 0.68]
Heterogeneity: Tau² = 0.31; Chi² = 26.54, df = 6 (P = 0.0002); I² = 77%								
Test for overall effect: Z = 0.85 (P = 0.39)								
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%								

Favours Control Favours PRP

Figure 3 Comparison of change in scores from baseline ultrasound (US) versus palpation (non-US) guided injections of PRP using the VAS pain scale outcome measure at less than two months follow up.

Despite statistically favourable outcomes for patients receiving a PRP injection (p <0.01) at two to three months, there was no evidence to support the use of ultrasound guidance over palpation alone (p = 0.62). (Fig. 4). Heterogeneity of the group differences was low with I^2 = 0%. In addition, we compared raw scores between treatment groups at two to three months and found no significant difference in treatment effect between groups (p = 0.22).

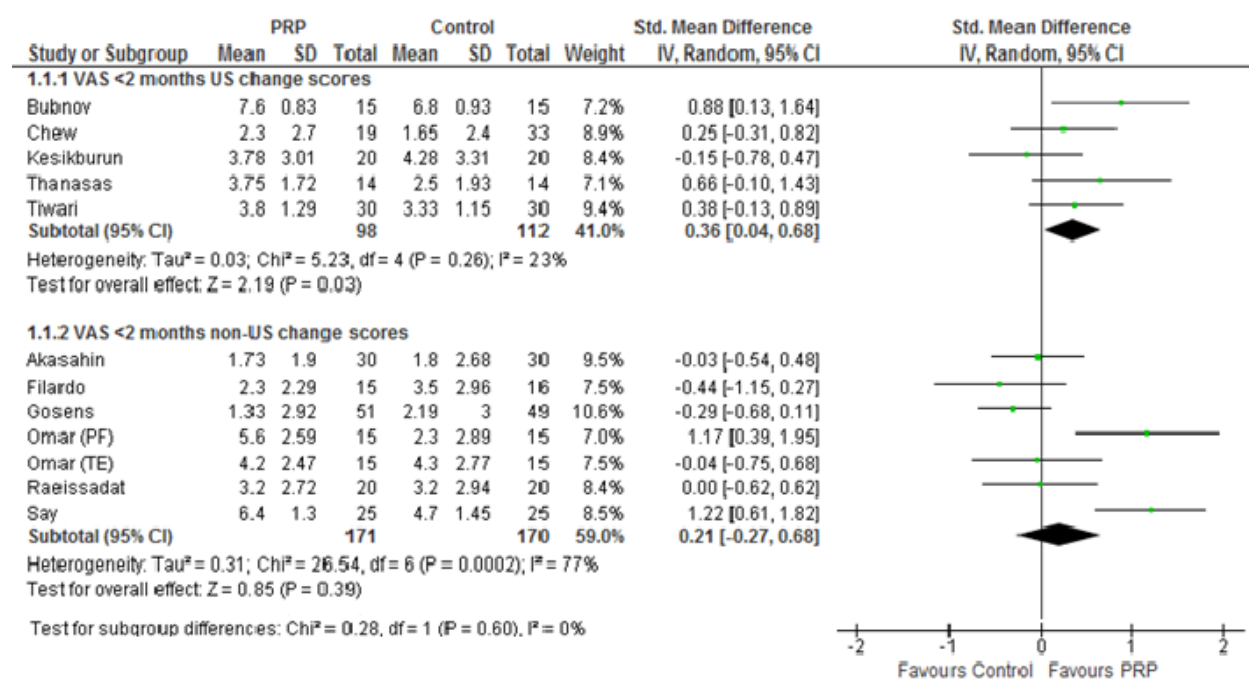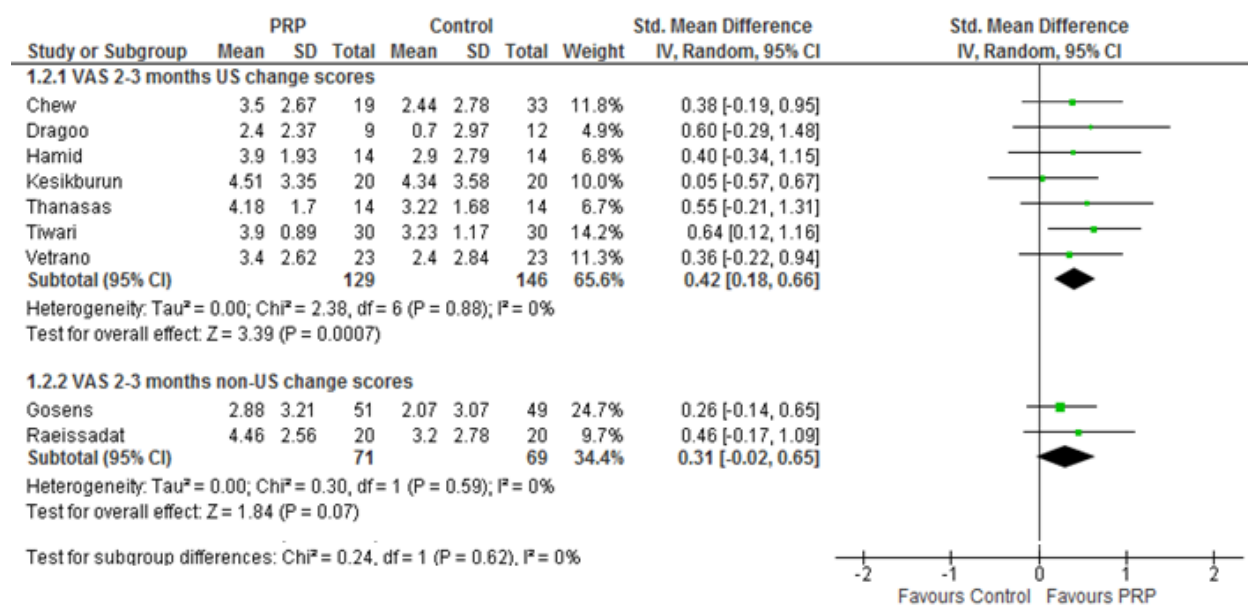| Study or Subgroup	PRP Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 VAS 2-3 months US change scores								
Chew	3.5	2.67	19	2.44	2.78	33	11.8%	0.38 [-0.19, 0.95]
Dragoo	2.4	2.37	9	0.7	2.97	12	4.9%	0.60 [-0.29, 1.48]
Hamid	3.9	1.93	14	2.9	2.79	14	6.8%	0.40 [-0.34, 1.15]
Kesikburun	4.51	3.35	20	4.34	3.58	20	10.0%	0.05 [-0.57, 0.67]
Thanasas	4.18	1.7	14	3.22	1.68	14	6.7%	0.55 [-0.21, 1.31]
Tiwari	3.9	0.89	30	3.23	1.17	30	14.2%	0.64 [0.12, 1.16]
Vetrano	3.4	2.62	23	2.4	2.84	23	11.3%	0.36 [-0.22, 0.94]
Subtotal (95% CI)			129			146	65.6%	0.42 [0.18, 0.66]
Heterogeneity: Tau² = 0.00; Chi² = 2.38, df = 6 (P = 0.88); I² = 0%								
Test for overall effect: Z = 3.39 (P = 0.0007)								
1.2.2 VAS 2-3 months non-US change scores								
Gosens	2.88	3.21	51	2.07	3.07	49	24.7%	0.26 [-0.14, 0.65]
Raeissadat	4.46	2.56	20	3.2	2.78	20	9.7%	0.46 [-0.17, 1.09]
Subtotal (95% CI)			71			69	34.4%	0.31 [-0.02, 0.65]
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.59); I² = 0%								
Test for overall effect: Z = 1.84 (P = 0.07)								
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%								

Figure 4 Comparison of change in scores from baseline ultrasound (US) versus palpation (non-US) guided injections of PRP using the VAS pain scale outcome measure at two to three months follow up.

Despite statistically favourable outcomes for patients receiving a PRP injection (p=0.0001) at six months, there was no evidence to support the use of ultrasound guidance over palpation alone (p=0.47). (Fig. 5). Heterogeneity of the group differences was low with I^2 = 0%. In addition, we compared true scores between treatment groups at six months and found no significant difference in treatment effect between groups (p = 0.64).
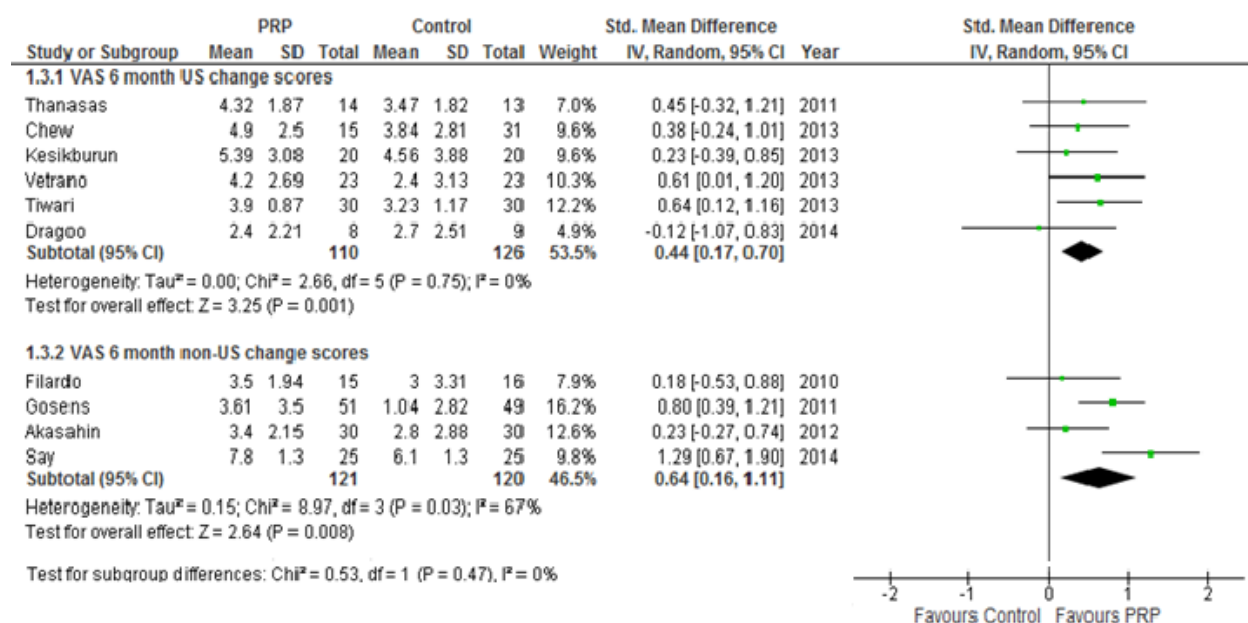
Figure 5 Comparison of change in scores from baseline ultrasound (US) vers of change in scores from baseline ultrasound (US) versus palpation (non-US) guided injections of PRP using the VAS pain scale outcome measure at six months follow up.

3.5.3 Disability and functional outcome scores

The outcome measures used in the studies included the DASH, SPADI, VISA-A, VISA-P, PRTEE, AFAS, and Liverpool Elbow Scale[1]*. Because the metric differed between studies, we used the standardized mean difference to pool the results. One of the studies included both the SPADI questionnaire, and the Western Ontario Rotator Cuff index (WORC) as outcome measures. We chose to use the data of the SPADI in our analysis as it was a region-specific

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* The DASH is a self-reported, region-specific, 30-item instrument that measures upper-extremity disability and symptoms on a scale of zero to 100 (0 = no disability). The SPADI is a self-reported, region-specific outcome that measures current shoulder pain and disability. The VISA-A is a self-reported, region-specific outcome that measures pain, function in daily living, and sporting activity in Achilles tendon pathology. The VISA-P measures a similar construct to the VASA-A but is specific to the patella tendon. The PRTEE is a 15-item questionnaire that measures forearm pain and disability in patients with lateral epicondylitis. The AFAS is a region-specific questionnaire of the foot and ankle that consists of nine items scored on a scale of 100 (100 = no disability). The Liverpool Elbow Scale is a region-specific questionnaire that assesses disability, including a question about pain.

questionnaire like the other included outcomes, as opposed to a disease-specific outcome measure like the WORC.

There was a statistically significant difference in treatment effect in favour of the palpation guided studies ($p = 0.01$) (Fig. 6). However, heterogeneity of the group differences was high with $I^2 = 83.5\%$. We attempted to reduce the heterogeneity by further subgroup analyses of *a priori* hypotheses for heterogeneity, but we were unable to adequately reduce I^2 to below the maximum 60% threshold. For example, the heterogeneity decreased to 62.2% with a $p = 0.10$ when we removed the sham and placebo studies. The removal of either low or high concentrations of PRP also did not change the heterogeneity. Additional comparison of the raw scores of disability and functional outcomes at six months produced a non-significant difference of treatment effect ($p = 0.16$) with a moderately low I^2 of 48.5%.
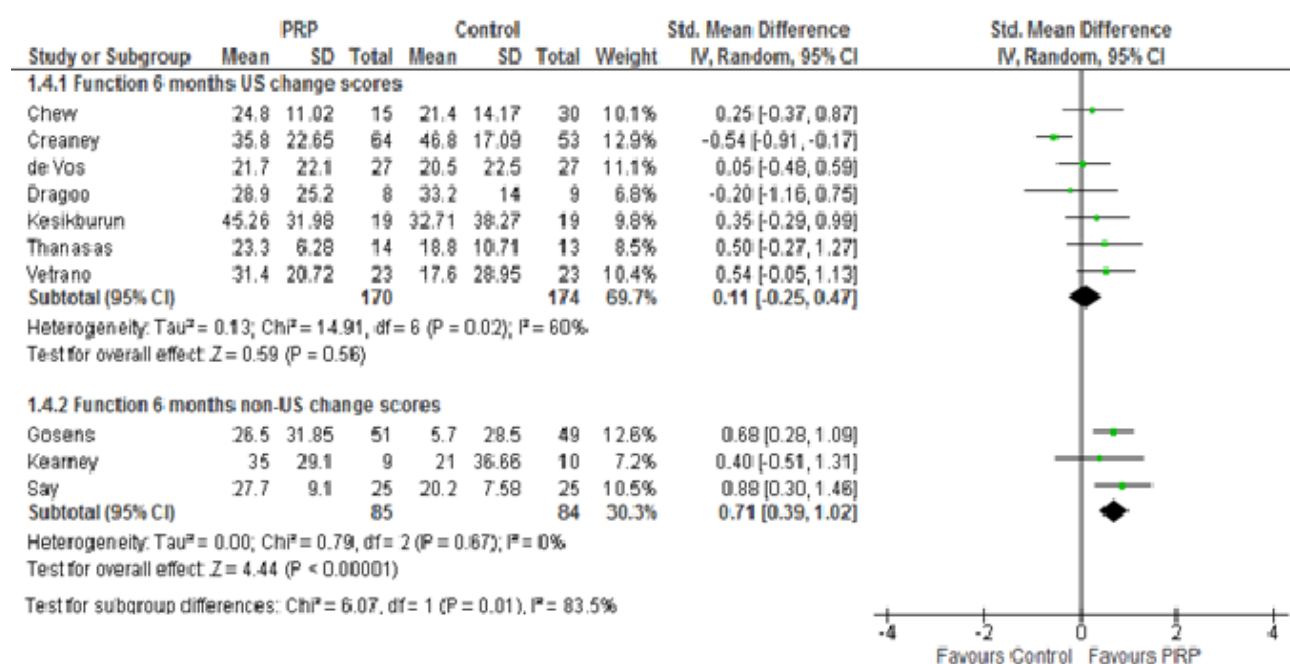

Figure 6 Comparison of change in scores from baseline for the ultrasound (US) versus palpation (non-US) guided injections of PRP using disability and functional outcomes at six months follow up.

3.6 Discussion

3.6.1 Summary of evidence

There are currently no published studies directly comparing the effectiveness of ultrasound versus palpation guided injections of PRP in musculoskeletal pathologies. In our systematic review and meta-analysis we compared these two techniques of PRP injection using an indirect analysis method. There was no significant difference in failure rates between ultrasound and palpation guided injections or for pain at less than two months, two to three months, or six months follow up. We found a significant difference between treatment groups in favor of palpation guided injections for disability and functional outcomes at six months follow up, however, there was high heterogeneity between treatment groups and therefore superiority of the palpation guided injection could not be definitively concluded.

We hypothesized that the administration of a PRP injection using ultrasound guidance would result in better outcomes. However, our results do not support this theory. Thus, there is no evidence to support the additional cost of equipment and the expertise required to perform injections under ultrasound guidance.

3.6.2 Limitations

The studies included in our systematic review and meta-analyses reiterated the need for higher powered and more rigorous randomized controlled trials to determine the effectiveness of PRP. The high levels of heterogeneity we found in our statistical analyses of disability and functional outcomes may be reflective of the intrinsic treatment and methodological variations within the included studies.

There were six different types of PRP preparation systems used, contributing to the heterogeneity of studies. These systems varied the speed and frequency of the spinning process, and the method for extraction (some maintain the leukocytes or buffy layer, while others do not)[37,53,62]

Furthermore, the different preparation systems yielded varying concentrations of PRP, ranging between two to six times higher than baseline blood. There is currently no standardized

concentration of platelets deemed essential for the effectiveness of PRP, adding to the heterogeneity of the treatment effect.

Additionally, the inclusion or omission of an anticoagulant, buffer, and/or an activator during the PRP preparation varied between studies and preparation systems. This also affected the concentration of platelets and associated growth factors, and may have introduced another cause for heterogeneity among treatment effect and study results.

The number of injections among studies ranged from one to as high as eight in one study[12], with most studies performing between one or two as part of the treatment protocol. There is still no consensus on the number of injections recommended for PRP treatment.

Five of the studies[15,38,39,41,47,54,57,65,66] included in our review received direct sponsorship, or were provided some form of compensation toward the study or author. Djulbegovic et al.[67] examined the quality of 136 studies evaluating the effectiveness of treatments in multiple myeloma and found that RCT's funded solely or in part by industry had a significantly greater effect of new treatments compared to studies funded by government or non-profit organizations. The reporting of results for these studies may have biased our analysis and contributed to the overall heterogeneity of the systematic review.

Finally, 11[11,12,37,41,48,51,53,55,59–61] of the included studies had a total sample size equal to or less than 30. Low sample sizes contribute greatly to the probability of Type II error, where the variability is still too great to statistically detect a sizable treatment effect and to Type I error whereby random sampling error captures larger treatment effects than truly exist in the population.

3.6.3 Conclusions

There is currently no evidence to support the use of ultrasound to guide needle placement when injecting PRP for resolution of symptoms from palpable tendon or muscle structures in musculoskeletal pathologies.

3.7 References

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Chapter 4 A Randomized Double-blind Clinical Trial to evaluate the use of Platelet-rich Plasma versus Corticosteroid Injection in Plantar Fasciitis

4.1 Abstract

Background: Plantar fasciitis is a chronic, degenerative breakdown of the plantar fascia that spans the sole of the foot. The pathology is associated with point tenderness at the medial side of the heel and pain and tightness with weight bearing. Corticosteroid (CS) injections is a fairly common treatment option after other non-operative treatments have failed. Platelet-rich plasma (PRP) may optimize the healing environment for tissue regeneration and repair such that an injection of PRP, may provide greater improvements in pain and function than corticosteroid injections.

Purpose: To compare the pain, function and quality of life in patients who have received a PRP injection versus a corticosteroid injection for the treatment of plantar fasciitis.

Methods: We conducted a randomized controlled trial (RCT) in patients with plantar fasciitis who were referred to our clinic from local primary care physicians. Patients were stratified by symptom duration (less than and greater than three months) and received either a PRP or CS injection. We measured outcomes at two weeks, six weeks, three months, six months and one year. Our primary outcome was the AOFAS ankle-hindfoot scale; secondary outcomes included the SF-12v2® Health Survey and the Plantar Fasciitis Pain and Disability (PFPD) scale.

Results: We screened 159 patients, of which 133 were eligible and randomized (PRP = 66, CS = 67). For the purpose of this thesis we included 114 patients in the analysis (PRP = 57, CS = 57). At six months the mean and standard deviation of the AOFAS Ankle-hindfoot scale was 67.1±18.3 for the PRP group and 70.8±17.6 for the CS group (mean difference -1.7, CI -7.6 to 4.2, $p = 0.6$). At one year the mean and standard deviation was 72.3±19.1 for the PRP group and 75.6±17.0 for the CS group (mean difference -1.3 CI -7.3 to 4.6, $p = 0.7$). We also found no statistically significant differences between treatment groups for any of the secondary outcome measures ($p > 0.05$).

Conclusion: PRP does not provide greater self-reported pain relief or function than CS injections in patients with plantar fasciitis.

4.2   Introduction

Plantar fasciitis is a chronic, degenerative breakdown of the plantar fascia, most commonly at its origin of the calcaneus. Injury of the structure is commonly caused by repetitive strain during locomotion which creates microtears of the fibers, and may include an inflammatory and associated repair response of the tissue[1,2].

Clinical diagnosis of plantar fasciitis includes patient complaint of point tenderness and pain in the medial plantar heel area of the foot with weight bearing[3]. The pain is especially severe during the first few steps in the morning, decreases with rest, and is exacerbated with prolonged weight bearing activities[4,5]. Ultrasound imaging has shown a thickening of the plantar fascia on the involved side by greater than 4mm compared to the uninvolved side in patients who are symptomatic[6].

More than one million individuals present to outpatient clinics with plantar fasciitis each year[7]. Approximately 30% of patients with plantar fasciitis will have bilateral pain, and 50% present with heel spurs which may or may not be symptomatic[5,8]. Although conservative treatment has been shown to be successful in 90% of patients, symptoms may last as long as six to 12 months before relief is attained obtain people afflicted with this disease can expect to have symptoms as long as six to 12 months[5,8,9].

The pathology is most prevalent in patients aged 45-64 years old, and more so in women than men[7]. Plantar fasciitis often presents in individuals with increased tensile load on the plantar fascia, such as running athletes or people with occupations that require prolonged standing. Poor biomechanics and anatomical variation, such as pes planus (flat feet) and pes cavus (high arches) are common predisposing factors to plantar fasciitis[4,5].

More than 80% of patients find symptom relief with non-operative care[1,10] including, physiotherapy, non-steroidal anti-inflammatory drugs, shoe orthotics or heel pads, night splints, shockwave therapy, and injections[4,5,9]. A corticosteroid (CS) injection may also be offered but usually only after failure of other non-operative treatments.

Corticosteroid injection is the current standard of treatment for patients who are resistant to acute treatment (ie. physical therapy). Current literature supports its use for short-term relief of pain. However, adverse events – including fat pad atrophy and rupture of the plantar fascia – have been linked to successive corticosteroid injections[5,8,11,12].

Li et al[13] conducted a systematic review and meta-analysis of studies that evaluated the efficacy of CS injections compared to a placebo for plantar fasciitis. They included four randomized controlled trials with a total 289 patients and reported a significant improvement of VAS pain scores in favour of the CS group at one month ($p < 0.05$), but no difference was found between treatments at two or three months post injection ($p > 0.05$). There was also no difference between treatments for the improvement of plantar fascia thickness ($p > 0.05$) on ultrasound evaluation. Given the adverse event profile of CS, it would be useful to find a safe and effective alternative.

Platelet-rich plasma (PRP) injections have emerged as a promising new treatment that may offer improved symptom relief compared to CS injections for patients with plantar fasciitis[14]. PRP is obtained through the centrifugation of human blood, which results in a high concentration of platelets suspended in plasma[15]. Platelets are rich in growth factors essential to the healing process of tissue. The injection of PRP into injured tissue is theorized to optimize the ideal healing environment for tissue regeneration and repair[16].

Hsiao et al[17] conducted a meta-analysis to compare the effectiveness of autologous blood-derived products (ABP's) (included PRP treatment), shockwave therapy, and CS injections for the treatment of plantar fasciitis. They included seven RCT's and three quasi-experimental studies for a total of 604 patients. There was no significant differences between the three treatment groups for VAS pain scores at three and six months post treatment ($p > 0.05$), but a subgroup analysis of PRP studies (other ABP's removed) versus CS treatments at three months revealed a significant improvement of VAS pain scores in the PRP compared to CS treatments at ($p < 0.05$).

Finally, Franceschi et al[18] conducted a systematic review to evaluate the effectiveness of PRP in the treatment of plantar fasciopathy. The review included eight studies: three RCT's, one cohort study, and four prospective case series. In the first RCT[19] comparing PRP (n = 10) to dextrose prolotherapy (n = 11), they found no significant difference between groups ($p > 0.05$) at two and six months for pain, disability, and activity limitation measured using the Foot Functional Index .

The second RCT[20] compared PRP (n = 15) to CS injections (n = 15) using the VAS pain scale and the Foot Health Status questionnaire at six weeks. The authors reported a statistically significant difference between treatments for both outcomes ($p < 0.05$) in favor of PRP. The third RCT[21] also compared PRP (n = 20) to a CS injection (n = 20) at three, six, 12 and 24 months follow up. The authors found a statistically significant improvement in AOFAS hindfoot scores in favor of the PRP group at each follow up over the two years patients were followed ($p < 0.05$). The prospective cohort study[22] compared PRP (n = 30) to CS (n = 30) injection using the VAS pain scale and the Roles and Maudsley score, a pain and activity limitations scale, at three and six months follow up. They found no statistically significant difference between groups ($p > 0.05$). The results of the systematic review suggest promising results for PRP as a treatment for plantar fasciitis, however, a methodologically rigorous randomized controlled trial with a large sample size will provide greater certainty about the superiority of PRP.

Therefore, we conducted a RCT in which we compared the effectiveness of PRP versus CS injections in patients with plantar fasciitis. We hypothesized that PRP may offer a greater reduction in pain and lead to improved function in patients with plantar fasciitis.

4.3   Methods

4.3.1   Study Design

Our study was a RCT that randomized patients to one of two groups (PRP or CS injection) using a computer-generated 1:1 randomization scheme, in permuted blocks of two and four, with stratification by duration of symptoms (< six months versus ≥ six months). The investigating physician, patient, and outcome assessor were all blinded to group allocation. Blood was drawn from all included patients by the nurse who then prepared and blinded the syringe prior to injection.

4.3.2   Patient Selection

We recruited patients from surrounding family physician offices using advertising posters (Appendix 2). Referrals were sent to the office of the investigating physician and patients were scheduled for a consultation at our sports medicine clinic. The investigating physician diagnosed

the patient with plantar fasciitis if the patient presented with pain with palpation of the medial calcaneal insertion of the plantar fascia that was worse in the morning and prolonged weight bearing, and subsided with rest.

Patients with plantar fasciitis were included if they were between the ages of 18 and 70 years and were willing to comply with the follow up protocol. Patients were ineligible if they were diagnosed with a tendon rupture, neurological or vascular insufficiencies in the painful heel, Paget disease or calcaneal fat pad atrophy, osteomyelitis, fracture of the calcaneus, ankle inflammation, recent infection in the treatment area, history of rheumatic diseases, collagenosis or metabolic disorders, immunosuppressive therapy or coagulation disturbance and/or therapy, long-term treatment with CSs, previous surgery of heel, malignant disease, diabetes mellitus, severe cardiac or respiratory disease, significant abnormalities in hepatic function.

The study protocol was explained and written consent was obtained. Our study protocol was approved by our institutional research ethics board and the trial was registered at clinicaltrials.gov (NCT01614223).

4.3.3 PRP and CS Preparation

All patients were seen at our clinic on Thursday mornings between 8:30am and 1:00pm. Our nurse (MY) extracted approximately 12cc's of blood from the patient's arm, which was then placed in an Arthrex ACP® double syringe system and spun in a table-top Rotafix 32A centrifuge at 1500 rpm for five minutes. This process of centrifugation separated the blood into a visible three-layer consistency of red blood components (bottom), a very thin, milky white leukocyte component (middle), and yellow plasma components (top). The nurse then extracted only the plasma from the top layer (between three and 4cc's) and blinded the syringe using opaque tape. The remaining fluid was discarded appropriately.

For the CS group, we added 2cc's of 2% Xylocaine to the 1cc solution of Celestone to equilibrate the weight with the PRP treatment to maintain blinding of the investigating physician. The CS solution was prepared in an opaquely blinded syringe identical to the size of the smaller syringe used in the Arthrex ACP® double syringe system.

4.3.4 Injection Method

We used the same method of injection for both the ACP® and CS treatments. The investigating physician (KW) palpated the point of most tenderness and marked the spot. The plantar surface and heel of the involved foot was then sterilized and prepped for injection. A local analgesic, Lidocaine (2% concentration) was injected superficially into the area. This was followed immediately by the ACP® or CS injection into the marked spot. If patients indicated that they had excessive pain three months after the first injection, we offered a second injection of the group allocated treatment.

4.3.5 Outcome Measures and Follow Up

Our primary outcome measure was the American orthopaedic foot and ankle society (AOFAS) scale. The AOFAS scale is a validated and reliable region-specific, quality of life and objective functional scale[23–25]. It is a combination of a patient-reported grading of pain, functional ability during activities of daily living, and physician assessed range of motion (ROM), stability, and ankle alignment. The scale is scored as an overall total out of 100, where a score of 100 represents the best possible outcome.

Secondary outcome measures included the Plantar Fasciitis Pain and Disability (PFPD) scale and the SF-12v2® Health Survey. The PFPD is a disease-specific pain and disability scale that has shown comparative validity and reliability with the Foot Function Index (FFI) and the visual analogue pain scale (VAS)[26,27]. The SF-12v2® is a well-known generic quality of life scale[28].

4.3.6 Sample Size Calculation

Based on the ability to detect a moderate effect size of 0.5 with 80% statistical power and 0.05 type one error, we calculated a sample size of 64 patients per group. To account for a drop-out rate of 10% we recruited a final sample size of 70 patients per treatment group.

4.3.7 Statistical Analysis

We followed the intention-to-treat (ITT) principle. We calculated the adjusted mean, adjusted between-group mean difference with 95% confidence interval, and associated probability values.

We used an analysis of covariance (ANCOVA) to analyze the primary outcome where the dependent variable was the AOFAS score at six months and one year post-treatment, the independent variable was the treatment group and the covariate was the baseline AOFAS score. We used the same analysis for the secondary outcomes. For patients with missing data points between visits we used regression to impute missing values. We included the last outcome carried forward (LOCF) in the analysis for patients who were lost to follow up. We determined the minimal clinically important difference (MCID) for all outcome measures as a between group difference of 20%[29]. We calculated a within-groups MCID by calculating the pooled standard deviation (SD) of the treatment groups at baseline, multiplied this value by a moderate effect size of 0.5. We then converted this value into a between-groups MCID by multiplying the within-groups MCID by 0.2 as described by Goldsmith et al[29].

4.4   Results

For the purpose of this thesis paper, we analyzed the data of patients who were at least 1 year post intervention (n=114). Between 2010 and 2015, 159 patients were screened for eligibility. Of these, 24 were ineligible: 11 did not have plantar fasciitis, eight did not want to be randomized, four had a concomitant disease, and one received a steroid injection two weeks prior to the baseline visit. Therefore a total of 133 patients were eligible, gave consent, and were randomized into treatment groups (Fig. 7).
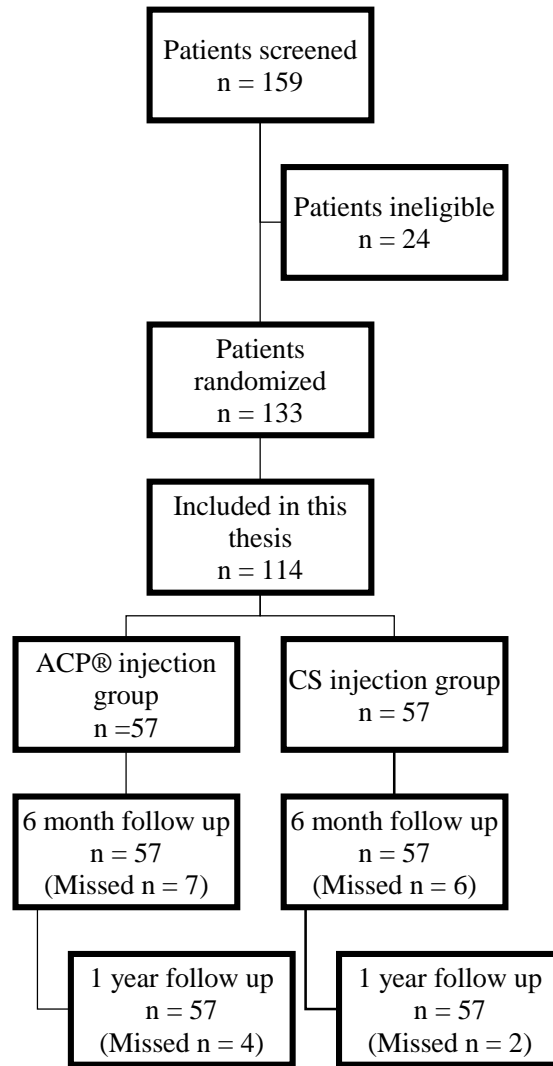
Figure 7 Study patient flow diagram of treatment groups.

Treatment groups were balanced for baseline demographics (Table 8). Independent groups t tests showed no statistically significant differences between treatment groups for baseline scores of the AOFAS ankle-hindfoot scale, SF12, and PFPD questionnaire (Table 9 and Fig. 8).

Demographic	ACP® Group n = 57	CS Group n = 57
Age (years)	52 ± 11	48 ± 9
Height (cm)	168 ± 12	168 ± 14
Weight (kg)	88 ± 18	84 ± 18
Sex (% Male)	25 (44%)	19 (33%)
Symptom duration (months)	37 ± 62	32 ± 63
Affected side:		
Right	20 (35%)	29 (51%)
Left	32 (56%)	26 (46%)
Both	5 (9%)	2 (4%)
Foot alignment		
Cavus	9 (16%)	8 (14%)
Planus	6 (11%)	11 (19%)
Neutral	42 (74%)	38 (67%)
Smoker	16 (28%)	16 (28%)
Previous treatments:		
Physical therapy	36 (63%)	36 (63%)
Orthoses:	42 (74%)	40 (70%)
Over the counter	5 (9%)	4 (7%)
Custom	37 (65%)	36 (63%)
Taping or heel pads	20 (35%)	18 (32%)
Shoe modification	7 (12%)	12 (21%)
Night splints	13 (23%)	19 (33%)
Topical analgesic or NSAIDs	9 (16%)	11 (19%)
Prescription analgesics or NSAIDs	9 (16%)	19 (33%)
Local anaesthetic injection	2 (4%)	3 (5%)
Electrocorporeal shockwave therapy	8 (14%)	9 (16%)
Corticosteroids	13 (23%)	17 (30%)
Other (acupuncture, cast, massage, weight loss, laser therapy)	0	9 (16%)

Table 8 Pre-intervention demographics for randomized patients. Values represent the mean ± standard deviation for variables measured using a continuous scale and the number and proportion for variables measured using a dichotomous scale.

4.4.1 Primary outcome

4.4.1.1 AOFAS

We found no statistically significant difference between treatment groups for improvement in pain and function for the AOFAS Ankle-hindfoot scale at six months or one year follow up. The adjusted mean differences were -1.7 (CI -7.6 to 4.1, p = 0.57) at six months and -1.3 (CI -7.3 to 4.6, p = 0.66) at one year.

	ACP®	CS	MD (95% CI)	p value
AOFAS				
Baseline	53.5±2.6	57.8 ± 2.6	-4.3 (-11.4 to 2.9)	0.24
2 weeks	60.9±1.7	64.3±1.7	-3.4 (-8.1 to 1.4)	0.16
6 weeks	64.4±2.0	64.3±2.0	0.1 (-5.5 to 5.7)	0.96
3 months	65.1±1.9	67.1±1.9	-2.0 (-7.4 to 3.3)	0.46
6 months	68.1±2.1	69.8±2.1	-1.7 (-7.6 to 4.1)	0.57
1 Year	73.3±2.1	74.6±2.1	-1.3 (-7.3 to 4.6)	0.66
PFPD				
Baseline	63.4±1.6	60.1±1.6	3.3 (-1.2 to 7.8)	0.15
2 Weeks	54.2±1.7	50.5±1.7	3.8 (-0.9 to 8.5)	0.12
6 Weeks	49.0±2.2	47.8±2.2	1.2 (-4.9 to 7.3)	0.70
3 Months	46.8±2.3	45.8±2.3	0.9 (-5.5 to 7.3)	0.78
6 Months	41.4±2.8	42.1±2.8	-0.7 (-8.7 to 7.2)	0.86
1 Year	33.5±2.6	36.3±2.6	-2.8 (-10.1 to 4.5)	0.45
SF12 PCS				
Baseline	40.8±1.3	42.1±1.3	-1.4 (-4.9 to 2.2)	0.44
2 Weeks	42.7±0.8	44.3±0.8	-1.7 (-3.9 to 0.6)	0.15
6 Weeks	42.8±0.9	44.2±0.9	1.3 (-3.9 to 1.2)	0.29
3 Months	43.9±1.0	44.3±1.0	-0.5 (-3.4 to 2.5)	0.76
6 Months	44.5±1.1	45.3±1.1	-0.8 (-3.8 to 2.2)	0.61
1 Year	46.9±1.1	46.7±1.1	0.2 (-2.9 to 3.2)	0.91
SF12 MCS				
Baseline	48.9±1.6	49.6±1.6	-0.7 (-5.3 to 3.9)	0.76
2 Weeks	49.9±0.9	48.6±0.9	1.3 (-1.1 to 3.7)	0.27
6 Weeks	50.4±1.0	49.5±1.0	0.9 (-1.9 to 3.8)	0.51
3 Months	50.1±1.0	49.9±1.0	0.2 (-2.8 to 3.1)	0.92
6 Months	51.7±1.1	50.5±1.1	1.2 (-1.8 to 4.2)	0.43
1 Year	52.3±1.1	51.4±1.1	0.9 (-2.2 to 4.1)	0.57

Table 9 AOFAS Ankle-hindfoot scale, Plantar Fasciitis Pain and Disability scale (PFPD), and SF12 Physical and Mental Component Summary (PCS and MCS) adjusted scores (mean ± standard error). Negative values are in favour of CS injections. MD = mean differ.
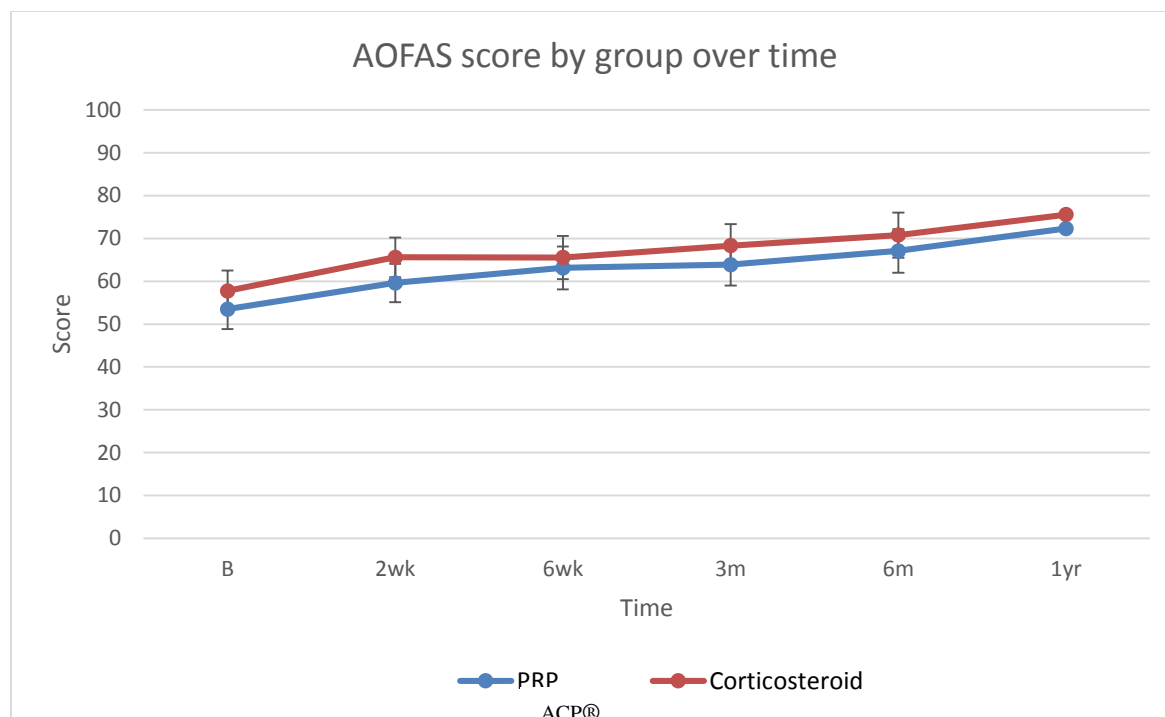
Figure 8 Unadjusted means and confidence intervals (error bars) for the AOFAS outcome measure over time. B = baseline, wk = week, m = month, yr = year

4.4.2 Secondary outcomes

4.4.2.1 Plantar Fasciitis Pain and Disability (PFPD)

We found no statistically significant difference between treatment groups for the disease-specific PFPD scale at six months or one year. The adjusted mean differences were -0.73 (CI -8.68 to 7.22, p = 0.86) at six months and -2.78 (CI -10.1 to 4.54, p = 0.45) at one year.

4.4.2.2 SF12 Physical Component

We found no statistically significant difference between treatment groups for the physical component score of the SF12 at six months or one year. The adjusted mean differences were -0.8 (CI -3.8 to 2.2, p = 0.61) at six months and 0.2 (CI -2.9 to 3.2, p = 0.91) at one year.

4.4.2.3 SF12 Mental Component

We found no statistically significant difference between treatment groups for the mental component score of the SF12 quality of life outcome measure at six months or one year. The adjusted mean differences were 1.2 (CI -1.82 to 4.22, p = 0.43) at six months and 0.92 (CI -2.24 to 4.08, p = 0.57) at one year

4.4.3 Adverse Events and Second Injection

Three patients in the ACP® group each received a second injection at three, six, and 12 months respectively. Two patients in the CS group received a second injection at six months. One patient in the CS group and one patient in the PRP had complete pain relief in the affected limb and requested the same injection on the contralateral foot. One patient in the CS group and three patients in the ACP® group had unresolved pain at the end of the study. One patient in the CS group ruptured their plantar fascia six months after completing the study.

4.5 Discussion

Chronic plantar heel pain is a debilitating condition that has a significant negative impact on both foot-specific and general health-related quality of life[30]. For patients who find no relief from non-operative care, injection therapy of steroids or autologous blood products may offer some relief of symptoms and promote healing[3,4,31]. In our study we found no statistically significant difference between injections of CS or PRP in the amount of improvement in self-reported pain and function as measured by the AOFAS Ankle-hindfoot scale in patients with plantar fasciitis. Secondary outcomes were also not significantly different between treatment groups.

The 95% confidence intervals around the mean difference for each outcome do not rule out the possibility that PRP is superior to CS. However, we can be certain that if there is a benefit of PRP, the difference not likely to be large and therefore is not likely to justify the cost.

On the other hand, CS injections in patients struggling with plantar fasciitis have not shown long term superior effectiveness compared to placebos[13] and repeated use of CS in tendons has been associated with adverse effects such as plantar fascia rupture and/or fat pad atrophy[32–34]. In our

study, one patient in the CS group had a rupture of their plantar fascia six months after their one year follow up. Thus, if PRP can offer similar benefits to CS without the added risk of tendon degeneration, it may offer a reasonable alternative to an injection of CS.

PRP is theorized to create an environment essential for healing tissue through the release of growth factors from platelets when the cells become activated during clotting. The collective body of literature evaluating the effectiveness of PRP compared to CS injections for patients with plantar fasciitis contains a range of different preparation systems with individualized preparation methods used to create the PRP[35–37]. This results in varying concentrations of platelets and may obscure the overall treatment effect. Additionally, there is a lack of well-designed RCT's with standardized outcomes and long term follow ups to support the conclusive evidence of the comparison between PRP and CS injections for plantar fasciitis.

In the network meta-analysis by Franceshi et al[18] that compared PRP versus other injections in patients with plantar fasciitis, authors included three RCT studies, and three comparative cohort studies. The total number of participants included in each study ranged from 30 to 61 patients whereas our study included almost double (n = 114) the number of patients compared to the study with the most participants. Two of the included studies were single-blind and the rest did not use blinding whereas we were able to blind the patient, physician, and outcomes assessor to group allocation. The maximum follow up period with the included studies was six months post-injection, whereas our study followed patients up to one year after treatment. For these reasons, we are confident that our conclusions represent the most rigorous findings to date.

Another recently published study[38] comparing the effectiveness of PRP (n = 25) versus CS (n = 25) injections in patients with plantar fasciitis, compared treatment groups at six weeks and six months using the VAS pain scale and the AOFAS scale. Authors found a statistically significant difference between groups for all outcomes at both follow up periods ($p < 0.05$) in favour of PRP. In evaluating the internal validity of the study, patients chose which treatment they preferred and were then allocated into groups accordingly. Although the groups were balanced for baseline demographics, the omission of randomization may have introduced a selection bias and influenced the results.

Shetty et al[39] also published the preliminary results of a non-randomized trial where authors compared PRP (n = 30) versus CS (n = 30) injections in patients with plantar fasciitis. The groups were compared at three months after the injection using the VAS pain scale, the Foot and Ankle Disability Index (FADI), and the AFAS. The authors found a statistically significant improvement of scores in favor of PRP for all outcomes at three months ($p < 0.05$). The process of group allocation was not described and no method of blinding was implemented.

4.5.1   Study Limitations

In our study, patients were allowed to add other forms of non-operative management (e.g. orthotics, laser therapy, massage, physiotherapy, etc.) for plantar fasciitis to their treatment regimen, with the exception of injections which made our study more pragmatic and applicable to regular practice where patients seek a variety of treatment options for plantar fasciitis. However, we did record the number of patients who sought physiotherapy during the study treatment period and found that they were balanced between groups (ACP® = 23, CS = 25).

The study was performed at a single-centre with a single surgeon performing all injections. Although the surgeon is a fellowship-trained physician with many years of experience, the addition of other centres and physicians may have added to the generalizability of the results.

We did not perform any ultrasound diagnostic evaluation of the plantar fascia to compare the thickness before and after treatment. Plantar fasciitis is known to be associated with a thickening of the plantar fascia[40], and evaluation of the improvement of the thickness between treatment groups may have been a useful tool.

We did not have a placebo group in our study, which limited our ability to make inferences about its superiority to no treatment at all. However, since we were trying to determine whether ACP could replace CS as a treatment for plantar fasciitis (given its adverse event profile), if we could show that ACP was similar or superior to corticosteroids then it is not necessary to compare ACP to placebo.

Individual variations of platelet concentration may have different effects on treatment outcomes[43]. Although we did not evaluate the concentration of platelets achieved for each

injection, other studies[44] conducted by this same group demonstrated consistent concentrations between two and three times greater than baseline blood which has been shown to be effective[41,42].

Despite meeting our *a priori* sample size requirements, our confidence intervals were too wide to allow definitive conclusions about the superiority of ACP® compared to CS). However, we can be certain that if there is a benefit of ACP® over CS that the effect is small; thus it is reasonable to adopt ACP® as part of usual treatment option prior to administration of CS[43]. The only other consideration is the cost to the patient and whether it is covered by public or third-party funding.

PRP preparation systems produce either leukocyte-rich (LR) or leukocyte-poor (LP) PRP. Leukocytes contain and produce cytokines which promote catabolic (molecular breakdown) cellular activity and inflammation[44] which is counteractive to the anabolic actions of the growth factors released by platelets in PRP. Thus, one expects that reduced leukocyte levels within a PRP solution may have a more positive effect on healing than leukocyte-rich PRP[44,45]. The presence or absence of inflammation in the damaged tissue is influential to the process of healing[46]. In acute pathologies where initial inflammatory activity is occurring at the site of tissue damage, additional leukocyte promotion may not be beneficial. However, in chronic conditions where the inflammatory process has subsided or no longer occurs, the addition of leukocytes may be advantageous in stimulating the initial healing process[47]. Plantar fasciitis has recently been redefined to classify the condition as plantar fasciosis when the symptoms are chronic without inflammation[2]. The absence of inflammation in the damaged tissue causes the healing response to include less inflammatory cellular activity than in an acute condition. For this reason, the ideal PRP solution for plantar fasciitis, given that it is a chronic condition, may need to include leukocytes to stimulate the necessary inflammatory response for healing to take place[48]. The ACP® solution used in our study did not contain leukocytes.

4.5.2 Future Directions

Directions for future research into the effectiveness of PRP injections in patients with plantar fasciitis should include a standardized physiotherapy, and the use of a PRP treatment that includes leukocytes. Plantar fasciitis is a chronic condition that is not always associated with

inflammation[2] and the presence of leukocytes which is known to promote inflammation may work in favor of creating the natural healing environment for the fascia.

4.6 Conclusion

We found no evidence thatACP is inferior to CS in patients with plantar fasciitisGiven the adverse event profile of CS it is reasonable for clinicians to use ACP prior to CS.

4.7   References

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5   Chapter 5 Summary

With an ever ageing population more active later in life, there is a demand for sports pathology treatment regimens that can both treat clinical symptoms and provide healing to the injured tissue for a continued active lifestyle. An injection of platelet-rich plasma (PRP) into injured tissue is theorized to provide an ideal healing environment through the introduction of growth factors imperative to tissue regeneration[1,2]. With improved tissue regeneration and enhanced overall healing of the pathology, patients should experience reduced pain, and improved function and quality of life. Over the last decade there have been a number of studies evaluating the effectiveness of PRP for sports medicine pathologies, however the variation in types of pathology, treatment methods, and PRP-specific treatment protocols have clouded the clarity in treatment effect.

Chapter 2: In our systematized review of the literature to evaluate the effectiveness of PRP in various tissue-specific pathologies, we found no definitive clinical evidence to support the use of PRP. For tendon healing, half of the studies found a significant treatment effect in favor of PRP while the other half found no difference. In the two studies we evaluated for the use of PRP in bone healing, the studies were again split with one finding a statistically significant effect in favor of PRP and the other finding no difference. Again, in muscle healing the two studies we evaluated were also split with one finding a significant difference in favor of PRP and the other finding no difference. The use of PRP in intra-articular injections of the knee did show some encouraging results, particularly in the treatment of osteoarthritis of the knee. We speculate that this may be because the PRP provides growth factors in an environment where the damaged cells are no longer able to maintain cell reparation through their own growth factor releasing mechanism[3–5].

Chapter 3: One area of dispute in the application of PRP injection is whether or not injections should be administered using ultrasound to guide needle placement. Proponents of PRP have argued that unless the investigator has taken measures to ensure that the PRP was administered

to the correct location, that conclusions about effectiveness (especially lack of effectiveness) are no more than speculative. To address this controversy, our second systematic review compared the effectiveness of PRP in ultrasound versus palpation guided injections for the non-operative treatment of tendon and muscle pathologies. We found no published studies directly comparing ultrasound versus palpation guided injections of PRP, which meant that we used an indirect analysis to make the comparison. We found no statistically significant differences between treatment methods for failure rates or pain scores at less than two months, two to three months, and six months post-injection. We did find a statistically significant difference in favor of palpation guided injections for functional scores at six months post-injection, but the heterogeneity of the comparison was high and so definitive superiority could not be concluded. Therefore, we found no evidence to support the claim that ultrasound guided injections of PRP offer greater outcomes and the additional cost and inaccessibility of the ultrasound equipment in the clinic setting work against its adoption into practice.

Finally, given the lack of high powered studies and unstandardized PRP preparation methods we set out to complete a methodologically rigorous RCT to compare the effectiveness of PRP injections compared to corticosteroid (CS) injections in patients with plantar fasciitis.

Chapter 4: Our study was a computer generated RCT where the patients, the physician administering the injection, and the outcomes assessor were blinded. We used the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale, the SF-12v2® Health Survey, and the Plantar Fasciitis Pain and Disability scale, all valid and reliable patient-reported outcome measures. We had a long term follow up of one year, with interval assessments at two weeks, six weeks, three months, and six months after the injection. We had a large sample size of 114 patients with only a 7% drop out rate. Following our intention-to-treat analysis, we found no statistically significant difference for our primary outcome (AOFAS) at six months or one year post-injection. In addition, we found no significant difference for any of our secondary outcomes at six months or one year. However, confidence intervals around the estimates of effect were large and could not rule out the possibility of a beneficial effect of PRP over CS. Our results do suggest however, that it is most likely that PRP injection provides similar pain relief and functional improvement compared to CS but without the serious side effects observed with CS; like tendon rupture which may justify its use.

5.1 Regulation of PRP Applications

In the United States, PRP is regulated by the Food and Drug Administration (FDA) and is classified as a Biologic under the Center for Biologics Evaluation and Research (CBER)[6]. Products in this class apply for approval using the 501 (k) application process that allows devices that are similar to other already approved devices to be introduced onto the market. The PRP preparation systems fall under this category and for this reason the available systems are both numerous and vary considerably in the way they are used and in the resulting components of the PRP product.

Originally, PRP systems were approved by the FDA for use in the mixing of the PRP product with bone graft materials for orthopaedic surgical use. The transfer of PRP into the clinical setting as an injectable treatment, termed "off label", has become acceptable in North America with the understanding that clinicians will use the treatment with self-determined ethical and evidential discretion to do no harm. However, controversy has arisen in the use of PRP that uses an activator such as thrombin and/or calcium to activate the clotting mechanism during the application of PRP[7] because this would be in addition to the treatment as initially approved. The activator changes the cellular composition of platelets and therefore produces a manipulation of the end product.

The conflict in the regulation of PRP systems has a direct effect on the quality of research and resulting evidence to support its use in clinical practice. Since the products approved under the 501 (k) application do not require evidence from laboratory, animal, and clinical studies, the current body of research has not undergone the stringent methodology controls and scrutiny as products classified as drugs. The research in the effectiveness of PRP has increased tremendously over the past decade, but the validity and reliability of the evidence is questionable.

5.2 Directions for future studies

The true measure of efficacy for the use of PRP in musculoskeletal pathologies has been diluted by the variation in methodology used in the published literature. Future studies evaluating the

effectiveness of PRP needs to adhere to certain standardized protocols to be included in a pooled collection of results that will provide the necessary evidence to change clinical practice.

5.3 Choosing a PRP preparation system

All PRP products are not equal, and comparison of the treatments produced by different systems should be considered thoroughly before comparing their effectiveness. For example, when we compare two studies with the same pathology and study design, but using different PRP preparation systems, one study may produce non-significant results while the other finds a statistically significant effect of PRP. This may have been the case in a comparison of our plantar fasciitis RCT where we found no significant difference between PRP and corticosteroid injections, versus Shetty et al[8] in which the authors found a statistically significant difference in favor of PRP for similar patient-reported functional outcomes when they also compared PRP to corticosteroid injections in patients with plantar fasciitis. In our study we used the ACP Double Syringe, Arthrex system which produced a concentration of two to three times higher than baseline blood. The other study used the SmartPrep, Harvest Technologies system which is known to produce platelet concentrations four to six times greater than baseline levels, and the protocol also requires the addition of an anti-coagulant and activator be added. Researchers need to focus their efforts on finding the most effective PRP solution for cell types that are important in healing the effected structure (e.g. tenocytes, myocytes, chondrocytes, osteocytes), followed by measuring the effect of that preparation in a specific tissue type (e.g. tendon, muscle, cartilage, bone), and finally, exploring the effectiveness for treating musculoskeletal pathologies within a specific patient population.

5.4 Acute versus chronic conditions

Tiwari et al[9] describes four different types of PRP treatments: leukocyte-poor or pure PRP, leukocyte PRP, pure platelet-rich fibrin clot, and leukocyte platelet-rich fibrin clot. All of these fall under the collective PRP treatment umbrella, however the solution content, concentration, and consistency vary considerably. For musculoskeletal pathologies, the healing of tissue is highly dependent on the stage of healing and the body's natural response of cellular activity and differentiation in the area of injury. Acute pathologies are associated with an inflammatory

response, whereas chronic conditions are associated with reduced inflammation or the absence of inflammation in the area. Since leukocytes are known to cause an inflammatory response in the local tissue, and the inclusion or removal of the cells may have a direct effect on the healing response of the injured tissue. Therefore, we suggest that investigators consider the stage of healing when selecting the type of PRP to treat that particular pathology.

The fibrin clot is used in the surgical application of PRP. During a surgical procedure the injured tissue is repaired and the area begins the acute phases of healing. The PRP solution applied here should also be one that should complement the acute healing phase which already includes an inflammatory response and may be adversely affected by the addition of leukocytes.

5.5 Requirements for future studies

Future research studies evaluating the effectiveness of PRP should include greater detail in the PRP preparation method and treatment protocol. This is necessary for the fair comparison across studies and valid pooling of data in meta-analyses. The PRP preparation system used, the inclusion or exclusion of leukocytes, and the use of anticoagulants and/or activators should be specified. The use of image-guidance for injection and a detailed description of how the treatment was applied should also be described.

5.6 Conclusion

The use of PRP treatments in musculoskeletal pathologies is a promising biological addition that should be further explored in clinical trials with higher levels of evidence. Researchers and clinicians should consider various aspects of PRP treatment and the options available that will produce the most successful treatment for patients in the clinical setting.

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Appendices

PRP System	Cascade, Musculoskeletal Tissue Foundation	RecoverTM Kit, Biomet (GPS II Platelet Separation System)	Magellan, Arteriocyte	ACP® Double Syringe, Arthrex	PRGF, BTI Biotechn-ology Institute	SmartPrep, Harvest Technologies	Prosys PRP Kit	MyCells® Autologous Platelet Preparation System	Orthokine®, Autologous Conditioned Serum	GenesisCS Component Concentrating System
Platelet Concentration	1-1.5x	3-8x	3-7x	2-3x	2-3x	4-6x	5-7x	2-3x	2-3x	6-10x
Anticoagulant	Yes	Yes	Yes	None	Yes	Yes	Yes	Yes	No	Yes
Centrifuge force	1100g	1100g	1200g	1500rpm	460g	400g	1600g and 2000g	1300 to 1500rpm	1000g	2400rpm
Centrifuge time (minutes)	6	15	17	5	8	14	3	10	10	12
Activator	None	None	None	None	Yes	Yes	No	No	No	No
Spin procedure	Single	Single	Single	Single	Single	Double	Double	Single	Single	Single
Leukocytes	No	Yes	Yes	No	No	Yes	No	No	No	No

Appendix 1Platelet-rich plasma preparation systems and PRP formulation

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Nicole Kaniki ███████████████

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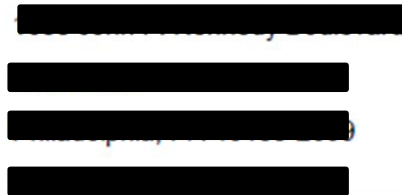If I may be of further assistance, please let me know.

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CINAHL	112		
		S6	S3 AND S4 AND S5
		S5	S1 OR S2
		S4	TX injection OR ultrasound OR "ultrasound-guided" OR "ultrasound guided" OR "ultrasound-guided injection" OR "ultrasound guided injection"
		S3	TX "platelet rich plasma" OR "platelet-rich plasma" OR "platelet-rich therapy" OR "platelet concentrate" OR "platelet gel" OR "growth factor*" OR "autologous plasma" OR "plasma rich in growth factor" OR "autologous conditioned plasma" OR "regenerative therapy" OR "platelet-derived growth factor" OR "platelet derived growth factor" OR "autologous platelet-rich plasma" OR "autologous therapy" OR platelet
		S2	TX muscle
		S1	TX tendon
PubMed	3000		(((((tendon) OR muscle)) AND (("platelet rich plasma" OR "platelet-rich plasma" OR "platelet-rich therapy" OR "platelet concentrate" OR "platelet gel" OR "growth factor*" OR "autologous plasma" OR "plasma rich in growth factor" OR "autologous conditioned plasma" OR "regenerative therapy" OR "platelet-derived growth factor" OR "platelet derived growth factor"

		OR "autologous platelet-rich plasma" OR "autologous therapy" OR platelet))) AND ((injection OR ultrasound OR "ultrasound-guided" OR "ultrasound guided" OR "ultrasound-guided injection" OR "ultrasound guided injection"))
Scopus	35	(tendon OR muscle) AND (platelet rich plasma OR platelet-rich plasma OR prp OR platelet-rich therapy OR platelet concentrate OR platelet gel OR growth factor OR autologous plasma OR plasma rich in growth factor OR prgf OR autologous conditioned plasma OR regenerative therapy OR pdgf OR platelet-derived growth factor OR platelet derived growth factor OR autologous platelet-rich plasma OR autologous therapy OR platelet) AND (injection OR ultrasound OR ultrasound-guided OR ultrasound guided OR ultrasound-guided injection OR ultrasound guided injection)

SPORTDiscus	121	S18	S15 AND S16 AND S17	
		S17	S13 OR S14	
		S16	TX injection OR ultrasound OR "ultrasound-guided" OR "ultrasound guided" OR "ultrasound-guided injection" OR "ultrasound guided injection"	
		S15	TX "platelet rich plasma" OR "platelet-rich plasma" OR "platelet-rich therapy" OR "platelet concentrate" OR "platelet gel" OR "growth factor*" OR	

		"autologous plasma" OR "plasma rich in growth factor" OR "autologous conditioned plasma" OR "regenerative therapy" OR "platelet-derived growth factor" OR "platelet derived growth factor" OR "autologous platelet-rich plasma" OR "autologous therapy" OR platelet S14 TX muscle S13 TX tendon	
Cochrane Database	**118**	#1 tendon #2 muscle #3 #1 or #2	

		#4 "platelet rich plasma" or "platelet-rich plasma" or "platelet-rich therapy" or "platelet concentrate" or "platelet gel" or "growth factor" or "autologous plasma" or "plasma rich in growth factor" or "autologous conditioned plasma" or "regenerative therapy" or "platelet-derived growth factor" or "platelet derived growth factor" or "autologous platelet-rich plasma" or "autologous therapy" or platelet #5 injection or ultrasound or "ultrasound-guided" or "ultrasound guided" or "ultrasound-guided injection" or "ultrasound guided injection" #6 #3 and #4 and #5	
Medline OVID	1583	2 muscle.mp. or Muscles/ 3 ("platelet rich plasma" or "platelet-rich plasma" or "platelet-rich therapy" or "platelet concentrate" or "platelet gel" or "growth factor" or "autologous plasma" or "plasma rich in growth factor" or "aulogous conditioned plasma" or "regenerative therapy" or "platelet-derived growth factor" or "platelet derived growth	

		factor" or "autologous platelet-rich plasma" or "autologous therapy" or platelet).af. 4 (injection or ultrasound or "ultrasound-guided " or "ultrasound guided " or "ultrasound-guided injection " or "ultrasound guided injection ").af. 7 tendon.mp. or Tendons/ 8 2 or 7 9 3 and 4 and 8	
Embase	3632	2. tendon.mp. or tendon injury/ or tendon rupture/ or tendon/ 3. muscle/ or muscle injury/ or skeletal muscle/ or muscle.mp. 4. 2 or 3 8. ("platelet rich plasma" or "platelet-rich plasma" or "platelet-rich therapy" or "platelet concentrate" or "platelet gel" or "growth factor" or "autologous plasma" or "plasma rich in growth factor" or "autologous conditioned plasma" or "regenerative therapy" or "platelet-derived growth factor" or "platelet derived growth factor" or "autologous platelet-rich plasma" or "autologous therapy" or platelet).af.	

		9. (injection or ultrasound or "ultrasound-guided" or "ultrasound guided" or "ultrasound-guided injection" or "ultrasound guided injection").af. 10. 4 and 8 and 9

Appendix 3 Systematic review summary of database results

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