No attributable effects of PRP on greater trochanteric pain syndrome

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ABSTRACT

AIMS: To assess whether a single platelet-rich plasma (PRP) injection would reduce pain intensity in chronic greater trochanteric pain syndrome (GTPS).

METHODS: Subjects with chronic lateral hip pain were randomised to either a PRP injection (intervention group) or a saline injection (control group) and both groups were prescribed identical eccentric exercise. Brief Pain Inventory (BPI), health professional consultation rate, medication use, Likert scale of progress, Expectation of Improvement Scale were assessed monthly for six months with a final follow-up one year after the intervention.

RESULTS: There were no differences in any outcomes between the two groups at any follow-up point, (all p>0.39).

CONCLUSION: A single injection of PRP resulted in no significant improvement for GTPS compared with a placebo injection.

reater trochanteric pain syndrome (GTPS) is a common and frequently debilitating condition presenting with pain at or around the greater trochanter, referred to the lateral thigh in some patients. The condition is often chronic, a retrospective study of 64 patients from the Netherlands having shown 76% symptomatic at one year, and 63% after five years. 1

Excluding lumbar or pelvic referred pain, the incidence of GTPS has been recorded at 1.8 per 1,000 adults per year in adults aged over 18¹ and a prevalence of 18% in a study of adults aged 50–75 years old with or at high risk of symptomatic knee osteoarthritis.² GTPS is estimated to occur in 20–35% in sufferers of chronic low back pain.³⁴ There is a strong gender bias with the female-to-male ratio 2–4:1,⁵ and the most frequently affected age group are those between the fourth and sixth decades.⁵

Diagnosis of GTPS is essentially a clinical diagnosis based on a history of lateral hip pain worse on side lying, first mobilising, going up or down stairs, and walking; and examination findings of focal tenderness over the superior aspect of the ipsilateral

greater trochanter. While imaging, particularly ultrasound and MRI, frequently demonstrates pathology, it contributes little to diagnosis as pathology is also present in 88% of asymptomatic people.⁶

GTPS can be difficult to treat. Seven open case series^{7–13} and three randomised studies^{14–16} appear to demonstrate relief from corticosteroids for most participants but any improvement had disappeared by 12 months.

Platelet-rich plasma is an autologous preparation, hence PRP is inherently safe and free from concerns over transmissible disease or allergy. Previous studies confirmed the safety of PRP with no significant complications, apart from transient post-injection soreness. ^{17–31}

The primary aim of this study was to assess the attributable effect of a single injection of platelet-rich plasma on pain intensity over 12 months in chronic greater trochanteric pain syndrome in a double blinded, randomised, placebo-controlled study. The primary measure used for this study was the change in reported pain intensity.



Secondary measures studied included function and sleep, as well as the effect on utilisation of health resources including consultation rates, medication use and interventions. Information gleaned from the study may allow a cost-effectiveness assessment of the intervention.

Method

Patients

Forty-eight patients with chronic (over three months') lateral hip pain from the Northland region of New Zealand with ages ranging from 18–70 years were studied with 12 months' follow-up. This study was approved by New Zealand Ministry of Health Northern B Health and Disability Ethics Committee (12/NTB/31) and was registered with Australian New Zealand Clinical Trials Registry (ANZCTR) with registration number ACTRN12612000982819. Informed consent was obtained from all participants prior to randomisation.

The clinical diagnosis for GTPS was based on the principal complaint of pain in the lateral aspect of the hip and local tenderness over the superior aspect of the greater trochanter at the insertion of the gluteus medius and minimus with the participant side lying with the hips flexed to approximately 60° and the most tender point marked. A trial injection of 2mls 1% Xylocaine at the focal tender point with participant-reported complete relief of symptoms within 10 minutes and lasting less than two hours was given to all participants and used as the definitive diagnostic criteria for borderline cases.

Exclusion criteria were: previous surgery in the same area, corticosteroid injection in the ipsilateral greater trochanteric region within the previous two months, diabetes, rheumatoid arthritis, osteoarthrosis of the hip (ACR 1991 criteria), infection, immunosuppression, severe cardiovascular disorder, coagulopathies, severe obesity (BMI ≥35), Pregnancy or breast feeding, Haemoglobin ≤100g/L, Platelets ≤105x10⁹/L, specific concurrent medication (anti-coagulants, fluoroguinolones or medications known to cause tendinopathy), corticosteroid, aspirin in previous three days, NSAIDs in previous 24 hours, anti-platelet drugs (such as Clopidogrel) in the past 14 days, high performance athletes, serious psychologic disorders or an inability to understand the questionnaires.

Enrolment was completed over a two-month period from mid-February to mid-April 2013 from consecutive referrals to a specialist musculoskeletal medicine private clinic and from the existing clinic database. There were 109 patients living in Northland screened, of whom 36 had insignificant pain, 13 were excluded on the basis of the exclusion criteria, 11 declined to participate or did not turn up to appointments and one failed venepuncture (Figure 1). All subjects provided written informed consent.

Procedures

The initial assessment included demographic details, a questionnaire (incorporating Brief Pain Inventory (under licence, MD Anderson Cancer Center Texas), health professional consultation rate, medication use in the past 14 days, Likert Scale of progress, Expectation of Improvement Scale), duration of symptoms, previous treatments (only treatments used by at least five participants reported), history of low back pain, history of hip pain). Participants were examined by the first investigator (GT) and included weight, height, BMI; pelvic level; gross spinal range of motion; prolonged 30-second Trendelenburg test; FABERE; point tenderness; pain elicited on passive and resisted hip movements. A full blood count (FBC) was obtained (Tables 1 and 2). The guestionnaire was repeated at 3, 6 and 12 months.

After the initial assessment 55mls of blood was drawn from the antecubital fossa with 1ml sent to the laboratory for full blood count including platelet numbers, and 54mls drawn into a syringe containing 6ml of ACD-A (citrate anticoagulant). The blood was passed to a New Zealand registered nurse who in a separate room randomised participants with the use of a block-randomised list with block sizes randomly chosen from two, four, six or eight, into either the active treatment group or control group. The randomisation code was computer-generated off site by the second investigator (JP). The randomisation was kept in a secret secure place separate from patient files and unavailable to other staff. For the treatment group, the collected blood was placed into a Recover™ platelet separation collecting system (Biomet Biologics,



Figure 1: Flow diagram for the Northland Lateral Hip Pain Study with a double-blinded random allocation of 48 patients to placebo or PRP injection arms with 12 months of follow-up.

Northland Lateral Hip Pain Study

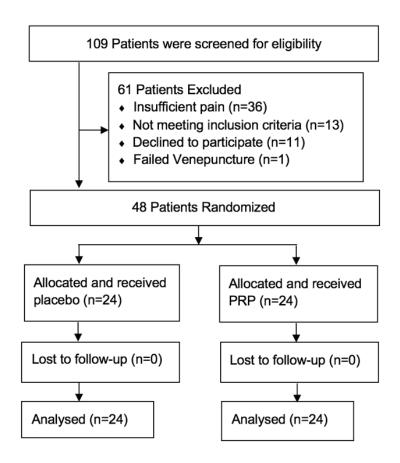


Table 1: Participant characteristics.

	Intervention	Control	Total	Р	
	24	24	48		
Age	54.3±10.5	56.3±9.6	55.3±10.0	0.50	
Female	22.0 (91.7%)	20.0 (83.3%)	42.0 (87.5%)	0.67	
Ethnicity					
European	21.0 (87.5%)	24.0 (100.0%)	45.0 (93.8%)	0.23	
Māori	1.0 (4.2%)	0.0 (0.0%)	1.0 (2.1%)	1.00	
ВМІ	28.8±4.7	29.1±4.2	28.9±4.4	0.85	
Haemoglobin	136.3±9.1	137.8±9.6	137.0±9.3	0.60	
Platelets	16.8±10.6	19.5±11.4	18.1±11.0	0.40	
Duration (months)	54.0±57.2	45.2±29.9	49.6±45.3	0.50	

Mean \pm sd or count (percentage) and P value from t test or Fisher's exact test for continuous and dichotomous data respectively.



Table 2: Pain characteristics at baseline.

	Intervention	Control	Total	Р
	24	24	48	
Location				•
Left side	11 (45.8%)	13 (54.2%)	24 (50.0%)	0.77
Right side	13 (54.2%)	11 (45.8%)	24 (50.0%)	0.77
Lateral thigh	15 (62.5%)	12 (50.0%)	27 (56.3%)	0.56
Lateral shin	2 (8.3%)	3 (12.5%)	5 (10.4%)	1
Groin	3 (12.5%)	3 (12.5%)	6 (12.5%)	1
Low back pain	11 (45.8%)	12 (50.0%)	23 (47.9%)	1
Treatment				
Topical	10 (41.7%)	9 (37.5%)	19 (39.6%)	1
Oral	15 (62.5%)	20 (83.3%)	35 (72.9%)	0.19
Steroid	16 (66.7%)	16 (66.7%)	32 (66.7%)	1
Physiotherapy	15 (62.5%)	13 (54.2%)	28 (58.3%)	0.77
Osteopathy	3 (12.5%)	7 (29.2%)	10 (20.8%)	0.29
Examination				
Trendelenburg	11 (45.8%)	5 (20.8%)	16 (33.3%)	0.12
Stance positive*	16 (88.9%)	19 (100.0%)	35 (94.6%)	0.23
Stance seconds*	9.1±7.9	10.7±9.5	9.9±8.7	0.57
FABERE (restriction)	6 (25.0%)	6 (25.0%)	12 (25.0%)	1
FABERE (pain)	18 (75.0%)	18 (75.0%)	36 (75.0%)	1
Tenderness	24 (100.0%)	24 (100.0%) 48 (100.0%)		1
Pain on IR	6 (25.0%)	5 (20.8%)	11 (22.9%)	1
Pain on ER	11 (45.8%)	12 (50.0%)	23 (47.9%)	1
Pain on Abd	7 (29.2%)	4 (16.7%)	11 (22.9%)	0.49
Pain on Add	3 (12.5%)	6 (25.0%)	9 (18.8%)	0.46
Pain on resisted ER	5 (20.8%)	14 (58.3%)	19 (39.6%)	0.02
Pain on resisted abduction	7 (29.2%)	8 (33.3%)	15 (31.3%)	1

 $\label{eq:mean policy} \mbox{Mean \pm sd or count (percentage) and P value from t test or Fisher's exact test for continuous and dichotomous data respectively. 5 (6) Control (treatment) patients not tested.}$

Warsaw, Indiana, US) and centrifuged using a FDA-approved Drucker centrifuge (Biomet Biologics, Warsaw, Indiana, US), with the platelet-rich plasma subsequently drawn off. To this was added 0.3ml of 8.4% sodium bicarbonate for buffering. Five millilitres of this PRP was added to 1ml 1% xylocaine for the treatment group. For the control group, 5mls isotonic saline was added to the 1ml

1% xylocaine. The syringes were carefully masked with tape by the nurse, leaving a small channel along the measurement edge of the barrel to allow volume judgement without being able to identify the contained material. The syringe was then passed back to the principle investigator for injection. The technique used was a single injection using a 1.5-inch 26g needle of 2mls into the



focal tender point at bone depth, and the remaining 3–4mls injected in three aliquots around this point. One millilitre of whole blood from the pre-centrifuge sample, and 1ml of the PRP component was analysed by a local IANZ-accredited laboratory for platelet counts.

All participants were advised to rest for 24 hours, and were then contacted by phone and recommended to resume usual activity. They were given an eccentric exercise programme³² to start after the initial 24 hours, including provocative leg lunges, single stance knee bends, and side lying eccentric flexion, side bending and extension. Participants were advised to perform 10-15 of each exercise up to twice daily but not to repeat the exercise until post-activity pain intensity returned to pre-activity baseline level. Participants were advised that they could use oral analgesia as required but asked to refrain from having manual therapy or injections for the duration of the trial. They could withdraw from the study at any point but were encouraged to continue without intervention for as long as possible.

Full written questionnaires were completed at entry, three months, six months, telephone questionnaires by an independent researcher (Numeric Rating Scale (NRS), Likert Scale of progress, adherence to exercise, medication use, health professional consultation rates) at one, two, four and five months, and email follow-up at 12 months.

Statistical analysis

Considering pain as a continuous response, this balanced case control study had 80% power at 5% type 1 error rate to detect a difference of 0.83 within group standard deviations, a large Cohen effect size.³³ There was no participant dropout throughout the trial, which was achieved

by maintaining regular contact with participants by telephone, email and post.

Initial demographics, pain location and treatment, and examination results were compared by t tests using the Satterthwaite adjustment for unequal variances or Fischer's exact test for continuous or dichotomous measurements respectively.

Post-intervention, the two arms were compared by t tests then analysis of covariance, firstly adjusting for the initial value only and secondly including covariates for age, (continuous), BMI (continuous), thigh pain (dichotomous), low back pain (dichotomous) and analgesia (continuous) at baseline and endpoint. At 12 months, analgesia was imputed by analgesia at six months. Analysis of covariance were performed for 3-month, 6-month and 12-month data, additionally a mixed model was fitted to each outcome using a random effect for subject over repeated measurements. No tests or models showed significant differences between arms, hence no adjustment was made for multiple testing.

All analysis was performed in R version 3.2.1 (Vienna, Austria), all tests were two tailed and considered significant at 5% type 1 error rate.

Results

Platelet concentration was able to be analysed from 23 samples and ranged from 1.12 to 7.67, with mean 4.9 (SD 1.8) (Table 3).

There was a reduction in worst, average and least pain over time (Figure 2), almost entirely in the first three to six months for most patients. No statistically significant evidence was found for a difference between control and treatment arms for any outcome at any time point whether with or without adjustment for age, BMI, pain location or analgesia (current and baseline) (Table 4).

Table 3: Haemoglobin, platelets and whole blood count pre- and post-centrifuge.

	Pre-centrifuge	Post-centrifuge	Concentration ratio
Haemoglobin	133.9±7.9	20.7±8.8	0.2±0.1
Platelets	254.9±55.3	1232.3±637.8	4.9±1.8
Whole blood count	6.5±1.9	29.5±9.0	4.5±1.0

Mean ± sd.



pain score 0 01 Worst Pain □ Placebo □ Treament 6 2 0 Average Pain 10 8 6 2 0 Least Pain 10 8 6 2 0

Figure 2: Pain levels.

Worst, average and least pain at baseline, 3, 6 and 12 months for placebo and treatment arms. Boxplots show median and interquartile range (IQR), whiskers extend to the furthest value inside 1.5xIQR. Lines join mean values at time points for each arm.

Table 4: Effect of treatment on pain adjusted for initial pain level.

Outcome	f²	6	СІ	Р	P adj
Worst pain					
3 months	0.011	-0.61	(-2.17, 0.95)	0.44	0.82
6 months	0.008	0.48	(-1.03, 1.99)	0.53	0.50
12 months	0.006	-0.46	(-2.18, 1.26)	0.59	0.34
Average pain					
3 months	0.007	-0.40	(-1.61, 0.81)	0.51	0.74
6 months	0.003	-0.23	(-1.36, 0.90)	0.68	0.20
12 months	0.003	-0.26	(-1.51, 1.00)	0.68	0.23
Least pain					
3 months	0.010	-0.36	(-1.19, 0.48)	0.39	0.71
6 months	0.000	-0.06	(-0.95, 0.82)	0.89	0.86
12 months	0.001	0.07	(-0.79, 0.93)	0.87	0.55

Coefficient (6), with 95% CI, f^2 and P value for treatment arm from analysis of covariance model for each outcome at 3, 6 and 12 months. P adj is the P value for treatment from an analysis of covariance model adjusted for covariates for age, BMI, pain duration, pain location and analgesia (baseline and current).



Table 5: Average pain over the course of the study.

	6	95% CI	Р
Age	-0.06	(-0.13, 0.00)	0.050
ВМІ	0.27	(0.09, 0.45)	0.007
Duration	-0.26	(-0.44, -0.09)	0.008
Month	-0.15	(-0.23, -0.06)	0.001
Treatment	0.48	(-0.77, 1.73)	0.441

Coefficients with 95% confidence intervals and P values for the fixed effects from the final model with a random effect for participant.

Mixed effects models with fixed effects for age, duration of pain, BMI, month and arm (placebo/treatment) and a random effect for subject, equivalent to a repeated measures anova, were fitted with and without the interaction between arm. Including the interaction term showed no significant interaction between month and arm (P=0.59), or arm (P=0.36) or improvement in model fit (Log ratio 0.31, P=0.85), models had AICs of 317.2 and 314.5 respectively. Fixed effect parameters for the model without interaction (Table 5) show that average pain decreases significantly with duration and timepoint increases with BMI; however, there is no evidence of an effect for autologous PRP injection (P=0.44). Similar results were obtained for least pain and worst pain (not shown).

Discussion

The present study shows a reduction in GTPS pain intensity in the first six months in both the intervention and control group. There was no statistically significant difference between the two arms. Consequently, we infer no effect of PRP injection of a clinically meaningful magnitude. The improvements in pain intensity in both arms of the study could be due to natural history, the result of the eccentric exercises which were given to both groups, or the placebo effect of the medical intervention.

There have been a number of labels previously for GTPS with the most contemporary being trochanteric bursitis. However, bursitis has been shown to be an inaccurate label with an absence of signs associated with bursitis of swelling, heat, crepitus or fluctuation, 11 no histologic evidence of bursitis, 34 infrequent bursal changes on

ultrasonic imaging³⁵ and no advantage of fluoroscopic-guided specific intra-bursal injections compared with blind injections.¹⁵

Histologic examination has frequently revealed tendinosis but not acute inflammation. Maffulli et al argue that this represents a "failed healing response". They argue that the histological changes are best described as "tendinosis" rather than "tendonitis" or "tendinitis" and define tendinopathy as the generic descriptor of the clinical conditions (both pain and pathological characteristics) associated with overuse in and around tendons. An editorial suggested that lessons learnt from other anatomic sites where tendinopathies occur could be extended to treatment of GTPS. 32

In recent years, there has been considerable interest in the use of intrinsic growth factors for accelerated healing in a number of applications, including tendinopathies. Platelets are a potential source of growth factors.37-40 Platelet rich concentrate has been shown to increase tenocyte population and enhance tendon growth in animal studies,41 and human tendon cells in culture. 37,42 Administration of platelets can be facilitated by the use of autologous whole blood or by concentrating platelet numbers by centrifugation or filtration to obtain platelet-rich plasma (PRP). The use of FDA-approved specific platelet harvesting centrifuges can be expected to increase the concentration of platelets by at a factor of 4-8.38,43 While one group showed a dose-response curve which indicated a sufficient cellular response to platelet concentrations when a four- to five-fold increase over baseline platelet numbers was achieved,44 both a single-blind45 and a double blind46 study of PRP compared with



autologous whole blood for chronic lateral elbow epicondylalgia found no statistical significance in outcome between the two treatment groups.

Utilisation of autologous blood injections, including PRP, has increased for a range of medical conditions, including tendinopathy, over the past two decades. There have been a number of reviews including a recent one by Wang et al.⁴⁷ Ali et al specifically reviewed the use of platelet-rich plasma in the treatment of greater trochanteric syndrome.⁴⁸

Fitzpatrick et al compared a single injection of PRP with corticosteroid over 12 weeks using the same collecting system as the authors.49 They used ultrasound-guided injections into the abnormal looking gluteal tendon and demonstrated good improvement in the corticosteroid group to six weeks, but subsequent deterioration, while there was continued improvement in the PRP group, sustained at one year in a follow up study.⁵⁰ Conversely, Riberio et al compared ultrasound-guided injection into the most tender aspect of the trochanteric bursa of PRP with corticosteroid over a two-month period and found no significant difference at any stage.51

In a third random controlled trial, Jacobson et al compared the effect of a single ultrasound-guided injection of PRP into the deepest aspect of tendon abnormality with another group treated with repeated fenestration and found subsequent improvement over the next three months in both groups with no statistically significant difference between them. 52

The published RCTs consistently demonstrate sustained improvement over time following single injections of platelet-rich plasma but no significant difference when compared with other injectable interventions such as normal saline (the current study) or fenestration.

While there is concept validity in the use of PRP in the management of tendinopathy, and seemingly widespread use, their use has not been vindicated by evidence provided so far, particularly in the lower limb tendinopathies and enthesopathies. The Northland GTPS PRP study was also double-blinded and placebo controlled, minimising reporting and observer bias and controlling for non-specific treatment effects.

There were 20 participants recruited into both treatment and control arms. Allowing for 20% dropout, the study was designed to demonstrate a difference between the two groups only if the effect size was large on Cohen's scale. It was reasoned that the significant financial cost of the intervention necessitated a similarly significant likelihood of positive therapeutic response. As it was, we recruited a total of 48 participants. Regular contact with participants contributed to no drop out at 12 months. The study had 80% power to detect an average difference of 1.8 units on the pain scale, the achieved between groups standard deviation (σ = 2.2 for average pain at 12 months) was very similar to that used for power calculations.26 It is possible that there is a significant but small effect due to PRP injections. Based on this study it would require over 200 patients in each arm of the study to have 80% power to detect the largest difference that was observed.

It is interesting that there were so few Māori in the study given the local population demographics and the number of Māori seen in the practice for other pain issues. To the investigators' knowledge, there are no cross-sectional studies of chronic pain in the Māori population, which remains a glaring deficiency in our understanding of the pain burden on the community.

The investigators chose not to do imaging prior to entry into the study, or to use imageguided injections. It was reasoned that imaging frequently provides false-positive results for lateral hip pain and is more useful for detecting other more rare pathology (eg, trochanteric osteitis) rather than making a positive contribution to the diagnosis of GTPS. The diagnosis of GTPS is a clinical one and hence we relied on clinical history taking and examination for diagnosis, and precise focal tenderness for injection placement. By injecting the bulk of the injectate at the site of maximal tenderness with smaller aliquots around this site, we attempted to reduce the risk of missing the target area. We were aiming at the point of maximal tenderness rather than image-diagnosed pathology, which could have been irrelevant. Nevertheless, it could be argued that this study included participants who may have other pathology which would not have responded to PRP in any case.



It has been calculated that there needs to be a four- to five-fold increase in baseline platelet numbers to stimulate a cellular response. ³⁸ In this study, there was a broad range of concentration in the post-centrifuge samples. Some investigators have used serial injections of PRP. This would add considerably to the cost of treatment, but potential remains for further investigation into treatment of GTPS. It is conceivable

that individuals respond differently to PRP and to different concentrations of PRP, but the authors are not aware of any clinical markers at this time that would predict a variable interindividual response to PRP.

This double-blinded study has demonstrated that there was no significant reduction in pain intensity from the use of a single injection of platelet-rich plasma for greater trochanteric pain syndrome.

Competing interests:

Nil.

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