■ KNEE

The effectiveness of leucocyte-poor platelet-rich plasma injections on symptomatic early osteoarthritis of the knee: the PEAK randomized controlled trial

E. Lewis,
K. Merghani,
I. Robertson,
J. Mulford,
B. Prentice,
R. Mathew,
P. Van Winden,
K. Ogden

From Launceston General Hospital, Launceston, Australia

Aims

Platelet-rich plasma (PRP) intra-articular injections may provide a simple and minimally invasive treatment for early-stage knee osteoarthritis (OA). This has led to an increase in its adoption as a treatment for knee OA, although there is uncertainty about its efficacy and benefit. We hypothesized that patients with early-stage symptomatic knee OA who receive multiple PRP injections will have better clinical outcomes than those receiving single PRP or placebo injections.

Methods

A double-blinded, randomized placebo-controlled trial was performed with three groups receiving either placebo injections (Normal Saline), one PRP injection followed by two placebo injections, or three PRP injections. Each injection was given one week apart. Outcomes were prospectively collected prior to intervention and then at six weeks, three months, six months, and 12 months post-intervention. Primary outcome measures were Knee Injury and Osteoarthritis Outcome Score (KOOS) and EuroQol five-dimension five-level index (EQ-5D-5L). Secondary outcomes included visual analogue scale for pain and patient subjective assessment of the injections.

Results

A total of 102 patients were recruited. The follow-up period was 12 months, at intervals of six weeks, 12 weeks, six months, and 12 months. KOOS-Total significantly improved in all groups at these time intervals compared to pre-injection. There was an improvement in EQ-5D-5L index scores in saline and single injection groups, but not in the multiple injection group. Comparison of treatment groups showed no additional beneficial effect of single or multiple PRP injections above that displayed in the saline injection group. Subjective patient satisfaction and recommendation of treatment received demonstrated a similar pattern in all the groups. There was no indication of superiority of either single or multiple PRP injections compared to saline injections.

Conclusion

There is no evidence that single or multiple PRP had any additional beneficial effect compared to saline injection up to 12 months' follow-up after treatment of early stage symptomatic OA of the knee.

Cite this article: *Bone Joint J* 2022;104-B(6):663–671.

Correspondence should be sent to E. Lewis; email: ms_emma_lewis@yahoo.com

doi:10.1302/0301-620X.104B6.BJJ-2021-1109.R2 $2.00

Bone Joint J 2022;104-B(6):663–671.

Introduction

Patients with symptomatic osteoarthritis (OA) of the knee represent a significant management challenge and burden to the health system.[1,2] These patients are presenting younger and have high expectations of treatment.[3] However, most traditional treatments are not consistently effective.[4] The hypothesis that early disease may be reversible has sparked interest in orthobiological therapies. More importantly, the clinical effect of orthobiologics on symptom improvement and disease-modifying effect is still debated.[5]

Orthobiologics are tissue-derived products, commonly based upon manipulation of platelets or stem cells to produce higher concentrations of beneficial substances than are found in normal tissue.[6] These products can be autologous or allogenic. Orthobiologics are applied to areas of pathology where they aim to deliver proregenerative growth factors and cytokines with the aim of promoting healing and decreasing inflammation. In vitro, and in animal models, they have shown improvements at histological, macroscopic, and clinical levels, however tangible evidence regarding their efficacy and functional improvement in humans remains controversial due to wide heterogeneity in the reported results. This has resulted in PRP not being supported or recommended by a number of guidelines and professional bodies.[7-14]

The use of PRP for degenerative arthritis has grown rapidly despite heterogeneity in the reported results and lack of standardization in preparation in PRP and treatment protocols.[15,16] How PRP works is debated; however, it is postulated that the possible therapeutic effect is largely due to anti-inflammatory effects from the local growth factors in PRP.[17] The local factors include interleukin-1 (IL-1) and epidermal growth factor (EGF), and bone morphogenetic protein (BMP) and insulin-like growth factor 1 (IGF-1), which stimulate fibrochondrocyte migration and proliferation.[18] Other potential mechanisms of action include cellular proliferation, anti-apoptotic activity, cartilage regeneration, angiogenesis, amplified activity at the trans-membrane receptors, and increased vascular permeability. These mechanisms are complex, but for knee arthritis it is thought that the growth factors and cytokines within platelets encourage formation of type II collagen, proteoglycans, and other extracellular matrix components, promoting adhesion between chondrocytes and discouraging proteolysis of the extracellular matrix microenvironment.[19] The role of leucocytes in PRP is not clear. There are different concentrations of leucocytes in PRP preparations, although a leucocyte-poor preparation is thought to be preferable in addressing OA.[11] An alternative hypothesized method of action suggested in the literature is the effect mediated through activation of biological pathways to increase growth factors, rather than simply by delivering them.[20]

Despite meta-analyses[21-25] and randomized trials on PRP in knee arthritis,[10,26-30] there is still a lack of certainty about its true effect on symptom control and disease modification. This debate exists due to the heterogeneity and risk of bias in previous studies. How much any measured benefit is due to a "placebo rich plasma" is debated. Previous studies suggest patients with early-stage OA may gain maximal benefit from PRP. There are few trials that have examined the dose required and whether multiple injections give better outcomes,[28-30] despite proponents and manufacturers of PRP often recommending three injections for best treatment effect. Previous studies have had methodological limitations such as unblinded patients and observers, short-term follow-up, and high loss to follow-up rates. This trial aims to address the unknown questions surrounding PRP use in early-stage knee OA, including the number of doses and the duration of effect, through a high-quality placebo-controlled, double-blinded, randomized clinical trial.

Methods

Study ethical approval was obtained from Tasmanian Health & Medical Human Research Ethics Committee (EC00337), and the study was registered as the PRP treatment in Early osteoArthritis of the Knee (PEAK) trial with Australian New Zealand Clinical Trials Registry (registration number ACTRN12617001162303).

Study design. This was a double-blinded, parallel-group, randomized placebo-controlled trial, consisting of three groups with ratios of 1 (placebo), 1.7 (single injection), and 1 (multiple injections).

Recruitment. Participants were recruited through self-referral, or referral from their general practitioner (GP). Flyers regarding the trial were distributed around the hospital and in GP practices throughout Launceston. Recruitment commenced on 1 September 2017 and was completed on 1 August 2018, with follow-up completed on 31 August 2019. Initial screening was performed by a research assistant (see Acknowledgements) to confirm inclusion/exclusion criteria.

Eligibility. Participants were recruited into the study if they were aged over 18 years, demonstrated a history of more than four months of pain and/or swelling in the knees with early radiological evidence of tibiofemoral OA that has a Kellgren-Lawrence (K-L) grade from 0 to 2.[31] Radiographs were assessed and classified according to the K-L grading system by the two senior authors (PVW, JM). If the knee was classified as Grade 0, the patient required MRI to confirm degenerative disease. If there was disparity between the senior authors, the grade was decided by a third reviewer (EL or BP).

Participation was denied and patients excluded if there was evidence of advanced OA of the knee, previous open knee surgery, anticoagulation, or any systemic disorder, such as rheumatological disease, severe cardiovascular disease, haematological disease, or infection.

Measures. Basic demographic information was collected, as well as K-L grade of the radiological appearance of the knee at recruitment.

Outcome measures. Outcome measures were collected pre-injection and at six weeks, 12 weeks, six months, and 12 months following intervention, by a research assistant who was blinded to intervention. The primary outcomes were Knee injury and Osteoarthritis Outcome Score (KOOS)[32] and EuroQol five-dimension five-level index (EQ-5D-5L).[33] The secondary outcomes were visual analogue scale (VAS) 1 to 10 for pain (whereby 1 signifies no pain and 10 signifies the worst pain imaginable), patient subjective assessment of the injection (Likert scale: 2 made it much better; 1 made it a little better; 0 no difference; -1 made it a little worse; -2 made it a lot worse), and whether they would recommend it (Likert scale: 2 most definitely; 1 probably; 0 not sure; -1 would be hesitant; -2 definitely not) (Supplementary Table i).

Randomization. Block randomization was employed, using a computer-generated random assignment sequence and concealed envelopes. The patient and the collector of the data were blinded to the injection regime received.

Interventions. Participants were randomized into one of the following groups: Group 1 received three placebo injections (Normal Saline); Group 2 received a single PRP injection

Table I. Demographic characteristics of the treatment groups.

Characteristic	Control	Single injection	Multiple injections	p-value
Sex, n (%)				
Male	12 (43)	20 (43)	9 (33)	0.732*
Female	16 (57)	27 (57)	18 (67)	
Mean age, yrs (SD)	60.1 (9.3)	55.1 (12.6)	59.4 (8.9)	0.099†
Mean BMI, kg/m² (SD)	29.9 (5.5)	29.3 (6.7)	29.7 (6.1)	0.927†
Mean symptom duration, mths (SD)	52.7 (57.3)	56.0 (66.4)	55.7 (66.8)	0.976†
KL grade, n				0.603*
0	0	4	1	
1	8	11	8	
2	17	23	13	

*Fisher's exact test.
†Fisher's F-test.
KL, Kellgren-Lawrence; SD, standard deviation.

followed by two placebo injections (Single); and Group 3 received three PRP injections (Multiple).

Irrespective of which group a patient was allocated to, they underwent venesection of 20 ml blood at each of the three injection appointments to ensure they were blinded to the treatment. The blood was either processed or discarded according to the patient allocation in the trial. The venesection and preparation of the PRP were performed by a doctor who was an unblinded clinician member of the research team. Patients were asked to wear a blindfold during injection. PRP was prepared using the Arthrex ACP syringe (leucocyte-poor) and centrifuge system (Arthrex, UK). This produced between 4 and 6 ml of PRP. For each placebo injection, 5 ml of 0.9% normal saline was used.

Sample size considerations. Based on the data from previous studies,[21,29] the trial was powered based on improvements in EQ-VAS scores as the most clinically relevant measure to the patient. This was based on an α of 0.025, power of 0.8, and standard deviation (SD) of EQ-VAS of 15. We assumed a final mean score of 50 (Control) to 62.5 (single PRP) to 75 (multiple PRP), with those intervals being the minimum relevant differences. The critical differences were between the control and single groups, and between the single and multiple groups; therefore, increased numbers of patients receiving single PRP injections were included to increase the efficiency of the study. The target population per group to adequately power the study was calculated as 26 in the placebo group, 45 single injection, and 26 multiple injection, allowing for a 10% non-completion rate (97 total patients) (Figure 1).

Baseline demographic data are shown in Table I. The mean age for the participants in the single PRP injection group was lower than in those in the other two groups. This potential confounder (although no confounding effect was found) was addressed as an adjustment variable in subsequent analyses.

Statistical analysis. Analysis was performed on an intention-to-treat basis. The effect of the alternative treatments on the primary outcomes (KOOS and EQ-5D-5L) and the secondary outcome of pain scores was estimated using repeated measures mixed-effect linear regression, adjusted for covariates. Covariates were selected by backward stepwise regression from the baseline variables (age, sex, BMI, symptom duration, comorbidities, and K-L grade). The mean levels (plus SDs) of outcome scores were calculated in the three treatment groups at five timepoints (pre-injection, six weeks, 12 weeks, six months, and 12 months) as were the differences between those estimates (plus 95% confidence intervals (CIs); p-values), both within and between group differences.

The scales used to measure the primary and secondary outcomes (Pain, KOOS, EQ-5D-5L, patient satisfaction, and judgement of value) were all rank-ordered. The degree to which those rank-ordered scales behaved as though they were interval scales was tested by using repeated-measures mixed effects ordered logistic regression, adjusted for the corresponding covariates for each outcome. In each case (linear regression and rank-ordered regression), the z-score test and p-values were closely similar, and so the natural value results derived from the linear regression analyses were shown in the results. Local swelling was compared using ordered logistic regression,

Missing data were substituted using multiple imputation: 20 repetitions using the Stata Bayesian multivariate approach, and assuming the missing data were missing at random (Supplementary Table ii). All analyses were performed using Stata MP2 v. 16.0 (StataCorp, USA).

To measure the effect of PRP, we considered that any effect of the saline injection is due to the procedure plus the natural fluctuations in scores following intra-articular injections. The effect of the single and multiple PRP injection is the difference between the saline results and the results of single and multiple PRP injections. A graph line for the saline injection will represent its effect, while the line for the single and multiple PRP injections is the additional effect of these injections. Values above zero mean additional benefit and values below zero mean worst values.

A post-hoc analysis was performed (not part of the original protocol) to estimate the minimum clinically important difference (MCID) using the satisfaction anchor question approach, for the purpose of guiding future study design of this participant-condition-treatment combination.[34] The mean outcome scale values, and mean difference (mean Δ) between the minimum improvement group and no improvement group were estimated using general linear modelling (all satisfaction responses were included in the regression model but only these groups reported in this table), adjusted for age, symptom duration, baseline BMI, and past history of cardiac disease, diabetes, GI disease, and depression and/or anxiety. The outcome scales used were KOOS-Total, Pain VAS, and EQ-5D-5L, each corrected to 0 to 100, where 100 meant best quality of life (QoL) or absence

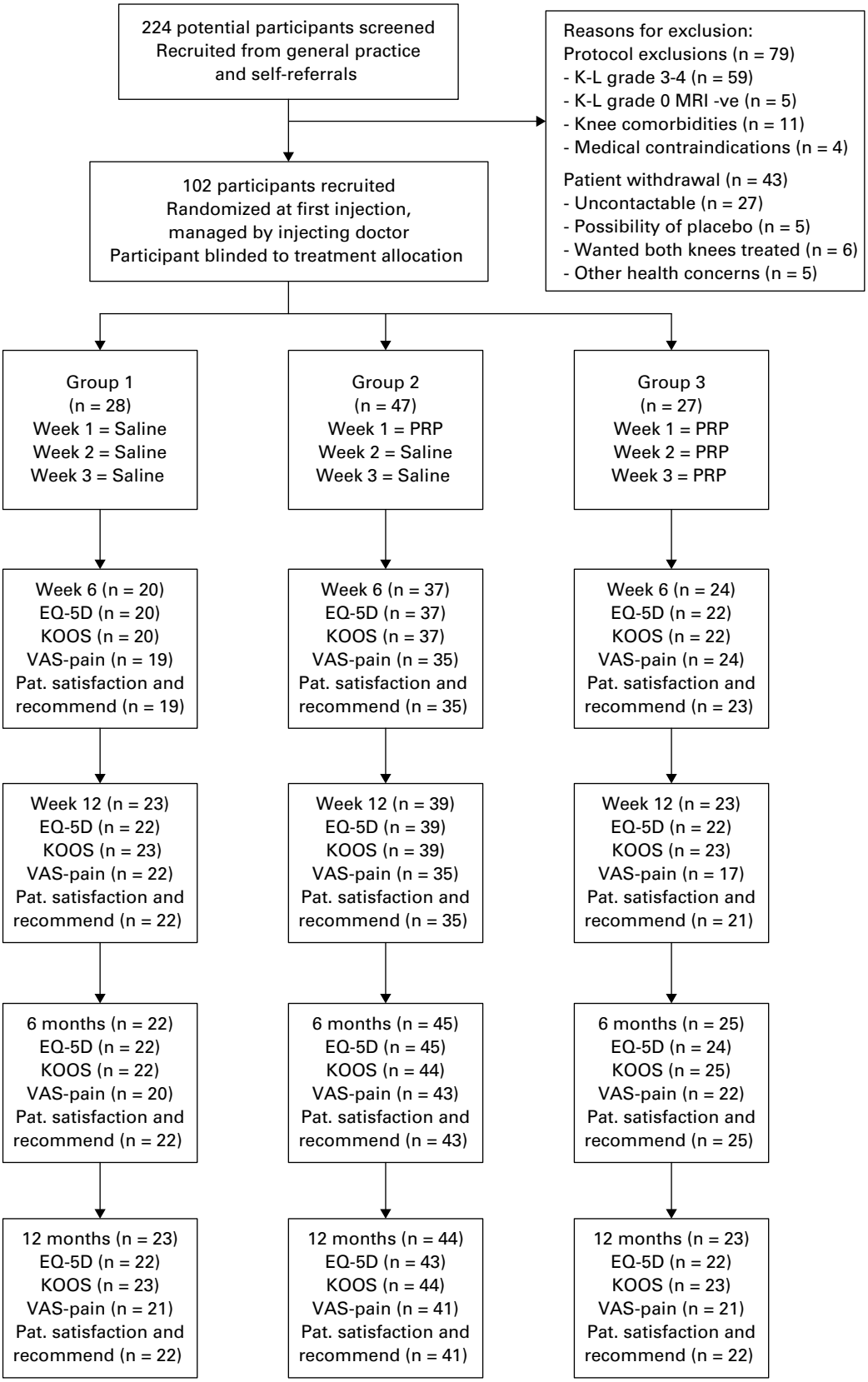

Fig. 1

CONSORT diagram of the study participation and exclusions. -ve, positive; EQ-5D, EuroQol five-dimension index; K-L, Kellgren-Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; PRP, platelet-rich plasma; VAS, visual analogue scale.

of pain (i.e. values reversed in order to achieve comparability between scale values), and 0 meant worst QoL and worst imaginable pain: the ten-point Pain VAS was reversed and converted pro-rata into a 0- to 100-point scale.

Results

In total, 102 patients were recruited (28 placebo injection, 47 single injection, and 27 multiple injection groups); 1.3% of the required patient characteristic data were missing, and 26.0% of the post-injection outcome assessment data were missing (Supplementary Table ii).

For the primary outcomes of KOOS-Total and EQ-5D-5L index scores, all treatment groups exhibited significant improvement at all follow-up times (Table II), although the early benefits appear to have been greatest in the saline injection group, and were slower to develop in the multiple injection group. Single and multiple PRP injections had a similar effect to saline injection, with no indication of superiority on the primary outcomes.

All sub-analysis scores of the components of KOOS, EQ-5D-5L, and VAS Pain scores are available in Supplementary Tables iv to vii. These show the sequence of analysis from the absolute levels of the scores at each time interval, the change in mean values within each treatment group across the time of follow-up, a comparison of the changes between the different treatment groups, and an estimate of the effect of active treatments (single or multiple PRP injections) in addition to the expected inactive saline injections.

In Figure 2, the graph line for the saline injection represents its effect, while the line for the single and multiple PRP injections is the additional effect of these injections. Values above zero indicate additional benefit, and values below zero indicate less benefit or worsening value. Saline injection was followed by statistically significant improvement in the KOOS-Total, with maximum improvement at 12 weeks (12.8 (95% CI 7.45 to 18.1); $p < 0.001$, mixed effects linear regression (see Supplementary Table iv for details)) followed by a steady decline to 52 weeks (7.9 (95% CI 2.6 to 13.2); $p = 0.004$). Single (-4.3 (95% CI -11.0 to 2.4); $p = 0.212$) and multiple (-8.8 (95% CI -16.4 to -1.2; $p = 0.023$) PRP injections were associated with an apparent small initial reduction in KOOS-Total at 12 weeks compared to saline injection. There was a possible clinically and statistically insignificant improvement in KOOS Symptoms scores after 18 weeks for single injection (7.5 (95% CI 1.3 to 13.6); $p = 0.017$) and 44 weeks for multiple PRP injections (7.8 (95% CI 0.9 to 14.7); $p = 0.027$). Similar findings were demonstrated in the effect of the injections on change in EQ-5D-5L.

The secondary outcome measure of pain using a VAS showed that all treatment groups exhibited statistically significant improvement at all follow-up times (Table II). Single and multiple PRP injections had a similar effect to saline injection with no indication of superiority.

Secondary outcomes showed no difference in any group, these being patient subjective assessment of the injection, whether it helped or they would recommend it (Supplementary Table vi and Figure a). At 12 months, the mean subjective scores were positive 0.66 (SD 0.85) for helped and 0.75 (SD 1.19) for recommended in the saline group; 0.81 (SD 0.85) for helped and 0.89 (SD 1.01) for recommended in the single injection group; and 0.68 (SD 0.66) for helped and 0.79 (SD 0.65) for recommended in the multiple injection group. There were no differences between groups.

Considering the local side effects compared with the saline injection group, there was significant swelling in the first time period after injection in the single (odds ratio (OR) 3.92 (95% CI 1.16 to 13.3); $p = 0.028$, ordered logistic regression) and multiple (OR 6.71 (95% CI 1.16 to 13.3); $p = 0.006$) PRP injection groups, which subsided at the second post-procedure observation time (single, $p = 0.843$; multiple, $p = 0.968$). No differences or changes were seen in levels of redness or bruising/bleeding between the different time periods and treatment groups. No injections were complicated by infection.

The estimated MCID at 12 months, representing the minimum improvement that the participants considered of value, was for KOOS-Total 6.3 units (95% CI 3.3 to 9.3; $p < 0.001$, mixed effects linear regression), for EQ-5D-5L score 6.4 units (95% CI 2.8 to 10.0; $p < 0.001$), and for the reverse Pain VAS score 5.8 units (95% CI 2.1 to 9.4; $p = 0.002$), each using a standardized 0- to 100-unit scale (Supplementary Table viii and Figure b).

A further exploratory analysis outside protocol was performed to determine whether the rate of minimal and substantial improvement was higher in participants from either of the PRP injection groups. We considered that examination of only those participants above minimum benefit threshold was inappropriate without consideration of those below the minimum adverse threshold. A non-parametric analysis was performed on the satisfaction scale, with parallel similar analyses performed on the EQ-5D-5L and KOOS-Total scale results at each of the four review timepoints. Those participants who received saline injection appeared not to have inferior responses to either of the PRP injection participant groups: the most optimistic result was that satisfaction scale results may have been higher in the single injection group compared to saline at six months (OR 1.46 (95% CI 0.51 to 4.24); $p = 0.484$, ordered logistic regression), although this is most likely a chance finding. At each timepoint, the OR for both multiple versus single injection, and multiple injection versus saline, was below 1.00 for the satisfaction scale, although no statistical certainty exists that this is a true effect. The wide CIs are the result of inadequate sample size for this analysis.

Discussion

The use of intra-articular PRP injection lends itself well to outpatient management of early-stage OA of the knee. The minimally invasive and autologous nature of the procedure, and ability to prepare in the outpatient setting, makes it an attractive treatment option.[19] The rapid expansion in the clinical indications for the use of PRP has preceded the establishment of research findings to support it.[13] In addition, the available literature is of variable quality, and suffers from bias and lack of procedural standardization.

As yet, no universal nomenclature has been adopted for PRP classification. Outcomes reported from this study relate to the leucocyte-poor ACP subtype of PRP injections. As such, these effects may not be predictive of outcomes using other PRP

Table II. Baseline values, change from pre-injection scores in outcome scores of Total Knee injury and Osteoarthritis Outcome Score, and EuroQol five-dimension five-level index within each treatment group at observation times (intention-to-treat), and difference between change in the saline injection group.

Variable	Saline		Single		Multiple	
	Δ (95% CI)*	p-value	Δ (95% CI)*	p-value	Δ (95% CI)*	p-value
KOOS-Total†						
Baseline value	63.8 (58.9 to 68.8)		60.9 (57.0 to 64.7)		54 (48.2 to 59.8)	
Change within each treatment group						
6 weeks	8.54 (3.23 to 13.8)	0.003	7.28 (3.18 to 11.4)	0.001	2.48 (-2.92 to 7.88)	0.37
12 weeks	12.8 (7.45 to 18.1)	< 0.001	8.47 (4.37 to 12.6)	< 0.001	3.95 (-1.46 to 9.35)	0.30
26 weeks	9.53 (4.22 to 14.8)	0.001	11.3 (7.17 to 15.4)	< 0.001	4.83 (-0.58 to 10.2)	0.24
52 weeks	7.9 (2.59 to 13.2)	0.004	10.2 (6.06 to 14.3)	< 0.001	8.61 (3.20 to 14.0)	0.007
Difference between Saline-injection and each of Single- and Multiple-injection groups						
6 weeks			-1.26 (-7.96 to 5.45)	0.71	-6.05 (-13.6 to 1.52)	0.12
12 weeks			-4.28 (-11.0 to 2.43)	0.21	-8.81 (-16.4 to -1.23)	0.023
26 weeks			1.74 (-4.96 to 8.44)	0.61	-4.71 (-12.3 to 2.87)	0.22
52 weeks			2.25 (-4.45 to 9.0)	0.51	0.7 (-6.87 to 8.3)	0.86
EQ-5D-5L‡						
Baseline value	0.775 (0.732 to 0.818)		0.73 (0.696 to 0.763)		0.732 (0.678 to 0.785)	
Change within each treatment group						
6 weeks	0.037 (-0.020 to 0.094)	0.40	0.057 (0.012 to 0.101)	0.036	-0.006 (-0.064 to 0.052)	0.85
12 weeks	0.076 (0.019 to 0.133)	0.036	0.037 (-0.007 to 0.081)	0.036	-0.002 (-0.060 to 0.056)	0.94
26 weeks	0.051 (-0.006 to 0.108)	0.243	0.059 (0.015 to 0.103)	0.036	-0.014 (-0.072 to 0.044)	0.63
52 weeks	0.015 (-0.042 to 0.072)	0.62	0.035 (-0.009 to 0.079)	0.12	-0.02 (-0.078 to 0.038)	0.51
Difference between Saline-injection and each of Single- and Multiple-injection groups						
6 weeks			0.019 (-0.053 to 0.091)	0.60	-0.043 (-0.124 to 0.038)	0.30
12 weeks			-0.039 (-0.111 to 0.033)	0.29	-0.078 (-0.160 to 0.003)	0.059
26 weeks			0.008 (-0.064 to 0.080)	0.83	-0.065 (-0.146 to 0.016)	0.12
52 weeks			0.021 (-0.051 to 0.093)	0.57	-0.034 (-0.116 to 0.047)	0.41

*Baseline scores; change from pre-injection scores within each treatment group; and difference between Saline-injection and each of Single- and Multiple-injection groups at observation times, with mean change (Δ) estimated by mixed effects linear regression adjusted for covariates, with missing data substituted by multiple imputation for intention-to-treat analysis, corrected for multiple comparisons by the Holm method.
†Range 0 to 100; adjustment covariates; duration of symptoms (log), BMI; past history of cardiac, gastrointestinal, liver diseases, diabetes, hypertension.
‡Range 0.0 to 1.0: adjustment covariates; age, duration of symptoms (log), BMI; past history of gastrointestinal, liver and neurological diseases, diabetes, K-L grade.
CI, confidence interval; EQ-5D-5L, EuroQol five-dimension five-level index; KOOS, Knee injury and Osteoarthritis Outcome Score.

formulations. This is a notable limitation in our study and the broader literature, as has been recently recognized.[35,36] A further limitation is the lack of specific component analysis of the PRP product produced.

Any modern treatment modality can carry an inherent benefit of placebo effect, and this may be most potent in the treatment of pain.[37] This was demonstrated previously in knee arthroscopy,[38] and orthobiologics are no exception. The lack of known therapeutic effect, but the well-described placebo benefit, of intra-articular saline injection renders it a suitable control group. Similarly, Saltzman et al[30] published a meta-analysis demonstrating statistically and clinically meaningful therapeutic effects of intra-articular injection of normal saline. They suggested that the saline injection provides quantification of the placebo effect as the minimum standard improvement that future trial therapies should surpass. We have accounted for this in our trial with a normal saline group used as a placebo arm, with participants blinded to group allocation.

The KOOS exhibited improvement across all the treatment groups over the follow-up period. There was also similar improvement in the EQ-5D-5L. These findings supported previously published studies demonstrating the efficacy of single and multiple PRP injections.[24,28] However, there was no statistical difference between the groups at any timepoint, indicating no additional clinically relevant medicinal benefit conferred from PRP injections relative to normal saline control. Our study therefore does not support the hypothesis that single and multiple PRP injections confer any detectable additional benefit to that of a placebo saline injection.

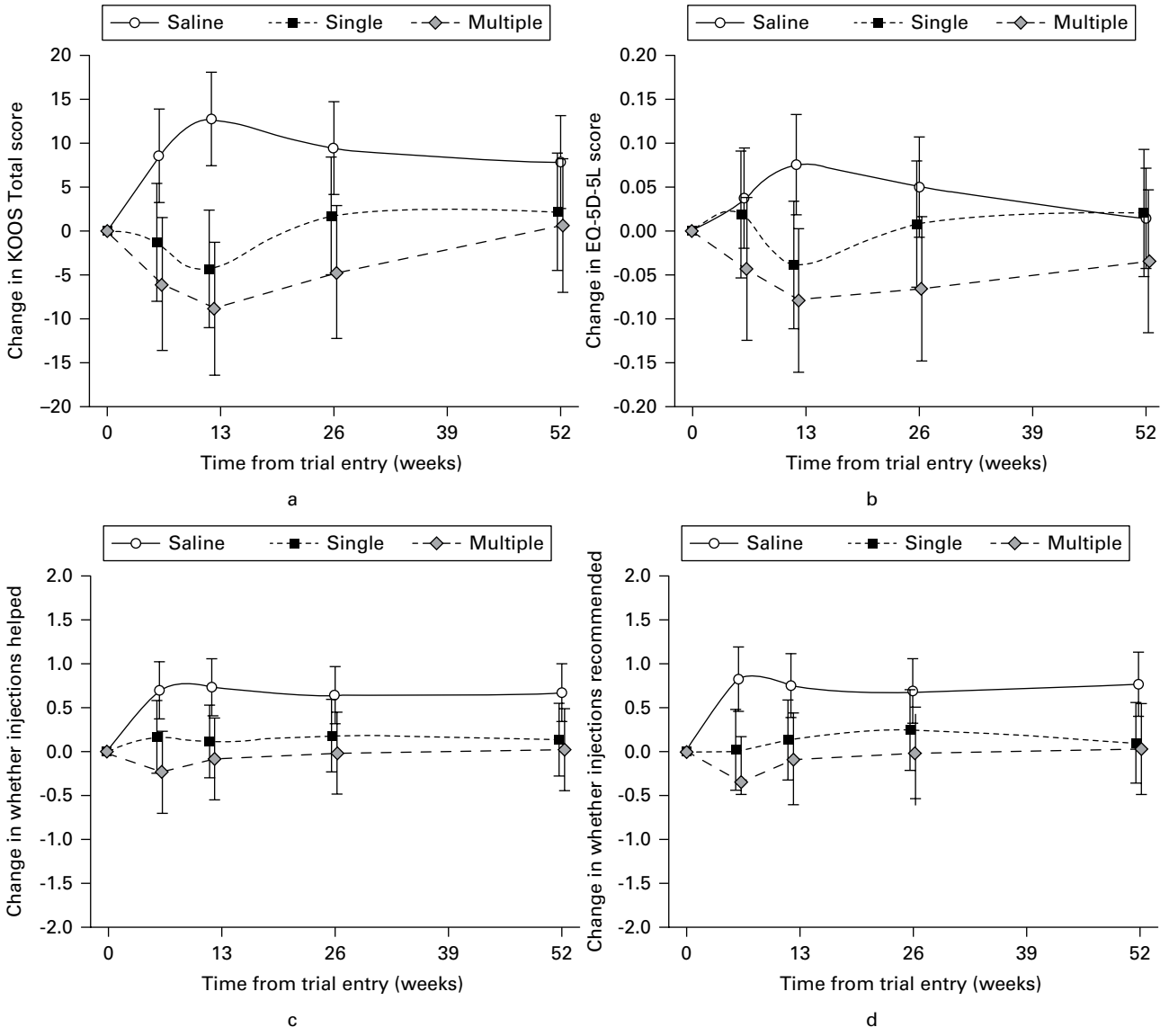

Fig. 2

Independent effects of saline injections, and the additional effects of single injections and multiple injections on outcomes of the platelet-rich plasma randomized controlled trial.

The majority of patients in this trial thought saline injections helped them, and would recommend the treatment. Single PRP injection might have marginally better patient-perceived benefit than saline injection, but the numbers were not large enough to represent significant effect. There is no evidence that multiple PRP injections were superior to saline injections. The pattern of patient opinions was consistent with knee functional and symptomatic measures.

We have demonstrated, in comparison to this control intervention, neither single nor multiple PRP injections offer additional improvements in pain relief, KOOS, or EQ-5D-5L. The single and multiple PRP injections were associated with an apparent small initial reduction in scores, i.e. worsening of the symptoms. This could be explained by the greater inflammatory response and increased synoviocyte cell death caused by the PRP injection.[39,40] This is also supported by the fact that these patients experienced greater swelling after PRP injection. Further research to identify responders from non-responders would also be useful in this domain.

Post-hoc analysis of our data estimated the MCID required by participants to justify non-surgical treatment of knee OA was in the range of 5.5 to 6.5 units of the KOOS-Total and EQ-5D-5L 0 to 100 scales, although the 95% CIs for these estimates were moderately large. This was considerably lower than the 12.5-unit difference included in the sample size calculation when designing this study. Using these numbers to perform a power analysis for a repeat of this study suggested the need for between 400 and 550 participants to detect a MCID across the 95% CI range of assumed values. These would be the minimum numbers required to detect any difference with wide CIs, and

much larger numbers would be required to narrow the 95% CIs to the extent that the upper and lower limits would support the same clinical decision, pragmatically requiring a meta-analysis of multiple randomized controlled trials.

In addition to the limitations highlighted previously, concerning the standardization of leucocyte-poor PRP, our study has some further limitations. A controlled no-treatment group would have been helpful to describe the natural history of the disease, map the natural fluctuations in pain scores that this cohort of patients can display, and could refute the argument that saline has therapeutic effects. However, the addition of such a group was not possible in the setting of patient-blinded study design. As stated, the sample size was inadequate for a clear demonstration of superiority, and non-inferiority would have been even more difficult to show. It is not possible to demonstrate correlation with optimum orthobiologic therapeutic effectiveness standards. Finally, data regarding exercise and physiotherapy programmes undertaken by the involved patients were not collected, which may add to the heterogeneity of the results.

In conclusion, there is no evidence from this trial that single or multiple PRP injections improve patient-reported outcomes compared to saline injection up to 12 months post-intervention. The estimated MCID would suggest the need for a much larger sample size to answer that therapeutic question.

Take home message

- This study provides 12-month follow-up with Knee injury and Osteoarthritis Outcome Score and EuroQol five-dimension five-level index outcomes for saline, single, and multiple platelet-rich plasma (PRP) injections for patients with knee osteoarthritis in its early stages in a double-blinded randomized control trial.
- Importantly, given the popularity of PRP injections for this condition, there is no evidence that single or multiple PRP had any additional beneficial effect compared to saline injection.

Supplementary material

The study protocol is attached in the supplementary material.

References

1. **Hunter DJ**, **Schofield D**, **Callander E**. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol*. 2014;10(7):437–441.
2. **Losina E**, **Paltiel AD**, **Weinstein AM**, **et al**. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. *Arthritis Care Res (Hoboken)*. 2015;67(2):203–215.
3. **Moatshe G**, **Morris ER**, **Cinque ME**, **et al**. Biological treatment of the knee with platelet-rich plasma or bone marrow aspirate concentrates: A review of the current status. *Acta Orthop*. 2017;88(6):670–674.
4. **Bennell KL**, **Hunter DJ**, **Hinman RS**. Management of osteoarthritis of the knee. *BMJ*. 2012;345:e4934.
5. **Heijink A**, **Gomoll AH**, **Madry H**, **et al**. Biomechanical considerations in the pathogenesis of osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(3):423–435.
6. **Dhillon MS**, **Behera P**, **Patel S**, **Shetty V**. Orthobiologics and platelet rich plasma. *Indian J Orthop*. 2014;48(1):1–9.
7. **Moatshe G**, **Morris ER**, **Cinque ME**, **et al**. Biological treatment of the knee with platelet-rich plasma or bone marrow aspirate concentrates: A review of the current status. *Acta Orthop*. 2017;88(6):670–674.
8. **O'Connell B**, **Wragg NM**, **Wilson SL**. The use of PRP injections in the management of knee osteoarthritis. *Cell Tissue Res*. 2019;376(2):143–152.
9. **Rahimzadeh P**, **Imani F**, **Faiz SHR**, **Entezary SR**, **Zamanabadi MN**, **Alebouyeh MR**. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. *Clin Interv Aging*. 2018;13:73–79.
10. **Rayegani SM**, **Raeissadat SA**, **Taheri MS**, **et al**. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. *Orthop Rev (Pavia)*. 2014;6(3):5405.
11. **Riboh JC**, **Saltzman BM**, **Yanke AB**, **Fortier L**, **Cole BJ**. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med*. 2016;44(3):792–800.
12. **Slimi F**, **Zribi W**, **Trigui M**, **et al**. The effectiveness of platelet-rich plasma gel on full-thickness cartilage defect repair in a rabbit model. *Bone Joint Res*. 2021;10(3):192–202.
13. **Chahla J**, **Cinque ME**, **Piuzzi NS**, **et al**. A call for standardization in platelet-rich plasma preparation protocols and composition reporting: A systematic review of the clinical orthopaedic literature. *J Bone Joint Surg Am*. 2017;99-A(20):1769–1779.
14. **No authors listed**. Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline. American Academy of Orthopaedic Surgeons. 2021. https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf (date last accessed 27 April 2022).
15. **Kolasinski SL**, **Neogi T**, **Hochberg MC**, **et al**. American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220–233.
16. **Salzler MJ**. Editorial Commentary: platelet-rich plasma: fountain of youth, cart before the horse, or both. *Arthroscopy*. 2018;34(5):1541–1542.
17. **LaPrade RF**, **Geeslin AG**, **Murray IR**, **et al**. Biologic treatments for sports injuries II think tank-current concepts, future research, and barriers to advancement, Part 1: biologics overview, ligament injury, tendinopathy. *Am J Sports Med*. 2016;44(12):3270–3283.
18. **Braun HJ**, **Wasterlain AS**, **Dragoo JL**. The use of PRP in ligament and meniscal healing. *Sports Med Arthrosc Rev*. 2013;21(4):206–212.
19. **Richards MM**, **Maxwell JS**, **Weng L**, **Angelos MG**, **Golzarian J**. Intra-articular treatment of knee osteoarthritis: from anti-inflammatories to products of regenerative medicine. *Phys Sportsmed*. 2016;44(2):101–108.
20. **Wasterlain AS**, **Braun HJ**, **Harris AHS**, **Kim H-J**, **Dragoo JL**. The systemic effects of platelet-rich plasma injection. *Am J Sports Med*. 2013;41(1):186–193.
21. **Filardo G**, **Kon E**, **Roffi A**, **Di Matteo B**, **Merli ML**, **Marcacci M**. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(9):2459–2474.
22. **Lai LP**, **Stitik TP**, **Foye PM**, **Georgy JS**, **Patibanda V**, **Chen B**. Use of platelet-rich plasma in intra-articular knee injections for osteoarthritis: a systematic review. *PM R*. 2015;7(6):637–648.
23. **Laudy ABM**, **Bakker EWP**, **Rekers M**, **Moen MH**. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *Br J Sports Med*. 2015;49(10):657–672.
24. **Meheux CJ**, **McCulloch PC**, **Lintner DM**, **Varner KE**, **Harris JD**. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. *Arthroscopy*. 2016;32(3):495–505.
25. **Tietze DC**, **Geissler K**, **Borchers J**. The effects of platelet-rich plasma in the treatment of large-joint osteoarthritis: a systematic review. *Phys Sportsmed*. 2014;42(2):27–37.
26. **Baltzer AWA**, **Moser C**, **Jansen SA**, **Krauspe R**. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. *Osteoarthr Cartil*. 2009;17(2):152–160.
27. **Dhillon M**, **Patel S**, **Bali K**. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis; author reply 865-866. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(5):863–864.
28. **Gobbi A**, **Lad D**, **Karnatzikos G**. The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(8):2170–2177.
29. **Görmeli G**, **Görmeli CA**, **Ataoglu B**, **Çolak C**, **Aslantürk O**, **Ertem K**. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(3):958–965.
30. **Saltzman BM**, **Leroux T**, **Meyer MA**, **et al**. The therapeutic effect of intra-articular normal saline injections for knee osteoarthritis: a meta-analysis of evidence level 1 studies. *Am J Sports Med*. 2017;45(11):2647–2653.
31. **KELLGREN JH**, **LAWRENCE JS**. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16(4):494–502.
32. **Roos EM**, **Lohmander LS**. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
33. **Herdman M**, **Gudex C**, **Lloyd A**, **et al**. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727–1736.

34. **Çelik D**, **Çoban Ö**, **Kılıçoğlu Ö**. Minimal clinically important difference of commonly used hip-, knee-, foot-, and ankle-specific questionnaires: a systematic review. *J Clin Epidemiol*. 2019;113:44–57.
35. **Chahla J**, **Cinque ME**, **Piuzzi NS**, **et al**. A call for standardization in platelet-rich plasma preparation protocols and composition reporting: A systematic review of the clinical orthopaedic literature. *J Bone Joint Surg Am*. 2017;99-A(20):1769–1779.
36. **Rossi LA**, **Murray IR**, **Chu CR**, **Muschler GF**, **Rodeo SA**, **Piuzzi NS**. Classification systems for platelet-rich plasma. *Bone Joint J*. 2019;101-B(8):891–896.
37. **Hróbjartsson A**, **Gøtzsche PC**. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med*. 2001;344(21):1594–1602.
38. **Siemieniuk RAC**, **Harris IA**, **Agoritsas T**, **et al**. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *Br J Sports Med*. 2018;52(5):313.
39. **Braun HJ**, **Kim HJ**, **Chu CR**, **Dragoo JL**. The effect of platelet-rich plasma formulations and blood products on human synoviocytes. *Am J Sports Med*. 2014;42(5):1204–1210.
40. **Braun HJ**, **Kim HJ**, **Chu CR**, **Dragoo JL**. The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy. *Am J Sports Med*. 2014;42(5):1204–1210.

Author information:
E. Lewis, MBBS, Orthopaedic Registrar
K. Merghani, MBBS, FRCS(T&O), Orthopaedic Fellow
J. Mulford, MBBS, FRACS(Orth), Orthopaedic Surgeon
B. Prentice, MBBS, Orthopaedic Registrar
R. Mathew, MBBS, Orthopaedic Registrar
P. Van Winden, MBBS, FRACS(Orth), Orthopaedic Surgeon
Launceston General Hospital, Launceston, Australia.

I. Robertson, M.Med.Sci., MPH, Medical Statistician
K. Ogden, MBBS, FRACGP, Senior Lecturer, General Practitioner
College of Health and Medicine, University of Tasmania, Launceston, Australia; Clifford Craig Foundation, Launceston General Hospital, Launceston, Australia.

Author contributions:
E. Lewis: Methodology, Investigation, Writing – original draft.
K. Merghani: Writing – original draft.
I. Robertson: Methodology, Formal analysis, Writing – original draft.
J. Mulford: Methodology, Writing – review & editing.
B. Prentice: Resources, Investigation, Writing – review & editing.
R. Mathew: Investigation, Writing – review & editing.
P. Van Winden: Methodology, Resources, Writing – review & editing.
K. Ogden: Methodology, Writing – review & editing.

Funding statement:
The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: a grant from the Clifford Craig Foundation, a private medical research charity, which covered the cost of study materials and a research nurse.

ICMJE COI statement:
I. Robertson is employed as a Medical Statistician by the Clifford Craig Foundation. R. Mathews reports funding for resources from the Clifford Craig Foundation for this study.

Acknowledgements:
The authors wish to acknowledge Jane Niekamp's contributions to this study as a research assistant.

Trial registration number:
Australian New Zealand Clinical Trials Registry Registration Number ACTRN12617001162303 Tasmanian Health & Medical Human Research Ethics Committee (EC00337).

This article was primary edited by D. Johnstone.