

Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis The RESTORE Randomized Clinical Trial

Kim L. Bennell, PhD; Kade L. Paterson, PhD; Ben R. Metcalf, BSc; Vicky Duong, DPT; Jillian Eyles, PhD; Jessica Kasza, PhD; Yuanyuan Wang, PhD; Flavia Cicuttini, PhD; Rachelle Buchbinder, PhD; Andrew Forbes, PhD; Anthony Harris, MSc; Shirley P. Yu, MPH; David Connell, MMed; James Linklater, MBBS; Bing Hui Wang, PhD; Win Min Oo, PhD; David J. Hunter, PhD

IMPORTANCE Most clinical guidelines do not recommend platelet-rich plasma (PRP) for knee osteoarthritis (OA) because of lack of high-quality evidence on efficacy for symptoms and joint structure, but the guidelines emphasize the need for rigorous studies. Despite this, use of PRP in knee OA is increasing.

OBJECTIVE To evaluate the effects of intra-articular PRP injections on symptoms and joint structure in patients with symptomatic mild to moderate radiographic medial knee OA.

DESIGN, SETTING, AND PARTICIPANTS This randomized, 2-group, placebo-controlled, participant-, injector-, and assessor-blinded clinical trial enrolled community-based participants ($n = 288$) aged 50 years or older with symptomatic medial knee OA (Kellgren and Lawrence grade 2 or 3) in Sydney and Melbourne, Australia, from August 24, 2017, to July 5, 2019. The 12-month follow-up was completed on July 22, 2020.

INTERVENTIONS Interventions involved 3 intra-articular injections at weekly intervals of either leukocyte-poor PRP using a commercially available product ($n = 144$ participants) or saline placebo ($n = 144$ participants).

MAIN OUTCOMES AND MEASURES The 2 primary outcomes were 12-month change in overall average knee pain scores (11-point scale; range, 0-10, with higher scores indicating worse pain; minimum clinically important difference of 1.8) and percentage change in medial tibial cartilage volume as assessed by magnetic resonance imaging (MRI). Thirty-one secondary outcomes (25 symptom related and 6 MRI assessed; minimum clinically important difference not known) evaluated pain, function, quality of life, global change, and joint structures at 2-month and/or 12-month follow-up.

RESULTS Among 288 patients who were randomized (mean age, 61.9 [SD, 6.5] years; 169 [59%] women), 269 (93%) completed the trial. In both groups, 140 participants (97%) received all 3 injections. After 12 months, treatment with PRP vs placebo injection resulted in a mean change in knee pain scores of -2.1 vs -1.8 points, respectively (difference, -0.4 [95% CI, -0.9 to 0.2] points; $P = .17$). The mean change in medial tibial cartilage volume was -1.4% vs -1.2%, respectively (difference, -0.2% [95% CI, -1.9% to 1.5%]; $P = .81$). Of 31 prespecified secondary outcomes, 29 showed no significant between-group differences.

CONCLUSIONS AND RELEVANCE Among patients with symptomatic mild to moderate radiographic knee OA, intra-articular injection of PRP, compared with injection of saline placebo, did not result in a significant difference in symptoms or joint structure at 12 months. These findings do not support use of PRP for the management of knee OA.

TRIAL REGISTRATION Australian New Zealand Clinical Trials Registry Identifier: ACTRN12617000853347

- + [Visual Abstract](#)
- ← [Editorial page 2012](#)
- + [Supplemental content](#)
- + [CME Quiz at \[jamacmlookup.com\]\(#\)](#)

Knee osteoarthritis (OA) affects approximately 260 million people worldwide and is a common cause of disability.¹ Effective and safe medical treatments are needed. Currently, no approved disease-modifying drugs exist, and nonoperative therapies are associated with only small to moderate benefits and may have serious adverse effects.^{2,3}

Platelet-rich plasma (PRP) is a safe autologous blood product containing high levels of growth factors and cytokines with potential to alter biological processes implicated in OA pathogenesis and symptoms.⁴ Although PRP is increasingly used to treat knee OA,⁵ evidence to support clinical benefits of PRP is limited. Some systematic reviews reported favorable pain and function outcomes associated with PRP compared with saline or hyaluronic acid^{6,7} and suggested that benefit was greatest in patients with mild to moderate radiographic disease.⁸ However, clinical trials of efficacy to date have been limited by a high risk of bias in PRP trials, particularly lack of blinding. Whether PRP influences joint structure is unclear.⁹⁻¹¹ Current OA clinical guidelines,^{2,3} including those from the American College of Rheumatology,³ recommend against PRP because of very low-certainty evidence and emphasize the need for rigorous studies.

This study evaluated the efficacy of intra-articular PRP injections on symptoms and joint structure in patients with knee OA. It was hypothesized that PRP would lead to greater improvements in knee pain severity and less medial tibial cartilage volume loss at 12 months compared with placebo saline injections.

Methods

Study Design

RESTORE was a 2-group, multisite, superiority randomized clinical trial (RCT). The institutional human ethics committees approved the study. Participants provided written informed consent. The trial protocol is available in [Supplement 1](#).¹² A checklist of minimum reporting requirements for PRP clinical studies is available in eTable 1 in [Supplement 2](#).¹³

Patients

Community-based volunteer participants in Melbourne and Sydney, Australia, were recruited from broadcast, print, and social media; clinicians; and the researchers' volunteer databases at the University of Melbourne and the University of Sydney. Eligible participants were aged 50 years or older; had knee pain most days of the past month; had an average knee pain score of 4 or higher on an 11-point numerical rating scale in the past week; and had mild to moderate radiographic tibiofemoral OA (Kellgren and Lawrence grade 2 or 3).¹⁴ Exclusion criteria ([Supplement 1](#)) included radiographic lateral joint space narrowing that was greater than medial,¹⁵ systemic or inflammatory disease, injection of a glucocorticoid in the past 3 months or hyaluronic acid in the past 6 months, past treatment with an autologous blood product or stem cell preparation, platelet count of $150 \times 10^3/\mu\text{L}$ or lower, bleeding disorder, or ongoing anticoagulation therapy. In cases of bilateral knee OA, the most symptomatic knee underwent the intervention.

Key Points

Question Does intra-articular injection of platelet-rich plasma (PRP), compared with placebo saline injection, improve symptoms and joint structure in patients with knee osteoarthritis?

Findings In this randomized clinical trial that included 288 adults aged 50 years or older with mild to moderate radiographic knee osteoarthritis, treatment with PRP vs placebo injection resulted in a mean change in knee pain scores of -2.1 vs -1.8 on an 11-point scale (range, 0-10) and a mean change in medial tibial cartilage volume of -1.4% vs -1.2% at 12 months. Neither comparison was statistically significant.

Meaning Among adults with mild to moderate knee osteoarthritis, treatment with PRP vs saline injection did not significantly improve knee pain or slow disease progression.

Randomization and Masking

The randomization schedule was prepared using computer-generated random numbers and stored by the National Health and Medical Research Council Clinical Trial Centre with permuted block sizes of 6 or 10, stratified by site (Melbourne or Sydney) and radiographic severity (Kellgren and Lawrence grade 2 or 3). Immediately before preparing the first injection, nurses telephoned the Clinical Trial Centre to reveal group allocation (1:1 ratio). Participants, injecting radiologists (D.C. and J.L.), assessors, and the biostatistician (J.K.) were blinded to group allocation.

Interventions

Potential participants completed online screening followed by telephone, radiographic, and laboratory-based screening before visiting a study site for clinical screening. Eligible participants completed baseline questionnaires and visited 1 of 2 radiology centers for magnetic resonance imaging (MRI). Follow-up questionnaires were completed at both 2- and 12-month follow-up. Follow-up MRI was performed at 12-month follow-up.

Participants were asked to discontinue nonsteroidal anti-inflammatory drugs and other analgesics for knee pain (except acetaminophen rescue pain relief) from 2 weeks before baseline assessment through 12-month follow-up.

Participants in both groups received 3 intra-articular knee injections (at weekly intervals) under ultrasound guidance using a medial patellofemoral approach by an experienced musculoskeletal radiologist,¹⁶ with the option of a subcutaneous local anesthetic injection. All participants underwent blood withdrawals to maintain blinding. Nurses prepared the injection (5 mL of fresh PRP or normal saline in a syringe with a 22-gauge needle) in a separate room, placing an opaque label around the syringe and needle base to mask contents from radiologists and participants. If an effusion was present and amenable to aspiration, this was performed using a separate syringe via the suprapatellar bursa. Following injection, passive knee flexion/extension was performed 5 times, and participants rested for 10 minutes.

Although the optimal PRP preparation protocol is not yet established, preparations in RCTs reporting symptom benefits in knee OA have generally used a single slower-speed centrifugation cycle for 5 minutes and injected fresh leukocyte-poor PRP at weekly intervals for 3 weeks.¹⁶ Thus, fresh PRP samples were

prepared at each weekly visit using a commercial product (Regen Lab SA) with single centrifugation at 1500g for 5 minutes. This protocol yields a platelet concentration factor of 1.6 to 5 times more than whole blood values, with approximately 80% platelet recovery, and is leukocyte poor.¹⁷ Details of the PRP characteristics according to recommended standards^{13,18} are available in eTable 2 in [Supplement 2](#).

Outcomes

The 2 primary outcomes were 12-month change in symptoms and 12-month percentage change in MRI-measured medial tibial cartilage volume, respectively. These 2 co-primary outcomes were interpreted separately. Average overall knee pain severity during the past week was assessed at baseline and at 12-month follow-up using a validated 11-point numerical rating scale with terminal descriptors of 0 (no pain) and 10 (worst pain possible). The minimum clinically important difference (MCID) for the 11-point scale is 1.8 points.¹⁹ Medial tibial cartilage volume was measured at baseline and 12 months with knee MRI using a 3T whole body system with a dedicated extremity coil and a T1-weighted, fat-suppressed, 3-dimensional gradient recall acquisition sequence (eTable 3 in [Supplement 2](#)). Each participant's paired image set was evaluated by a single assessor (blinded to time sequence and treatment allocation)¹² with excellent reliability (20 MRIs measured twice in blinded order; intraclass correlation coefficient, 0.92 [95% CI, 0.82-0.97]). The MCID for the MRI outcome is unknown.

Prespecified secondary self-reported symptom-related outcomes were as follows: (1) 2-month change in average overall knee pain severity; (2) 2- and 12-month changes in knee pain severity during walking over the past week as measured on an 11-point scale; (3) 2- and 12-month changes in scores on the intermittent pain subscale of the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire²⁰ (5-point Likert scale; range, 0-100, with higher scores indicating worse pain; MCID, 18.4); (4) 2- and 12-month changes in scores on the constant pain subscale of the ICOAP (MCID, 18.7); (5) 2- and 12-month changes in scores on the pain subscale of the Knee Injury and Osteoarthritis Outcome Score²¹ (KOOS) (5-point Likert scales; range, 0-100, with lower scores indicating worse outcomes; MCID, 15.4); (6) 2- and 12-month changes in scores on the other symptoms subscale of the KOOS (MCID, 15.1); (7) 2- and 12-month changes in scores on the function in daily living subscale of the KOOS (MCID, 17); (8) 2- and 12-month changes in scores on the function in sport and recreation subscale of the KOOS (MCID, 11.2); (9) 2- and 12-month changes in scores on the knee-related quality-of-life subscale of the KOOS (MCID, 16.5); (10) 2- and 12-month changes in health-related quality-of-life scores on the Assessment of Quality of Life-8 Dimension instrument²² (range, -0.04 to 1.00, with higher scores indicating better quality of life; MCID, 0.06); (11) 2- and 12-month global ratings of change in overall status via 7-point Likert scales with terminal descriptors of "much worse" to "much better,"²³ with ratings of "moderately better" or "much better" classified as improvement; (12) 2- and 12-month global ratings of change in pain via 7-point Likert scales as described for change in overall status; and (13) 2- and 12-month global ratings of change in physical function via 7-point Likert scales as described for change in overall status.

Secondary MRI outcomes at 12 months were the results of the MRI Osteoarthritis Knee Score²⁴ for (1) meniscal morphology (any region worsening at 12 months; scored as yes or no; MCID not available); (2) intercondylar synovitis incorporating synovitis and effusion (worsening at 12 months; scored as yes or no; MCID not available); (3) cartilage morphology (number of areas worsening in thickness; categorized as 0, 1, 2, or ≥ 3 ; MCID not available); (4) whole knee effusion (categorized as worsened, no change, or improved; MCID not available); (5) progression of medial distal femur and proximal tibia bone marrow lesion size (scored as 0-3 per region, with higher scores indicating greater size; MCID not available); and (6) progression of cartilage defects (scored as 0-4 per region, with higher scores indicating greater cartilage defects; MCID not available). Progression (yes or no) was defined as a score increase of 1 or greater from baseline in either compartment.

Other baseline measures, such as age, sex, body mass index, symptom duration, and symptoms in other joints, were collected as described in the trial protocol ([Supplement 1](#)). Adherence was defined by number of injections administered. Cointerventions, such as pain medications, physical therapies, joint injections, and knee surgery, were self-reported at 2 and 12 months. Adverse events were self-reported following each injection and at 2 and 12 months.

Growth factor and cytokine concentrations were analyzed in PRP aliquots in a consecutive subset of participants from both sites ($n = 59$) (eAppendix 1 in [Supplement 2](#)).

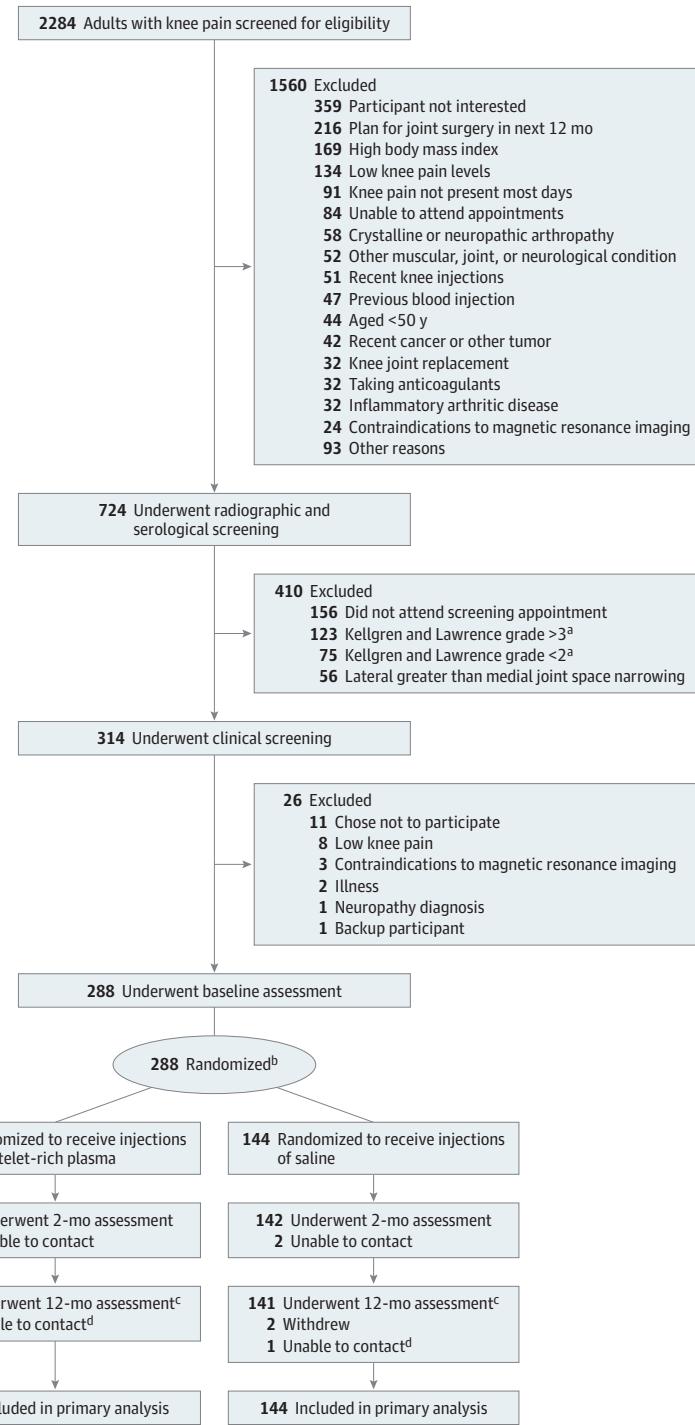
Sample Size Calculation

The study aimed to detect a 40% reduction in medial tibial cartilage volume loss in the PRP group, compared with the placebo group, since this level of reduction could delay knee replacement.²⁵ We anticipated a 2.8% (SD, 3.5%) loss of medial tibial cartilage volume in the placebo group, a 1.7% loss in the PRP group,²⁶ and a baseline to 12-month score correlation of 0.50. Using analysis of covariance adjusted for baseline, 115 participants per group were needed for 80% power with a 2-sided $\alpha = .05$ significance level. This provided greater than 99% power to detect a change in pain scores of at least 1.8 points, consistent with the MCID,¹⁹ assuming a between-participant SD of 2.4 and a baseline to 12-month correlation of 0.29.²⁶ Thus, anticipating approximately 20% attrition, 144 participants per group ($n = 288$ total) were required.

Statistical Analysis

Missing outcomes were imputed using chained equations with predictive mean matching and 5 nearest neighbors for continuous outcomes, and logistic or multinomial regression imputation models for binary improvement or categorical outcomes. Continuous outcomes at 2 and 12 months were imputed together, including baseline outcomes and characteristics as described in eAppendix 2 in [Supplement 2](#). Because of the tendency for perfect prediction (whereby the covariate completely separates outcomes, leading to failure of the imputation procedure), binary and categorical variables were imputed separately, adjusting for baseline levels of continuous outcomes and other characteristics when possible. Data were imputed for each group separately. Estimates from 20 imputed data sets were combined using Rubin rules.²⁷

Figure 1. Flow of Participants Through the Trial



^a On the Kellgren and Lawrence scale of radiographic osteoarthritis disease severity, grade 0 indicates no radiographic features of osteoarthritis; grade 1, doubtful joint space narrowing and possible osteophytic lipping; grade 2, definite osteophytes and possible joint space narrowing; grade 3, multiple osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity; and grade 4, large osteophytes, marked joint space narrowing, severe sclerosis, and definite deformity of bone ends.

^b Stratified for site (Melbourne or Sydney) and Kellgren and Lawrence grade (2 or 3).

^c Indicates the number of participants that completed at least 1 of the primary outcome measurements at 12 months.

^d Two participants in the platelet-rich plasma group and 2 in the placebo group rejoined at 12 months after being unable to contact at the 2-month assessment.

Table 1. Baseline Participant Characteristics

Characteristics	Platelet-rich plasma (n = 144)	Placebo (n = 144)
Age, mean (SD), y	62.2 (6.3)	61.6 (6.6)
Sex, No. (%)		
Female	85 (59.0)	84 (58.3)
Male	59 (41.0)	60 (41.7)
Height, mean (SD), m	167.6 (10.2)	167.3 (9.6)
Weight, mean (SD), kg	81.8 (13.6)	83.0 (14.4)
Body mass index, mean (SD) ^a	29.0 (3.7)	29.6 (4.5)
Kellgren and Lawrence grade of radiographic severity, No. (%) ^b		
2	69 (47.9)	72 (50.0)
3	75 (52.1)	72 (50.0)
Knee alignment, mean (SD), degrees ^c	180.4 (3.4) [n = 112]	180.9 (3.6) [n = 121]
Currently employed, No. (%)	87 (60.4)	93 (64.6)
Symptom duration, median (IQR), y	5.0 (2.0-12.0)	6.0 (2.5-10)
Unilateral symptoms, No. (%)	48 (33.3)	47 (32.6)
Problems in other joints, No. (%)		
Back	76 (52.8)	73 (50.7)
Hand	53 (36.8)	59 (41.0)
Neck	45 (31.3)	61 (42.4)
Foot	44 (30.6)	40 (27.8)
Shoulder	41 (28.5)	41 (28.5)
Hip	41 (28.5)	32 (22.2)
Current pain medication use, No. (%) ^d	99 (68.8)	87 (60.4)
Acetaminophen alone or in combined formulations	56 (38.9)	49 (34.0)
Topical anti-inflammatory drugs	38 (26.4)	22 (15.3)
Nonsteroidal anti-inflammatory drugs	30 (20.8)	25 (17.4)
Oral opioids	3 (2.1)	3 (2.1)
Oral corticosteroids	2 (1.4)	3 (2.1)
Treatment expectation, No. (%) ^e		
No effect	5 (3.5)	0 (0)
Improvement		
Minimal	15 (10.4)	13 (9.0)
Moderate	63 (43.8)	68 (47.2)
Large	55 (38.2)	55 (38.2)
Complete recovery	6 (4.2)	8 (5.6)
painDETECT results, No. (%) ^f		
Nociceptive knee pain	102 (70.8)	108 (75.0)
Unclear	34 (23.6)	26 (18.1)
Neuropathic-like knee pain	8 (5.6)	10 (6.9)
Physical Activity Scale for the Elderly score, median (IQR) ^g	163.1 (109.4-235.5)	170.8 (118.5-230.0)
Overall knee pain score, mean (SD) ^h	5.7 (1.5)	5.7 (1.5)

(continued)

Comparative analyses were performed using Stata version 15.1 (StataCorp). All participants were analyzed in their originally randomized groups, regardless of adherence. Models included terms for stratifying variables and baseline measures of the outcome (except global change). For the primary outcome of knee pain and the secondary continuous outcomes, the difference in mean change (follow-up minus

Table 1. Baseline Participant Characteristics (continued)

Characteristics	Platelet-rich plasma (n = 144)	Placebo (n = 144)
Medial tibial cartilage volume, mean (SD), mm ³ ⁱ	1337 (488)	1309 (479)
Medial tibial plateau cross-sectional area, mean (SD), cm ² ^j	22.9 (3.8)	23.3 (3.8)
Presence of knee effusion, No. (%) ^k	63 (43.8)	53 (36.8)

^a Calculated as weight in kilograms divided by height in meters squared.

^b The Kellgren and Lawrence system grades radiographic osteoarthritis disease severity from 0 to 4. Grade 2 indicates presence of osteophytes and possible joint space narrowing; grade 3, multiple osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity.

^c Measured as anatomical axis from standing radiograph with 180° indicating neutral alignment; <180°, varus alignment; and >180°, valgus alignment.

^d Defined as taken at least once per week over the prior month.

^e Treatment expectation was assessed by a 5-point Likert scale with participants asked "What effect do you think injections of platelet-rich plasma will have on your knee?"

^f painDETECT is a 13-item screening survey for neuropathic-like pain. Total range, 0-38; category ranges: 0-12 indicates nociceptive pain; 13-18, unclear; and 19-38, neuropathic-like pain.

^g The Physical Activity Scale for the Elderly is a 12-item questionnaire that asks about leisure, household, and occupational activity over the past week. Scores range from 0 to more than 400, with higher scores indicating higher physical activity.

^h Measured on an 11-point numeric rating scale for average knee pain in the past week. Score range is 0 (no pain) to 10 (worst pain possible); higher scores indicate worse pain.

ⁱ A single rater (blinded to group and time point) measured medial tibial cartilage volume from sagittal magnetic resonance images (MRI) by manually drawing disarticulation contours around the cartilage boundaries on each section using OsiriX software. These data were resampled by bilinear and cubic interpolation for the final 3-dimensional rendering. The cartilage plate volume was determined by summing the pertinent voxels within the resultant binary volume.

^j Medial tibial plateau cross-sectional area was measured manually from axial MRI on the 2 consecutive images closest to the tibial cartilage by a single rater using OsiriX software. The mean of these 2 areas was used as an estimate of tibial plateau bone area.

^k Graded from MRI images and scored by a single rater (blinded to group) using the MRI Osteoarthritis Knee Score effusion subscore, with 0 indicating normal; 1, small; 2, medium; and 3, large. Presence of knee effusion was defined as a score of 2 or 3.

baseline) was compared between the 2 groups using mixed linear regression including an interaction between month (time point) and treatment group and random effects for participants. Outcomes from 2 and 12 months were analyzed in a single model. For the primary structural outcome, the difference in annual percentage change was compared between groups using linear regression. Binary outcomes were analyzed via binomial regression models with a log-link fit using generalized estimating equations to account for multiple measurements per participant, including terms for month and treatment group and an interaction between them. A 2-sided significance level of $\alpha = .05$ was applied. Because of the potential for type I error due to multiple comparisons, secondary outcomes should be interpreted as exploratory. Post hoc complete-case analyses were also performed using methods described above, including all available data and participants in their originally randomized groups.

The statistical analysis plan (*Supplement 3*) describes sensitivity analyses that included excluding participants treated before a centrifuge speed change (n = 30) and controlling for

Table 2. Continuous Outcomes at Baseline and 12 Months by Treatment Group^a

Outcomes	Values, mean (SD)			Placebo (n = 144)			Difference in change between groups, mean (95% CI) ^b	P value
	Platelet-rich plasma (n = 144)		Within-group change	Placebo (n = 144)		Within-group change		
	Baseline	12 mo		Baseline	12 mo			
Primary outcomes								
Overall knee pain score ^{c,d}	5.7 (1.5)	3.5 (2.6)	-2.1 (2.7)	5.7 (1.5)	3.9 (2.6)	-1.8 (2.5)	-0.4 (-0.9 to 0.2)	.17
Annual change in medial tibial cartilage volume, % ^{e,f}		-1.4 (7.2)	-1.4 (7.2)		-1.2 (6.8)	-1.2 (6.8)	-0.2 (-1.9 to 1.5)	.81
Secondary outcomes								
Knee pain while walking ^{c,d}	5.8 (2.1)	3.8 (2.6)	-2.0 (2.6)	5.7 (2.1)	4.1 (2.8)	-1.6 (2.8)	-0.4 (-1.0 to 0.2)	.21
Intermittent and Constant Osteoarthritis Pain score ^{d,g}								
Constant pain	6.7 (4.1)	3.9 (4.1)	-2.8 (4.8)	6.7 (3.6)	3.9 (4.4)	-2.7 (4.5)	-0.1 (-1.0 to 0.8)	.84
Intermittent pain	10.6 (4.1)	7.4 (4.6)	-3.2 (5.3)	10.4 (3.2)	7.5 (5.2)	-2.9 (4.8)	-0.2 (-1.3 to 0.8)	.68
Knee Injury and Osteoarthritis Outcome Score ^{f,h}								
Pain	52.9 (15.2)	68.0 (18.2)	15.1 (18.9)	53.5 (13.5)	65.4 (19.9)	11.9 (17.6)	3.1 (-0.8 to 6.9)	.12
Other symptoms	53.9 (15.9)	67.2 (18.9)	13.3 (19.0)	53.3 (16.6)	63.7 (20.1)	10.4 (17.0)	3.3 (-0.5 to 7.1)	.09
Function in daily living	58.7 (16.9)	72.6 (18.4)	13.9 (18.9)	58.8 (16.3)	71.4 (19.7)	12.6 (17.6)	1.3 (-2.5 to 5.2)	.49
Function in sport and recreation	30.1 (19.3)	45.2 (25.3)	15.1 (25.1)	26.0 (18.7)	40.9 (24.9)	14.9 (21.4)	1.9 (-3.0 to 6.9)	.44
Knee-related quality of life	33.8 (15.8)	51.1 (20.1)	17.2 (20.5)	34.2 (16.8)	48.3 (22.0)	14.1 (19.7)	3.0 (-1.3 to 7.3)	.17
Assessment of Quality of Life-8 Dimension score ^{f,i}	0.72 (0.15)	0.76 (0.16)	0.04 (0.13)	0.72 (0.16)	0.76 (0.17)	0.04 (0.12)	-0.00 (-0.03 to 0.03)	.91

^a Missing outcomes were imputed. Twenty data sets were imputed separately by group using predictive mean matching with the 5 nearest neighbors, with results combined using Rubin rules.

^b Adjusted for baseline value of the outcome, stratifying variables (site and Kellgren and Lawrence grade), and clustering of 2- and 12-month outcomes within participants (except annual percentage change in medial tibial cartilage volume given no 2-month data).

^c Measured on an 11-point numeric rating scale for average knee pain in the past week. Score range is 0 (no pain) to 10 (worst pain possible); higher scores indicate worse pain; the minimum clinically important difference (MCID) is 1.8.

^d A negative within-group change indicates improvement. For difference in change between groups, a negative difference favors the platelet-rich plasma group.

^e A single rater (blinded to group and time point) measured medial tibial cartilage volume from sagittal magnetic resonance imaging (MRI) by manually drawing disarticulation contours around the cartilage boundaries on each section using OsiriX software. These data were resampled by bilinear and cubic interpolation for the final 3-dimensional rendering. The cartilage plate volume was determined by summing the pertinent voxels within the resultant binary volume. Annual percentage change in cartilage volume was calculated

as (follow-up cartilage volume - baseline cartilage volume)/(baseline cartilage volume × time between MRI scans) × 100. Because the outcome measure is annual percentage change, there are no baseline values.

^f A positive within-group change indicates improvement. For difference in change between groups, a positive difference favors the platelet-rich plasma group.

^g The Intermittent and Constant Osteoarthritis Pain score is an 11-item, 2-subscale questionnaire for knee and hip osteoarthritis, with each item scored 0 (no pain) to 4 (extreme pain). The constant pain subscale range is 0 to 20; the intermittent pain subscale range is 0 to 24; higher scores indicate worse pain; the MCID is 18.5.

^h The Knee Injury and Osteoarthritis Outcome Score is a knee-specific questionnaire with 42 items covering 5 subscales. Total subscale scores range from 0 to 100, with 0 indicating extreme problems and 100, no problems. The MCIDs are as follows: pain, 15.4; other symptoms, 15.1; function in daily living, 17.0; function in sport and recreation, 11.2; and knee-related quality of life, 16.5.

ⁱ The Assessment of Quality of Life-8 Dimension is a 35-item questionnaire regarding health-related quality of life in the past week. The score range is -0.04 to 1.0; higher scores indicate better quality of life; the MCID is 0.06.

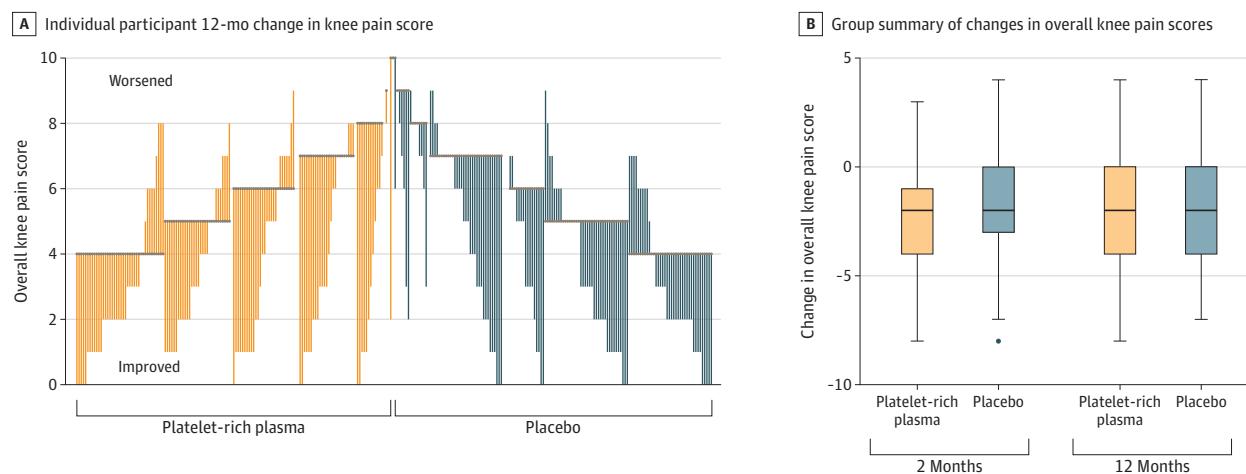
aspiration immediately prior to injection, a post hoc analysis. Additional analyses were performed to evaluate participant blinding using the James Blinding Index (blinding being successful if the 95% CI lies completely between 0.5 and 1.0)²⁸ and assessment of whether PRP effects on the primary outcomes at 12 months were moderated by Kellgren and Lawrence grade (2 or 3), effusion (yes or no), body mass index, or knee alignment. It was hypothesized that PRP benefits would be greater in participants with Kellgren and Lawrence grade 2 (compared with grade 3), absence of effusion (compared with presence of effusion), lower body mass index (compared with higher body mass index), and higher knee alignment angle (less varus malalignment). For each continuous moderator and outcome pair, the “mfp” command in Stata²⁹ was used to investigate the potential for nonlinear relationships with the model. For each pair, terms for the moderator and the interaction between randomized group and moderator were included with

stratifying variables and a group term. Planned estimation of treatment effects assuming full adherence was not performed because of the high rate of adherence.

Results

Figure 1 summarizes participant flow. A total of 288 participants from among 2284 individuals screened were enrolled between August 24, 2017, and July 5, 2019. Twelve-month follow-up was completed on July 22, 2020. Baseline participant characteristics and treatment expectations were comparable between groups (**Table 1**). At 12 months, 10 participants (6 in the PRP group and 4 in the placebo group) had missing data on the primary pain outcome and 16 participants (4 in the PRP group and 12 in the placebo group) had missing data on the structural outcome. Those missing data for both (n = 19)

Figure 2. Overall Knee Pain Individual Participant 12-Month Changes and Group Summary of Changes



A, Each vertical line represents an individual participant, with participants ordered by baseline value (gray dots) and vertical lines extending up (worsened) or down (improved) to the 12-month values. B, Box plots show the summary of changes by

group at each time point. Box tops and bottoms indicate the IQRs of the distribution; horizontal lines, medians; and whiskers, furthest points within 1.5× the IQRs. The data point outside of the whiskers is an outlier.

were comparable with those with complete data (eTable 4 in *Supplement 2*).

In each group, 140 participants (97.2%) received all 3 injections, with slightly more use of local anesthetic and less use of aspiration in the PRP group (eTable 5 in *Supplement 2*). Levels of growth factors and cytokines in the PRP preparations are shown in eTable 6 in *Supplement 2*. There were high concentrations of growth factors and cytokines that promote tissue healing and inhibit inflammatory processes (eg, platelet-derived growth factor BB, interleukin 1 receptor antagonist, and transforming growth factor β), and low concentrations of proinflammatory cytokines (eg, interleukin 1 β , interleukin 6, and matrix metalloproteinase 9). Cointerventions were comparable between groups (eTable 5 in *Supplement 2*). The James Blinding Index indicated successful blinding beyond chance (mean, 0.71 [95% CI, 0.65-0.76] for participants and 0.74 [95% CI, 0.69-0.79] for the individuals administering the injections).

Primary Outcomes

At 12 months, PRP injection was not more effective than saline placebo injection on either primary outcome (**Table 2** and **Figure 2**). For change in pain scores, the between-group mean difference was not statistically significant (-0.4 [95% CI, -0.9 to 0.2] points), favoring PRP. In within-group analyses, each group had a mean change in pain scores (PRP group, -2.1 [SD, 2.7]; placebo group, -1.8 [SD, 2.5] points) that exceeded the MCID. For percentage change in medial tibial cartilage volume, the between-group mean difference was not statistically significant (-0.2% [95% CI, -1.9% to 1.5%]), with a mean change of -1.4% (SD, 7.2%) in the PRP group and a mean change of -1.2% (SD, 7.2%) in the placebo group.

Secondary Outcomes

There was no statistically significant beneficial effect of PRP on overall pain at the 2-month secondary time point

(eTable 7 in *Supplement 2*). None of the other 24 secondary outcomes that measured symptoms at 2 and 12 months were statistically significantly different between the 2 groups, except for global improvement (**Table 2** and **Table 3**; eTable 7 in *Supplement 2*). The number of participants in the PRP group who reported global improvement overall was statistically significantly greater than in the placebo group at 2 months (PRP group, 68/141 [48.2%] vs placebo group, 51/141 [36.2%]; risk ratio, 1.37 [95% CI, 1.05-1.80]; $P = .02$).

More participants in the PRP group than in the placebo group reported global improvement in function at 12-month follow-up (PRP group, 59/138 [42.8%] vs placebo group, 45/140 [32.1%]; risk ratio, 1.36 [95% CI, 1.00-1.86]; $P = .05$) (**Table 3**). None of the 6 secondary structural outcomes showed statistically significant benefits of PRP at 12-month follow-up (**Table 3**). The number of participants in the PRP group who had 3 or more areas of cartilage thinning was statistically significantly greater than in the placebo group (PRP group, 24/140 [17.1%] vs placebo group, 9/133 [6.8%]; risk ratio, 2.71 [95% CI, 1.16-6.34]; $P = .02$).

Post hoc complete-case analyses (eTables 8-10 in *Supplement 2*) and sensitivity analyses accounting for PRP centrifuge speed (eTable 11 in *Supplement 2*) and use of aspiration (eTable 12 in *Supplement 2*) yielded similar results. There was no evidence that Kellgren and Lawrence grade, body mass index, knee effusion, or knee alignment significantly moderated the effects of PRP on the 2 primary outcomes at 12-month follow-up (eTables 13 and 14 in *Supplement 2*).

Adverse Events

Adverse events were minor and transient. There were no serious related adverse events. More participants in the PRP group than in the placebo group reported knee joint pain, swelling, and stiffness after injections (eTable 5 in *Supplement 2*).

Table 3. Global Improvement and Other Joint Structural Outcomes

Outcomes	No./total (%) ^a		Absolute difference (95% CI) ^b	Risk ratio (95% CI) ^b	P value
	Platelet-rich plasma	Placebo			
Global change at 2 mo^c					
Improved overall	68/141 (48.2)	51/141 (36.2)	13.07 (2.15 to 23.98)	1.37 (1.05-1.80)	.02
Improved pain	66/141 (46.8)	53/141 (37.6)	10.02 (-1.10 to 21.15)	1.27 (0.97-1.67)	.08
Improved function	53/141 (37.6)	46/141 (32.6)	5.58 (-5.24 to 16.40)	1.17 (0.86-1.61)	.31
Global change at 12 mo^c					
Improved overall	64/138 (46.4)	52/140 (37.1)	9.55 (-1.45 to 20.55)	1.27 (0.96-1.67)	.09
Improved pain	64/138 (46.4)	50/140 (35.7)	11.20 (-0.01 to 22.41)	1.32 (0.99-1.75)	.05
Improved function	59/138 (42.8)	45/140 (32.1)	11.19 (0.17 to 22.21)	1.36 (1.00-1.86)	.05
MRI Osteoarthritis Knee Score subscores at 12 mo^{d,e}					
Worse meniscus morphology ^f	37/140 (26.43)	37/133 (27.82)	-1.76 (-12.21 to 8.69)	0.94 (0.63-1.38)	.74
Worse intercondylar synovitis ^g	12/140 (8.57)	17/133 (12.78)	-3.62 (-9.91 to 2.66)	0.67 (0.34-1.33)	.26
No. of areas of cartilage thinning^h					
0	72/140 (51.4)	71/133 (53.4)		1.0 [Reference]	
1	27/140 (19.3)	37/133 (27.8)		0.72 (0.39-1.31)	.27
2	17/140 (12.1)	16/133 (12.0)		1.06 (0.49-2.28)	.88
≥3	24/140 (17.1)	9/133 (6.8)		2.71 (1.16-6.34)	.02
Change in whole knee effusionⁱ					
Improved	31/140 (22.1)	32/133 (24.1)		0.87 (0.48-1.56)	.63
No change	84/140 (60.0)	76/133 (57.1)		1.0 [Reference]	
Worsened	25/140 (17.9)	25/133 (18.8)		0.90 (0.47-1.71)	.74
Other MRI measures at 12 mo^e					
Bone marrow lesion progression ^j	34/140 (24.3)	25/132 (18.9)	4.68 (-4.21 to 13.57)	1.26 (0.81-1.98)	.31
Cartilage defects progression ^k	25/140 (17.9)	15/132 (11.4)	6.31 (-1.99 to 14.62)	1.55 (0.86-2.79)	.14

Abbreviation: MRI, magnetic resonance imaging.

^a Counts and proportions are based on complete case data.

^b Missing outcomes were imputed. Twenty data sets were imputed separately by group using predictive mean matching with the 5 nearest neighbors, with results combined using Rubin rules. Absolute differences greater than 0 and risk ratios greater than 1 indicate that the risk of the outcome is greater in the platelet-rich plasma group.

^c Rated using 7-point Likert scales with terminal descriptors of "much worse" to "much better." Participants were asked to indicate the overall change in their study knee, change in knee pain, and change in function compared with baseline, with ratings of "moderately better" or "much better" classified as improved. Absolute differences and risk ratios were adjusted for stratification variables (site and Kellgren and Lawrence grade) and clustering of 2- and 12-month outcomes within participants.

^d The MRI Osteoarthritis Knee Score is a semiquantitative MRI scoring tool for knee osteoarthritis. It was assessed by a single rater (blinded to group) grading baseline and 12-month MRI images.

^e Absolute differences and risk ratios were adjusted for baseline scores and stratification variables (site and Kellgren and Lawrence grade).

^f Three regions were scored from 0 to 9 for morphological features for each meniscus, and defined as worse if any region of either the medial or lateral meniscus was scored higher at 12 months than at baseline.

^g Incorporating synovitis and effusion and scored from 0 to 3, with 0 being normal; 1, mild; 2, moderate; and 3, severe. Defined as worse if the score was higher at 12 months than at baseline.

^h Fourteen regions each scored from 0 to 3, with 0 indicating no area with cartilage loss; 1, less than 10% of cartilage surface area with loss; 2, 10% to 75% of cartilage surface area with loss; and 3, greater than 75% of cartilage surface area with loss. Data are the number of regions for which the score was higher at 12 months than at baseline.

ⁱ Scored from 0 to 3, with 0 being normal; 1, small; 2, medium; and 3, large. Improved was defined as a lower score at 12 months than at baseline, no change was defined as the same score, and worsened was defined as a higher score.

^j Assessed by a single rater (blinded to group and time point) grading baseline and 12-month MRI images. Bone marrow lesions were graded in the medial distal femur and medial proximal tibia as 0 to 3 (0, absent; 1, occupies less than one-third of the region; 2, occupies one-third to two-thirds of the region; and 3, occupies greater than two-thirds of the region). Progression was defined as an increase in bone marrow lesion grade of 1 or greater in either the medial distal femur or medial proximal tibia between baseline and 12 months.

^k Assessed by a single rater (blinded to group and time point) grading baseline and 12-month MRI images. Cartilage defects were graded in the medial tibia and medial femur as 0 to 4 (0, normal cartilage; 1, focal blistering and intracartilaginous low-signal-intensity area with an intact surface and bottom; 2, irregularities on the surface or bottom and loss of thickness of less than 50%; 3, deep ulceration with loss of thickness of more than 50%; and 4, full-thickness chondral wear with exposure of subchondral bone). Progression was defined as a score increase of 1 or greater in either the medial tibia or medial femur between baseline and 12 months.

Discussion

In this RCT, knee injections of PRP did not significantly improve knee pain or reduce medial tibial cartilage volume loss at 12-month follow-up, compared with placebo saline injections, in people with symptomatic mild to moderate radio-

graphic knee OA. Most secondary outcomes also showed no statistically significant benefit.

There was no evidence of a statistically significant between-group difference in change in overall knee pain between PRP and placebo, with 95% CIs excluding a clinically important effect. Pain scores improved by approximately 32% to 37% in both groups, and the absolute improvement in this pain

measure exceeded the MCID. The results did not differ by body mass index, presence of knee effusion, Kellgren and Lawrence grade, or knee alignment. Thus, the trial results do not support use of this procedure (with a mean cost per injection reported as \$2032)⁵ for treating knee OA.

These results are not consistent with the statistically significant benefits of PRP compared with placebo for knee OA symptoms reported previously in a systematic review and meta-analysis of 5 RCTs.³⁰ This discrepancy may be due to differences in methodology such as PRP preparation method and injection regimen, outcome measures, and patient characteristics, as well as design issues affecting risk of bias. It is possible that the lack of blinding in prior trials influenced the reported improvement in symptoms.

The lack of a statistically significant benefit of PRP for the primary structural outcome suggests that PRP does not slow disease progression and is unlikely to reflect a type II error. Although the sample size was designed to detect a 40% reduction in percentage of cartilage volume loss over 12 months with PRP (anticipated 2.8% absolute loss in the placebo group vs 1.7% loss in the PRP group), the actual between-group difference was small (a 0.2% absolute difference) and favored the placebo group.

Analyses showed that the PRP preparation used in this study contained elevated concentrations of growth factors and cytokines that promote tissue healing and inhibit inflammatory processes, proposed mechanisms by which PRP achieves its effects. Despite elevated concentrations of these “active ingredients,” symptom and structural benefits were not evident.

Only 3 prior RCTs included structural outcomes.⁹⁻¹¹ However, sample sizes of these prior RCTs were small and may have lacked statistical power. In 1 trial of 98 participants, no statistically significant difference in MRI-assessed knee cartilage thickness at 12 months was reported with PRP (n = 33) compared with hyaluronic acid (n = 32) or nonsteroidal anti-inflammatory drugs (n = 33).⁹ In 2 other RCTs, femoral cartilage thick-

ness measured by ultrasound at 6 months was not significantly different between PRP (n = 30) and saline (n = 30),¹⁰ while PRP (n = 44) significantly improved ultrasound-assessed synovial hypertrophy/vascularity and effusion at 3 and 6 months compared with hyaluronic acid (n = 45).¹¹

This study has several strengths, including the RCT design with a large sample size; relatively long follow-up; masking of participants, injectors, assessors, and the biostatistician to treatment group; excellent adherence and retention; use of validated outcome measures of symptoms and joint structure^{31,32}; measurement of relevant PRP growth factors and cytokines (one of very few RCTs to include this); and reporting of parameters recommended for PRP studies.^{13,18}

Limitations

This study has several limitations. First, PRP preparations are heterogeneous and lack standardization. Results from this trial may not be generalizable to other PRP preparations. However, a commercially available PRP product was used in this trial with a preparation and schedule that appears more efficacious for OA.^{16,33} Second, this trial included patients with mild to moderate radiographic knee OA because prior evidence suggested that they may have greater benefits from PRP.⁸ Results reported herein may not be generalizable to more severe disease. Third, participants in this community-based sample may not represent those recruited exclusively from medical settings.

Conclusions

Among patients with symptomatic mild to moderate radiographic knee OA, intra-articular injection of PRP, compared with injection of saline placebo, did not result in a significant difference in symptoms or joint structure at 12 months. These findings do not support use of PRP for the management of knee OA.

ARTICLE INFORMATION

Accepted for Publication: October 12, 2021.

Author Affiliations: Centre for Health, Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia (Bennell, Paterson, Metcalf); Rheumatology Department, Royal North Shore Hospital, Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, New South Wales, Australia (Duong, Eyles, Yu, Oo, Hunter); Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (Kasza, Y. Wang, Cicuttini, Forbes); Rheumatology Department, Alfred Hospital, Melbourne, Victoria, Australia (Cicuttini); Monash Department of Clinical Epidemiology, Cabrini Institute, Melbourne, Victoria, Australia (Buchbinder); Centre for Health Economics, Monash University, Melbourne, Victoria, Australia (Harris); Imaging @ Olympic Park, Melbourne, Victoria, Australia (Connell); Castlereagh Imaging, Sydney, New South Wales,

Australia (Linklater); Monash Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (B. H. Wang); Biomarker Discovery Laboratory, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia (B. H. Wang); Department of Physical Medicine and Rehabilitation, University of Medicine, Mandalay, Myanmar (Oo).

Author Contributions: Drs Bennell and Kasza had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bennell and Paterson are co-first authors and contributed equally to the article.

Concept and design: Bennell, Paterson, Kasza, Y. Wang, Cicuttini, Buchbinder, Harris, Connell, Linklater, Hunter.

Acquisition, analysis, or interpretation of data: Bennell, Metcalf, Duong, Eyles, Kasza, Y. Wang, Cicuttini, Buchbinder, Forbes, Yu, Connell, Linklater, B. Wang, Oo, Hunter.

Drafting of the manuscript: Bennell, Paterson, Metcalf, Kasza, Linklater.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Metcalf, Kasza, Forbes.

Obtained funding: Bennell, Y. Wang, Buchbinder, Hunter.

Administrative, technical, or material support: Paterson, Metcalf, Duong, Eyles, Cicuttini, Harris, Yu, Linklater, B. Wang.

Supervision: Bennell, Paterson, Eyles, Y. Wang, Cicuttini, Connell, Linklater, Hunter.

Conflict of Interest Disclosures: Dr Bennell reported receiving personal fees from Wolters Kluwer for production of UpToDate knee OA clinical guidelines. Dr Paterson reported receiving grants from the Australian National Health and Medical Research Council (NHMRC) outside the submitted work. Dr Buchbinder report receiving funding from the NHMRC outside the submitted work. Dr Yu reported receiving royalties from Wolters Kluwer for contributions to UpToDate. Mr Connell reported providing PRP injections in clinical practice (Imaging @ Olympic Park). Dr Linklater reported providing

PRP injections in clinical practice (Castlereagh Imaging). Dr Hunter reported receiving personal fees for scientific advisory board membership from Biobone, Novartis, Tissuegene, Pfizer, and Lilly. No other disclosures were reported.

Funding/Support: The study was funded by NHMRC project grant 1106274. Regen Lab SA provided the commercial kits free of charge.

Role of the Funder/Sponsor: The NHMRC, the University of Melbourne, and Regen Lab SA had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank Paris Arlegui (Imaging @ Olympic Park), for administrative assistance; Jade McTernan, BSC, Naomi Haverty, BSN, and Tom Entwistle, MBBS (all from Imaging @ Olympic Park), and Annie Phillips, DipAppSci, Jennie Noakes, BMed, and Danielle Pryke, GDip (all from Castlereagh Imaging), for assisting with administration of PRP injections; and Sarah Robbins, BPhty (University of Sydney), for assisting with project management. Their roles were supported through the NHMRC research grant.

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789–1858. doi:10.1016/S0140-6736(18)32279-7
2. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578–1589. doi:10.1016/j.joca.2019.06.011
3. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 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. doi:10.1002/art.41142
4. Fice MP, Miller JC, Christian R, et al. The role of platelet-rich plasma in cartilage pathology: an updated systematic review of the basic science evidence. *Arthroscopy*. 2019;35(3):961–976.e3. doi:10.1016/j.arthro.2018.10.125
5. Werner BC, Cancienne JM, Browning R, Verma NN, Cole BJ. An analysis of current treatment trends in platelet-rich plasma therapy in the Medicare database. *Orthop J Sports Med*. 2020;8(2):2325967119900811. doi:10.1177/2325967119900811
6. Hohmann E, Tetsworth K, Glatt V. Is platelet-rich plasma effective for the treatment of knee osteoarthritis? a systematic review and meta-analysis of level 1 and 2 randomized controlled trials. *Eur J Orthop Surg Traumatol*. 2020;30(6):955–967. doi:10.1007/s00590-020-02623-4
7. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res*. 2017;12(1):16. doi:10.1186/s13018-017-0521-3
8. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;41(2):356–364. doi:10.1177/0363546512471299
9. Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín MA. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. *J Orthop Traumatol*. 2018;19(1):3. doi:10.1186/s10195-018-0501-3
10. Elik H, Doğu B, Yılmaz F, Begoglu FA, Kurancı B. The efficiency of platelet-rich plasma treatment in patients with knee osteoarthritis. *J Back Musculoskeletal Rehabil*. 2020;33(1):127–138. doi:10.3233/BMR-181374
11. Ahmad HS, Farrag SE, Okasha AE, et al. Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. *Int J Rheum Dis*. 2018;21(5):960–966. doi:10.1111/1756-185X.13315
12. Paterson KL, Hunter DJ, Metcalf BR, et al. Efficacy of intra-articular injections of platelet-rich plasma as a symptom- and disease-modifying treatment for knee osteoarthritis—the RESTORE trial protocol. *BMC Musculoskelet Disord*. 2018;19(1):272. doi:10.1186/s12891-018-2205-5
13. Murray IR, Geeslin AG, Goudie EB, Petriglione FA, LaPrade RF. Minimum information for studies evaluating biologics in orthopaedics (MIBO): platelet-rich plasma and mesenchymal stem cells. *J Bone Joint Surg Am*. 2017;99(10):809–819. doi:10.2106/JBJS.I.00793
14. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16(4):494–502. doi:10.1136/ard.16.4.494
15. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15(suppl A):A1–A56. doi:10.1016/j.joca.2006.11.009
16. Bennell KL, Hunter DJ, Paterson KL. Platelet-rich plasma for the management of hip and knee osteoarthritis. *Curr Rheumatol Rep*. 2017;19(5):24. doi:10.1007/s11926-017-0652-x
17. RegenBCT Tube Performance. Version 3. Regen Lab; February 25, 2015.
18. Kon E, Di Matteo B, Delgado D, et al. Platelet-rich plasma for the treatment of knee osteoarthritis: an expert opinion and proposal for a novel classification and coding system. *Expert Opin Biol Ther*. 2020;20(12):1447–1460. doi:10.1080/14712598.2020.1798925
19. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials, II: tables for calculating sample size for clinical trials. *J Rheumatol*. 1992;19(3):444–450.
20. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure—an OARSI/OMERACT initiative. *Osteoarthritis Cartilage*. 2008;16(4):409–414. doi:10.1016/j.joca.2007.12.015
21. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28(2):88–96. doi:10.2519/jospt.1998.28.2.88
22. Richardson J, Iezzi A, Khan MA, Maxwell A. Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument. *Patient*. 2014;7(1):85–96. doi:10.1007/s40271-013-0036-x
23. ten Klooster PM, Drossaers-Bakker KW, Taal E, van de Laar MA. Patient-Perceived Satisfactory Improvement (PPS): interpreting meaningful change in pain from the patient's perspective. *Pain*. 2006;121(1–2):151–157. doi:10.1016/j.pain.2005.12.021
24. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis Cartilage*. 2011;19(8):990–1002. doi:10.1016/j.joca.2011.05.004
25. Cicuttini FM, Jones G, Forbes A, Wluka AE. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. *Ann Rheum Dis*. 2004;63(9):1124–1127. doi:10.1136/ard.2004.021253
26. Bennell KL, Bowles KA, Payne C, et al. Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ*. 2011;342(7808):d2912. doi:10.1136/bmj.d2912
27. Carpenter JG, Kenward MG. *Multiple Imputation and Its Application*. John Wiley & Sons Ltd; 2013. doi:10.1002/9781119942283
28. James KE, Bloch DA, Lee KK, Kraemer HC, Fuller RK. An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation—a VA cooperative study. *Stat Med*. 1996;15(13):1421–1434. doi:10.1002/(SICI)1097-0258(19960715)15:13<1421::AID-SIM266>3.0.CO;2-H
29. Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med*. 2004;23(16):2509–2525. doi:10.1002/sim.1815
30. Hong M, Cheng C, Sun X, et al. Efficacy and safety of intra-articular platelet-rich plasma in osteoarthritis knee: a systematic review and meta-analysis. *Biomed Res Int*. 2021;2021:2191926. doi:10.1155/2021/2191926
31. McAlindon TE, Driban JB, Henrotin Y, et al. OARSI clinical trials recommendations: design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(5):747–760. doi:10.1016/j.joca.2015.03.005
32. Hunter DJ, Altman RD, Cicuttini F, et al. OARSI clinical trials recommendations: knee imaging in clinical trials in osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(5):698–715. doi:10.1016/j.joca.2015.03.012
33. Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med*. 2021;49(1):249–260. doi:10.1177/0363546520909397