Original Investigation NOT ON PRP, BUT PLATELET POOR!

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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

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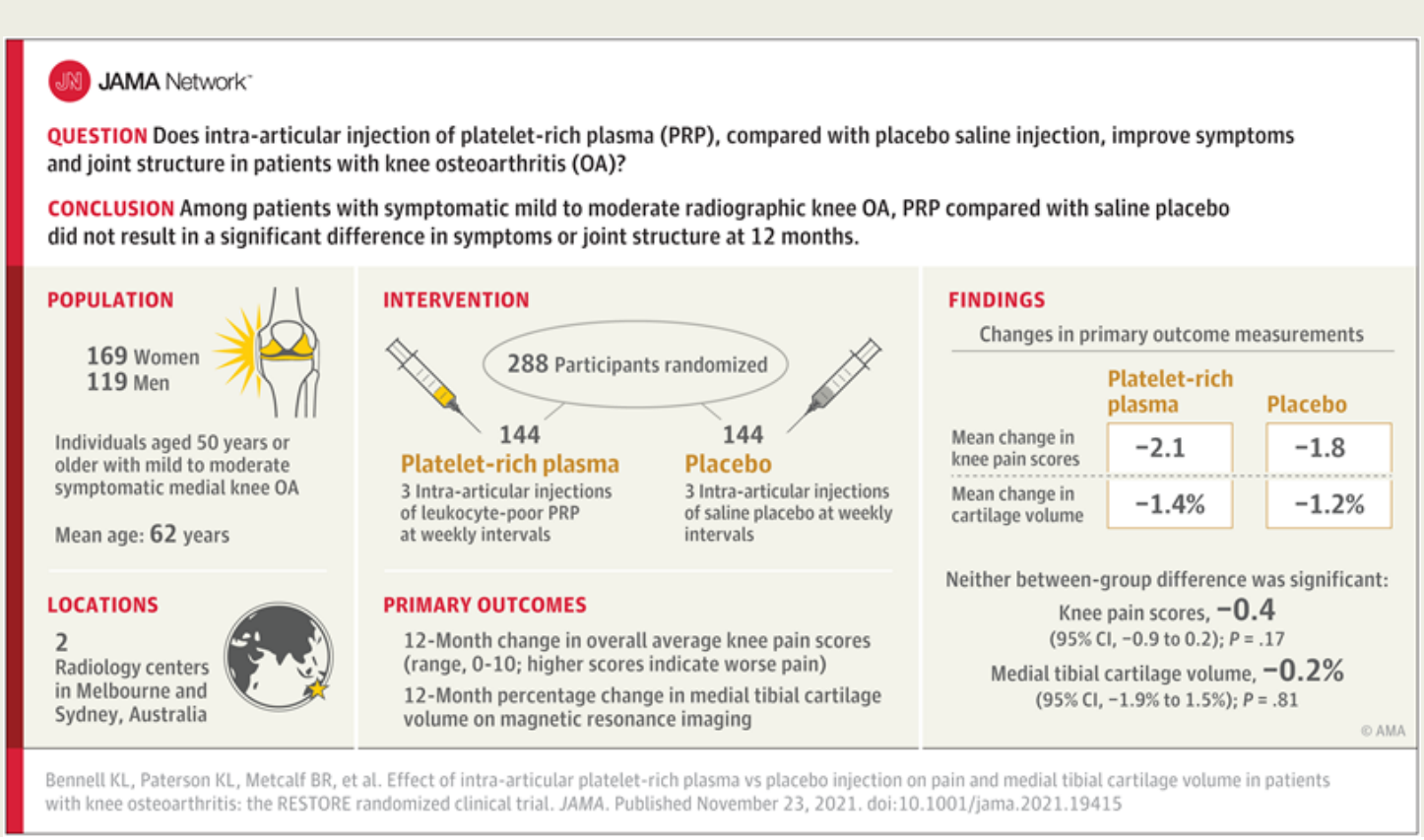

Key Points

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.

Abstract

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). JAY'S COMMENT. So they ordered something by mail, when it must be less than 60 minutes, and then used the trash I throw away. Then they call it rich when it's poor. HOW did this get past peer review.

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

Introduction

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 × 10^3/μL or lower, bleeding disorder, or ongoing anticoagulation therapy. In cases of bilateral knee OA, the most symptomatic knee underwent the intervention.

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 1500*g* 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) questionnaire[20] (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 Score[21] (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 instrument[22] (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 Score[24] for (1) meniscal morphology (any region worsening at 12 months; scored as yes or no; MCID not available); (2) intercondylar synovosis 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]

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 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 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 “mfpi” command in Stata[29] 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) 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 1β, interleukin 6, and matrix metallopeptidase 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).

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 radiographic 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 thickness 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.

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

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

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