Bone Marrow Aspirate Concentrate Is Equivalent to Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis at 1 Year

A Prospective, Randomized Trial

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Background: Approximately 47 million people in the United States have been diagnosed with arthritis. Autologous platelet-rich plasma (PRP) injections have been documented to alleviate symptoms related to knee osteoarthritis (OA) in randomized controlled trials, systematic reviews, and meta-analyses. Autologous bone marrow aspirate concentrate (BMC) injections have also emerged as a treatment option for knee OA, with a limited clinical evidence base.

Purpose: To compare the efficacy of BMC to PRP for the treatment of knee OA regarding pain and function at multiple time points up to 12 months after an injection. We hypothesized that BMC will be more effective in improving outcomes in patients with knee OA.

Study Design: Randomized controlled trial; Level of evidence, 2

Methods: A total of 90 participants aged between 18 and 80 years with symptomatic knee OA (Kellgren-Lawrence grades 1-3) were randomized into 2 study groups: PRP and BMC. Both groups completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and subjective International Knee Documentation Committee (IKDC) questionnaires before and 1, 3, 6, 9, and 12 months after a single intra-articular injection of leukocyte-rich PRP or BMC.

Results: There were no statistically significant differences in baseline IKDC or WOMAC scores between the 2 groups. All IKDC and WOMAC scores for both the PRP and BMC groups significantly improved from baseline to 1 month after the injection (P < .001). These improvements were sustained for 12 months after the injection, with no difference between PRP and BMC at any time point.

Conclusion: Both PRP and BMC were effective in improving patient-reported outcomes in patients with mild to moderate knee OA for at least 12 months; neither treatment provided a superior clinical benefit. Autologous PRP and BMC showed promising clinical potential as therapeutic agents for the treatment of OA, and while PRP has strong clinical evidence to support its efficacy, BMC has limited support. This study did not prove BMC to be superior to PRP, providing guidance to clinicians treating OA. It is possible that the results were affected by patients knowing that there was no control group.

Registration: NCT03289416 (ClinicalTrials.gov identifier).

Keywords: platelet-rich plasma; bone marrow aspirate; bone marrow concentrate; regenerative medicine; osteoarthritis
for surgical treatments. For these and other reasons, many patients choose nonoperative treatments, and there has been great interest in injections classified as regenerative. There is a current unmet clinical need to improve the quality of life of patients suffering from all stages of OA, and for these patients, injection therapies have a developing role.

Although commonly used for the treatment of knee OA, the clinical efficacy of HA and corticosteroid injections to treat knee OA has been questioned. This has led to the development of additional injection options, such as autologous blood– and bone marrow–derived products. Leukocyte-poor platelet-rich plasma (LP-PRP) has preclinical basic science, randomized controlled comparative clinical, and meta-analysis studies supporting its safety and efficacy. Bone marrow aspirate concentrate (BMC), a more cellular and protein-rich product, has also emerged as a treatment. A benchtop comparative study of the components of PRP and BMC has suggested that BMC contains a higher number of cells that will culture/differentiate, often referred to as stem cells, and a higher concentration of potentially advantageous chemokines. A higher cellular component of cells that can be grown in culture suggests a higher potential for tissue regeneration and anti-inflammatory effects; however, clinical superiority remains theoretical. The full clinical potential of BMC is unclear, but studies have shown promise with preclinical animal studies for cartilage repair, clinical case series for the treatment of OA, and clinical studies suggesting a role in open implantation for cartilage repair.

Clinical comparisons of PRP and BMC are lacking. The main objective of this study was to compare, with validated patient-reported outcomes, the effectiveness of BMC to PRP for the treatment of knee OA after a single injection. We hypothesized that BMC will outperform PRP at multiple time points after an injection.

METHODS

Participants

This study was approved by the affiliated hospital’s institutional review board, which oversees the facility where the study was performed. Participants aged between 18 and 80 years with evidence of knee OA were screened for eligibility in the study (N = 110). All participants were informed of the experimental procedures, risks, and benefits of the study and provided written informed consent before the screening appointment. Participants were instructed not to take any prescription over-the-counter NSAIDs for 3 weeks before the screening appointment. NSAID use was not monitored or regulated after treatment.

Patients were screened with a 4-view radiographic series of the knee (long-leg, lateral, sunrise, and bilateral Rosenberg views), and they were included in the study if they had pain or swelling of the knee of at least 4 months in duration and a Kellgren-Lawrence grade between 1 and 3 on the radiographic evaluation. The population studied is typical of patients with knee OA who typically inquire about orthobiologic injections. Exclusion criteria included patients with a major mechanical axis deviation of more than 50% to either compartment (varus or valgus), a corticosteroid injection within 3 months or an HA injection within 6 months, or a history of any of the following medical conditions: diabetes, autoimmune disorders, disorders requiring immunosuppression, rheumatoid arthritis, hemophilic arthropathy, infectious arthritis, Charcot knee, Paget disease of the femur or tibia, history of cancer, ongoing infectious diseases, or significant cardiovascular, renal, or hepatic diseases.

Participants were enrolled over the course of 4 years. There were 91 participants who met the inclusion and exclusion criteria; 1 declined to participate. A total of 90 participants were randomized using a computer-generated sequence into 2 groups: BMC (n = 49) and PRP (n = 41); enrollment was stopped at 90 participants. All participants received the allocated treatment (Figure 1). In the BMC group, 4 participants withdrew, and in the PRP group, 1 participant withdrew, while 1 was lost to follow-up, leaving 84 participants in the study. Participant characteristics are summarized in Table 1. There were no significant differences between the groups in these characteristics.

Patient-Reported Outcomes

Both groups completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and subjective International Knee Documentation Committee (IKDC) questionnaires before any treatment. An a priori power analysis (G*Power 3.1.9.3) revealed that a sample

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5References 5, 7, 10, 13, 25, 29, 30, 35, 36, 38-40, 42, 44, 46, 47, 49.
size of 25 and 50 patients in each group was necessary to detect large effects using a power of 0.8 and alpha of 0.05 using the WOMAC and IKDC, respectively. Participants also completed the WOMAC and IKDC questionnaires at 1, 3, 6, 9, and 12 months after the allocated injection.

Injection Protocol

Group 1 (BMC group) received a single intra-articular injection of BMC. Group 2 (PRP group) received a single intra-articular injection of PRP. Because of the invasive nature of obtaining marrow aspirate, blinding of the participants and clinicians was not feasible. All injections and all associated procedures were performed in the clinic setting by either the first author (A.W.A.: 34 PRP, 40 BMC) or the last author (J.G.H.: 7 PRP, 9 BMC).

The harvest of blood for PRP production involved standard, antecubital venipuncture with a 60-mL syringe pre-loaded with 10 mL of sodium citrate anticoagulant. Blood was processed at the point of care with a dual-spin protocol/disposable (PurePRP; EmCyte) to make leukocyte-rich (LR-PRP), which is monocyte/lymphocyte rich and neutrophil poor. The blood was loaded into a first cylinder disposable and centrifuged for 1.5 minutes at 3800 rpm, according to the instructions for use. A 2-layer soft stack, that is, platelet plasma suspension above the red cell layer, was produced. The top platelet plasma suspension was aspirated off until red blood cells filled the aspiration pipe and was then loaded into a second disposable and centrifuged for 5 minutes at 3800 rpm, creating a platelet-poor plasma (PPP) top layer and platelet buffy coat at the bottom of the disposable. PPP was aspirated off, leaving approximately 7 mL of pure PRP. The plasma and platelet buffy coat were resuspended into the remaining plasma by swirling, and the final PRP, approximately 7 mL, was aspirated into the injection syringe.

For bone marrow harvest, two 30-mL syringes and a traditional 11-gauge, 11-cm Jamshidi needle (Ranfac) were prerinsed with heparin. The two 30-mL syringes were loaded with 5 mL of sodium citrate anticoagulant in each syringe. Aspiration was performed from a bone puncture at the posterior superior iliac spine with the Jamshidi needle. For bone marrow aspiration, participants were placed into the lateral decubitus position. The posterior superior iliac spine was localized with ultrasound and prepared with ChloraPrep (chlorhexidine gluconate; BD). The skin, subcutaneous tissues, and periosteum were anesthetized with 1% lidocaine, and no systemic analgesics or anxiolytics

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**TABLE 1**

| Participant Characteristics<sup>a</sup> | All (n = 84) | BMC (n = 45) | PRP (n = 39) |
|----------------------------------------|-------------|-------------|-------------|
| Sex, male/female, n                   | 49/35       | 27/18       | 22/17       |
| Age, y                                 | 54.1 ± 11.9 | 55.8 ± 11.3 | 52.2 ± 12.4 |
| Height, cm                            | 173.9 ± 11.7| 175.2 ± 11.1| 172.3 ± 12.3|
| Weight, kg                            | 86.7 ± 20.5 | 89.5 ± 20.6 | 83.5 ± 20.3 |
| Body mass index, kg/m<sup>2</sup>     | 28.2 ± 5.7  | 27.7 ± 5.0  | 27.9 ± 5.8  |
| Kellgren-Lawrence grade               | 1.8 ± 0.7   | 1.8 ± 0.7   | 1.9 ± 0.7   |

<sup>a</sup>Values are reported as mean ± SD unless otherwise indicated.

BMC, bone marrow aspirate concentrate; PRP, platelet-rich plasma.
were required. The needle was used to puncture the posterior superior iliac spine, advanced 3 to 5 cm, and aspiration performed while withdrawing and rotating the needle. Aspiration was performed until the 30-mL mark was reached on the first syringe, and then the needle was advanced a second time in a divergent trajectory. Aspiration was repeated with the second 30-mL syringe while withdrawing and rotating the needle. Bone marrow was processed at the point of care with a dual-spin protocol/disposable (PureBMC; EmCyte). The bone marrow was loaded into a first cylinder disposable through a bone marrow aspiration filter, according to the instructions for use. It was then centrifuged for 2.5 minutes at 3800 rpm. This produced a 3-layer hard stack: platelet plasma suspension, early buffy coat, and red cell layer. The top plasma layer and 2-mL buffy coat were aspirated off and loaded into a concentrating accessory disposable. A second centrifuge was performed for 7 minutes at 3800 rpm, creating a PPP top layer and BMC buffy coat at the bottom of the disposable. PPP was aspirated off, leaving approximately 7 mL of plasma and the BMC buffy coat. The BMC buffy coat was reconstituted into the plasma by swirling, and the final BMC, approximately 7 mL, was loaded into the injection syringe. Intra-articular injections were performed as a standard sterile procedure with ultrasound guidance and a superolateral, parapatellar approach.23

This study was initiated before guidelines were issued for minimal reporting of biologic product studies; the reporting standards were published near the conclusion of the study. For this reason, 4 participants, 3 in the BMC group and 1 in the PRP group, were selected to have cellular analysis of the product. For this analysis, a small sample (1 mL) of the whole blood or bone marrow aspirate and BMC or PRP was separated and sent to an independent laboratory for analysis (BSR Laboratories). The laboratory analysis included obtaining a complete blood count for all samples with the addition of flow cytometry for human CD34+ hematopoietic stem/progenitor analysis and colony-forming unit–fibroblast (CFU-F) for bone marrow aspirate and BMC after the cell culture protocol of the laboratory.

After the injection, participants were given follow-up care instructions that included no use of NSAIDs for at least 7 days and partial weightbearing on the limb for 2 to 3 days, followed by the initiation of a standard physical therapy program at 1 week after the injection for 4 weeks.

Statistical Analysis

Separate 2 (group) × 6 (time) mixed-design analyses of variance (ANOVAs) were used to detect differences between groups and among time points for the WOMAC and IKDC. If the Mauchly test of sphericity was statistically significant (P < .05), the Huynh-Feldt adjustment was used to correct for the violation of sphericity. Statistical significance was set a priori at P < .05. All analyses were conducted using SPSS version 24.0 software (IBM).

RESULTS

The mixed-design ANOVAs revealed a significant effect of time on the IKDC score (F3.79,310.88 = 31.928; P < .001; \( \eta_p^2 = 0.280 \)), with no differences between the BMC and PRP groups. Both groups significantly improved from baseline to 1-month follow-up, and scores plateaued at 3 months, remaining consistent with no further significant improvement through 6, 9, and 12 months (Figure 2A and Table 2). For the BMC group, mean scores after 1 month improved by 30.0 points for the IKDC and 43.9 for the WOMAC, and for the PRP group, the scores improved by 23.2 points for the IKDC and 39.3 for the WOMAC.

A significant effect of time was observed on all WOMAC subscales: WOMAC total (F3.88,318.09 = 31.165; P < .001; \( \eta_p^2 = 0.262 \)), WOMAC pain (F4.18,342.65 = 24.735; P < .001; \( \eta_p^2 = 0.232 \)), WOMAC stiffness (F4.18,342.88 = 32.306; P < .001; \( \eta_p^2 = 0.283 \)), and WOMAC function (F4.00,327.80 = 25.389; P < .001; \( \eta_p^2 = 0.236 \)). Both groups significantly improved on all WOMAC subscales from baseline to 1-month follow-up, with no further significant improvement in scores (Figure 2B and Table 2). Scores remained significantly improved between baseline and 3, 6, 9, and 12 months after both BMC and PRP injections.

Results from the composition analysis of the samples sent for independent review are presented in Table 3. The
results of the cellular composition analysis showed an increase in platelet, white blood cell, CD34+, and CFU-F counts with concentration, with an expected decrease in the red blood cell count.

**DISCUSSION**

The objective of this study was to compare the efficacy of PRP to BMC for the treatment of knee OA. This study showed significant improvement in WOMAC and IKDC scores for both the PRP and BMC groups as early as 4 weeks after the injection, and the improvement remained through to 12-month follow-up. The most important finding of this study is that BMC was not superior to PRP for the treatment of OA out to 12 months, contrary to our hypothesis. To our knowledge, this is the first direct clinical comparative study of PRP and BMC. For the BMC group, mean scores at 1-month follow-up improved by 30.0 points for the IKDC and 43.9 for the WOMAC, and for the PRP group, the scores improved by 23.2 points for the IKDC and 39.3 for the WOMAC. The improvement in WOMAC (minimal detectable change = 22.8) and IKDC (minimal detectable change = 13.7) scores was clinically significant for established values in OA.2,17

PRP has a pyramid of developmental work, starting with preclinical benchtop and animal studies, continuing with high level of evidence clinical trials, and ending with systematic reviews. In benchtop studies, PRP has clear mechanisms of action to improve the catabolic and inflammatory environment of OA.7,35,47 Animal studies have reflected benchtop principles, with histological and morphological findings documenting a beneficial effect on the synovium and cartilage.7,25,26,49

Clinical studies have established safety and efficacy for PRP, with comparison including HA and saline as
controls. The body of evidence has progressed to meta-analyses and systematic reviews. One study for comparison, by Smith, involved United States Food and Drug Administration observations, employed stricter inclusion/exclusion criteria than the current study, and reported similar findings out to 12 months. Smith reported on 114 participants screened to yield 30 participants and then randomized into 2 groups. A series of 3 weekly injections of LP-PRP was compared with saline as a control; the WOMAC served as the primary efficacy outcome measure. No adverse events were reported, and at the conclusion, WOMAC scores for the participants receiving LP-PRP had improved by 78% from baseline, whereas scores for the placebo group had improved by only 7%. The current study illustrates similar improvement in WOMAC scores as reported by Smith. By contrast, however, the current study had less restrictive selection criteria, had a scenario more consistent with clinical practice, and studied a single injection instead of a series.

Systematic reviews and meta-analyses provide further evidence and are clarifying a consensus that PRP is an effective intra-articular treatment for knee OA. A 2017 systematic review of the literature found 29 well-designed studies including 26 evaluating knee OA and 3 evaluating hip OA. The compilation included 9 prospective randomized controlled trials (RCTs; 8 knee and 1 hip), 4 prospective comparative studies, 14 case series, and 2 retrospective comparative studies. As a control group, HA was used in 11 studies (7 RCTs, 2 prospective comparative studies, and 2 retrospective comparative studies). Only 2 RCTs, 1 for the knee and 1 for the hip, did not report the significant superiority of PRP compared with the control group that received HA. Also, 9 of 11 HA studies showed significantly better results in the PRP group. Conclusively, PRP has been shown consistently to be safe and effective for improvements in pain and function for patients with sustained benefit lasting ≥12 months. The current study further supports this conclusion. Additionally, in this study, BMC showed similar improvement as PRP out to 12 months.

Developing orthopaedic literature has produced opinions that LP-PRP is the preferred preparation for knee OA because variable results have been found with LR-PRP. Kon et al conducted a prospective comparative trial in 150 patients comparing a series of 3 LR-PRP injections to 2 different preparations of HA. The PRP group showed stronger and longer efficacy than the HA groups. The study involved 5-mL injection volumes, a 600% increase in platelets from baseline whole blood, and a 2-spin preparation method. Leukocyte values with differentials were not reported. These authors followed with an RCT comparing PRP to a high–molecular weight HA in 192 participants and did not find superior clinical improvement in the PRP group. In that study, platelets were increased by a factor of 4.6 and leukocytes by a factor of 1.1. Leukocyte differentials were not reported. Our study involved LR-PRP, which was prepared to be 7 mL, monocyte/lymphocyte rich, and neutrophil poor. The findings of the current study reaffirm leukocyte differential and product volume as 2 variables that affect PRP effectiveness and warrant further study. The volume reported by Smith in his RCT of LP-PRP was 3 to 8 mL.

Evidence firmly supporting the clinical use of BMC for knee OA is lacking. Overall, 2 studies from a single data registry cohort and an additional case series are the only studies supporting its clinical efficacy. Centeno et al reported on 840 procedures involving BMC, divided into 2 groups: 616 procedures performed on 518 patients in the first group and 224 procedures performed on 163 patients in the second group. The first group received an injection of hypertonic dextrose solution, followed 2 to 5 days later by an injection of bone marrow concentrate, PPP, and platelet lysate. The platelet lysate was created by storing buffy coat–based PRP at −20°C. The second group received the same injections as the first group in addition to a lipoaspirate point-of-care product injected with the BMC solution. The lipoaspirate component was prepared from 5 to 15 mL of lipoaspirate. Outcomes included the numerical pain rating scale score at an average of 6.5 months and a lower extremity functional scale (LEFS) score at an average of

### TABLE 3

| Sample | RBC, 10^6/mL | Platelet, 10^9/mL | WBC, 10^9/mL | CD34+, Cells/mL | CFU-F, Cells/mL | RBC, 10^6/mL | Platelet, 10^9/mL | WBC, 10^9/mL | CD34+, Cells/mL | CFU-F, Cells/mL |
|--------|--------------|------------------|--------------|----------------|----------------|--------------|----------------|--------------|----------------|----------------|
| 1      | 3120         | 175              | 15.9         | 33,373         | 42             | 1020         | 410            | 41.6         | 112,558        | 86             |
| 2      | 2310         | 64               | 18.7         | 40,827         | 37             | 1250         | 337            | 46.6         | 1130           | 75             |
| 3      | 3480         | 64               | 113,470      | 309,910        | 136            | 410          | 141            | 2.3/11.9     | 0.4            |                |

| Whole Blood | Platelet-Rich Plasma | |
|-------------|----------------------|---------------|
| Sample      | RBC, 10^6/mL | Platelet, 10^9/mL | WBC, 10^9/mL | Mono/Lym, 10^9/mL | Gran, 10^6/mL | RBC, 10^6/mL | Platelet, 10^9/mL | WBC, 10^9/mL | Mono/Lym, 10^9/mL | Gran, 10^6/mL |
| 4           | 4.03         | 238              | 8.5          | 1.1/2.0         | 5.3           | 0.12         | 1216             | 14.7         | 2.3/11.9        | 0.4           |

*CFU-F, colony-forming unit–fibroblast; Gran, granulocyte; Lym, lymphocyte; Mono, monocyte; RBC, red blood cell; WBC, white blood cell.*
rates, a harvest technique advocated by Hernigou et al. The BMA technique used by Shapiro et al.1 involved 52 mL of bone marrow aspirate, 8 mL of anticoagulant citrate dextrose solution-A (ACDA), and an automated concentration system. The BMA technique used by Shapiro et al. included bilateral iliac crests and small-volume aspiration; this could have introduced reporting bias in the treatment, given the invasive nature of bone marrow aspiration. A second limitation was that a single BMC injection for mild to moderate knee OA was not superior to a single PRP injection for improvement in pain and function, questioning the value of the increased invasiveness of the BMC procedure when compared with PRP. We do not have any data to support whether PRP or BMC injections are superior to placebo. In clinical practice, we have noted trends regarding the reimbursement of biologic products. HA injections are covered by most insurance companies, PRP costs on average US $714,43 and BMC costs on average US $3000.

One limitation of this study was the lack of blinding. Neither the participants nor practitioners were blinded to the treatment, given the invasive nature of bone marrow aspiration; this could have introduced reporting bias in the patient-reported outcomes. A second limitation was that there was no control group, and the patients knew that there was no control group; therefore, their survey responses may have been biased. Previous studies have shown a dramatic placebo effect when analyzing the effects of biologics. An additional critique is that a comparative arm of steroids or HA was not provided and would have further improved this study’s real-world applicability. The length of follow-up was 12 months, and it is possible that a longer follow-up would show a difference between BMC and PRP outcomes. Our intent is to continue to follow this cohort for another year.

A third limitation was the lack of product sampling throughout the study. A recent consensus statement has developed a minimal reporting requirement for biologic studies; however, this study was initiated before the consensus statement. While we tested 4 samples, it is hard to develop any comparison of the PRP to BMC product differences in cellular compositions. Also, our experience with this study highlighted variability when sending samples for culturing. There is a chance that viability data were affected by sending samples to a remote laboratory. Since this study’s conclusion, we have brought in house the ability to test samples with an automated hemocytometer, flow cytometry, microscopy, and culturing. This study included patients with essentially no joint space narrowing (Kellgren-Lawrence grade 1) and excluded patients with changes in underlying bone shapes (Kellgren-Lawrence grade 4); therefore, we cannot conclude whether either technique would be effective for severe OA. Additionally, the study was not powered to compare the results of the treatment for different Kellgren-Lawrence grades. Finally, we used LR-PRP, whereas subject leader experts have been advocating LP-PRP. Results may be different with LP-PRP.

CONCLUSION

This study demonstrated that both PRP and BMC were effective in improving patient-reported outcomes in patients with mild to moderate knee arthritis for at least 12 months. Through the 12-month period, neither treatment provided a superior clinical benefit.

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