Bone Marrow Aspirate Concentrate Is Equivalent to Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis at 2 Years

A Prospective Randomized Trial

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Background: Autologous platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMC) are being used clinically as therapeutic agents for the treatment of knee osteoarthritis.

Purpose/Hypothesis: The purpose of this study was to compare the efficacy of BMC and PRP on pain and function in patients with knee osteoarthritis up to 24 months after injection. It was hypothesized that patients receiving BMC would have better sustained outcomes than those receiving PRP.

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

Methods: A total of 90 participants aged between 18 and 80 years with symptomatic knee osteoarthritis (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) questionnaire before and 1, 3, 6, 9, 12, 18, and 24 months after a single intra-articular injection of leukocyte-rich PRP or BMC. A linear mixed-effects model was performed to quantify the effects over time and the difference between the groups. This model has the random effect for time to assess the extent in which the change over time differs from one person to another.

Results: An overall 84 patients completed questionnaires from baseline to 12 months; however, 17 patients (n = 9; PRP group) were lost to follow-up at 18 months and 25 (n = 13; PRP group) at 24 months. There were no statistically significant differences in IKDC ($P = .909$; 95% CI, −6.26 to 7.03) or WOMAC ($P = .789$; 95% CI, −6.26 to 4.77) scores over time between the groups. Both groups had significantly improved IKDC ($P < .001$; 95% CI, 0.275-0.596) and WOMAC ($P = .001$; 95% CI, −0.41 to −0.13) scores from baseline to 24 months after the injection. These improvements plateaued at 3 months and were sustained for 24 months after the injection, with no difference between PRP and BMC at any time point.

Conclusions: For the treatment of osteoarthritis, PRP and BMC performed similarly out to 24 months. BMC was not superior to PRP.

Registration: NCT03289416 (ClincalTrials.gov identifier).

Keywords: bone marrow aspirate; bone marrow aspirate concentrate; osteoarthritis; platelet-rich plasma; regenerative medicine

Osteoarthritis (OA) is a chronic joint disease that results in structural damage to articular cartilage and bone.[16] OA causes increased pain and decreased function and quality of life that can be debilitating for patients. Obesity, aging, and hormonal and genetic factors contribute to OA[11,38] and previous joint injury to posttraumatic OA.[22] In the United States, 80% of the population will have radiographic evidence of OA by the age of 65 years.[12,25,33] Additionally, 5.6 million individuals in the United States have posttraumatic OA, which accounts for $3 billion in annual direct medical costs.[3] The costs associated with treating OA can lead to significant financial burden for patients over the course of their lives.

Glucocorticoids, hyaluronic acid, and nonsteroidal anti-inflammatory drugs (NSAIDs) are pharmacological options

in the nonsurgical management of OA; exercise and weight loss are additional medical recommendations. Platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMC) are autologous cell-based therapies that are becoming more frequently used for the treatment of many orthopaedic conditions including OA. The cellular components of PRP and BMC differ, as BMC is a more cellular product because the starting tissue of bone marrow is more cellular than whole blood.[15] When compared with PRP, BMC also has significant concentrations of interleukin 1 receptor antagonist (IL-1ra), which acts to inhibit IL-1, a proinflammatory chemokine associated with negative effects of OA.[4,15] The higher cellular and IL-1ra content of BMC suggests that it would be more effective in the management of OA.

The purpose of this study was to compare the efficacy of BMC and PRP on pain and function in patients with knee OA up to 24 months after a single injection. It was hypothesized that patients receiving BMC would have better outcomes up to 24 months than those receiving leukocyte-rich PRP. The 12-month data from this study have been reported,[2] and similar improvements in patient-reported outcomes were found.

METHODS

Participants

Participants between the ages of 18 and 80 years with evidence of knee OA were screened for eligibility in the study (n = 110). This study was approved by the affiliative hospital's institutional review board, which oversees the facility where the study was performed. All participants were informed of the experimental procedures, risks, and benefits of the study and provided informed consent before the screening appointment. Participants were instructed not to take any prescription or 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 radiograph series of the knee (long-leg, lateral, sunrise, and bilateral Rosenberg views). Patients were included in the study if they had pain or swelling of the knee of at least 4 months and a Kellgren-Lawrence score[25,28] between 1 and 3 on radiograph evaluation. The determination of the Kellgren-Lawrence score was performed by the enrolling physicians, an

orthopaedic surgeon who was fellowship trained in sports medicine, and a orthopaedist who was fellowship trained in nonoperative sports medicine (A.W.A. and J.G.H.). The population studied is typical of patients with knee OA who inquire about orthobiologic injections. Exclusion criteria included (1) major mechanical axis deviation >50% into either compartment (varus or valgus); (2) a corticosteroid injection within 3 months or a hyaluronic acid injection within 6 months; or (3) 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, previous cancer, and ongoing infectious disease, as well as significant cardiovascular, renal, or hepatic disease. Funding for the execution of the study and disposables were provided to the Andrews Research & Education Foundation from EmCyte. The study was registered with ClinicalTrials.gov (NCT03289416). Participants were enrolled over the course of 4 years.

Patient-Reported Outcomes

Both groups completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[4] and the International Knee Documentation Committee (IKDC) subjective score[20] before any treatment. The outcome scores were limited to pain and function to optimize the data captured and the willingness of participants to complete multiple questionnaires. As representatives in nonoperative and operative sports medicine, we were familiar with the WOMAC and IKDC. An a priori power analysis (G*Power 3.1.9.3) revealed that a sample size of 25 patients in each group for the WOMAC and 50 patients in each group for the IKDC was necessary to detect large effects using a power of 0.8 and alpha of .05. As the study was designed, we proposed enrolling 120 patients to appropriately power the WOMAC and the IKDC scores and allow for expected losses to follow-up; however, as the funds were acquired to perform the study, limitations regarding the number of participants were set. Since the WOMAC was the primary outcome measure, the study was deemed powered to reflect its suggested sample size while anticipating for loss of follow-up over 2 years. In retrospect, at this point in the study we could have used the WOMAC and Knee injury and Osteoarthritis Outcome

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Score instead, which may have been a better study design. Participants completed the WOMAC and IKDC questionnaires at 1, 3, 6, 9, 12, 18, and 24 months after the allocated injection.

Injection Protocol

The BMC group received a single intra-articular injection of BMC. The PRP group received a single intra-articular injection of PRP. Given 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).

Harvest of blood for PRP production involved standard antecubital venipuncture with a 60-mL syringe preloaded with 10 mL of sodium citrate anticoagulant. Blood was processed at the point of care with a dual-spin protocol (PurePRP; EmCyte Corporation) to make a leukocyte-rich PRP, which is monocyte/lymphocyte rich and neutrophil poor. The blood was loaded into a first disposable cylinder and centrifuged for 1.5 minutes at 3800 rpm, according to the instructions for use. A 2-layer soft stack was produced (ie, platelet plasma suspension above red cell layer). The top platelet plasma suspension was aspirated off until red blood cells filled the aspiration pipe; then, it was loaded into a second disposable and centrifuged for 5 minutes at 3800 rpm, creating a platelet-poor plasma top layer and platelet buffy coat at the bottom of the disposable. Platelet-poor plasma 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 length, Jamshidi biopsy needle (Ranfac Corporation) were prerinsed with heparin. The two 30-mL syringes were each loaded with 5 mL of sodium citrate anticoagulant. Aspiration was performed from a bone puncture at the posterior superior iliac spine with the biopsy 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 were required. The needle was used to puncture the posterior superior iliac spine and advanced 3 to 5 cm. Aspiration followed an "aspirate, rotate, aspirate" technique, which included withdrawing the needle approximately 5 to 10 mm after 5 to 10 mL of harvest. Similar methods have been described and quantitively studied: comparison of BMC, as harvested with this technique, with PRP has shown a more cellular product, and comparison of this technique with a multiple–puncture site technique has shown similar harvest.[4,27] Aspiration was performed until the 30-mL mark was reached on the first syringe. The blunt stylet was reinserted, and the needle

was advanced a second time in a divergent trajectory. Aspiration was repeated with a second 30-mL syringe with the same aspirate, rotate, aspirate and withdrawal technique. Bone marrow was processed at the point of care with a dual-spin protocol/disposable (PureBMC; EmCyte Corporation). 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 of 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 platelet-poor plasma top layer and BMC buffy coat at the bottom of the disposable. Platelet-poor plasma was aspirated off, leaving approximately 7 mL of plasma and the 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 following a standard sterile procedure, ultrasound guidance, and a superolateral parapatellar approach.

Four 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). 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 for the bone marrow aspirate and BMC, following the cell culture protocol of the laboratory.

After the injection, participants were given follow-up care instructions, which included no use of NSAIDs for at least 7 days after the injection 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

A linear mixed-effects model was used to quantify the effects over time and the difference between the groups regarding the WOMAC and IKDC scales and subscales. This model is also known as a multilevel linear model or hierarchical linear model.[14] The advantage of using a linear mixed-effects model is to provide a flexible approach to handle correlated longitudinal data and outcomes that are missing completely at random.[17,31] The model is presented as follows:

$$y_{ijk} = \beta_0 + \beta_1 t_k + \beta_2 groups_i + u_{0j} + u_{1j}t_k + \epsilon_{ijk}$$

where y_{ijk} is the score at time $t_k (k = 1, \ldots, 8)$ for patient j in group i ($i = 1$ for BMC; $i = 2$ for PRP), $\beta_i (i = 0, 1, 2)$ are fixed effects, $u_{0j} \sim N(0, \sigma_{u_0}^2)$ and $u_{1j} \sim N(0, \sigma_{u_1}^2)$ are random effects, and $\epsilon_{ijk} \sim N(0, \sigma_\epsilon^2)$ is the random error term. The
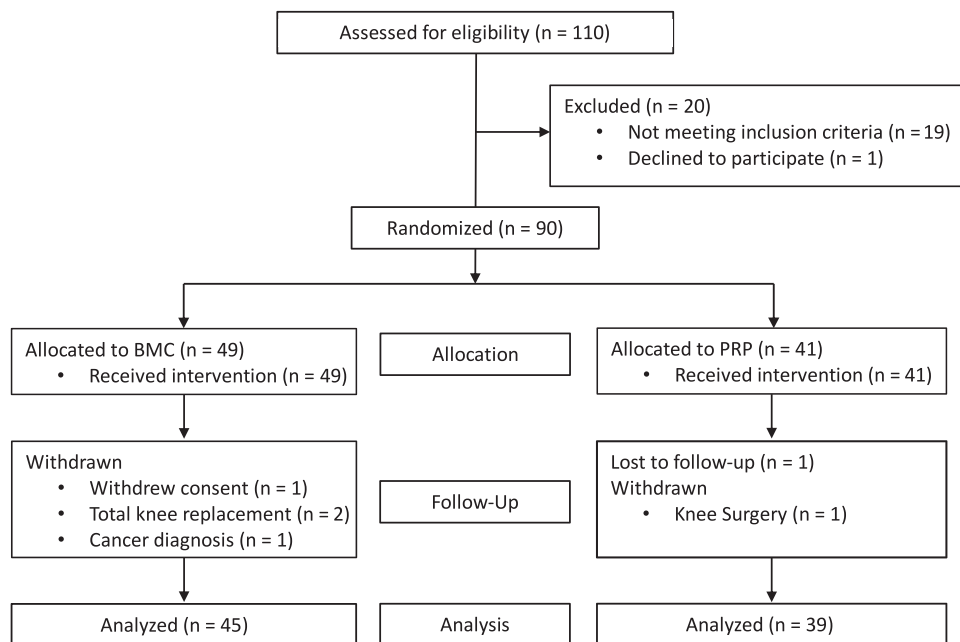
Figure 1. Flowchart. BMC, bone marrow aspirate concentrate; PRP, platelet-rich plasma.

group (BMC and PRP) is a fixed effect, testing if a statistical difference exists between the groups' mean scores.

Loss to follow-up often occurs in randomized controlled trials. The effect of loss to follow-up on the results depends on (1) the level of loss to follow-up and (2) the missing data mechanisms. There are 3 missingness mechanisms: missing completely at random, missing at random, and missing not at random. In applications, missing completely at random means that the outcomes could be missing and the reasons for the missingness are unrelated to the questions that we seek to investigate. The missing data could be also missing at random and/or not at random if there was differential loss to follow-up by exposure status (missing at random) or outcome status (missing not at random). In other words, the "missing at random" mechanism is caused by the variable itself; that is, missing values are dependent on the unobserved values of the variable. The crucial assumption about missing at random is that the missingness is related to the other observed variables; therefore, the probability distribution of the variable (where the missing values exist) given the other variables is identical whether the variable is observed or not. For example, multiple imputation uses this information to handle missing values. The "missing not at random" mechanism is where the data are missing because of their dependence to unobserved variables. To handle missing values, multiple imputation is a common method. Multiple imputation is a simulation-based approach that replaces each missing value with a set of plausible values, say k, constructing k complete data sets. The statistical analyses of the k data sets are then combined to create a final estimate incorporating the variability of the data.

RESULTS

A total of 91 participants met the inclusion and exclusion criteria; 1 declined to participate. Enrollment was stopped once 90 participants were enrolled. Ninety participants were randomized using a computer-generated sequence into 2 groups: BMC (n = 49) and PRP (n = 41). All participants received the allocated treatment (Figure 1). There were 84 patients who completed questionnaires from baseline to 12 months, and 17 (n = 9; PRP group) were lost to follow-up at 18 months and 25 (n = 13; PRP group) at 24 months. At 24 months, 68% (28/41) of the PRP group and 76% (37/49) of the BMC group completed the WOMAC survey. At 24 months, 76% (31/41) of the PRP group and 76% (37/49) of the BMC group completed the IKDC survey. Therefore, 65 and 68 patients ended up completing the WOMAC and IKDC from baseline to 24 months, respectively. Figure 2 presents the rates of loss to follow-up for the WOMAC and IKDC, indicating that there were more dropouts in the PRP group after 12 months (Table 1).

For the IKDC scores, the effect of time was statistically significant ($P < .0001$; 95% CI, 0.275-0.596). Time was positively related to IKDC scores such that they increase over time (Table 2). There was no significant difference between the means of IKDC scores for the PRP and BMC groups ($P = .9$; 95% CI, −6.26 to 7.03) (Figure 3). The random effect for time evaluates the extent to which the change over time differs from patient to patient. The standard deviation of the random effect for time was 0.47 (95% CI, 0.31-0.7), and the confidence interval does not include zero; therefore, we can conclude that change of IKDC scores over time does significantly differ across individuals in the data. The mean change in the IKDC subjective
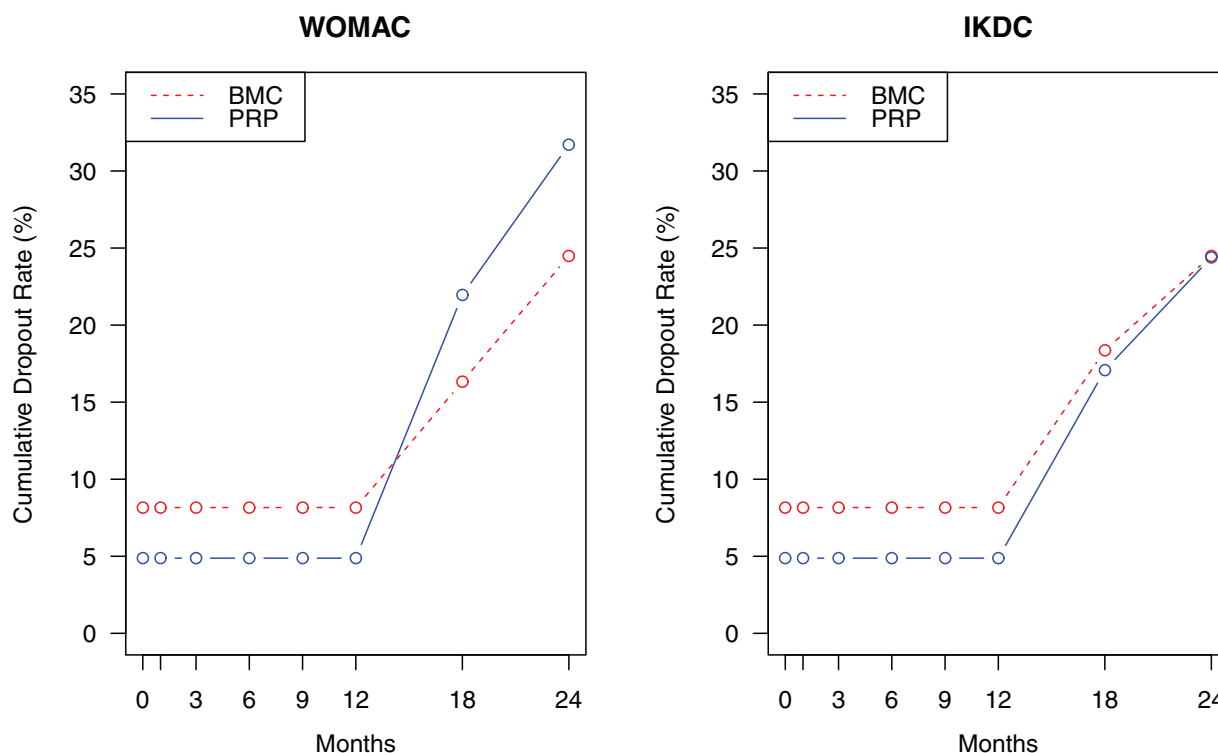
WOMAC

IKDC

Figure 2. Rates of loss to follow-up for WOMAC and IKDC scores. BMC, bone marrow aspirate concentrate; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

TABLE 1
Participant Characteristics[a]

Characteristic	Participants, No. or Mean ± SD		
	Sample (n = 84)	BMC (n = 45)	PRP (n = 39)
Sex, male:female	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	28.2 ± 5.7	27.7 ± 5.0	27.9 ± 5.8
Kellgren-Lawrence score	1.8 ± 0.7	1.8 ± 0.7	1.9 ± 0.7

[a]BMC, bone marrow aspirate concentrate; PRP, platelet-rich plasma.

knee form score was 5.9, 18.1, and 38.7 for those who considered themselves slightly better, somewhat better, and greatly better, respectively. At 24 months, IKDC scores were 16.6 points higher than baseline in the BMC group and 16 points higher than baseline in the PRP group.

For the overall WOMAC scores, the effect of time was statistically significant ($P < .0001$; 95% CI, −0.41 to −0.13). Time was negatively related to WOMAC scores such that they decrease over time (Table 2). No significant differences existed between the PRP and BMC groups with respect to overall WOMAC scores ($P = .78$; 95% CI, −6.26 to 4.77) (Figure 4). The random effect for time is

significant (SD, 0.28; 95% CI, 0.12-0.62) such that the change rates over time differ among individuals. Table 3 presents descriptive statistics of all WOMAC scores.

These improvements (IKDC increase and WOMAC decrease) plateaued at 3 months and were sustained for 24 months after the injection, with no significant difference between PRP and BMC at any time point.

A significant effect of time was observed on all WOMAC subscales: pain ($P < .0001$; 95% CI, −0.09 to −0.03), stiffness ($P < .001$; 95% CI, −0.04 to −0.01), and function ($P < .001$; 95% CI, −0.29 to −0.09). Both groups had significant improvements at 1-month follow-up, which were maintained to 24 months. The fixed effect for groups was not statistically significant for any WOMAC subscale: pain ($P = .5$; 95% CI, −1.40 to 0.69), stiffness ($P = .53$; 95% CI, −0.64 to 0.33), and function ($P = .98$; 95% CI, −3.96 to 3.84). See Appendix Table A1 and A2 (available in the online version of this article).

Assessing the Missing Data

The WOMAC and IKDC scores showed similar behaviors over time for the 2 groups (BMC and PRP). Figure 2 shows 24% and 32% dropout over a 24-month period for the BMC and PRP groups, respectively. The statistical modeling conducted here indicated no statistical differences between the groups, but the question is whether this finding is credible considering the rates for loss of follow-up over the 24
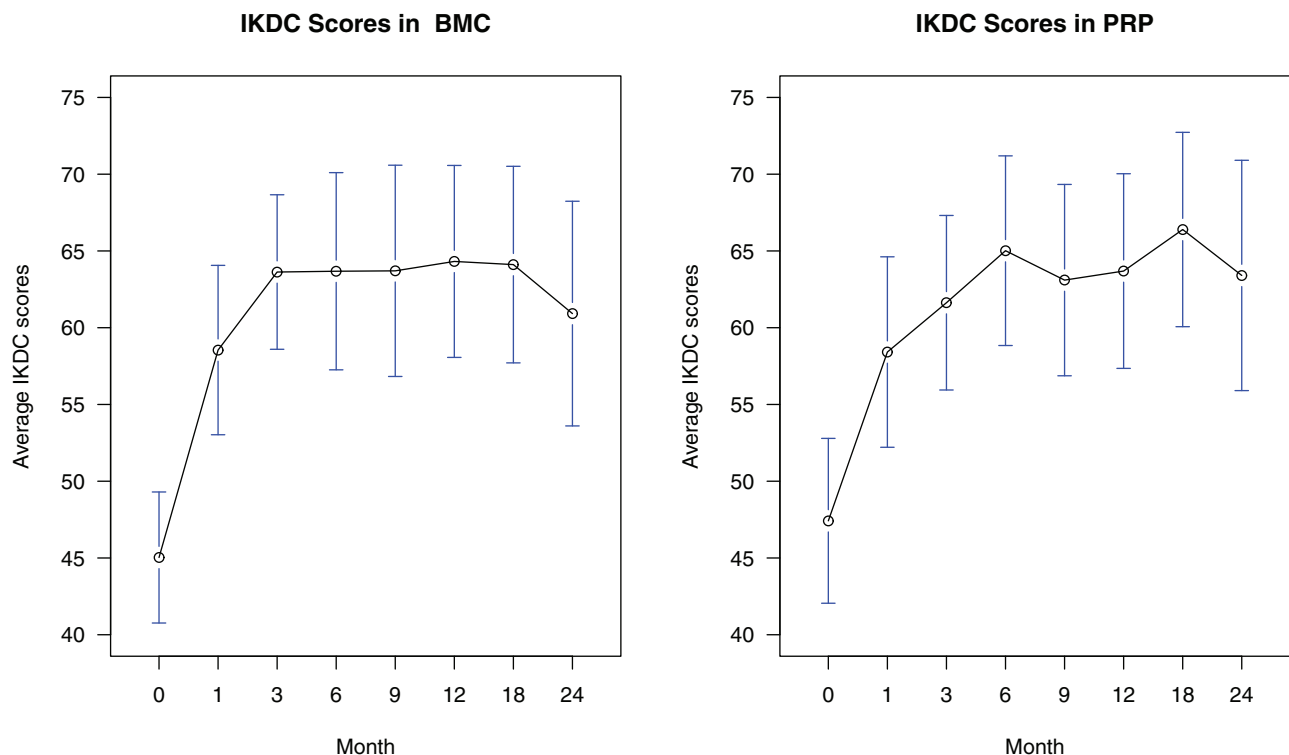
IKDC Scores in BMC

IKDC Scores in PRP

Figure 3. Mean IKDC scores over time with 95% CIs. BMC, bone marrow aspirate concentrate; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma.

TABLE 2
Linear Mixed-Effects Models for WOMAC and IKDC Scores[a]

	Estimate	SE	*df*	*t*	*P* Value	Random Effects, SD (95% CI)
IKDC						
Intercept	56.83	2.28	561	24.89	<.0001	13.92 (11.54-16.77)
Time	0.44	0.08	561	5.35	<.0001	0.47 (0.31-0.7)
Group (PRP)	0.38	3.34	82	0.11	.909	—
WOMAC						
Intercept	22.92	1.93	557	11.82	<.0001	11.63 (9.26-14.07)
Time	−0.27	0.07	557	−3.93	<.0001	0.28 (0.12-0.62)
Group (PRP)	−0.74	2.77	82	−0.27	.789	—

[a]IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Dashes indicate that the statistical model does not include random effects for the 'group' variable. 'Group' is a fixed effects variable.

months. To address this question, the data were plotted by dropout status (completers vs dropouts) and by group (BMC vs PRP) and are shown in Figures 5 and 6 for the IKDC and WOMAC, respectively.

From Figures 5 and 6, the completers demonstrated very similar averages for WOMAC and IKDC scores over time. Furthermore, the figures suggest that dropout may be missing completely at random because the average scores are similar for dropouts and completers. Most important, this pattern of loss to follow-up showed almost identical average scores in the 2 groups before the dropout occurred. The assumption of missing completely at random is reasonable in this case. Therefore, the analysis that we

conducted using linear mixed model should be sufficient to handle missing values where the mechanism is missing completely at random.

Cellular Composition Analysis

Results from the composition analysis of the samples sent for independent review are presented in Table 4. The results of the cellular composition analysis showed an increase in the platelet, white blood cell, CD34 + , and colony-forming unit–fibroblast counts with concentration, with an expected decrease in red blood cells.

TABLE 3
WOMAC Scores for the BMC and PRP Groups[a]

WOMAC	Baseline	1 mo	3 mo	6 mo	9 mo	12 mo	18 mo	24 mo
Overall								
BMC	35.3 ± 18.1	19.8 ± 14.3[b]	15.2 ± 13.3[b]	19.4 ± 18.6[b]	17.6 ± 16.1[b]	19.4 ± 16.2[b]	18.7 ± 16.0	20.8 ± 17.1
Δ Baseline, %		43.9	56.9	45.0	50.1	45.0	47.0	41.1
PRP	32.1 ± 17.9	19.5 ± 16.3[b]	18.2 ± 15.3[b]	16.2 ± 13.6[b]	18.4 ± 17.1[b]	16.8 ± 16.9[b]	16.3 ± 13.2	19.8 ± 15.2
Δ Baseline, %		39.3	43.3	49.5	42.7	47.7	49.2	38.3
Pain								
BMC	7.0 ± 3.3	3.9 ± 3.4[b]	3.2 ± 3.1[b]	4.1 ± 4.0[b]	3.2 ± 3.3[b]	3.5 ± 3.1[b]	3.7 ± 3.0	3.8 ± 3.4
Δ Baseline, %		44.3	54.3	41.4	54.3	50.0	47.1	45.7
PRP	6.2 ± 3.8	3.8 ± 3.3[b]	3.5 ± 3.1[b]	2.6 ± 2.7[b]	3.5 ± 3.5[b]	2.9 ± 3.1[b]	3.2 ± 2.8	3.7 ± 3.4
Δ Baseline, %		38.7	43.5	58.1	43.5	53.2	48.4	40.3
Stiffness								
BMC	3.8 ± 1.6	2.1 ± 1.5[b]	1.8 ± 1.5[b]	1.9 ± 1.7[b]	2.1 ± 1.6[b]	2.3 ± 1.6[b]	2.1 ± 1.6	2.2 ± 1.5
Δ Baseline, %		44.7	52.6	50	44.7	39.5	44.7	42.1
PRP	3.4 ± 1.5	2.1 ± 1.4[b]	1.9 ± 1.4[b]	1.7 ± 1.4[b]	1.8 ± 1.6[b]	1.8 ± 1.5[b]	1.8 ± 1.5	2.3 ± 1.7
Δ Baseline, %		38.2	44.1	50.0	47.1	47.1	47.1	32.4
Function								
BMC	22.9 ± 13.2	12.9 ± 9.3[b]	9.5 ± 9.3[b]	12.5 ± 12.4[b]	11.5 ± 11.1[b]	12.8 ± 11.6[b]	12.0 ± 11.3	13.2 ± 11.9
Δ Baseline, %		43.7	58.5	45.4	49.8	44.1	47.6	42.4
PRP	21.3 ± 12.5	12.7 ± 11.8[b]	12.2 ± 11.4[b]	11.2 ± 9.9[b]	12.4 ± 12.2[b]	11.3 ± 12.2[b]	10.6 ± 9.0	12.1 ± 10.7
Δ Baseline, %		40.4	42.7	47.4	41.8	46.9	50.2	43.2

[a]Values are reported as mean ± SD unless otherwise noted. BMC, bone marrow aspirate concentrate; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
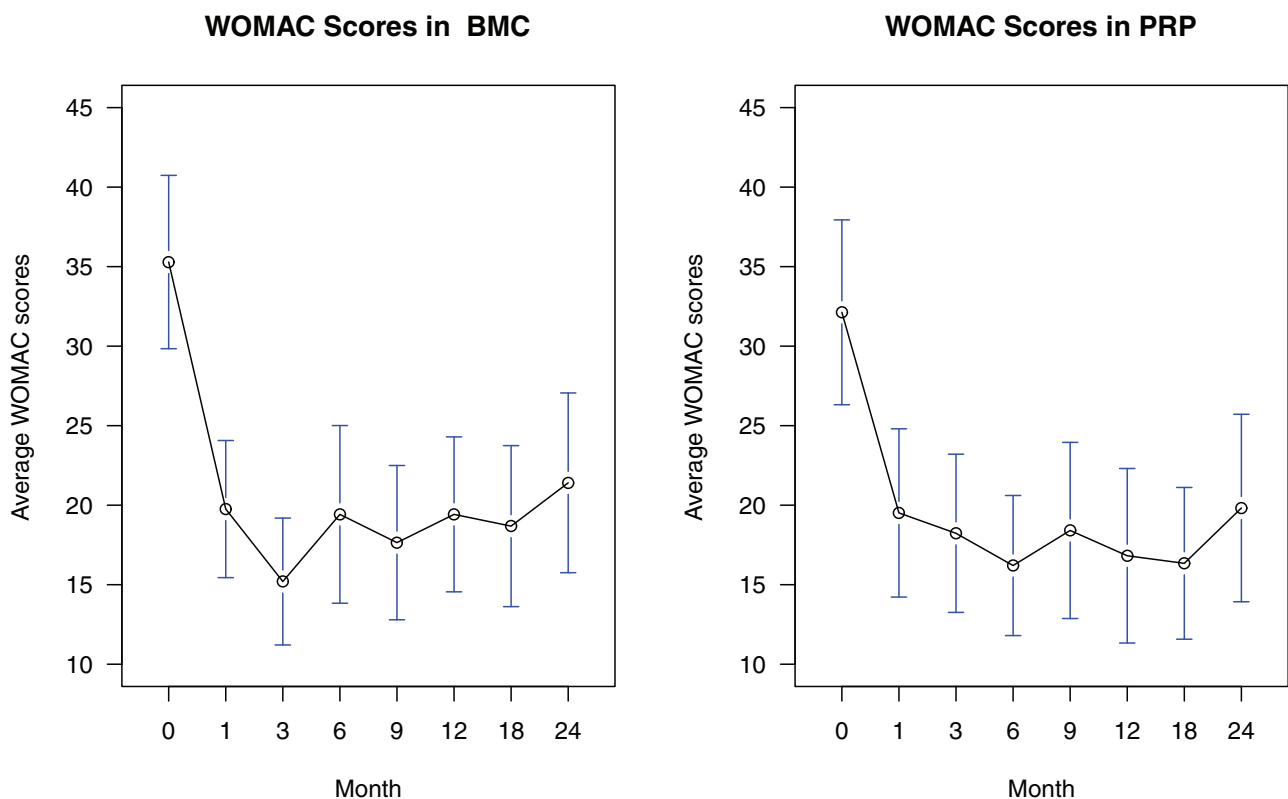[b]$P < .05$ vs baseline.

Figure 4. Mean WOMAC scores over time with 95% CIs. BMC, bone marrow aspirate concentrate; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index
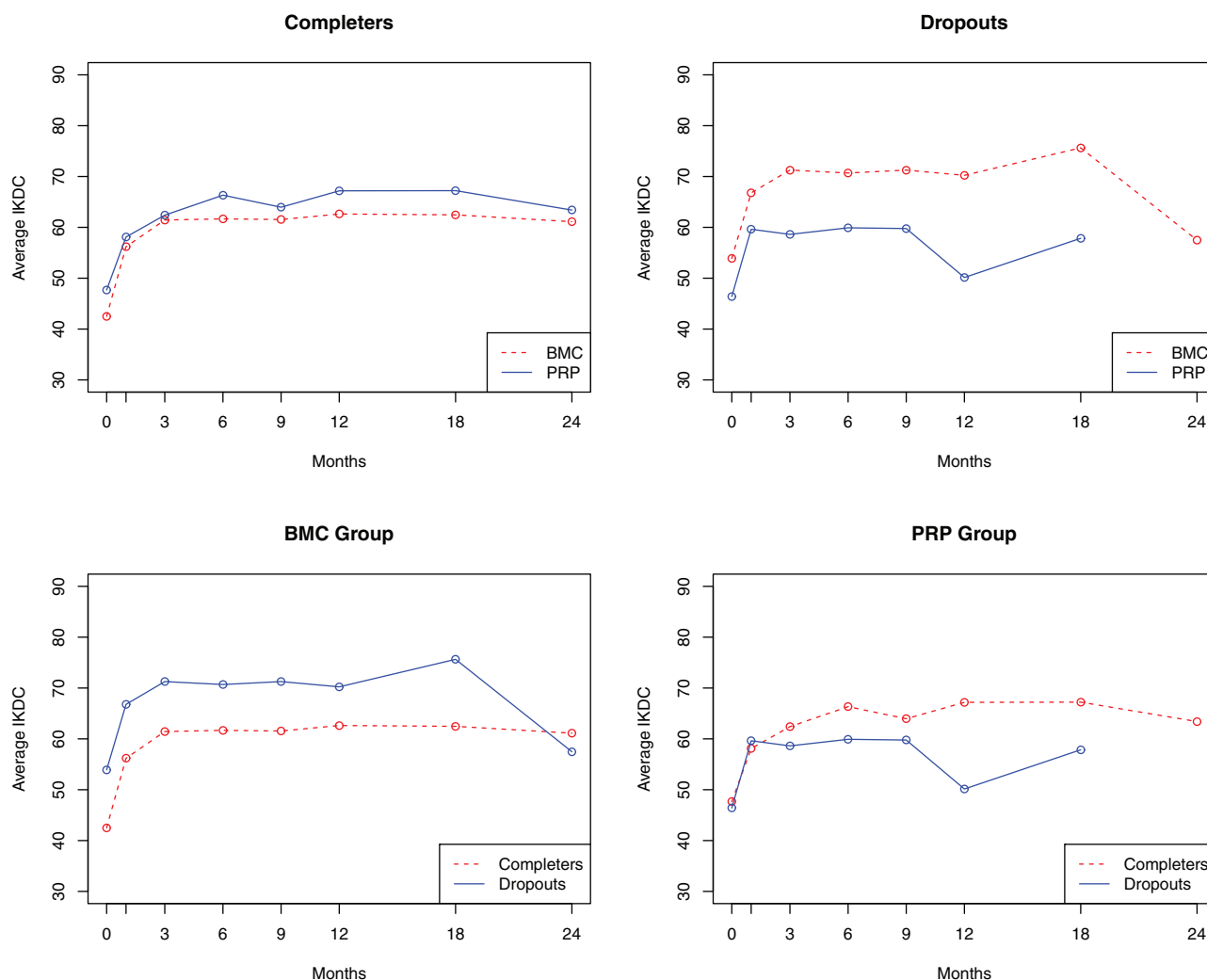
Figure 5. Mean IKDC scores over time: BMC vs PRP and completers vs dropouts. BMC, bone marrow aspirate concentrate; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma.

DISCUSSION

The most important finding of this study is that PRP and BMC performed similarly in pain and function scores for 24 months. Significant improvements in WOMAC overall and WOMAC pain, stiffness, and function were observed at 1 month after injection, and at 3 months the improvement plateaued for the remainder of the 24-month follow-up. At 24 months, IKDC scores were 16.6 points (37%) higher than baseline in the BMC group and 16 points (34%) higher than baseline in the PRP group. These improvements in IKDC scores exceeded the minimal detectable change of 12.8, a change described as significant in a validation study involving numerous conditions of the knee including OA.[19] WOMAC scores at 24 months improved by 14.5 points (41%) from baseline in the BMC group and 12.4 points (38%) in the PRP group. WOMAC scores exceeded the minimum clinically important difference (MCID) for clinical significance.[8] There were no differences in patient outcomes between the PRP and BMC

groups. For these reasons, it is difficult to argue for the added morbidity and expense of a bone marrow aspirate when considering treatments for knee OA in the general population with OA. Our hypothesis—that improvements in pain and function would last longer in patients receiving BMC—was not supported at the 24-month time point. Standard of care consisting of physical therapy, hyaluronic acid injections, or placebo could also produce similar outcomes in patients with knee OA.

The improvements in WOMAC and IKDC scores must be tempered by the 2 major flaws of this study: a high loss to follow-up and no placebo group. While statistical significance was found, the clinical importance of the change must be considered. In a study investigating the WOMAC in a population with total knee arthroplasty, the MCID was 11 for pain, 9 for function, 8 for stiffness, and 10 for the total WOMAC score. The minimal important change was 21 for pain, 16 for function, 13 for stiffness, and 17 for the total WOMAC score.[8] In a population with OA treated with nonoperative measures of physical
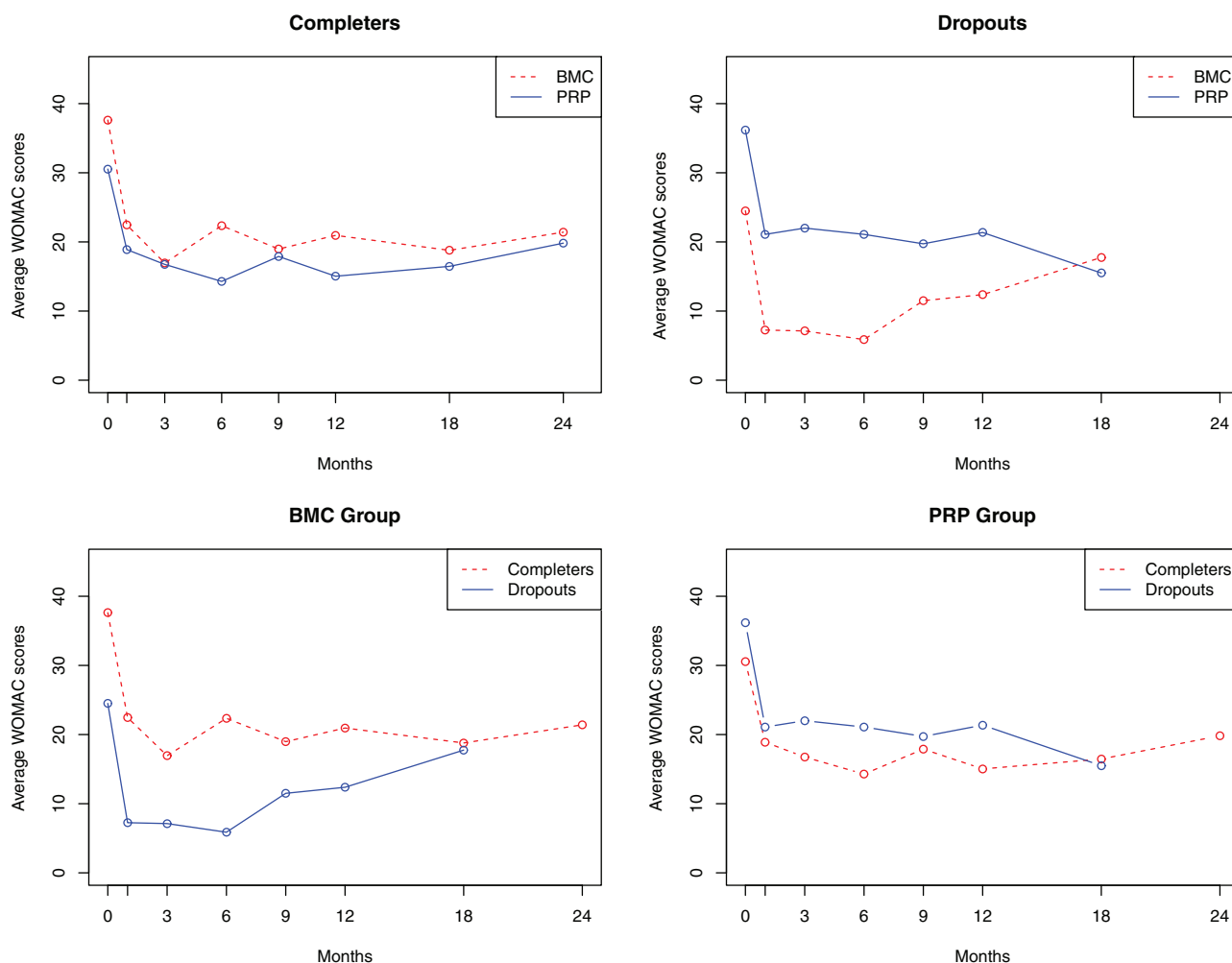
Figure 6. Average WOMAC scores over time: BMC vs PRP and completers vs dropouts. BMC, bone marrow aspirate concentrate; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

therapy and medical treatments, the minimal important change was 9.8 points for what patients would consider a small change, 9.8 points for a medium change, and 10.1 points for a large change.[1] In this study, the WOMAC scores at 24 months improved by 14.5 points from baseline in the BMC group and 12.4 points from baseline in the PRP group. The MCID for the IKDC has not been studied strictly in a population with OA. However, the original validation study for the IKDC included a percentage of patients with OA and compared mean changes in scores with patients' perceived global ratings of change. The mean change in the IKDC subjective knee form score was 5.9, 18.1, and 38.7 for those who considered themselves slightly better, somewhat better, and greatly better, respectively. At 24 months, IKDC scores were 16.6 points higher than baseline in the BMC group and 16 points higher than baseline in the PRP group.

PRP has benchtop and clinical evidence that supports its use for the indication of OA. In benchtop studies, PRP has a clear mechanism of action to improve the catabolic and inflammatory environment of OA.[20] Clinical trials in

humans have established safety and efficacy in case series, comparative cohort, and randomized controlled trials,[13,21,29,36] and systematic reviews of the literature.[9,24] Recent systematic reviews and meta-analyses have concluded greater clinical improvements in pain and function with PRP injections as compared with controls, with only 1 review concluding that there may be an increased risk of local adverse reactions after multiple PRP injections.[9,24] Since studies using leukocyte-rich PRP have reported variable results, leukocyte-poor PRP has become the preferred preparation for knee OA.[13,21,29] However, variability in the leukocyte-rich PRP studies highlights the variability in reporting and manufacturing techniques as well as the need for improved future reporting. The current study used a buffy coat–based system to create a leukocyte-rich PRP that was monocyte/lymphocyte rich and neutrophil poor.

The current evidence evaluating the effectiveness of intra-articular BMC for the treatment of OA includes 4 retrospective case series,[30,32,35,37] 3 noncontrolled retrospective comparative studies,[5,6,23] and 1 randomized

TABLE 4
Results of Cellular Composition Analysis[a]

Sample	RBC[b]	Platelets[b]	WBC[b]	CD34 +[c]	CFU-F[c]	RBC[b]	Platelets[b]	WBC[b]	CD34 +[c]	CFU-F[c]
			Bone marrow aspirate					**Bone marrow aspirate concentrate**		
1	3120	175	15.9	33,373	42	1020	492	41.6	90,305	194
2	2310	64	18.7	40,827	37	1250	337	46.6	112,558	86
3	3480	64		113,470	57	1130	410		309,910	136
				MONO/LYM[b]	GRAN[b]				MONO/LYM[b]	GRAN[b]
			Whole blood					**Platelet-rich plasma**		
4	4.03	238	8.5	1.1/2	5.3	0.12	1216	14.7	2.3/11.9	0.4

[a]This table was previously presented with 1-year results.[2] CFU-F, colony-forming unit–fibroblast; GRAN, granulocytes; LYM, lymphocytes; MONO, monocytes; RBC, red blood cells; WBC, white blood cells.
[b] $\times 10^6$/mL.
[c]Cells/mL.

controlled trial.[34] A recent systematic review concluded that studies were poor quality, varied in production and application methods, and contained a risk of bias.[10] The 4 retrospective case series found improved pain and function scores, with 2 of the 4 including multiple injections. The randomized controlled trial involved bilateral knee OA, with 1 knee receiving BMC and the other receiving saline as a control. The methodology for bone marrow aspiration was similar to the technique in the current study with the exception of harvest from both iliac crests. Improvement in both knees was noted, but there was no difference in patient-reported pain between knees, with outcome scores followed until 6 months.[34] This current study followed patients until the 24-month time point.

There are 3 noncontrolled retrospective comparative studies involving BMC for comparison. Centeno et al[6] compared the response of BMC in the treatment of 424 osteoarthritic knees up to 12 months after injection. Approximately, 10 to 15 mL of bone marrow aspirate was harvested bilaterally from the posterior superior iliac crest from 3 or 4 puncture sites on each side; the samples were processed and then injected into the knee. Patients were fitted with either an off-loader or a patellar brace and returned to full activity over a 6-week period. Patients receiving BMC with a cell count $>4 \times 10^8$ were considered to have higher cell counts, and those with cell counts $\leq 4 \times 10^8$ had lower counts. Regardless of cellular dose, patients had significant improvement in Lower Extremity Functional Scale (LEFS) and IKDC scores. Patients in the higher cell count group had less pain than the lower cell count group, although no differences were observed in LEFS or IKDC scores. It is possible that the LEFS and IKDC instruments are neither sensitive nor specific enough for this condition to differentiate change after treatment. Cell counts may have been affected by patient age, as those with higher cell counts were younger than those with lower counts. The current study followed a single puncture site on 1 iliac crest site, which contrasts the 3 or 4 puncture sites from the bilateral iliac crests in the Centeno et al[6] study.

The 2 remaining noncontrolled comparative studies evaluated the effectiveness of adipose tissue injections.[5,23] Centeno et al[5] studied the use of BMC and PRP with and without a lipoaspirate graft to treat knee OA. Bone marrow aspirate was obtained from the posterior superior iliac crest (616 procedures), and in 224 procedures lipoaspirate was added to the BMC product. Significant improvements in pain and function were observed over time in both treatment groups. In both treatment groups, the decrease in pain exceeded the MCID of 1.2 for the Numeric Pain Rating Scale. Additionally, patients receiving the BMC product with added lipoaspirate reported improved function for the LEFS that exceeded the MCID of 9. Interestingly, the group receiving only BMC and PRP had LEFS scores that did not exceed the MCID. However, patients in this treatment group did have a greater positive percentage improvement than the lipoaspirate group, leading the authors to speculate that there is no additional benefit to adding lipoaspirate to the BMC product.

Mautner et al[23] retrospectively reviewed prospectively collected data from 110 patients treated with either BMC or a micronized adipose tissue injection for symptomatic knee OA. Patients in this cohort had Kellgren-Lawrence grades of 1 (n = 5), 2 (n = 23), 3 (n = 55), and 4 (n = 18). Patients in the BMC and micronized adipose tissue treatment groups showed improvement pre- vs postprocedure in the Knee injury and Osteoarthritis Outcome Score, Emory Quality of Life questionnaire, and visual analog scale. Similar to our results, there were no differences in pain or function between groups, which may help to justify the numerous treatment options that are beneficial for OA.

The results of this study suggest that there may be little difference between BMC and PRP over a 2-year period, which questions the added morbidity and cost of harvesting BMC. A systematic review of BMC did not demonstrate a significant benefit over other more commonly administered treatments.[10] BMC is an invasive and more costly procedure than PRP; thus, the value of using BMC for knee OA should be considered when treating patients. A cost analysis of BMC versus repeat PRP injections with follow-up data has not been examined. Hyaluronic acid injections are covered by most insurance companies, whereas PRP and BMC are not currently covered. PRP has an average out-of-pocket cost of $714,[28] and BMC costs on average $3000. When one considers the costs of BMC and PRP in patients with knee OA, multiple injections of PRP over

time to treat symptoms may be a more cost-effective treatment strategy. Patients could elect to receive 4 PRP injections over the course of treatment for the same cost of a single BMC injection, and a controlled laboratory study evaluating for disease modification at the histologic level determined that a series of 3 injections of PRP was superior to a single injection.[7]

It is probable that the method of BMC harvest affects clinical efficacy. This study employed a technique that has been quantitatively studied and is often used in orthopaedic clinics. Quantitative analysis of BMC with a single-puncture technique and with rotation of the needle after 5-mL aspiration and continued aspiration has been studied and compared with PRP. Not only did BMC as harvested with this technique represent a more cellular product, including markers of mesenchymal stem cells, but it also contained more IL-1ra.[4] An additional study compared 1 puncture site with multiple divergent advancements against a multiple–puncture site technique, with comparable cell harvests.[27] In contrast, 2 additional controlled laboratory studies suggest that small aliquots and multiple osseous locations would be superior to the technique employed.[18,26] It is quite possible that the results would be different with a different BMC harvest. However, this study will still aid clinicians who are currently harvesting with this BMC technique. Clinical studies comparing the harvest methods would help develop this further.

Given the invasive nature of bone marrow aspiration, we were unable to blind participants and the practitioners to the treatment group, which may have introduced reporting bias. The patients may also have given biased survey responses because they knew that there was no control group in the study. Shapiro et al[34] observed a significant placebo effect when comparing outcomes between BMA and a placebo injection in patients with knee OA. It is possible that if Shapiro et al[34] had followed participants longer, the placebo effect would have become clearer. For the current study, a comparative arm of steroid or hyaluronic acid would have produced a stronger study; however, saline-controlled studies produce difficulties with patient enrollment. Another limitation of this study is the rate of patients lost to follow-up, which may have had an effect on the data. Only 65 patients completed the WOMAC and 68 patients completed the IKDC at 24 months. More patients in the PRP group were lost to follow-up compared to the BMC group. Why patients were lost to follow-up was not tracked, so it is possible that they received additional treatment for continued pain or functional limitations. The recent consensus statement developed for Minimum Information for studies reporting Biologics (MIBO) highlights an additional limitation. The current study was initiated before the MIBO guidelines. Enrollment for the study was from February 2016 to December 2017. MIBO was published in 2017, when enrollment was nearing completion. Ideal accommodations to appropriately quantify the PRP and BMC products for the remaining participants in this study were sought after MIBO was published but were not attained. Practical accommodations were based on financial constraints and outsourcing availability of the cellular analysis. Patients enrolled in the current study

also had no joint space narrowing (Kellgren-Lawrence 1) and patients with severe narrowing (Kellgren-Lawrence 4) were excluded; therefore, the results may be different in patients with severe OA. Our sample size was not large enough to compare treatment outcomes among Kellgren-Lawrence grades.

CONCLUSION

For the treatment of knee OA, PRP and BMC performed similarly out to 24 months. BMC was not superior to PRP.

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