Bone Marrow Concentrate Injection Treatment Improves Short-term Outcomes in Symptomatic Hip Osteoarthritis Patients

A Pilot Study

Kaitlyn E. Whitney,*† BSc, Karen K. Briggs,† MPH, MBA, Carolyn Chamness,* PA, Ioanna K. Bolia,† MD, MS, Johnny Huard,† PhD, Marc J. Philippon,*‡ MD, and Thos A. Evans,* MD

Investigation performed at The Steadman Clinic and Steadman Philippon Research Institute, Vail, Colorado, USA

Background: Osteoarthritis (OA) is one of the leading causes of disability in the United States, the hip being the second most affected weightbearing joint. Autologous bone marrow concentrate (BMC) is a promising alternative therapy to conventional treatments, with the potential to mitigate inflammation and improve joint function.

Purpose: To investigate the effectiveness of a single intra-articular BMC injection for patients with symptomatic hip OA.

Study Design: Case series; Level of evidence, 4.

Methods: A total of 24 patients diagnosed with symptomatic hip OA who elected to undergo a single BMC injection were prospectively enrolled in the study. Patients were excluded if they reported a preinjection Numeric Rating Scale (NRS) score for pain with activity of < 6 points out of 10. The Western Ontario and McMaster Universities Arthritis Index (WOMAC), modified Harris Hip Score (mHHS), Hip Outcome Score–Activities of Daily Living (HOS-ADL), 12-Item Short Form Health Survey (SF-12), and NRS pain scores were collected before and after the procedure (6 weeks, 3 months, and 6 months). Joint space and Tönnis OA grade scores were recorded on preinjection anteroposterior pelvis radiographs.

Results: A total of 18 hips from 16 patients (7 male and 9 female) (mean age, 57.6 ± 11; mean body mass index, 25.9 ± 3.6 kg/m²) were used in the final analysis. Significant improvements were observed in NRS pain with activity (from 8 to 4.5; P < .001) and without activity (from 5 to 1; P < .001), WOMAC (from 31 to 16; P = .006), mHHS (from 63 to 80; P = .004), and HOS-ADL (from 71 to 85; P = .014) over 6 months. At 6 months, all patients maintained their improvements and did not return to preprocedure status. BMI significantly correlated with baseline WOMAC scores (P = .012) and inversely correlated with 6-month SF-12 Physical Component Summary (P = .038). Tönnis grades 2 and 3 were inversely correlated with 6-week SF-12 Mental Component Summary (P = .008) and 3-month pain with activity (P = .032). No serious adverse events were reported from the BMC harvest or injection procedure.

Conclusion: A single BMC injection can significantly improve subjective pain and function scores up to 6 months in patients with symptomatic hip OA. Further studies are warranted to evaluate BMC treatment against other therapeutics in a larger sample size and compare the biological signature profiles that may be responsible for the therapeutic effect.

Keywords: hip; osteoarthritis (OA); bone marrow aspirate (BMA); bone marrow concentrate (BMC); patient-reported outcomes (PROs)

Hip osteoarthritis (OA) is one of the leading causes of disability in the United States, affecting 1 in every 4 adults over the age of 50 years.20,24 Hip OA leads to substantial lifelong socioeconomic burdens as a result of chronic pain and disability.27,30 There are practical advantages to using unloader bracing, physical therapy, and over-the-counter medications as a first line of conservative treatment to improve clinical symptoms in early hip OA.22,26,28,35,45 However, for patients suffering from moderate-to-severe hip OA who do not respond to the first line of conservative treatment, conventional therapies including, but not limited to, corticosteroids, hyaluronates, glucosamine, chondroitin sulphate, and prescribed medications are generally accepted interventions to minimize pain and to improve joint function and physical activity.23,35,45 There is evidence that nonoperative treatment strategies can be effective in treating symptoms.
of hip OA; however, according to the American Academy of Orthopaedic Surgeons’ recent practice guidelines, there is no conclusive recommendation for commonly used conventional therapies because of the lack of clinical predictors and short-lived palliative effect on hip OA symptoms. Unconventional treatment modalities (ie, targeted single-molecule treatment, platelet-rich plasma, and cell-based therapies) have been developed over the past decade in parallel with a better understanding of biochemical and mechanical factors that contribute to the progression of hip OA. Currently, there is no evidence that a biological therapy can delay the degenerative cascade in OA; however, physicians treating patients with hip OA continue to seek alternative therapies to manage symptoms and improve quality of life and joint function until total hip arthroplasty is necessary.

Bone marrow concentrate (BMC) is one such alternative that has been proven safe and clinically effective for the treatment of knee OA symptoms. For decades, bone marrow (BM) has served as the primary biological therapy used to combat various diseases and conditions, ranging from cancer to autoimmune disorders. In 2005, the US Food and Drug Administration (FDA) issued guidance documents on “minimally manipulated” cellular and genetic therapies. Under the FDA’s Human Cells, Tissues and Tissue-Based Products provisions, the biological properties in BM can be concentrated using a manual methodology or automated point-of-care device and prepared for reinjection the same day. Utilizing the BM niche that is composed of stromal cells, hematopoietic stem cells, perivascular cells, and other blood cells, as well as naturally occurring growth factors and cytokines, might be a therapeutic option to alleviate arthritic conditions.

Limited research is available on the therapeutic efficacy of BMC injection therapy for patients with symptomatic hip OA. The purpose of this study was to determine the therapeutic efficacy of a single intra-articular BMC injection for patients with symptomatic hip OA. We hypothesized that there would be improvements in patient-reported outcomes (PROs), including pain and function, up to 6 months after the intra-articular BMC injection procedure.

METHODS

Patient Enrollment

This study received institutional review board approval. A total of 24 patients between 18 and 80 years of age who were diagnosed with unilateral or bilateral hip OA at the time of their evaluation were prospectively consented and enrolled. The patients in this pilot study had elected to undergo a single BMC injection with out-of-pocket expenses (average cost US$2300) before study enrollment. All patients were screened and enrolled over a 2-year period (2016-2018). Inclusion criteria included ≤2 mm of joint space on anteroposterior pelvic radiograph at 1 of 3 defined weightbearing positions, unilateral or bilateral anterior groin pain, chronic gluteal and/or inner groin hip pain symptoms, and a minimum 6 points out of 10 on a Numeric Rating Scale (NRS) for pain with activity. Patients were excluded if they had an active form of cancer, osteonecrosis, rheumatoid arthritis, or hip avascular necrosis. Other exclusion factors included ≥2 mm of hip joint space at all 3 defined weightbearing positions, a center-edge angle of <20° due to dysplasia, and/or a history of any hip procedure or injection treatment within the previous 6 months. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was adhered to for the design of the study.

Outcome Measures

PRO scores, including NRS pain score, modified Harris Hip Score (mHHS), Hip Outcome Score–Activities of Daily Living (HOS-ADL), 12-Item Short Form Health Survey (SF-12) Physical Component Summary (PCS) and Mental Component Summary (MCS), and Western Ontario and McMaster Universities Arthritis Index (WOMAC), were collected at preprocedure (baseline) and postprocedure 6-week, 3-month, and 6-month time points. Joint space and Tonnis OA grade scores were recorded on the preinjection anteroposterior pelvic radiographs, as previously described. Characteristic information, including patient age, sex, body mass index (BMI), and comorbidities, were collected from all patients. The data were extracted and analyzed by a single investigator (K.K.B.) from an electronic database and transferred to a separate spreadsheet for statistical analysis. This study followed the MIBO (Minimum Information for Studies Evaluating Biologics in Orthopaedics) guidelines.

Bone Marrow Aspirate Harvest, Processing, and Injection Procedures

All samples were processed and reinjected on the same day of the bone marrow aspirate (BMA) harvest. A CellDyn
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R. Steven Medeiros, F. John Malanga, Myron S. Bukhari, Kenneth M. Aschenbrenner, R. Morgan D. Smith

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Harvest Procedure. All of the BMA procedures were performed in a clinical setting by the same experienced physician (T.A.E). The BMA was harvested using the same technique as previously described. A Briefly, the patient was placed in the prone position, and the harvest site was steriley prepped and draped. The bone landmarks of the posterior superior iliac crest were located by palpation and confirmed using ultrasound guidance. Local anesthetics were administered into the superficial layers of the skin. A BMA kit (Arrow OnControl; Teleflex) was opened, and a battery-powered aspiration drill (Arrow OnControl) was steriley draped. Then, an 11-gauge ported aspiration needle was percutaneously inserted through the skin and subcutaneous tissues until reaching the posterior superior iliac crest. The battery-powered drill was then used to insert the ported aspiration needle into the medullary cavity of the posterior superior iliac crest. A syringe preloaded with 1 mL of anticoagulant citrate dextrose solution formula A (ACD-A) was injected into the site to minimize coagulation. Approximately 60-120 mL of BMA was collected in 30-mL syringes preloaded with 5 mL of ACD-A, and the trocar needle was rotated every 5-10 mL of BMA. The BMA samples were then taken to a separate clinical laboratory for processing.

Processing Procedure. A centrifugation and manual extraction methodology was used to prepare BMC. Under a biosafety hood, the BMA was distributed into 50-mL conical tubes and approximately 0.8 mL was pipetted into a microcentrifuge tube for hematology analysis using the CellDyn Ruby. The BMA was centrifuged at 2400 rpm for 10 minutes using an IEC Centra-CL2 benchtop centrifuge (Thermo IEC). After completion of the soft-spin centrifugation, the buffy coat leukocyte layer and a small volume of the platelet-poor plasma layer were extracted from the conical tube. The layers were combined into one 50-mL conical tube for a second centrifugation at 3400 rpm for 6 minutes. After the hard-spin centrifugation, the WBC layer and a small volume of plasma were extracted and transferred to a separate conical tube. A total volume of 6-12 mL of BMC was produced, and approximately 0.8 mL was used for hematology analysis to assess the final BMC product. Activation and storing solutions were not used in the final BMC product. The final BMC product was reinjected in a liquid state at room temperature within 4 hours of the BM harvest.

Injection Procedure. In an examination room, the patient was placed in a supine position and the hip was prepared and draped in a sterile fashion. After local anesthetics, a 22-gauge needle of 3.5-inches was advanced toward the head-neck junction under ultrasound guidance. Then, 6-12 mL of BMC was injected into the intra-articular space under ultrasound guidance. After the procedure, patients were weightbearing as tolerated and were asked to avoid high-impact sport for 6 weeks. In addition, patients were instructed to avoid use of nonsteroidal anti-inflammatory medications and to ice the joint for a minimum of 2 weeks.

Statistical Analysis

An a priori power analysis was conducted and formulated by previous literature. Specifically, Gosens et al found that pain scores were significantly reduced in the platelet-rich plasma group compared with the steroid group. Our primary hypothesis was that a similar effect would be observed in NRS pain scores among patients with moderate-to-severe degenerative hip treated with a single intra-articular BMC injection. Based on prior experience, we expected a minimum 25% improvement. Assuming a 2.5-point mean improvement in NRS pain scores or a 25-point improvement in HOS-ADL, we expected a group standard deviation of 3.0 or 30, a pre-to-post correlation of 0.5, and a Bonferroni-adjusted alpha level of .0167, and it was calculated that 14 participants would be sufficient to provide 80% power for our primary comparisons. To account for dropouts and conversions to total hip arthroplasty, 24 patients were enrolled. Preprocedure and minimum 6-month follow-up measures, as well as characteristic factors, were statistically compared among groups using repeated-measures analysis of variance. Participants who did not complete questionnaires up to a minimum of 6 months were withdrawn from the study. A paired t test was performed to compare CBCs. Statistical analyses were performed with SPSS software (Version 11, SPSS).

RESULTS

Patient Characteristics

A total of 24 patients met the inclusion criteria and agreed to participate in the study. Of these, 1 patient did not complete the consent process, 2 patients failed the eligibility criteria because of rheumatoid arthritis and Tönnis grade 1 score and were withdrawn from the study, and 3 patients (12.5%) were lost to follow-up within 6 weeks after injection. Of the remaining 18 patients, 2 (11%) required a total hip arthroplasty after injection (Table 1). One female patient required total hip arthroplasty 4 months after their BMC injection and 1 male patient underwent total hip arthroplasty approximately 6 months after BMC injection treatment.

A total of 16 patients (7 male and 9 female; 18 hips) with an mean age of 57.6 ± 11 years (range, 41-76) and mean BMI of 25.9 ± 3.6 kg/m² completed all PRO surveys and were a minimum of 6 months from their autologous BMC intra-articular hip injection. On preinjection radiographs, 6 hips had Tönnis grade 2, and 12 hips had Tönnis grade 3. Patient characteristics are shown in Table 2.

Bone Marrow Characteristics

Cell surface markers were not assessed in this study; however, a CBC was obtained from 14 BMA and 14 BMC samples. Of the 16 patients, there were 2 with missing CBC...
TABLE 1
Details on 2 Patients Who Underwent Total Hip Arthroplasty After a Single Injection of BMCa

| Patient | Age, y | BMI, kg/m² | Sex | Tönnis Grade | HOS-ADL | mHHS | WOMAC | NRS Pain | SF-12 PCS | SF-12 MCS |
|---------|--------|------------|-----|--------------|--------|------|-------|----------|----------|----------|
| 1       | 63     | 26.6       | F   | 2            | 71/73  | 62/65| 27/22 | 77       | 33.7/49.4| 66.8/61.1|
| 2       | 47     | 28.5       | M   | 2            | 62/68  | 48/48| 31/39 | 77       | 16.4/13.8| 48/56.5  |

aData represent patient characteristics and patient-reported outcome results. Outcome scores include Hip Outcome Score–Activities of Daily Living (HOS-ADL), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Numeric Rating Scale (NRS) for pain, and 12-Item Short Form Health Survey (SF-12) Mental Component Summary (MCS) and Physical Component Summary (PCS). BMC, bone marrow concentrate; BMI, body mass index; F, female; M, male; mHHS, modified Harris Hip Score.

TABLE 2
Patient Characteristics, Treatment History, and Joint Condition Information (N = 16)a

| Age, y, mean (range) | 57.6 (41-76) |
|----------------------|--------------|
| Sex (n)              |              |
| Female               | 9            |
| Male                 | 7            |
| BMI, kg/m² (mean ± SD) | 25.9 ± 3.6 |
| Comorbidities (n)    |              |
| Hypertension         | 6            |
| Hyperlipidemia       | 4            |
| Diabetes             | 1            |
| Mental health conditions | 2           |
| Thyroid disorder     | 3            |
| Tobacco/smoking (n)  |              |
| Former               | 4            |
| Never                | 12           |
| Injection <6 months before BMC procedure | 10 |
| Injection >6 months before BMC procedure | 7 |
| Tönnis grade (n)     |              |
| Grade 2              | 6            |
| Grade 3              | 12           |

aData are reported as No. unless otherwise indicated. Not including 2 participants who went on to total hip arthroplasty. BMC, bone marrow concentrate; BMI, body mass index.

The most significant finding from this study was that patients with symptomatic hip OA who underwent a single intra-articular BMC injection reported significantly less pain with and without activity at 6 weeks, 3 months, and 6 months. Patients demonstrated a significant decrease in pain and improvements in function, as shown by an increase in HOS-ADL scores. In addition, there was a significant improvement in WOMAC, mHHS, and SF-12 PCS scores. These results suggest that BMC therapy for the treatment of hip OA can improve hip function and reduce pain over 6 months.

Historically, BM mesenchymal stem cells (BM-MSCs) have been primarily targeted for therapeutic purposes because of their ability to regenerate damaged tissue and secrete anabolic factors, such as interleukin-1 receptor antagonist (IL-1Ra), IL-10, and transforming growth factor beta isoforms 1 and 2, that promote tissue repair mechanisms through intrinsic signaling pathways.29,38,42 The US federal guidelines prohibit the clinical use of isolated and expanded BM-MSCs, unless otherwise approved for specific clinical conditions by the FDA. In addition to the low quantity of BM-MSCs in BMA,32 there are several other challenges using adult BM-MSCs in that age and donor...
characteristics affect their cellular content, function, and potency. Contemporary literature suggests that the regenerative effects of MSCs are mediated by secreted factors, making BMC therapy a compelling source of bio-regenerative effects of MSCs are secreted by small molecular weight proteins that can be released from MSCs into the extracellular matrix, where they can interact with nearby cells and promote tissue repair.

TABLE 3
Complete Blood Count Results From BMA and BMC Samples in 16 Patients (18 Hips) and 2 Patients Who Converted to Total Hip Arthroplasty

| Patient | BMA (Baseline) | BMC (Final Product) |
|---------|----------------|---------------------|
|         | PLT (10^3/L)   | WBC (10^3/L) | Monocytes (10^3/L) | Neutrophils (10^3/L) | RBC (10^6/L) | Harvest Vol. (mL) | PLT (10^3/L) | WBC (10^3/L) | Monocytes (10^3/L) | Neutrophils (10^3/L) | RBC (10^6/L) | Final Vol. (mL) |
| 1       | 253            | 9.23          | 0.633          | 5.59          | 4.55          | 60           | 367           | 18.06          | 1.71          | 4.31          | 3.02          | 7.5          |
| 2       | 2.29           | 5.77          | 0.332          | 3.93          | 3.43          | 60           | 496           | 18.7           | 0.991         | 12            | 4.48          | 8            |
| 3       | 43.7           | 4.71          | 0.258          | 1.95          | 4.28          | 90           | 77.5          | 17             | 0.521         | 9.27          | 3.66          | 8            |
| 4       | 57.1           | 11.1          | 0.332          | 4.53          | 3.91          | 60           | 463           | 62.7           | —             | 3.05          | 6            |
| 5       | 194            | 11.7          | 0.765          | 5.84          | 4.61          | 60           | 411           | 31.1           | 1.63          | 14.3          | 3.84          | 8            |
| 6       | 52.6           | 5.47          | 0.266          | 2.23          | 4.21          | 90           | 128           | 30.6           | 1            | 13.2          | 5.81          | 7            |
| 7       | 348            | 8.38          | 0.814          | 4.86          | 4.2           | 70           | 1109          | 24.8           | 1.78          | 14.2          | 6.32          | 8            |
| 8       | 166            | 18.4          | 0.766          | 9.22          | 5.52          | 100          | 685           | 87.9           | 5.1           | 36.7          | 3.16          | 12           |
| 9       | 132            | 16            | 0.596          | 8.77          | 3.92          | 84           | 147           | 87.4           | 4.45          | 55.9          | 4.8           | 6            |

| Patient | Preinjection | 6 wk post-injection | 3 mo Postinjection | 6 mo Postinjection |
|---------|--------------|---------------------|-------------------|-------------------|
|         | (n = 14)     | (n = 16)            | (n = 16)          | (n = 16)          |
| SF-12 PCS | 43.5 ± 8 | 42 ± 9 | 43.7 ± 9 | 46.5 ± 9 | .29 |
| SF-12 MCS | 50.3 ± 9 | 55.7 ± 7 | 55.7 ± 8 | 54.8 ± 7 | .12 |
| NRS pain at rest (median) | 5 ± 2 | 2 ± 2 | 1.5 ± 1.6 | 1 ± 1 | <.001 |
| NRS pain with activity (median) | 8 ± 1 | 6 ± 2 | 2.5 ± 2.5 | 4.5 ± 2 | <.001 |
| WOMAC | 31 ± 19 | 25 ± 13 | 22 ± 14 | 16 ± 14 | .006 |
| mHHS | 63 ± 19 | 73 ± 15 | 79 ± 15 | 80 ± 15 | .004 |

aData represent platelet, total white blood cell (WBC), monocyte, neutrophil, and red blood cell (RBC) counts from 14 patients. The shaded rows represent the 2 patients who converted to total hip arthroplasty. BMA, bone marrow aspirate; BMC, bone marrow concentrate; PLT, platelet.

bTwo patients had missing complete blood count (CBC) data. Dashes represent missing data.

TABLE 4
Patient-Reported Outcomes in All Patients Who Completed 6-Week, 3-Month, and 6-Month Questionnaires

| Patient-Reported Outcome Score | Preinjection | 6 wk post-injection | 3 mo Postinjection | 6 mo Postinjection | P |
|-------------------------------|-------------|---------------------|-------------------|-------------------|---|
| SF-12 PCS                     | 43.5 ± 8    | 42 ± 9              | 43.7 ± 9          | 46.5 ± 9          | .29 |
| SF-12 MCS                     | 50.3 ± 9    | 55.7 ± 7            | 55.7 ± 8          | 54.8 ± 7          | .12 |
| NRS pain at rest (median)     | 5 ± 2       | 2 ± 2               | 1.5 ± 1.6         | 1 ± 1             | <.001 |
| NRS pain with activity (median) | 8 ± 1     | 6 ± 2               | 2.5 ± 2.5         | 4.5 ± 2           | <.001 |
| WOMAC                         | 31 ± 19     | 25 ± 13             | 22 ± 14           | 16 ± 14           | .006 |
| mHHS                          | 63 ± 19     | 73 ± 15             | 79 ± 15           | 80 ± 15           | .004 |

aResults are reported in mean or median ± SD. P values were calculated by repeated-measures analysis of variance. Bolded P values are statistically significant. HOS-ADL, Hip Outcome Score–Activities of Daily Living; mHHS, modified Harris Hip Score; NRS, Numeric Rating Scale; SF-12, 12-Item Short Form Health Survey; MCS, Mental Component Summary; PCS Physical Component Summary; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

bSignificant difference compared with preinjection (P < .05).
BMC as an orthobiological modality by identifying the contents that are responsible for mitigating inflammation and pain, along with the appropriate timing and number of successive treatments.

Improving joint function while decreasing pain in patients with hip OA by utilizing self-derived biological properties within BMC offers a very compelling therapeutic strategy to enable patients to return to predisease function and activity level. The importance of physical activity for individuals with degenerative joint disease and its relation to age-related diseases has been well described. Treating hip OA symptoms with BMC as opposed to conventional treatments may be an effective treatment modality in preventing comorbidity development and promoting physical activity. Our results suggest that BMC treatment has a beneficial effect on hip outcomes and function, but further evaluation of postprocedure physical activity should be considered in future studies.

Limitations to this study were primarily the small sample size, lack of a control group, and short duration of follow-up. While the small sample size was determined a priori, a larger sample size may have helped identify other factors associated with improvement or failure. The duration of the study was set at 6 months because patients generally will decide to undergo a total hip arthroplasty by 6 months if the alternative treatments are unsuccessful. In our study, 2 patients ultimately converted to total hip arthroplasty approximately 6 months after a single BMC injection; thus, injection treatment may have, in fact, delayed surgical intervention. Whether there is a significant placebo effect because of the lack of a control group remains unclear, but the significant changes in PROs does support that a single BMC injection is a safe, alternative option to delay further invasive treatment interventions. Moreover, we recognize that the lack of a comparative group and the potential bias could have had an effect on PRO results, as these patients had elected to undergo an out-of-pocket, experimental procedure. In addition, medication information and secondary injection treatment (6 months post-BMC injection) were not collected in this study. However, this pilot study was able to demonstrate the safety and short-term therapeutic efficacy of a single BMC injection in patients who had failed other nonoperative treatments.

Furthermore, cell surface markers (ie, MSC surface antigens) and protein concentrations were not measured in this study; however, blood cell concentrations in BMA and BMC were measured. We anticipate that various BMC components, such as hematopoietic, perivascular/endothelial MSCs, correlate with clinical outcomes. The long-term goal would be to establish a signature profile (percentage of various progenitor/stem cells) to use as a tool to determine and predict the therapeutic efficacy of BMC. Ziegler et al recently found that BMA and BMC contain higher concentrations of anti-inflammatory proteins, such as IL-1Ra, than in peripheral blood and other platelet-rich plasma preparations. It is important to note that these factors may be involved in mediating catabolic factors and improving hip OA symptoms and function. Last, we observed blood cell heterogeneity among our patients, which has been observed by Birbrair and Frenette. A standardized methodology that yields a consistent number of nucleated cells and has been optimized to cause a therapeutic response is necessary to reduce treatment variability.

CONCLUSION

A single BMC injection can significantly improve subjective pain and function scores up to 6 months in patients with symptomatic hip OA. There were no serious adverse events or complications reported during this study. Further studies are warranted to evaluate BMC treatment against other therapeutics in a larger sample size to compare the biological signature profiles that may be responsible for the therapeutic effect.

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