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Original Research

Early Clinical Outcomes of Intra-Articular Injections of Bone Marrow Aspirate Concentrate for the Treatment of Early Osteoarthritis of the Hip, and Knee: A Cohort Study

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Abstract

Background: Bone marrow aspirate concentrate (BMC) is one of the few cell-based therapies available as a possible biological treatment for early osteoarthritis (OA). Its efficacy, safety, and benefit compared with other treatments are still to be determined.
Objective: To assess the clinical outcomes of patients undergoing intra-articular injection of BMC for the treatment of early knee and hip OA.
Design: Prospective, cohort study.
Setting: Single institution, quaternary level of care.
Patients: Nineteen patients (16 female and 3 male), totaling 25 joints (10 knees, 15 hips), treated with intra-articular BMC for early OA between 2014 and 2016. The mean age at time of the procedure was 58 $\pm$ 12.7 years (range, 30-80 years). The mean follow-up was 13.2 $\pm$ 6.3 months (range, 6-24 months). Inclusion criteria included $\geq$18 years; knee OA, Kellgren—Lawrence grade I-II; hip OA, Tönnis grade I-II; first-time intra-articular BMC therapy, after unsuccessful symptomatic and conservative treatments (ie, physical therapy, analgesics and anti-inflammatory drugs) for 6 months. Exclusion criteria included pregnancy; malignancy; rheumatologic diseases; infection; Kellgren—Lawrence grade III-IV; Tönnis grade III; and previous intra-articular injections or surgery.
Interventions: All patients had autologous bone marrow aspirate harvested from the iliac crest and centrifuged to achieve BMC, for intra-articular injection.
Main Outcome Measurements: The hypothesis was formulated before the study. Patient-reported outcomes measures were assessed preoperatively and at last follow-up using the Western Ontario and McMaster Universities Arthritis Index.
Results: Western Ontario and McMaster Universities Arthritis Index improved from a baseline of 40.8 $\pm$ 18.3% to 20.6 $\pm$ 17% ($P < .001$) at final follow-up. The satisfaction rate was 63.2%. The minimal clinically important difference threshold of 9.15 points was reached by 64% of the patients. Two patients were converted to total hip arthroplasty at 8 months after BMC injection.
Conclusions: Intra-articular injections of BMC for the treatment of early knee or hip OA were safe and demonstrated satisfactory results in 63.2% of patients. Future studies are necessary to determine the efficacy of this technique and its safety profile.
Level of Evidence: II

Introduction

Osteoarthritis (OA) is one of the leading causes in both disabling (ie, pain and decreased range of motion) and generated economic burden (ie, long-term treatment costs for the patient and the society) in musculoskeletal conditions, with knee and hip joints most commonly affected [1-5]. Regenerative and biological therapies continue to provide new insights within the field of orthopedics. These therapies may expand the available options of nonsurgical or minimally invasive treatments for patients with early OA and other joint diseases [6]. Bone marrow aspirate concentrate (BMC) has been proposed as a possible biological treatment for symptomatic focal chondral defects and OA of the knee [7-12], femoral head osteonecrosis [13-17], as well as

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other musculoskeletal conditions [18,19]. Bone marrow aspirates (BMAs) typically are obtained from the iliac crest [20,21]. Then, BMC is processed by centrifugation (density separation) of the BMA sample, which yields in a small volume a greater concentration of nucleated cells (including stem and progenitor cells, 0.001%-0.01% of mononuclear cells [10,22,23]) in addition to an increased concentration of platelets, growth factors, and cytokines (platelet-derived growth factor, transforming growth factor-beta 2, vascular endothelial growth factor, etc) [12].

Therefore, BMC could potentially result in anti-inflammatory and anabolic effects once injected in an OA joint [24]. In comparison with platelet-rich plasma, BMC has been shown to carry a greater concentration of several growth factors and cytokines, including vascular endothelial growth factor, interleukin-8, and interleukin-1RA [24-27]. All of these are involved in either angiogenesis, chondrocyte metabolism, homing of stem cells, or are anti-inflammatory [27].

In addition, autologous BMC is one of the few cell-based treatments that can be used in accordance with Food and Drug Administration regulations. The process of centrifugation has been viewed as minimal manipulation; therefore, performing BMA and obtaining BMC for autologous injection during the same procedure qualifies as a Category 1 "non-HCT/P" because the cell product involves a specifically exempted product (bone marrow), is autologous, used for a homologous purpose, and is not combined with other articles [28]. Clearly, there is a strong potential for the use and continuous investigation of BMC for the treatment of articular cartilage disease; however, their value needs to be determined [9]. Therefore, the purpose of this study was to assess the clinical outcomes, satisfaction, and safety of patients undergoing intra=articular injection of BMC for the treatment of early knee or hip OA.

Methods

Patients

This single-institution study was approved by the institutional review board. Between December 2014 and June 2016, a surgeon (C.P.-G.) prospectively enrolled patients undergoing an intra-articular injection of BMC for the treatment of early knee and/or hip OA. Knee and hip OA was radiographically confirmed by the use of anteroposterior and lateral views of the corresponding joint. These patients were identified and offered participation in this study. Medical records of patients were analyzed. Data were obtained from a clinical electronic database. Inclusion criteria included patients $\geq$18 years old undergoing first-time intra-articular BMC therapy; primary diagnosis: early knee OA, Kellgren—Lawrence (K-L) grade I-II, and/or early hip OA, Tönnis grade I-II; and did not respond to nonoperative treatments including physical therapy and nonsteroidal anti-inflammatory drugs for at least 6 months. Exclusion criteria included age $<$18 years old; pregnancy; malignancy; rheumatologic diseases; infection; K-L grade III-IV; Tönnis grade III; joint space narrowing $<$2 mm; patients previously treated with intra-articular steroids injections; avascular necrosis of the femoral head; and previous surgery in the affected joint. Patient demographics (age, sex, and body mass index) and comorbidities (smoking status, osteoporosis, hypothyroidism, and diabetes) were documented. The data were extracted by a single investigator (F.R.-F.) and entered in a created electronic database for statistical analysis. Data quality control was performed by the principal investigator (C.P.-G.).

Procedures

Bone Marrow Aspirate Concentrate

The technique was performed as previously described [20,21,29]. All patients were placed in the dorsal supine position on the operating table while under sedation. The anterior superior iliac spine was identified. A skin incision was performed, followed by cortical perforation, and multiple 2- to 4-mL bone marrow aspiration samples were collected from the anterior iliac crest advancing every 5-10 mm via a bone marrow aspiration needle. This was done either perpendicularly (to the iliac crest), advancing in a fan-like projection followed by aspiration, or parallel (to inner and outer tables of the iliac crest), advancing in a fan-like projection between both tables. A total of 120 mL of bone marrow was obtained. The sample was centrifuged at 1400 *g* for 15 minutes (BioCUE Platelet Concentration System; Zimmer Biomet, Warsaw, IN) to create a final BMC volume of 12 mL. This formulation was then injected intra-articularly into the knee or hip joint under radiographic or ultrasound guidance.

All patients were allowed immediate full weight-bearing activity and encouraged to perform gradual physical activity. Patients were asked not to take nonsteroidal anti-inflammatory drugs for 3 weeks post-operatively. Ice therapy was indicated. Major and minor complications, under the Clavien—Dindo classification, were documented throughout the follow-up period [30].

Patient-Reported Outcome Measures

Patients completed the Western Ontario and McMaster Universities Arthritis Index (WOMAC) preoperatively and at 6, 12, 18, and 24 months. Patients who underwent conversion to total joint replacement or persisted with pain that resulted in additional treatment or intervention were considered as failures. The WOMAC score is a survey divided in 3 sections: pain, stiffness, and physical function. The total score is summed to a total of 0 to 96, and a percentage is calculated. The

score is directly proportional to patient symptoms, with greater scores indicating worse outcomes [31]. The minimal clinically important difference (MCID) was calculated based on a distribution-based approach to represent the smallest change in patient-reported outcome measures that is important to patients [32]. The MCID threshold was considered to be half a standard deviation (SD) of the baseline score to be a clinically important change in quality of life [33].

In addition, satisfaction rate was assessed as yes (satisfied) or no (unsatisfied) via the question: "Where you satisfied with the procedure outcomes?" to see the percentage of patients satisfied and unsatisfied with the outcomes at latest follow-up. Based on this response, the effect size (ES) was calculated as score changed divided by baseline SD to determine the responsiveness to treatment [34]. For interpretation, Cohen [35] proposed the following benchmarks: 0.2 (small effect), 0.5 (moderate effect), and 0.8 (large effect). The ES is expected be small in those with no improvement and large in those with great improvement [36].

Statistical Analysis

Statistical analysis included the Student *t* tests and analysis of variance for the assessment of the treatment effect by mean difference between postoperative versus preoperative WOMAC scores. The analysis was performed using Sigma Plot 11.0 software (Systat Software Inc, San Jose, CA). Data are reported as mean ± SD (range), and *P* values $\leq$.05 were considered statistically significant.

Results

In total, 19 patients (16 female and 3 male) were enrolled, accounting for a total of 25 joints (10 knees, 15 hips). None of the patients were lost to follow-up. Two patients (1 male, 1 female) underwent bilateral hip procedures, 1 female patient underwent hip and knee procedures, and 3 female patients underwent bilateral knee procedures, totaling 6 patients with 2 joints treated. The mean age at date of surgery and mean latest postoperative follow-up time was 58 ± 12.7 years (range, 30-80 years) and 13.2 ± 6.3 months (range, 6-24 months), respectively (Table 1).

All patients completed the WOMAC preoperatively, at 6 months, and at latest follow-up. At 6 months postoperatively, scores improved abruptly ($P < .001$). At mean latest follow-up, scores remained low and significant ($P < .001$). No significant difference was found between the 6-month follow-up and the mean latest follow-up points ($P = .6$). The percentage of patients experiencing important improvement based on the MCID threshold of 9.15 was 64% (Table 2 and Figure 1).

Regarding the patients' satisfaction rate, 12 patients (16 joints: 5 knees, 11 hips; 63.2%) were satisfied with the procedure. These patients regained function and agreed that they felt significant improvement during the first 6 months postinjection. A total of 7 patients (9 joints: 5 knees, 4 hips; 36.8%), 2 of whom had bilateral knees treated, experienced mild improvement, no improvement, or worsening of symptoms after treatment. Two of the unsatisfied patients were converted to total hip arthroplasty (THA) at 8 months postoperatively. The responsiveness measured with the standardized ES based on the WOMAC scores for satisfied and unsatisfied subgroups showed small effect in the unsatisfied group and a large effect for the satisfied group and both subgroups combined (Table 3).

Table 1
Demographics

Baseline Characteristics	Study Group (N = 19)
Age at DOS, y	58 ± 12.7 (30-80)
Sex, n (%)	
Male	3 (16%)
Female	16 (84%)
Joints, n (%)	
Knee(s)	10 (40%)
Hip(s)	15 (60%)
BMI, kg/m^2	25.9 ± 6 (19.4-39.7)
Osteoporosis, n (%)	5 (26.3%)
Smoking status, n (%)	
Never	12 (63.2%)
Former, >10 y	5 (26.3%)
Current	2 (10.5%)
Diabetes, n (%)	2 (10.5%)
Hypothyroidism, n (%)	4 (21.1%)

Results for age and BMI are reported as a mean ± SD (range).
N/n = number; DOS = date of surgery; BMI = body mass index.

Complications and Failures

No patient developed major complications. However, 11 patients experienced 1 or 2 minor complications: mild pain at the site of BMC extraction during the first 24 postoperative hours (3 cases; 15.8%), hip joint discomfort during the first days after the procedure (7 cases; 36.8%), pain during the first 2 weeks after BMC injection (5 cases; 26.3%), and swelling (1 case; 5.2%). Seven patients were unsatisfied, and 2 of them converted to THA (10.5%). One of the patients who converted to THA was 65 years old and had multiple comorbidities: diabetes, obesity, and osteoporosis.

Discussion

The goal of the study was to assess the clinical outcomes, satisfaction, and safety of patients undergoing intra-articular injection of BMC for the treatment of symptomatic early knee and hip OA. Based on the results of this study, intra-articular injections of BMC improved clinical symptoms in 12 patients (63.2%) included in this cohort. Improvements mostly were observed during the first 6 months postinjection and

Table 2
Preoperative and Postoperative WOMAC

Time Point	WOMAC	Postoperative at 6-Month Follow-Up vs Preoperative	Postoperative at Mean Latest Follow-Up vs Preoperative	MCID
Preoperative (N = 19)	40.8% ± 18.3 (5.2-71)	Mean difference 21.6 ± 5.1; 95% CI 11.3-32; $P < .001$	Mean difference 20.2 ± 5; 95% CI 10.2-30.3; $P < .001$	9.15
6-mo follow-up (N = 19)	19.2% ± 18.2 (1-56.2)			
Latest postoperative follow-up, 13.2 ± 6.3 mo (6-24); (N = 19)	20.6% ± 17 (1-54)			

Results are reported as a mean ± SD (range).
WOMAC = Western Ontario and McMaster Universities Arthritis Index; MCID = minimal clinically important difference; N = number of patients; CI = confidence interval.

remained throughout the follow-up periods. The most common reported adverse effects were temporary pain during the first 2 weeks after BMC injection (5 cases; 26.3%) and anterior hip joint discomfort during the first days after the procedure (7 cases; 36.8%). The calculated MCID value (9.15) was smaller than the mean differences at both time points (6 months and latest follow-up), and 64% of the patients reached this threshold. It seems to represent a true minimal difference for patients experiencing a significant improvement. Regarding the assessment of responsiveness to treatment by the calculated standardized ES, BMC treatment had a substantial effect in patients who reported better WOMAC scores and were satisfied.

Few clinical studies have reported on the use of BMA in patients with OA, with most of these studies focusing on knee OA [7,37-40]. Although these studies used different formulations and some included patients receiving adjuvant therapy, each of these studies have reported positive outcomes after BMA treatment, with patients improving physical activity and quality of life. Hauser and Orlofsky [37], using whole BMA and hyperosmotic dextrose injections in a case series of 7 patients

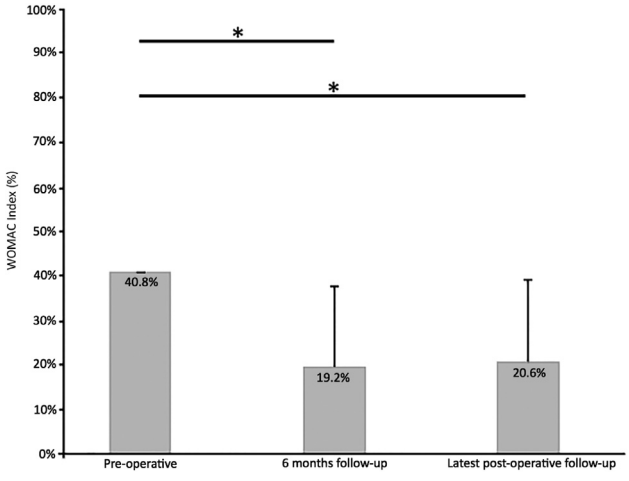

Figure 1. Bar chart showing WOMAC Index (mean and standard deviation) at preoperative and postoperative follow-ups. *Significant differences ($P \leq .05$) between preoperative and respective postoperative follow-ups. WOMAC, Western Ontario and McMaster Universities Arthritis Index.

(mean age, 64 years) with OA (7 hips, 6 knees, and 1 ankle), and using an original questionnaire [37] as outcome measure, reported a substantial improvement in function and pain relief in all patients with no adverse events. However, in discordance with the present study, the treatment period ranged from 2 to 12 months and the patients received multiple whole BMA injections (range 2-7), with no centrifuge density separation to harness the majority of stem cells [37].

In another case series by Kim et al [38], 41 patients (75 knees) with a mean age of 60.7 years underwent BMC injections. The outcomes were measured with the visual analog scale and functional tests. At a mean follow-up of 8.7 months, all patients showed clinical improvement, with satisfactory results in 70.7% of patients. However, more invasive concomitant therapy was used in this study, including adipose tissue injection, arthroscopic debridement, microfracture, and high tibial osteotomy. Interestingly, the authors found that patients with inferior results had a greater severity of OA, K-L grade IV, suggesting that advanced OA may be more reticent to BMC therapy. The side effects encountered in this study, joint inflammation and pain, were similar those found in the present study.

In a retrospective study by Centeno et al [39], a total of 840 knees in 2 treatment groups, 616 BMC alone and 224 BMC plus adipose graft, with a mean age of 54.3 and 59.9 years and a mean follow-up of 10.4 and 10.7 months, respectively, were assessed and compared. The results were measured with a subjective improvement rating scale, the Lower Extremity Functional Scale, and Numeric Pain Scale (NPS). The authors reported good results in both groups ($P \leq .001$), although patients treated with BMC alone demonstrated significantly better subjective percentage improvement scale scores ($P = .03$). In addition, better outcomes were found in patients with K-L grade II than with K-L grade III or IV.

Furthermore, in a multicenter analysis done by Centeno et al [40], clinical outcomes for 216 hips treated with BMC plus platelet-rich plasma for OA were appraised. Clinical outcomes were evaluated with the Oxford Hip Scale (OHS), NPS, and an original percentage improvement questionnaire. The mean age was 57 years

Table 3
Standardized ES based on participant response to satisfaction and respective WOMAC scores

Subgroups Based on Satisfaction (Yes or No)	N (%)	ES ± SD (95% CI)
Yes/satisfied	12 (63.2%)	3.36 ± 0.57 (2.25-4.47)
No/unsatisfied	7 (36.8%)	0.24 ± 0.54 (−0.64-1.12)
Satisfied + unsatisfied	19 (100%)	1.13 ± 0.3 (0.53-1.72)

Results are reported as ES ± SD (95% CI).
ES = effect size; WOMAC = Western Ontario and McMaster Universities Arthritis Index; N = number; SD = standard deviation; CI = confidence interval.

(divided in 2 groups, ≤55 and >55 years old), and the mean follow-up was 4.9 months for the OHS, 5.9 months for NPS, and 9 months for the percentage improvement questionnaire. The number of joints meeting the improvement thresholds for each one of these measuring scales was 64%, 59%, and 43%, respectively. Although the rate of survey response was low, the OHS increased in 57 procedures ($P < .001$), and the NPS decreased in 81 procedures ($P < .001$). The group ≤55 years were substantially more likely to report improvement with OHS and 50% or greater percentage improvement scale. Age did not affect NPS outcome, nor did K-L grade for OHS and NPS. Response to intra-articular injection of BMC might depend on age [40]. Similar to our study, the most commonly reported side effects of both studies by Centeno et al were pain and joint swelling [39,40].

In a recent randomized controlled trial by Shapiro et al [7], 25 patients with bilateral knee OA and a median age of 60 years underwent BMC therapy with platelet-poor plasma in one knee and a placebo injection of saline in the contralateral knee. Using the Intermittent and Constant Osteoarthritis Pain and visual analog scale questionnaires, Shapiro et al found that both groups demonstrated improvement ($P \leq .02$) but no intergroup difference in pain relief ($P = .09$) [7]. Interestingly, this is the only study to our knowledge that compared a treatment group with a placebo group and both had pain relief.

Bone marrow has been an extensively studied source of stem and progenitor cells [41-44] and is currently one of the few cell-based treatments for OA compliant with Food and Drug Administration regulations [28]. However, BMC formulations vary between patients and also depending on the protocol and device used to process the sample. These sources of variation make comparisons between reports challenging [45]. Therefore, it is important to standardize quantitative methods for BMC processing, characterization, and delivery and to report standardized clinical and structural outcomes to determine the value of these treatments [12,46]. Previous studies have shown that patients treated with BMC for OA or focal chondral defects experience symptoms improvement with mild side effects [9,47-50]. The phenomenon responsible for the pain relief is still to be determined but may be related to the stem cell paracrine and immunomodulatory effect or the anti-inflammatory effect of the growth factors included with BMC [51-53]. It is important to note that less-encouraging results were seen in patients with severe OA (K-L grade IV), which raises concern about the need to establish the adequate recipients for these treatments [38,39].

In conjunction with the aforementioned studies, the findings of the present study provide a broader base to the current knowledge of outcomes related to BMC intra-injections for the treatment of OA. Although these studies often used heterogeneous BMC preparations, adjuvant therapies, and different outcome measuring scales, the overall response to these are positive and encouraging results. In addition, the BMC sample have not been characterized in most cases [27], which limits the correlation of cellular composition with clinical outcomes.

The present study had some limitations. The sample size was small, and a control group was not used for comparison of outcomes. The mean follow-up duration was relatively short, and long-term follow-up is necessary to determine the true efficacy of this procedure. As stated previously, BMC characterization was not performed; therefore, we could not account for the different quality of BMC samples between and within patients. In addition, no biological analysis was performed (eg, cellular composition, colony-forming units, growth factors, surface markers) before BMC injection at time of surgery to analyze the "potency" of each formulation and, hence, correlate to outcomes. Future studies should address this cornerstone when analyzing outcomes of BMC therapy. The strengths of this study include one of the first clinical outcome studies reporting on the use of BMC therapy for patients with early OA and adds knowledge to the growing literature in this subject.

Conclusions

Intra-articular injections of BMC for the treatment of symptomatic early knee or hip OA appears to be safe. However, outcomes are unpredictable, given that only 63.2% of the patients were satisfied after the treatment. No major complications occurred at early follow-up. Further prospective randomized comparison

cohorts are necessary to determine the efficacy of BMC intra-articular injection in patients with early hip and knee OA.

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Disclosure

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