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Bone marrow aspirate injection for osteoarthritis of the hip; A pilot study

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ABSTRACT

Objectives: Bone marrow aspirate (BMA) intra-articular injection is a minimally invasive orthobiologic treatment option for osteoarthritis (OA). Hip OA affects a significant portion of the population and has a paucity of data surrounding orthobiologic treatments. The primary objective of this study was to delineate the clinical impact of bone marrow aspirate intra-articular injections on decreasing pain and improving function in patients with hip OA.

Methods: A single-center, retrospective analysis of thirty-one patients, aged 32 to 83 (62.4 ± 16.5), with Kellgren-Lawrence (KL) Hip OA grading of 2–4 (mean 2.9 ± 0.7), who underwent intra-articular bone marrow aspirate injection into the hip and were followed for twelve months. Evaluation was at baseline, 12 weeks, 6 months, and 12 months using the Numerical Rating Scale (NRS) for pain and the Hip Disability and Osteoarthritis Outcome Score Jr (HOOS-Jr) for function. The proportion of responders, as defined by a ≥50% reduction in NRS pain score, was assessed at 12 weeks, 6 months and 12 months.

Results: At 6 and 12 months follow-up, there was a statistically significant improvement in NRS scores ($P < 0.05$). Stratifying by KL grade, subjects with KL grades 2 and 3 experienced statistically significant improvement in NRS scores at 6 and 12 months. Patients with KL grade 4 showed significant improvement in pain at 12 months. Forty-two percent of patients at 6 months and 61% at 12 months reported ≥50% reduction in pain. When stratifying by KL grade, 80% and 71% of KL2 and KL3 grades respectively were responders by 12 months. Patients experienced statistically significant improvement in HOOS-Jr scores at 6 and 12 months.

Conclusion: In patient with mild, moderate, and severe hip OA, BMA may be an alternative treatment that improves pain and function in patients for as long as 12 months. In addition, BMA may also be an effective, lower cost option to more expensive BMAC preparations.

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis and is defined as a progressive degenerative process affecting the joints in our body [1]. In 2017, OA was estimated to have affected over 300 million people on a global scale [2]. Although the knee is the most common joint diagnosed with OA, hip OA also affects a significant portion of the population, with studies reporting a prevalence as high as 9.2% among adults aged 45 years and older in the United States in 2009 [3,4]. The prevalence of hip OA in individuals under the age of 50 is higher in men, but the condition becomes female-predominant when over 50 years of age [5]. Classically, treatment options include physical therapy, anti-inflammatory medication, joint injection, with either steroid or viscosupplementation, and joint replacement. While the majority of hip replacements occur in patients over age 65, studies indicate that as the prevalence of hip OA continues to increase, greater than 50% of total hip arthroplasties will be performed in patients younger than 65 by 2030 [6].

Many argue that there is a large gap in the treatment options available between that of conservative management and surgical intervention for hip OA. To address this gap and offer more options to patients with this condition, there has been increasing interest in the field of Regenerative Medicine. Currently, there are several biologically based treatments being offered for the treatment of OA. Platelet rich plasma (PRP), bone marrow derived stem cells, which includes both aspirate alone (BMA) and aspirate concentrate (BMAC), and adipose derived stem cells are among the most common treatments currently under investigation. These products are delivered directly to the area of injury in an attempt to alter the biologic environment within the joint to promote regeneration and harness the body's innate healing potential for the purpose of relieving pain and improving function. Bone marrow and adipose tissue are two

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areas of the body that are currently being utilized to harvest autologous mesenchymal stem cells (MSCs) for the treatment of musculoskeletal conditions. MSCs are derived from pericytes and are thought to function as medicinal signaling cells in vivo [7]. From the recent work of Caplan et al., it has been postulated that MSCs establish a regenerative environment via anti-apoptotic, anti-scarring, mitotic and angiogenic effects [7]. Following bone marrow harvesting, centrifugation of BMA is performed to further concentrate the aspirate and produce BMAC. The evidence for the use of these treatments for osteoarthritis continues to grow, however the majority of data has centered around the knee joint. BMAC has shown promising results for pain reduction and improved function in knee OA, although there is ongoing debate on whether it is superior to other commonly used orthobiologics, such as PRP and microfragmented adipose tissue [8,9]. Furthermore, evidence for treatment of OA outside of the knee joint, such as in the hip, is severely lacking.

Research to date has been largely focused on BMAC, as opposed to BMA, as the primary therapeutic treatment derived from bone marrow. However, recent advancements in aspiration technology have allowed improved concentrations of harvested cells without the need for centrifugation [10]. Given the paucity of data reporting the effect of BMA on OA in the hip, the aim of this investigation is to report the clinical impact of image-guided BMA injections for the treatment of hip OA.

2. Methods

This study was performed at a single-center outpatient rehabilitation office at a large tertiary care hospital. After institutional review board approval was obtained, the records of patients diagnosed with hip osteoarthritis and treated with BMA between January 2017 and January 2021 were obtained using International Classification of Diseases (ICD-9) codes and Current Procedural Terminology (CPT) codes. Patients were included in the study if they met the following criteria: age 18–99 years, had undergone the BMA procedure after having hip pain for at least four months, at least one positive physical exam maneuver(s) including internal rotation over pressure (IROP) and hip flexion adduction and internal rotation (FADIR), diagnosis of hip osteoarthritis on plain radiograph, failure to improve satisfactorily (defined by the patient as intolerable pain and functional limitations) with physical therapy (minimum three months). Exclusion criteria included patients with a prior history of hip surgery and those who refused BMA and therefore didn't undergo the procedure. In addition, patients who received a steroid injection into the hip within three months, were taking NSAIDs or antiplatelet medications, or had any signs of infection were also excluded from the study. After a thorough review of the medical records, thirty-one patients fulfilled the inclusion criteria.

2.1. Hip osteoarthritis classification

The Kellgren and Lawrence (KL) system is a method of classifying the severity of knee osteoarthritis (OA) using five grades [11].

- grade 0: no radiographic features of OA are present;
- grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping;
- grade 2: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph;
- grade 3: multiple osteophytes, definite JSN, sclerosis, possible bony deformity;
- grade 4: large osteophytes, marked JSN, severe sclerosis, and definite bony deformity.

2.2. Bone marrow aspirate: preparation

A single, fellowship-trained, board-certified physiatrist performed the procedure. For the aspiration, the patient was placed in the prone position. The fluoroscope was used to maximally profile the posterior iliac bone utilizing an oblique anterior-posterior projection with the image detector obliquely rotated towards the contralateral iliac bone (Fig. 1). Once the posterior iliac bone is profiled, a skin needle entry site (osseous target site) is selected and marked along the middle third posterior iliac bone at the central medullary space. Once subcutaneous and periosteal anesthesia is achieved, intermittent fluoroscopy is used to ensure that the biopsy needle follows a coaxial trajectory, parallel to the X-ray beam, into the posterior iliac bone at the planned osseous entry site and then along the long axis of the iliac bone in the anterior-posterior plane.

Following optimal fluoroscopic positioning, bone marrow aspiration was conducted from the posterior iliac crest using the Marrow Cellution Bone Marrow Harvesting Device (Ranfac Corp., Avon, MA) consistent with the manufacturer's instructions, best practice guidelines and expert consensus technique. Firstly, 10 cc's of 1000 units/mL heparin were withdrawn into a 10-mL syringe. After the syringe was connected to the introducer needle, heparin was injected until the introducer needle was fully rinsed and then it was aspirated back into the syringe. This process was repeated for the longer aspiration needle. All stylets were then rinsed with heparin. Following this, 1.0 mL heparin was added to the 10-mL collection syringe. Once proper localization was confirmed under fluoroscopic guidance, the introducer needle with sharp stylet was inserted just past the cortex into the medullary space. The sharp stylet was removed, and a syringe was attached. An initial 1 mL of bone marrow was aspirated to ensure proper needle tip positioning. The syringe was removed, and an 11-gauge blunt stylet was inserted and locked into the device. The introducer needle was then advanced approximately 2 cm. The blunt stylet was removed and a smaller 14-gauge aspiration cannula was inserted. The smaller gauge aspiration cannula minimizes bleeding and uptake of less desirable peripheral blood. Following this, a syringe is attached, and 1.0 mL of bone marrow is aspirated. Next, the physician then held the outer housing in place while rotating with the opposite hand 180° to raise the cannula tip 0.375 cm into a new, more superficial, location. This rotation/aspiration technique was repeated 5–6 times to obtain approximately 6–8 mL of BMA harvested near the cortex, which houses the largest number of stem/progenitor cells [10].

2.3. BMA injection technique

Injection of BMA was performed using two (fluoroscopic or ultrasound) imaging-guided techniques. For the fluoroscopically guided procedure, the patient was placed in a supine position and prepped and draped in typical sterile fashion. Using antero-posterior fluoroscopic imaging, the skin was marked at a spot over the center of the femoral neck. A skin wheal using a 25-gauge needle was made, and deeper structures were anesthetized using local anesthetic. Once anesthetized, a 22-gauge, 3.5-inch spinal needle was directed toward the junction of the femoral head and neck (Fig. 2). Once osseous contact was made, 1–2 cc's of radio-opaque contrast medium was injected to confirm intra-articular flow. Reasons for using the antero-posterior fluoroscopic approach include its ability to allow the anterior musculature to relax offering a procedural advantage, as well as for comfort when patients cannot tolerate the lateral decubitus position for a lateral approach. Using ultrasound guidance, the anterior hip joint was directly visualized by placing the transducer longitudinally at the femoral head-neck junction (Fig. 3). Following the sterile prep, the skin and subcutaneous tissues were anesthetized, using 3 mL of 1% lidocaine attached to a 3.5-inch 22-gauge spinal needle was inserted approximately 3 cm. Using sterile ultrasound gel, the needle was guided through this anesthetized track toward the anterior joint capsule. Once the capsule was penetrated, the syringe containing the BMA was attached, and the injectate was delivered. A detailed depiction of the procedural technique with images has been previously described by Yasar et al. [12]. BMA was injected into the intra-articular and subcapsular space. Approximately 6–8 cc of bone marrow aspirate was injected into the joint until resistance was met, at which point 1–2 cc was injected into the extracapsular space. Immediately after the procedure, the needle was removed, and a sterile Band-Aid

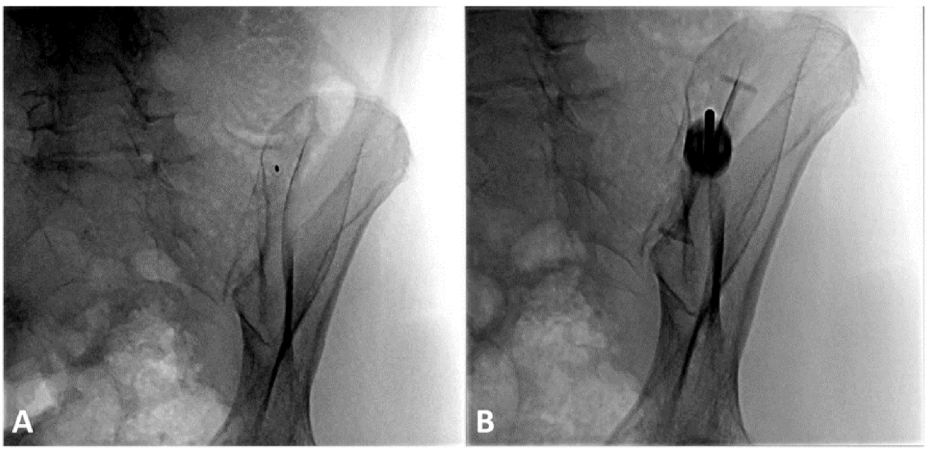

Fig. 1. Fluoroscopic guided posterior iliac bone marrow aspiration. A: Posterior iliac osseous target. B: Insertion of the marrow cellutions aspiration device.

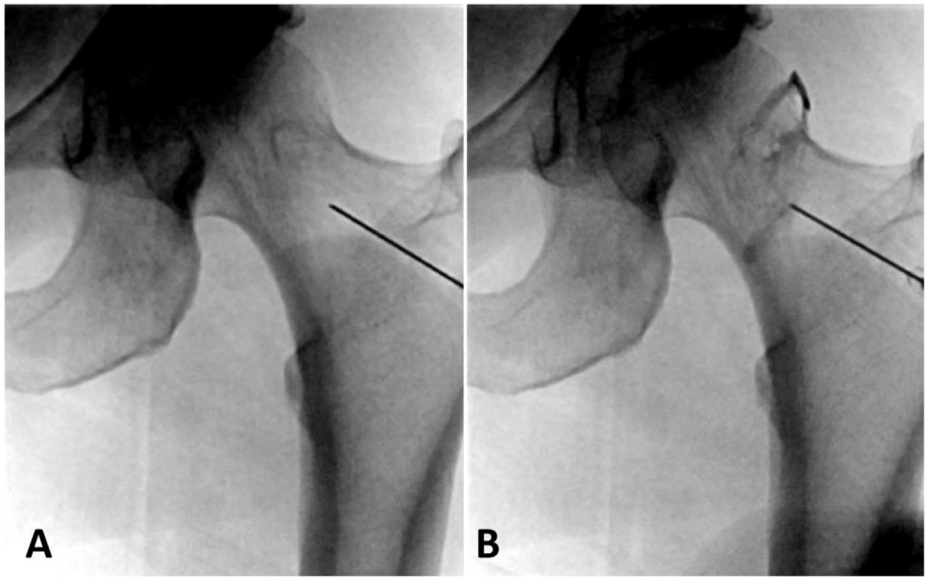

Fig. 2. Fluoroscopic guided intra-articular hip injection via an anterior approach. A) pre injection. B) confirmation of intra-articular contrast flow prior to injection.

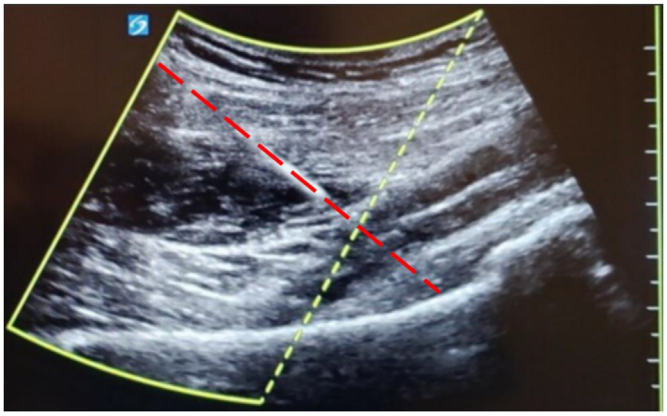

Fig. 3. Ultrasound guided intra-articular injection of the hip. (Red dashed line representing needle). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

was placed over the injection site.

2.4. Post BMA protocol

Patients conducted a standard post procedure protocol which includes progressive and evolving precautions, therapy goals, home exercises from Day 1–28 post procedure, as detailed in appendix A below.

2.5. Evaluation measures

This study evaluated reduction in hip pain, as quantified by a scale of 1–10 numerical rating scale (NRS) for pain intensity; lower scores were indicative of less pain. The Hip Disability and Osteoarthritis Outcome Score Jr (HOOS-Jr) was also used as a tool to evaluate function and pain. The HOOS-Jr is modified from the longer HOOS score which was designed as a means to evaluate the opinion of adults with hip disability, regardless of the presence of osteoarthritis [13]. The HOOS-Jr is a six item questionnaire which focuses on 3 subcategories: joint pain, stiffness, and function. Each item is answered on a scale of 0–4. Sums of the raw score (0−24) are then converted to an interval score ranges from 0 to 100 using the chart below (Table 1), where 0 represents total hip disability and 100 represents perfect hip function. Response to treatment was also assessed and defined as patients who reported a $\geq$50% improvement on pain scores assessed at each time interval.

Table 1
HOOS Jr. score conversion chart.

Raw summed score (0–24)	Interval score (0–100 scale)
0	100.00
1	92.340
2	85.257
3	80.550
4	76.776
5	73.472
6	70.426
7	67.516
8	64.664
9	61.815
10	58.930
11	55.985
12	52.965
13	49.858
14	46.652
15	43.335
16	39.902
17	36.363
18	32.735
19	29.009
20	25.103
21	20.805
22	15.633
23	8.104
24	0.00

2.6. Statistical analysis

Descriptive statistics (including mean, standard deviation, median, range, frequency, and percentage) were calculated to characterize the patient population. The one-sample paired *t*-test was used to compare NRS and HOOS-Jr values between 1) pre-injection (baseline) and 12 weeks after the procedure, 2) pre-injection (baseline) and 6 months after the procedure, and 3) pre-injection (baseline) and 12 months after the procedure. In addition, patients were stratified by Kellgren-Lawrence classification, and a one-sample paired *t*-test was used to compare NRS values between 1) pre-injection (baseline) and 12 weeks after the procedure, 2) pre-injection (baseline) and 6 months after the procedure, and 3) pre-injection (baseline) and 12 months after the procedure.

For responder analysis, a chi-square test was used to compare the proportion of responders to nonresponders in terms of radiographic grade of hip arthritis, defined by the Kellgren-Lawrence scale. Statistical significance was defined at a P value of <5% ($P < 0.05$).

3. Results

A total of thirty-one subjects qualified for this study and underwent bone marrow aspirate injection for osteoarthritis of the hip. The average patient age (range) was 62.4 ± 16.5 (32–83) years, with 52% of patients being female and 48% male. The baseline NRS as a group was 6.2 ± 2.0. Demographic data, along with stratification based on Kellgren-Lawrence scale, can be found in Table 2.

Table 2
Baseline demographic information (N = 31).

Age, mean ± SD, y	62.5 ± 16.5
Gender, No. (%)	
Male	15 (48.4)
Female	16 (51.6)
NRS Pain score at baseline, mean ± SD	6.2 ± 2.0
Kellgren-Lawrence Hip Grading, mean ± SD	2.9 ± 0.7
Kellgren Lawrence Hip Grading, No. (%)	
0	0 (0)
1	0 (0)
2	10 (32)
3	14 (45)
4	7 (23)

3.1. Numerical rating scale scores (cohort)

The average NRS score for the group was 6.2 ± 2.0 at baseline. At 12 weeks, 6 months, and 12 months, it was 5.9 ± 2.1, 3.8 ± 2.6, and 3.0 ± 1.4 respectively. Although there was no significant improvement in pain at 12 weeks ($P = 0.4$), there was a statistically significant improvement at both 6 month and 12 month follow-up ($P < 0.05$) (Table 3).

3.2. Numerical rating scale scores (stratified by Kellgren-Lawrence)

No patients showed significant improvement in pain at 12 weeks. However, in patients whose radiographic hip arthritis grade was KL grades 2 and 3, there was a significant improvement in pain at both 6 months and 12 months (Tables 4 and 5). Conversely, patients who suffered from severe hip arthritis (KL grade 4) only showed statistically significant improvement in pain at 12 months (Table 6).

3.3. Responder analysis

Response to bone marrow aspirate for the treatment of hip arthritis was defined by a ≥50% reduction in pain scores compared to baseline levels. We also analyzed those that had at least a ≥30% reduction in pain. When analyzing the group as a whole, 42% of the group at 6 months and 61% of the group at 12 months reported ≥50% reduction in pain, and 52% of the group at 6 months and 77% of the group at 12 months reported at least a ≥30% reduction in pain (Table 7). Tables 8 and 9 further specify the number of patients in each KL grade that responded to treatment (≥50% reduction in pain scores) or achieved at least 30% reduction in pain at each time point. By 12 months follow up, those with KL2 and KL3 showed an 80% and 71% response rate respectively.

Table 3
Change in NRS from baseline.

Baseline	12 wk	Baseline vs 12 wk, 95% CI; *P*	6 mo	Baseline vs 6 mo, 95% CI; *P*	12 mo	Baseline vs 12 mo, 95% CI; *P*
6.2 ± 2.0	5.9 ± 2.1	−0.5 to 3.3; 0.4	3.8 ± 2.6[a]	0.7 to 4.1; <0.05[a]	3.0 ± 1.4[a]	3.2 to 4.8; <0.05[a]

CI = confidence interval; NRS = Numerical Rating Scale.
[a] Statistically significant.

Table 4
Change in NRS from baseline (Kellgren/Lawrence Grade 2).

N = 7						
Baseline	12 wk	Baseline vs 12 wk, 95% CI; *P*	6 mo	Baseline vs 6 mo, 95% CI; *P*	12 mo	Baseline vs 12 mo, 95% CI; *P*
6.5 ± 2.0	5.1 ± 1.7	0.5 to 3.3; 0.1	3.0 ± 2.8	0.7 to 6.3; <0.05[a]	3.0 ± 1.8	1.6 to 5.4; <0.05[a]

CI = confidence interval; NRS = Numerical Rating Scale.
[a] Paired *t*-test.

Table 5
Change in NRS from baseline (Kellgren/Lawrence Grade 3).

N = 14						
Baseline	12 wk	Baseline vs 12 wk, 95% CI; *P*	6 mo	Baseline vs 6 mo, 95% CI; *P*	12 mo	Baseline vs 12 mo, 95% CI; *P*
6.4 ± 2.1	6.4 ± 2.3	−1.6 to 1.5; 0.9	3.6 ± 2.6	1.3 to 4.2; <0.05[a]	2.5 ± 1.0	2.4 to 5.3; <0.05[a]

CI = confidence interval; NRS = Numerical Rating Scale.
[a] Paired *t*-test.

Table 6
Change in NRS from baseline (Kellgren/Lawrence Grade 4).

N = 10						
Baseline	12 wk	Baseline vs 12 wk, 95% CI; *P*	6 mo	Baseline vs 6 mo, 95% CI; *P*	12 mo	Baseline vs 12 mo, 95% CI; *P*
5.6 ± 1.6	5.9 ± 2.0	−1.7 to 1.1; 0.6	5.3 ± 1.9	−1.3 to 1.9; 0.7	3.9 ± 1.2	0.4 to 3.0; <0.05[a]

CI = confidence interval; NRS = Numerical Rating Scale.
[a] Paired *t*-test.

Table 7
NRS % reduction from baseline.

	NRS 12 wk, No. (%)	95% CI	NRS 6 mo, No. (%)	95% CI	NRS 12 mo, No. (%)	95% CI
≥50% reduction (Responders)	5 (16%)	2.2 to 10.2	13 (42%)	8.1 to 18.4	19 (61%)	13.6 to 23.6
≥30% reduction	7 (23%)	3.5 to 12.3	16 (52%)	10.8 to 21.1	24 (77%)	18.7 to 27.5

CI = confidence interval; NRS = numerical rating scale.
Responders are defined as having ≥50% reduction on NRS (Numerical Rating Scale).
≥30% reduction on NRS (Numerical Rating Scale).

Table 8
Responder characteristics based on K-L Grade at 12 weeks, 6 months, and 12 months.

	Kellgren-Lawrence Grade 2	Kellgren-Lawrence Grade 3	Kellgren-Lawrence Grade 4
Responders at 12 weeks	3 (30%) *1.1 to 6.0*	2 (14%) *0.56 to 5.6*	0 (0%) *0 to 2.5*
Responders at 6 months	6 (60%) *3.1 to 8.3*	7 (70%) *3.8 to 10.2*	0 (0%) *0 to 2.5*
Responders at 12 months	8 (80%) *4.9 to 9.4*	10 (71%) *6.4 to 12.4*	1 (14%) *0.18 to 3.6*

Responders are defined as having ≥50% reduction on NRS (Numerical Rating Scale).
Percentages are displayed in parentheses; 95% confidence intervals are displayed in italics.

Table 9
≥30% reduction in pain stratified by K-L Grade at 12 weeks, 6 months, and 12 months.

	Kellgren-Lawrence Grade 2	Kellgren-Lawrence Grade 3	Kellgren-Lawrence Grade 4
≥30% reduction at 12 weeks	4 (40%) *1.7 to 6.9*	3 (14%) *0.56 to 5.6*	0 (0%) *0 to 2.5*
≥30% reduction at 6 months	6 (60%) *3.1 to 8.3*	9 (70%) *3.8 to 10.2*	1 (14%) *0.18 to 3.6*
≥30% reduction at 12 months	8 (80%) *4.9 to 9.4*	12 (86%) *6.4 to 12.4*	4 (57%) *1.8 to 5.9*

≥30% reduction on NRS (Numerical Rating Scale).
Percentages are displayed in parentheses; 95% confidence intervals are displayed in italics.

Table 10
Change in HOOS, JR score from Baseline.

	Baseline	12 wk	6 mo	12 mo
HOOS, JR Score	17.9 ± 3.9	16.1 ± 4.6	11.6 ± 4.6[a]	9.2 ± 5.1[a]

HOOS, JR = Hip Disability and Osteoarthritis Outcome Score, Joint Replacement.
[a] Statistically significant at $P > 0.05$.

Patients with KL4 grade OA showed a 14% response rate (Table 8). Furthermore, by 12 months follow up, 80% of patients with KL2, 86% of patients with KL3, and 57% of patients with KL4 grade OA showed at least 30% improvement in pain (Table 9).

3.4. Hip Disability and Osteoarthritis Outcome Score, joint replacement

When analyzing functional outcomes, the HOOS, JR scale was used. The group as a whole revealed statistically significant improvement in function from baseline at the 6 month and 12 month follow-up, but no statistically significant improvement at the 12 week follow-up (Table 10).

4. Discussion

There are several orthobiologic treatment options available including PRP, BMA, BMAC and adipose derived stems cells. The purpose of this study was to delineate the clinical impact of BMA on decreasing pain and improving function in patients with hip OA. Retrospective analysis of each of the 31 patients revealed that at 12 weeks post-injection, there was no statistically significant improvement in NRS or HOOS Jr. In contrast, subsequent follow-up at 6 and 12 months revealed a statistically significant improvement in both measures. We defined response to the treatment as a greater than or equal to 50% reduction in pain compared to their baseline. We also analyzed which patients had at least a 30% reduction in their pain. From this analysis, we found that there was a 42% response rate at 6 months post procedure which increased to a 61% response rate by 12 months. When evaluating 30% reduction in pain, 52% of the cohort by 6 months and 77% of the cohort by 12 months experienced at least a 30% reduction in pain. This demonstrates the time-dependent effect of BMA in improving pain and function in patients with hip OA. Additionally, stratification of patients by KL grades showed that patients with KL grade 2 or 3 had more favorable response rates when compared with KL grade 4. By 12 months, 80% of patients with KL grade 2, and 71% of KL grade 3 were classified as responders to treatment. Only one patient with KL grade 4 was a responder by 12 months. However, we did find that 57% of patients with KL grade 4 did experience at least 30% reduction in pain with BMA treatment by 12 months follow-up. Lastly, using the HOOS-Jr scale, statistically significant functional improvement was noted at 6 and 12 months follow-up.

The results of this study have several clinical implications. First, the data suggests that BMA injection can provide long-term pain relief and functional restoration (as much as 6–12 months) while avoiding the complications/risks, prolonged recovery time, and added cost associated with surgical intervention. Second, patients with KL grades 2–3 experienced an earlier and more significant reduction in pain (compared to KL grade 4), which suggests that earlier intervention with BMA can significantly improve quality of life in patients with hip OA. Finally, these findings may encourage clinicians to shift toward using BMA rather than intra-articular corticosteroid injections (CSI).

Although CSI are commonly used to relieve pain and restore function in patients with OA, they only provide short-term benefits and may contribute to cartilage degeneration and disease progression [14]. In contrast, studies have shown that orthobiologics (such as HA, PRP, and BMAC) regulate inflammation and promote cartilage healing, which would improve the joint complex itself rather than simply mitigating pain [15–20]. According to a recent meta-analysis, intra-articular

injections of PRP resulted in the best overall outcome (with regards to both pain and function) compared to CSI, HA, and placebo for patients with knee OA from 3 to 12 months post-injection [21]. A 2021 retrospective analysis concluded that BMAC was safe and superior when compared with PRP in knee OA [22]. Given the biomechanical and physiological differences between the hip and knee joints, it is important to provide evidence for orthobiologic treatments that is specific to hip OA.

Current research regarding the therapeutic efficacy of BMAC for symptom management in patients with hip OA is severely lacking. Singh et al. found PRP to be helpful in reducing pain and improving function in a retrospective analysis of 36 patients who received a single intra-articular injection of PRP for hip OA [23]. To our knowledge, there is only one study that investigated the role of BMAC in pain and function in hip OA, which showed a statistically significant improvement in both outcome measures for up to 6 months [24]. However, the sample size was limited to 18 hips and a shorter duration of follow-up compared to our study's duration of 1 year.

A unique aspect of this study was our use of a single site 'Marrow Cellutions' Bone Marrow aspiration system (MC system) which did not involve concentration of the aspirate as is done in BMAC preparations. Scarpone et al. showed that the MC system produced concentration of CFU-fs, $CD34^+$ cells and CD117+ cells that were comparable or greater to BMAC [10]. There have been no studies documenting the superiority of BMAC vs BMA without concentration, however BMA is less costly and easier to institute. The MC system uses multiple small volume harvests from a single puncture, using lateral flow from multiple sites near the cortex, which has been shown to house the largest number of stem/-progenitor cells [10,25,26]. It has been shown that single site, large volume (2 mL or great) aspiration results in significant infiltration of peripheral blood which contains few MSCs and lower CFU-f and $CD34^+$ cell counts. The MC system utilizes a cannula with a closed distal end which limits peripheral blood infiltration and reduces total harvest volume required [26,27]. Therefore, our study highlights the potential for BMA without concentrate to serve as an alternative injectate that is more feasible in clinical practice, though further research is needed to investigate the comparative efficacy.

In addition, our injection technique highlights a novel approach that delivers a portion of the injectate to the intra-articular space as well as the extra-articular space within the joint capsule. It has been established that osteoarthritis is a condition which affects multiple aspects of the joint, including tissues such as the subchondral bone, synovium, and joint capsule [28]. We suspect that our injection technique promotes healing processes throughout the entire joint complex. However, further studies are necessary to delineate the concrete benefit of this approach.

Limitations of this study include its retrospective design, which by nature prevents blinding and establishment of a control group. This has the potential to introduce recall bias into the study. In addition, we were unable to quantify the harvested cell counts used, which prevented further analysis and identification of a potential dose response correlation. Lastly, the out-of-pocket cost of the BMA kit may have introduced bias regarding the perceived treatment effect due to the financial input from patients. However, this cost was limited given that a philanthropic grant covered the procedural and facility costs.

5. Conclusion

Further research is required to demonstrate the efficacy of intra-articular injection of BMA for hip OA. Considerations for future studies includes obtaining detailed cellular aspiration concentrations in order to evaluate any potential dose response variables and to ensure standard treatment across all participants. In addition, head-to-head comparison between BMA and BMAC are warranted to compare efficacy. This study suggests that BMA may be an alternative treatment for patients with not only mild to moderate, but also severe hip OA in regard to improving pain and function from 6 month to 12 months. This data suggests that BMA can potentially delay or prevent invasive and expensive joint replacement surgery. A larger prospective, randomized controlled trial is warranted in order to further characterize the efficacy of BMA for the treatment of hip OA.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. : Post Bone Marrow Aspirate Injection Protocol

Post Procedure	Precautions	Therapy Goals	Home Program
Days 1 to 2	• For lower extremities, WBAT (Weight Bearing As Tolerated), but PWB (Partial Weight Bearing) is allowed for patients with moderate to severe pain • Avoid NSAIDs	• Gentle ROM (range of motion) • Wound monitoring	• Bracing if indicated by physician • Gentle ROM (range of motion) if pain is not severe
Days 3 to 7	• WBAT • Avoid excessive loading of the joint • Avoid NSAIDS	• Continue ROM • Enhance blood perfusion through modalities (moist heat, ultrasound, etc.) • Begin low grade closed chain program (foot or hand on the ground/ equipment)	• Start/continue ROM • For lower extremities, can start partial squats/ lunges/activities if pain is not severe (body weight only)
Days 8 to 14	• WBAT • Avoid impact activities • Avoid heavy weight lifting to affected joint • Avoid NSAIDS	• May start light OKC (open kinetic chain) (foot or hand off the ground) exercises • Continue ROM work • Continue modalities as needed	• For lower extremities, continue squats/lunges (can add resistance); start leg curl/extension exercises with light weight • May start swimming and biking (low resistance)
Days 14 to 28	• May restart NSAIDS if needed for pain control • Avoid impact activities	• Progress OKC and functional exercise program • Light agility training • Proprioception exercises	• Can increase biking/swimming activities • May resume light aerobic activities such as walking • Weight lifting/strength training as tolerated

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