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Positive early clinical outcomes of bone marrow aspirate concentrate for osteoarthritis using a novel fenestrated trocar

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Background: This study sought to assess early clinical outcomes for knee osteoarthritis (OA) patients undergoing bone marrow aspirate concentrate (BMAC) treatment using a novel closed-end, fenestrated trocar (FT) that does not require centrifugation.

Methods: A prospective cohort of 17 knee OA patients undergoing BMAC treatment with the FT system from March 2018 to March 2019 was retrospectively evaluated. Approximately 10 mL of BMAC was harvested, no centrifugation was performed, and the BMAC was injected into the affected knee. Clinical outcomes were assessed at baseline, six weeks, and 12 weeks. This study has no affiliation with/vested-interest in the FT system.

Results: There were significant improvements in nearly all outcomes from baseline to 12 weeks. Specific improvements included Knee Injury and OA Outcome Score (KOOS) activities-of-daily-living (61.1 ± 9.2 [mean ± 95% confidence interval] to 89.3 ± 6, $p = 0.001$), quality-of-life (32.7 ± 9.3 to 66.1 ± 17.9, $p = 0.003$), sports/recreation (36.9 ± 10.6 to 72.6 ± 26.3, $p = 0.006$), and pain (53.8 ± 9.3 to 83 ± 10.2, $p = 0.001$); Lysholm scores (55.5 ± 8.4 to 77.3 ± 10.5, $p = 0.009$); and visual analog pain scores (5.68 ± 1.14 to 2.07 ± 1.86, $p = 0.003$). Individually, at least 75% of patients exhibited improvement in all KOOS categories at six weeks and at least 85% at 12 weeks.

Conclusions: BMAC treatment with an FT system that does not require centrifugation resulted in significant improvements in early pain and function scores for knee OA. The symptomatic improvements in this study were similar to or greater than what has been reported using traditional needles. These data may provide clinicians with comfort in using an FT system and provide motivation for future randomized-controlled trials comparing aspiration techniques.

1. Introduction

Knee osteoarthritis (OA) is a chronic debilitating condition that accounts for over 80% of the OA burden in the United States [1]. The disease is increasing in prevalence partly due to an aging population and rising rates of obesity [2]. Total knee arthroplasty is successful surgery for alleviating pain and restoring functional activity in patients with end-stage OA [3], particularly when non-operative measures fail. Unfortunately, functional limitations and the possibility of future revision surgery limit its utility for

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young or active patients [4]. Consequently, there is growing interest in minimally invasive methods to prevent, delay, or reverse knee OA, such as the use of bone marrow aspirate concentrate (BMAC) treatments [5–13].

The preparation of BMAC, however, is subject to significant variability [14,15], including in the: volume of aspirate, use of a carrier (e.g., adipose, platelet-rich plasma [PRP], or hyaluronic acid) [5,10], location of harvesting site [16], number of harvesting sites [17], centrifugation system [18], and needle used [19]. As the use of BMAC treatments continues to rise, optimization of these factors is increasingly important. Currently, typical BMA procedures entail aspiration of 50–60 mL of bone marrow from the iliac crest using an open-ended needle (e.g., the Jamshidi needle), followed by centrifugation to yield BMAC, which is then injected into the joint [20,21].

The centrifugation step in this sequence aims to increase the number of stem/progenitor cells from the large volume of aspirate [18]; however, the density separation achieved with centrifugation cannot distinguish between nucleated peripheral blood cells and the progenitor cells in the bone marrow [19]. In addition, the use of an open-ended needle may result in 1) draws of greater than one to two milliliters from a single-site and 2) draws from the center of the iliac bone as compared to the inner cortical plate. Both of these procedural variations may decrease the ratio of progenitor to peripheral blood cells [18,21–25]. Moreover, centrifugation creates additional handling steps with opportunities for contamination, as well as increases the total procedure time required of both the clinician and patient.

A novel fenestrated trocar (FT) system (Marrow Cellution, Ranfac, Avon, MA) seeks to overcome these challenges by providing a one-step procedure that delivers a high concentration of progenitor cells. The FT system has a blunt, closed-end with multiple lateral side ports, which allow for small draws from several different sites near the inner cortical plate, the location believed to have the highest concentration of bone marrow progenitor cells [23–25]. By combining these multiple techniques to maximize the amount of progenitor cells in the aspiration step, centrifugation is purportedly unnecessary with the FT system.

In fact, the FT system was recently shown to yield significantly higher colony forming unit (CFU) concentrations—the best available marker for connective tissue progenitors (CTPs) in freshly isolated cell populations [26]—than traditional BMAC techniques [19]. However, no data are available on the clinical outcomes of patients undergoing BMAC with any FT or centrifugation-free system. It is plausible that centrifugation or the required filtration may decrease cell viability or anabolic potential, even with comparable laboratory data, and thus clinical outcomes may be superior with the FT system. Conversely, the clinical benefit of BMAC injections may come largely from factors beyond the progenitor cells (e.g., growth factors, connective tissue progenitors, cytokines, and platelets, among other possibilities) [14], and thus the superior CFU lab values achieved with the FT system may not translate to clinical benefit. The purpose of this pilot study was thus to examine early pain and functional outcomes among patients with knee OA undergoing BMAC treatment with the FT system. We hypothesized that patients undergoing BMAC with the FT system would experience significant improvements in pain and function scores and that these improvements would be similar to what has been reported for traditional BMAC techniques [5,10,27].

2. Methods

After institutional review board approval, a prospective cohort of knee OA patients undergoing BMAC treatment with the FT system from March 2018 to March 2019 was retrospectively evaluated. Inclusion criteria for patients to have received BMAC therapy consisted of patients aged 18–79 years with radiographically confirmed Kellgren–Lawrence I–III knee OA (no bone-on-bone) who had failed at least six weeks of conservative therapy (i.e., activity modification, weight loss, brace, nonsteroidal anti-inflammatory drugs, and corticosteroid injection). Exclusion criteria are listed in Table 1 but broadly consisted of other ligamentous, meniscal, or mechanical issues; body mass index >35 kg/m^2; smoking; and significant medical comorbidities. No association, funding, or support was provided from Ranfac Corporation or any other source.

Table 1
Exclusion criteria.

• Anterior/posterior cruciate ligament deficiencies
• History of meniscal injury other than degenerative meniscal tears
• Presence of a degenerative meniscal tear causing mechanical symptoms such as locking, buckling, or give-way
• Major mechanical axis deviation of more than 50% into either compartment (varus or valgus) or 7°
• Intra-articular injection to affected knee within 3 months of BMAC injection or HA within 6 months
• Body mass index of 35 or more; 18.5 or less (malnourished)
• Active infection and ongoing infectious diseases, including HIV and hepatitis
• Clinically significant diabetes, cardiovascular, hepatic, or renal disease
• Malignancy
• Use of anti-inflammatory medications, including herbal therapies, within 7 days of BMAC injection
• Use of anti-rheumatic medications, including methotrexate and other antimetabolites, within 3 months of BMAC injection
• History of radiation therapy
• History of or current drug or alcohol use disorder
• Current cigarette smokers
• History of anemia, bleeding disorders, or inflammatory joint disease (rheumatoid arthritis, infectious arthritis, hemophilic arthropathy, Charcot's knee)
• History of metabolic bone disease (osteoporosis, osteomalacia, rickets, osteitis fibrosa cystica, Paget's disease of bone)
• Pregnant or currently breast-feeding

2.1. Trocar

The FT system, in comparison to a traditional needle, is depicted in Figure 1. A photograph is provided in Figure 2. It appears similar to a traditional open-ended BMA trocar, with the exception of the location of the aspiration port(s) and having a closed-end. Traditional trocars aspirate from the distal tip of the device, while the FT system has multiple ports angled in different directions along the sides of the distal portion of its length. After positioning the trocar into the desired initial position in the medullary cavity, the placement stylet is replaced with an aspiration canula that closes the tip of the trocar and allows for aspiration from the fenestrations in the trocar's sides. This design aims to minimize contamination of peripheral blood into the aspirate that may be present from an open-ended device, instead aspirating small draws from maximally preserved bone marrow architecture.

2.2. Technique

All patients were prepped and draped in a sterile fashion. Approximately 10 mL of BMAC was taken from the anterior iliac crest following the manufacturer's instructions. Namely, the device was initially positioned into to the medullary space with the sharp stylet filling the lumen of the trocar, similar to traditional BMA procedures. After entering the medullary space, the sharp stylet was removed, and one milliliter of bone marrow was aspirated from the open tip of the trocar to ensure proper localization. Thereafter, the blunt stylet was inserted, and the device was advanced to the proper depth along the insertion trajectory. Finally, the aspiration cannula was inserted, closing the trocar's open end and allowing for BMA from the trocar's side ports. After each one milliliter draw, the aspiration ports were mechanically repositioned approximately 0.75 cm out of the body with the completion of a 360° counterclockwise turn of the handle. Draws were made using quick sharp pulls on the plunger. As this technique allows for aspiration from many different geographies within the medullary space from a single insertion trajectory, only one insertion site was required for all patients. The BMAC was then injected into the affected knee under ultrasound guidance; no centrifugation was performed.

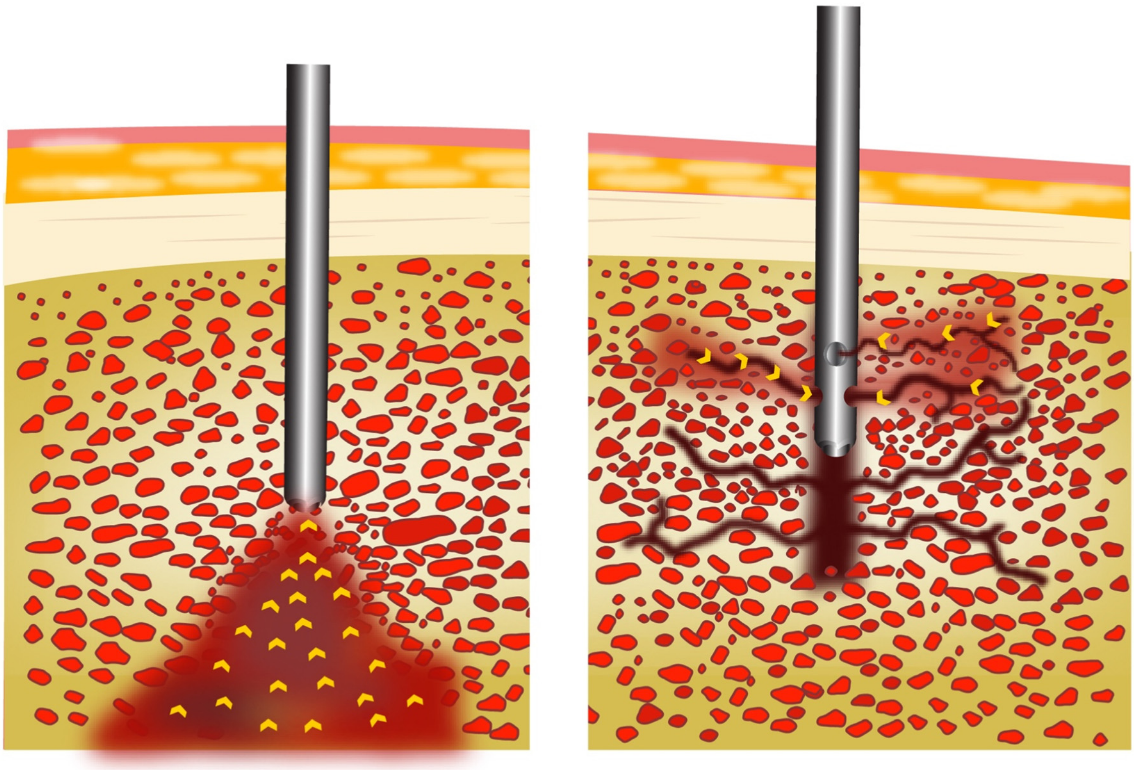

Figure 1. Image depicting a traditional open-ended needle (left) and the blunt, fenestrated trocar system (right). The fenestrated trocar system has a closed-end and multiple side ports. This design aims to allow for small concurrent draws from multiple locations in the bone marrow, preserving marrow architecture and minimizing pooling of peripheral blood, in hopes of achieving higher concentrations of progenitor cells. After each one to two milliliter draw, the trocar handle is turned 360° counterclockwise, which retracts the device approximately 0.75 cm out of the body, and subsequent draws are made from these new locations in the marrow (in contrast to subsequent draws being from the same general insertion trajectory with a traditional, open-ended needle).

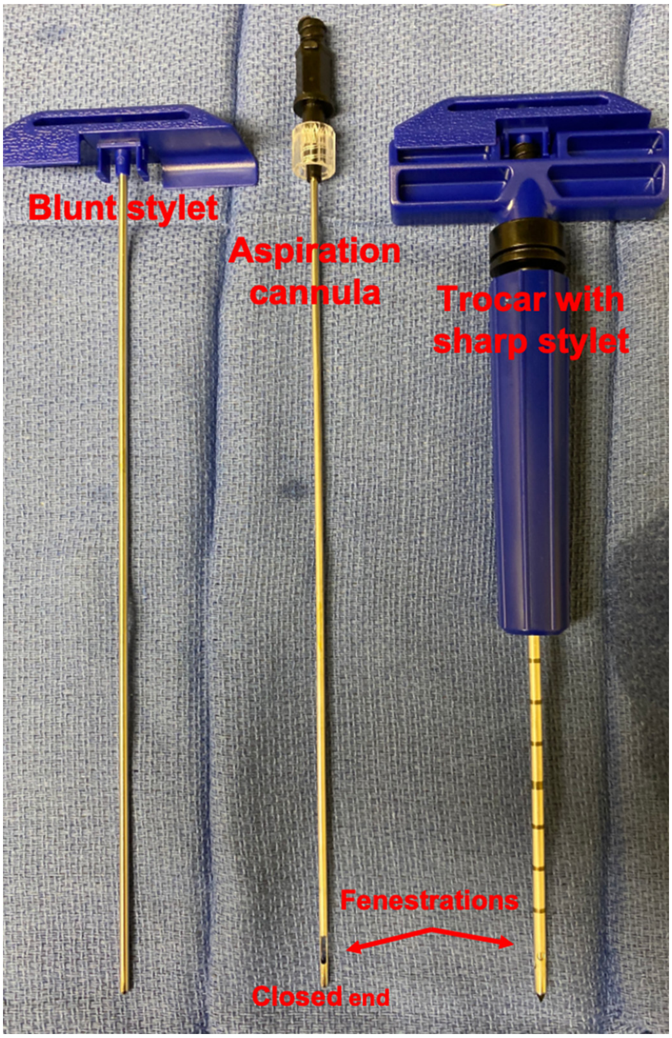

Figure 2. This photograph shows the components of the fenestrated trocar system, which consist of a trocar, a sharp stylet, a blunt stylet, and an aspiration cannula (to which a 10 mL syringe attaches). The trocar is shown with the sharp stylet in place, in preparation for the first step of the procedure. The procedure begins with medullary space penetration being achieved with the sharp stylet. The blunt stylet is then inserted for further progression. Finally, after the device is positioned to the desired depth, the blunt stylet is removed and the aspiration cannula is inserted. This cannula closes the trocar's distal end, while opening the trocar's side ports to allow for marrow aspiration.

2.3. Outcomes

Multiple patient-reported outcome measures (PROMs) were recorded at baseline, six-week follow-up, and 12-week follow-up. The primary outcome measure in this study was the Knee Injury and Osteoarthritis Outcome Score (KOOS), which measures outcomes across five domains: pain, symptoms, activities of daily living, sports and recreation function, and knee-related quality of life [28]. The KOOS was chosen as the primary outcome metric as it is an extension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) that is designed specifically for younger and/or more active patients with knee injury or osteoarthritis [28,29]. Secondary outcomes included the Lysholm Knee Score [30], which evaluates knee pain and function [31] and the visual analog pain scale (VAS) [32], a metric scale shown to well-correlate with OA pain [33,34].

2.4. Statistics

Continuous variables are presented as mean ± 95% confidence interval (CI). For each PROM, differences between baseline, six-week, and 12-week follow-up scores were assessed with one-way analysis of variance (ANOVA). When significant, Tukey's honest significant difference tests were then employed for post-hoc comparison testing between specific time points (e.g., baseline vs. six weeks, baseline vs. 12 weeks). All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC) or Microsoft Excel (Microsoft, Redmond, WA), and $p < 0.05$ was considered significant.

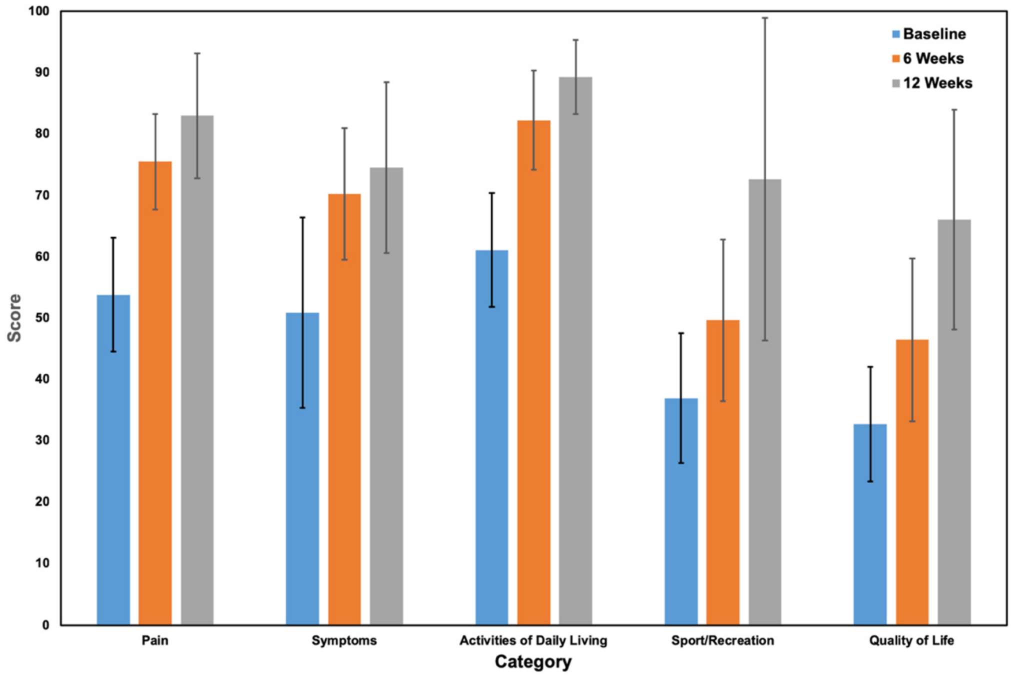

Figure 3. Knee Osteoarthritis Outcome Score (KOOS) scores at baseline, six weeks, and 12 weeks. All scores were significantly improved at 12 weeks compared to baseline ($p \le 0.009$ for all), except KOOS symptoms ($p = 0.053$). Activities of daily living and pain were significantly improved at six weeks ($p = 0.001$ for both).

3. Results

Seventeen patients were included (10 women, 7 men; median 54 years, range 46–77). KOOS scores steadily improved from baseline to six weeks to 12 weeks (Figure 3). All five KOOS domains were significantly improved at 12 weeks except KOOS symptoms which approached significance ($p = 0.053$). Specifically, KOOS activities-of-daily-living scores significantly increased from 61.1 ± 9.2 (mean ± 95% CI) at baseline to 89.3 ± 6 ($p < 0.001$) at 12 weeks. KOOS quality of life (32.7 ± 9.3 to 66.1 ± 17.9, $p = 0.002$) and KOOS sports/recreation scores (36.9 ± 10.6 to 72.6 ± 26.3, $p = 0.004$) both approximately doubled during the 12-week period. KOOS pain scores improved from 53.8 ± 9.3 at baseline to 83 ± 10.2 ($p < 0.001$) at 12 weeks. Individually, at least 75% of patients exhibited improvement at six weeks and at least 85% at 12 weeks for *all five* KOOS categories.

Results were similar for the secondary outcomes (Table 2). Lysholm scores significantly improved 39.3% from 55.5 ± 8.4 to 77.3 ± 10.5 ($p = 0.009$) over 12 weeks. VAS scores significantly improved by 63.6% from a mean baseline score of 5.68 ± 1.14 to 2.07 ± 1.86 ($p = 0.003$) at 12 weeks. There were no adverse events.

4. Discussion

The use of cell therapy techniques, such as BMAC injections, has dramatically increased in the past five to ten years [35]. Consequently, a number of factors are being investigated in an effort to improve outcomes of this procedure. In a recent study comparing traditional open-ended needle aspiration followed by centrifugation to a single puncture FT with multiple lateral flows without centrifugation, Scarpone et al. [19] found that the lateral flow mechanism yielded significantly higher CFU concentrations than the traditional aspiration technique with centrifugation. Whether this system provides any clinical benefit, however, was unknown. In this pilot-study, we find that patients significantly improved in all pain and functional outcome measures after BMAC treatment using the FT system. These data provide motivation for future randomized control trials (RCTs) comparing these two techniques.

The most important finding of this study was the significant improvement in all prospectively collected PROMs data relative to baseline. Moreover, the results with the FT-system were similar to those of traditional BMAC techniques [5,10,27]. For example, in an early report using BMAC for knee OA with an adipose carrier, Kim et al. [5] found significant improvement in KOOS scores from a mean of 43.1 (±6.3) at baseline to 64.9 (±5.6) at three-month follow-up, slightly below the 24–30 point improvements in KOOS domains over the same time frame in this study. In their prospective, placebo-controlled trial using traditional BMAC technique, Shapiro et al. [10] found that VAS pain scores significantly decreased in BMAC knees from a mean of 3.1 at baseline to 0.9 at three months, in comparison to 5.7 at baseline to 1.9 at three months seen here. Most recently, similar pain and function improvements were reported by Rodriguez-Fontan et al. [27] in a cohort of 19 patients undergoing traditional BMAC therapy for knee or hip OA (mean improvement from baseline to six-month follow-up of 21.6 [±5.1] in WOMAC score).

When coupled with previously reported laboratory data demonstrating higher levels of CFUs with the FT system [19], the current results may give clinicians comfort in using this system. The lines of potential benefit of an FT/centrifuge-free system are

Table 2
Patient reported outcome measures at baseline, six weeks, and 12 weeks.

Score	Baseline	6 weeks	12 weeks	*p*-ANOVA	*p*-Baseline vs. 6 weeks	*p*-Baseline vs. 12 weeks
KOOS						
Activities of daily living	61.1 ± 9.2	82.3 ± 8.1	89.3 ± 6	<0.001	0.001	<0.001
Pain	53.8 ± 9.3	75.5 ± 7.8	83 ± 10.2	<0.001	0.001	<0.001
Quality of life	32.7 ± 9.3	46.4 ± 13.3	66.1 ± 17.9	0.003	0.16	0.002
Sports/recreation	36.9 ± 10.6	49.6 ± 13.2	72.6 ± 26.3	0.006	0.29	0.004
Symptoms	50.9 ± 15.5	70.2 ± 10.7	74.5 ± 13.9	0.03	0.056	0.053
Lysholm score	55.5 ± 8.4	71.9 ± 9.2	77.3 ± 10.5	0.003	0.02	0.009
Visual analog pain score	5.68 ± 1.14	3.18 ± 1.64	2.07 ± 1.86	0.002	0.02	0.003

KOOS = Knee Osteoarthritis Outcome Score; ANOVA = analysis of variance.

two-fold. First, there is potential for superior clinical outcomes, given that the FT system avoids centrifugation and the associated filtration and handling steps. This study provides no evidence to support this benefit, and a head-to-head RCT would be needed to demonstrate this effect. The second benefit is time-savings for the clinician and patient by not requiring the additional procedure time to concentrate the BMA. Given that BMAC procedures are currently not covered by most insurance companies, out-of-pocket paying patients may desire to have their procedure done as quickly as possible. Similarly, the decreased time requirement may allow clinicians to see more patients.

Although this study was limited to short-term clinical outcomes, we found that patients were continuing to improve at three months. These results may highlight that the anti-inflammatory and regenerative mechanisms of cell therapy take time to act. In addition, it is encouraging that these patients were maintaining their results. It is known that in patients with knee OA, the benefit of corticosteroid injections may wane starting at approximately three months [36]. In our study, not only was the benefit in pain and function maintained at three months, but it appeared to still be improving. Future work is indicated to capture longer term clinical outcomes using the FT system (e.g., six months, one year, two years). Not only will this work provide information on the duration of benefit from BMAC therapy, but it also may provide insight on how BMAC therapies should be utilized. For example, it is unclear whether one-time treatment vs. recurring treatments are more efficacious, whether BMAC may be effective for long-term pain relief, or even a preventative measure against surgical intervention.

Finally, not only does this study add to the growing body of evidence supporting cell therapy techniques for the symptomatic treatment of OA in general [37], it is one of few studies to-date to examine clinical outcomes of BMAC for OA without the use of an adjuvant carrier. For example, an adipose carrier was utilized in the report by Kim et al. [5], while a platelet-poor-plasma carrier was used in the report by Shapiro et al. [10]. A previous study by Centeno et al. [9] using registry data found similar PROM improvements between patients undergoing BMAC with an adipose or PRP carrier; however, the benefit of BMAC for knee OA without a carrier is largely unknown. This is a clinically important question given that both PRP and adipose themselves have been shown to provide symptomatic relief in OA [37–39]. Therefore, not only do the positive clinical outcomes in this study stimulate the need for additional RCTs on aspiration technique, they also support additional study of the relative benefit of adjuvant carriers.

This study is not without limitations. Most importantly, this study was not designed to assess superiority of one aspiration technique or another. These are pilot (e.g., phase II) data, which demonstrated a positive clinical response in this patient cohort using the FT system. Although the effect sizes are comparable to what has been reported in other studies using traditional BMAC techniques, an RCT—with both laboratory and clinical outcome data—formally comparing FT and traditional BMAC techniques is warranted. Next, it is not possible to say whether the benefits in the study were due to the BMAC treatment or placebo. To date, Shapiro et al. (discussed above), is the only placebo-controlled trial that has been performed on BMAC for OA [10]. Given that mesenchymal stem cells are known to home to sites of injury [40,41], even in this placebo-controlled study it was impossible to say whether the benefit was due to placebo or a systemic effect of the therapy, as significant improvements did not differ between knees. Elucidating the exact mechanism of action of BMAC therapy continues to be a critically important task for researchers moving forward; nonetheless, this study adds to the growing body of literature supporting a positive effect of cell therapies for OA. Third, like most BMAC studies [14], there were no laboratory data obtained in this study on clinical outcomes; however, a higher concentration of CFUs with the FT system was recently reported in a separate, unaffiliated study [19]. We build on these results by providing supporting clinical data that this technique not only has good laboratory values but also positive clinical outcomes. Finally, in our practice we have found that patients tolerate aspiration from the anterior iliac crest better than from the posterior crest, and thus, we utilize this technique. While we have not found the posterior crest to yield better clinical outcomes in our own internal PROM data monitoring, previous reports have indicated that the posterior approach may yield superior laboratory outcomes [16]. If anything, then, the results of clinical benefit with the FT system in this study may be underestimated.

In conclusion, as BMAC therapies for knee OA continue to grow in use, optimization of the procedure is increasingly important. Here we demonstrate positive pain and function outcomes for patients receiving BMAC therapy with a fenestrated trocar system that does not require centrifugation. These data may provide clinicians with comfort in using an FT/centrifuge-free system and provide motivation for an RCT comparing aspiration systems.

Declaration of competing interest

All authors report no conflicts of interest.

The authors have no affiliation with the manufacturer or any other party related to the Marrow Cellution trocar examined in this study.

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