**Long-Term Outcomes of Bone Marrow Aspirate Concentrate Injections for Knee Osteoarthritis**

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## Abstract

Background: Preliminary research indicates that bone marrow aspirate concentrate (BMAC), containing mesenchymal stem cells and growth factors, may be a therapeutic option for knee osteoarthritis (OA). While short-term outcomes (<1 year) show improvements in pain and functionality, long-term outcomes (>3 years) of repeated BMAC injections remain incompletely characterized.

Objectives: This study evaluates outcomes of intra-articular BMAC injections for knee OA, focusing on pain, functionality, and overall perceived improvement during long-term follow-up.

Design: Retrospective analysis of prospective clinical data from a private regenerative medicine clinic.

Methods: Long-term outcomes were evaluated in 43 patients (46 knees) with knee osteoarthritis treated with intra-articular BMAC injections between 2016 and 2018. Patients aged 22-85 years (mean 63.2) received one to four treatments (mean 2.65) at two-to-four week intervals. Outcomes included resting pain, active pain, functionality, and perceived improvement, assessed at baseline and at long-term follow-up. Final follow-up occurred, on average, about 3.48 years (42 months) after the last treatment. Changes from baseline were analyzed using Wilcoxon signed-rank tests.

Results: Significant long-term improvements were observed in active pain and functionality compared to baseline ($p<0.05$). Mean active pain decreased from 6.85 to 3.35 out of 10 at final follow-up. Functionality improved progressively with additional injections, with patients receiving four treatments experiencing the greatest improvements. While resting pain trended toward improvement, it did not reach statistical significance. Overall, patients reported a mean improvement of 60.41% following their final treatment, with those receiving four injections reporting an average improvement of 82.4%.

Conclusions: In this cohort, BMAC injections were associated with sustained long-term reductions in active pain and functional improvements. These findings support repeated BMAC injections as a viable nonoperative option for symptomatic knee OA and warrant further investigation through controlled prospective studies.

## Keywords

Stem cells; knee osteoarthritis; bone marrow aspirate concentrate; orthobiologics; nonoperative therapy; regenerative medicine

## Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis and a pervasive joint disorder worldwide (Felson et al., 2000). In 2019, osteoarthritis affected over 500 million people worldwide, an increase of 113% from 1990 (Long et al., 2022). The knee is the most commonly affected joint, accounting for approximately 60% of OA cases (Long et al., 2022). In the United States, symptomatic knee OA affects approximately 10% of men and 13% of women over the age of 60 (Zhang & Jordan, 2010).

Knee OA is characterized by progressive degeneration of articular cartilage, which can lead to disability (Brody, 2015). The most common symptoms of knee OA include muscle weakness, knee stiffness and swelling, reduced range of motion, and pain that worsens over time as the disease progresses (Hunter & Bierma-Zeinstra, 2019; Hsu & Siwiec, 2024). Osteoarthritis is classified into primary and secondary types. Primary osteoarthritis arises without an identifiable cause, whereas secondary osteoarthritis develops in response to abnormal joint loading or underlying conditions that impair articular cartilage integrity, including rheumatoid arthritis (Hsu & Siwiec, 2024).

Current first-line treatments for knee OA include nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections (Dantas et al., 2021; Hunter & Bierma-Zeinstra, 2019; Ringdahl & Pandit, 2011). While these interventions may provide temporary symptom relief, none have been shown to modify disease progression (Dantas et al., 2021). Moreover, repeated IACS injections have been

associated with accelerated breakdown of articular cartilage, which exacerbates OA (Guermazi et al., 2023). Corticosteroids also cause notable cartilage deterioration and chondrocyte toxicity at high doses in both in vitro and in vivo models (Wernecke et al., 2015). IACS injections are typically precursors to a surgical operation, as this treatment does not reverse OA but only mediates the adverse effects of the condition (Guermazi et al., 2023).

Total knee arthroplasty (TKA), a surgical joint replacement procedure, is typically considered a last resort in managing knee OA (Lim & Thahir, 2021; Ringdahl & Pandit, 2011). Although TKA may minimize the pain associated with osteoarthritis, a substantial proportion of patients experience persistent functional limitations, chronic pain, or require revision surgery (Bade et al., 2010; Walsh et al., 1998). In comparison to normal healthy adults, TKA patients have 18% slower walking speed, 40% decrease in quadriceps strength, and climb stairs 51% slower than they were able to before their operation (Bade et al., 2010). While the primary aim of TKA is pain relief, approximately 20% of patients continue to suffer from chronic pain years after their surgery, affecting all aspects of their health-related quality of life (Wylde et al., 2018). In addition, knee replacements tend to have poor long-term durability, failing due to loosening, infection, persistent pain, and instability (Evans et al., 2019). Consequently, patients may need to have revisional surgeries, with younger, more active individuals or those with higher BMI at increased risk (Bayliss et al., 2017; Hossain, Patel & Haddad, 2010). Post-operative complications may occur, and addressing these issues often necessitates subjecting the patient to multiple surgical interventions during their lifetime. These limitations have prompted interest in biologic and regenerative approaches aimed at improving symptoms while delaying or avoiding surgical intervention.

Bone marrow aspirate concentrate (BMAC) injections are a regenerative procedure that has gained recognition among clinicians for their promising potential in treating OA. BMAC contains growth factors, platelets, and mesenchymal stem cells (MSCs), all of which have regenerative properties that stimulate new tissue growth and can alleviate OA symptoms (Sampson et al., 2013). Previous research in this field demonstrated that BMAC treatments provide numerous clinical benefits, including pain relief and

functionality improvements for patients with knee OA in a short period of time (Han et al., 2024). One study demonstrated that BMAC therapy was more effective than PRP therapy in reducing pain and improving functionality in the first year after treatment (El-Kadiry et al., 2022). In 2018, Darrow Stem Cell Institute highlighted the short-term outcomes of BMAC for patients with symptomatic knee OA and found that patients responded well to 4 biweekly BMAC treatments (Shaw et al., 2018). Patients experienced significant improvement in both symptoms and functionality. In another study, 34 knees with osteoarthritis were treated with one mononuclear bone marrow-derived cell injection and were assessed on symptoms before, 3 months after, 6 months after, and 1 year after the injection (Goncars et al., 2019). At the one-year follow-up, results showed that patients responded well to treatment and exhibited significantly reduced pain levels and OA symptoms. However, data examining the durability of these outcomes over multiple years remains limited.

This study aims to evaluate the long-term, as opposed to the usual shorter-term, clinical outcomes of patients with knee osteoarthritis treated with one to four intra-articular BMAC injections, with particular attention to pain, function, and patient-reported improvement over extended follow-up.

## Methods

### Study Design and Patients

This study presents a retrospective analysis of prospectively collected clinical data from a private sports medicine and regenerative medicine clinic. Patients with symptomatic knee osteoarthritis confirmed by radiographic imaging (MRI and/or X-ray) were treated with intra-articular BMAC injections between July 2016 and December 2018. A total of 50 patients (57 knees) initially underwent treatment. Of this initial cohort, 43 patients (46 knees) who did not undergo knee arthroplasty during the follow-up period were included in the final analysis, ensuring the focus remained on non-replaced knees throughout the study period. Patients ranged in age from 22 to 85 years (mean 63.2 years). Among the included knees, 20 were from female patients and 26 from male patients.

Patients received between one and four BMAC treatments per knee, with an average of 2.65 treatments. Bilateral knee treatment was performed in six patients, one female and five males. Despite recommendations for injections spaced approximately 14 days apart, logistical issues between patients and the physician resulted in longer average intervals, with a mean spacing of approximately 28 days between treatments. Altogether, 43 patients underwent a total of 122 treatments (involving 46 knees). There was complete questionnaire participation both before and after each treatment session. Before each treatment, written informed consent for the treatment and the subsequent use of de-identified data for research purposes was obtained from all patients. Comprehensive patient characteristics are shown in Table 1.

**Table 1. Baseline patient characteristics**

| | N | MEAN (SD) |
|---|---|---|
| Age | 46 | 63.91 (13.78) |
| Body mass index (BMI) | 46 | 28.14 (3.97) |
| Gender, % | | |
| Male | 26 | 56.52 |
| Female | 20 | 43.48 |

**Procedure: BMAC Injection**

Patients were positioned prone, and the skin above the posterior superior iliac spine (PSIS) was sterilized using 10% povidone-iodine and 4% chlorhexidine gluconate (Hibiclens) solutions. Local anesthesia was administered, comprising 10 cc of 1% lidocaine and 2 cc of 8.4% sodium bicarbonate around the patient's PSIS. Once complete anesthesia was achieved, an 11-gauge, 4-inch disposable needle with fenestration was employed to penetrate the PSIS using a drill. A 20 cc syringe, pre-loaded with one cc of heparin (1000 USP units/mL), was utilized to extract 19 cc of BMAC while the needle was turned slowly to

optimize stem cell yield. Following collection, the sample was centrifuged to isolate the mononuclear cell layer, excluding visible red blood cells. To alleviate patient discomfort during and after the treatment, 1 cc of ropivacaine was added to every 5 cc of centrifuged BMAC. Ropivacaine, in contrast to lidocaine, has been shown to have minimal toxicity toward MSCs (Rahnama et al., 2013). The knee joint was sterilized locally with 10% povidone-iodine and 4% Hibiclens, following which the 6-cc BMAC was injected via a 25-gauge needle under ultrasound guidance. Joint effusions, when present, were aspirated prior to injection using an 18-gauge needle. During and after treatment, patients were instructed to refrain from using anti-inflammatory medications to prevent interference with the differentiation of MSCs into osteogenic cells.

**Outcomes**

This study focused on assessing changes in resting pain, active pain (measured via the numerical pain scale [NPS]), overall perceived improvement (reported as a percentage), and joint functionality (assessed using a validated questionnaire derived from the Lower Extremity Functional Scale). Patient-reported outcomes were collected at baseline and before each subsequent injection, as well as at long-term follow-up (see Figure 1). The final follow-up occurred on average at 3.48 years after their last treatment. For patients who completed all four treatments, the final data collection took place at an average of 407.36 days (1.12 years) after the patient's final treatment and ranged from 57 days to 1,833 days. The NPS, utilized to gauge resting and active pain, employed a scale ranging from 0 (representing no pain) to 10 (indicating extreme pain). Furthermore, the form included a subjective measure of the patient's overall improvement post-treatment, graded on a scale from 0-100%.

**Statistical Analysis**

Baseline and post-treatment outcomes were compared using Wilcoxon signed-rank tests. Each knee was treated as an independent unit of analysis. Given the restricted sample size, covariates were not considered in this analysis. Statistical significance was defined as $p < 0.05$. Analyses were performed using GraphPad Prism.

**Figure 1. Patient Questionnaire (Lower Extremity Functional Scale and Numerical Pain Scale)**

**Lower Extremity Functionality Questions**

*Please describe the deg ree of difficulty you have performing these activities with your injured lower body part*

| | Activities | Extreme Difficulty | Quite a Bit of Difficulty | Moderate Difficulty | A Little Bit of Difficulty | No Difficulty | N/A |
|---|---|---|---|---|---|---|---|
| 1 | Job, housework, or school activities | 0 | 1 | 2 | 3 | 4 | N/A |
| 2 | Hobbies, recreational, or sport activities | 0 | 1 | 2 | 3 | 4 | N/A |
| 3 | Squatting | 0 | 1 | 2 | 3 | 4 | N/A |
| 4 | Walking two blocks | 0 | 1 | 2 | 3 | 4 | N/A |
| 5 | Going up stairs | 0 | 1 | 2 | 3 | 4 | N/A |
| 6 | Rolling over in bed | 0 | 1 | 2 | 3 | 4 | N/A |
| 7 | Standing for an extended period of time | 0 | 1 | 2 | 3 | 4 | N/A |
| 8 | Lifting a heavy objecting | 0 | 1 | 2 | 3 | 4 | N/A |
| 9 | Getting in and out of your car | 0 | 1 | 2 | 3 | 4 | N/A |
| 10 | Bending to the floor | 0 | 1 | 2 | 3 | 4 | N/A |

**Total:_____**

Resting Pain Level: 0 (No pain) 1 2 3 4 5 6 7 8 9 10 (Extreme pain)

Active Pain Level: 0 (No pain) 1 2 3 4 5 6 7 8 9 10 (Extreme pain)

Improvement Since Date of First Treatment (%) 0 10 20 30 40 50 60 70 80 90 100

## Results

A total of 46 knees from 43 patients were analyzed, representing 122 BMAC injections. One patient received a single injection, 23 patients received two injections, 9 patients received three injections, and 10 patients received four injections. Long-term post-injection surveys on all knees showed that resting pain, active pain, and functionality scores all improved significantly ($p<0.05$) from baseline (the period before a knee's first BMAC injection) (Table 2).

**Table 2. Mean resting pain, active pain, total improvement percentage, and functionality score before and after bone marrow concentrate injections, N = 46 knees**

| | Treatment | |
|---|---|---|
| | Baseline | Long-term |
| Resting pain (0-10) | 2.09 | 1.43[0] |
| Mean (SD) | (2.21) | (2.45) |
| Active pain (0-10) | 6.85 | 3.35[0] |
| Mean (SD) | (2.42) | (2.86) |
| Total improvement (%) | — | 60.41% |
| Mean (SD) | | (37.24) |
| Functionality score (0-40) | 20.96 | 27.80[0] |
| Mean (SD) | (9.26) | (8.87) |

[0]Statistically significant ($P$ <.05) compared with baseline outcomes.

Patients experienced a significant reduction in resting pain after the first BMAC injection, as compared to baseline. After the second BMAC injection, patients still reported a significant reduction from baseline resting pain, but there was no significant reduction in resting pain as compared to after the first injection. After the third and fourth BMAC injections, the average pain was reduced from baseline by 0.62 and 1.40 points, respectively, and the average pain from the first to fourth injection was reduced by 0.47 points.

Despite the reductions in average resting pain, the third and fourth BMAC injections themselves did not cause statistically significant changes when compared to the first and second injections, likely due to insufficient sample size: only 21 out of 46 knees had three injections, and only 10 had four injections. Further, 17 had a baseline resting pain of zero, and 11 knees had a baseline resting pain of one, allowing little to no room for the possibility of a reduction in resting pain score for a large portion of the knees.

In contrast, active pain improved significantly regardless of the number of injections administered. Notably, mean active pain following the third injection was 4.33 points lower than baseline active pain. Mean active pain also decreased significantly from the first to the third injection. From baseline to the long-term final follow-up, active pain decreased from a mean of 6.85 before treatments to 3.35 after treatments. Among the 46 knees assessed, 28 were initially reported to have an active pain level of seven or higher on a 10-point scale. In contrast, only eleven knees were reported to have an active pain level of seven or higher at the final follow-up. Ten of these eleven knees received only two injections, and the remaining knee received three. Zero knees that received four injections were reported to have a final active pain of seven or higher.

Subjectively rated long-term outcomes demonstrated a mean overall improvement of 60.41% among patients who received between one and four BMAC treatments. Notably, patients who underwent four treatments reported a higher mean overall improvement of 82.4%. This variable was measured as a patient-reported percentage instead of a continuous outcome that would be measured at baseline, and hence no formal hypothesis test against a baseline value was conducted. Since overall improvement is an indicator of self-examination of change as opposed to a pre- and post-intervention, paired measurement, statistical evaluations, including the Wilcoxon signed-rank test, cannot be used. Still, the reported improvement over an extended percentage among treated knees remains consistent, and there is clinical evidence of the relevance of BMAC therapy in managing knee osteoarthritis long-term. These results correspond with the objective changes in active pain and functionality scores, which indicate that the perceived benefit of patients is linked with the quantifiable clinical outcomes.

In regard to functionality, patients exhibited a significantly greater score in the long-term after completing 2 or more treatments in comparison to baseline. Baseline functionality averaged 20.96 ± 9.26 when there were no injections. After one injection, mean functionality increased to 25.17 ± 9.17, representing an average improvement of +4.22 from baseline. After two injections, functionality further increased to 27.29 ± 9.01, which is +6.20 from baseline. Patients receiving three injections demonstrated a mean functionality of 27.38 ± 8.54, which is +6.14 from baseline, while those receiving four injections reached 31.70 ± 7.33, corresponding to a +11.20 improvement from baseline.

Importantly, not all patients received four treatments. The dataset includes knees that received between one and four injections, and long-term outcomes reflect the maximum number of injections completed per knee rather than a uniform treatment protocol. Functional gains were therefore analyzed stratified by the number of injections received, rather than assuming equal exposure across patients. The overall improvement in functionality across time was statistically significant, indicating that the observed changes are unlikely to be due to chance alone.

Overall, statistically significant improvements were observed in resting pain, active pain, and functionality compared to baseline ($p<0.05$). However, some sequential injection comparisons did not reach statistical significance, mainly due to limited sample sizes in higher injection groups and the presence of low initial baseline pain scores, which limited the ability to detect improvement.

**Table 3. Resting pain, active pain, total improvement percentage, and functionality score by bone marrow concentrate injections received, N = 46 knees.**

| | TREATMENT NUMBER | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Resting pain (0-10) | 2.09 | 1.15 | 1.29 | 1.10 | 0.30 |
| Mean (SD) | (2.21) | (1.55) | (2.04) | (2.41) | (0.67) |
| Active pain (0-10) | 6.85 | 4.11 | 3.73 | 2.62 | 3.10 |
| Mean (SD) | (2.42) | (2.73) | (2.87) | (2.58) | (1.97) |
| Total improvement (%) | — | 45.39% | 54.09% | 61.67% | 82.40% |
| Mean (SD) | | (32.38) | (42.36) | (36.41) | (15.56) |
| Functionality score (0-40) | 20.96 | 25.17 | 27.29 | 27.38 | 31.70 |
| Mean (SD) | (9.26) | (9.17) | (9.01) | (8.54) | (7.33) |

**Table 4. Changes in resting pain, active pain, total improvement percentage, and functionality outcomes compared with baseline, N = 46 knees.**

| | TREATMENT NUMBER | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Change in resting NPS | -0.93[0] | -0.69[0] | -0.62 | -1.40 |
| Mean (SD) | (2.82) | (3.02) | (3.06) | (1.71) |
| Change in active NPS | -2.74[0] | -3.07[0] | -4.33[0,1] | -3.40[0] |
| Mean (SD) | (2.73) | (3.62) | (3.98) | (2.72) |
| Total improvement (%) | 45.39% | 54.09% | 61.67%[1] | 82.40%[1,2,3] |
| Mean (SD) | (32.38) | (42.36) | (36.41) | (15.56) |
| Change in functionality score | 4.22[0] | 6.20[0,1] | 6.14[0] | 11.20[0,1,2] |
| Mean (SD) | (4.79) | (10.11) | (7.42) | (10.89) |

[0]Statistically significant ($P < .05$) compared with baseline outcomes.

[1]Statistically significant ($P < .05$) compared with outcomes after the first injection.

[2]Statistically significant ($P < .05$) compared with outcome after the second injection.

[3]Statistically significant ($P < .05$) compared with outcome after the third injection.

## Discussion

This study unveils significant long-term outcomes wherein patients reported substantial reductions in active pain, subjective improvement, and notable improvements in functionality. Although the reduction in resting pain was not statistically significant, the observed trend toward pain reduction suggests that BMAC injections may help to alleviate discomfort during rest, thereby improving patients' overall comfort and well-being. Further research is needed to validate these findings and elucidate the effectiveness of BMAC injections in providing pain relief during rest. Interestingly, our 2018 study measured the same variable and indicated short-term benefits, suggesting that multiple injections might yield superior efficacy compared to a single BMAC injection (Shaw et al., 2018). The results at the final follow-up of the 2018 study exhibited statistically significant differences after the fourth treatment compared to baseline, following the first, second, and third treatments (Shaw et al., 2018).

The greater and more consistent reduction observed in active pain compared to resting pain suggests that BMAC therapy may preferably improve pain associated with joint loading and movement rather than baseline nociceptive pain. Active pain in knee osteoarthritis may be more responsive to the regenerative and anti-inflammatory effects of the stem cells present in BMAC, as shown in clinical studies demonstrating reductions in OA symptoms following BM MNC treatment (Han et al., 2024). In contrast, resting pain may reflect chronic structural degeneration or central pain sensitization, which may be less amenable to localized biologic intervention.

Functionality scores improved from baseline to 3.48 years post-treatment, indicating better ability to perform daily activities. Consistent with functionality scores, active Numeric Pain Scale (NPS) results echoed similar trends. Mean active pain decreased by 2.74, 3.07, 4.33, and 3.49 points after Treatments 1–4, respectively. The observed trend toward greater functional improvement and reductions in active pain with increasing numbers of BMAC injections suggests a cumulative or dose-dependent therapeutic effect. However, further research is warranted to ensure this effect is significant in a larger patient sample size.

These results confirm that the short-term improvements reported previously (Shaw et al., 2018) persist long-term (over 3+ years). Both of these studies carry substantial clinical implications for managing Osteoarthritis (OA) using BMAC injections, elucidating both short-term and enduring effects. If BMAC treatments become more accessible or covered by insurance, an increase in patients opting for BMAC sessions rather than surgery for OA management could be anticipated. Moreover, this study highlights that patients injected with BMAC experienced significant pain relief and functionality in the long term.

The persistence of improvements at long-term follow-up indicates that the clinical benefits of BMAC injections may extend well beyond the immediate post-treatment period. From a clinical perspective, these findings suggest that BMAC injections may represent a meaningful nonoperative option for patients seeking to delay or avoid total knee arthroplasty.

This study demonstrates that pain relief and functional improvements persist over time, underscoring BMAC's sustained and enduring effects in the long term. By providing sustained symptom relief and functional gains, BMAC warrants serious consideration in clinical practice and should be a priority for further research and policy evaluation.

Several limitations constrain the study's outcomes. Notably, the absence of a control group and reliance on self-reported responses for subjective variables may introduce bias. Furthermore, the lack of treatment randomization, inadequate data on nucleated cell count, and a relatively small sample size impose limitations on the generalizability of the findings. In future investigations, a larger sample size might help achieve statistical significance for the reduction in resting pain and improve external validity. To address the potential biases associated with phone-based evaluations and to overcome limitations such as self-report bias and the inability to perform physical assessments, future studies should consider incorporating in-person assessments to offer a more comprehensive evaluation of treatment efficacy.

Looking forward, BMAC injection treatments could be used not only as a primary treatment but as a healing tool following knee joint surgery due to their ability to prevent post-surgical Knee OA. Knee OA can occur even following knee joint surgery, so this would be an optimal way to prevent and slow the progression of Knee OA by promoting joint recovery (Roemer et al., 2018).

## Conclusion

The long-term outcomes of our report demonstrate that patients with knee osteoarthritis experienced less active pain and were able to perform daily activities with less difficulty after receiving 1 to 4 BMAC injections. This study found that the procedures were well-tolerated, with no adverse events or complications reported among the patients during or after the treatments. Patients who completed all four injections reported the greatest improvement, with mean overall functional gains reaching 82%, highlighting a potential dose-response relationship. These findings suggest that BMAC therapy may provide a meaningful non-surgical method for managing knee osteoarthritis, offering alternatives to procedures such as total knee arthroplasty. Further studies with a larger patient pool and controlled designs are warranted to confirm these results and to determine optimal treatment protocols, including the number and timing of injections.

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## Statements and Declarations

Ethical considerations: This study was a retrospective analysis of de-identified clinical data collected during routine patient care at a private clinic. The study did not involve prospective intervention or experimentation beyond standard clinical practice. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Consent to participate: Written informed consent for treatment and for the use of de-identified clinical data for research purposes was obtained from all patients prior to treatment.

Consent for publication: The manuscript does not contain any identifiable patient information. All data were fully de-identified. Therefore, consent for publication is not applicable.

Conflict of Interest: M.D. is the primary physician at Darrow Stem Cell Institute, where all study procedures were performed.

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Data availability: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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