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ORIGINAL ARTICLE

Bone Marrow Aspirate Concentrate for Treatment of Primary Knee Osteoarthritis: A Prospective, Single-Center, Non-randomized Study with 2-Year Follow-Up

Madhan Jeyaraman[1,2,3,4] · Naveen Jeyaraman[1] · Swaminathan Ramasubramanian[5] · Rajni Ranjan[6] · Saurabh Kumar Jha[2,7] · Ashim Gupta[4,8,9,10]

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Abstract

Introduction Knee osteoarthritis (OA) is a widespread, disabling condition with no intervention to fully restore cartilage or halt progression. Bone marrow aspirate concentrate (BMAC), an autologous product from bone marrow aspiration, has shown promise as a regenerative therapy due to its cell composition and chondrogenic effects. Our study aims to assess the functional outcomes, including pain, function, satisfaction, and complications post-BMAC injection in knee OA patients.

Materials and Methods In this prospective, single-center study, 63 patients with grade II–III knee OA (Kellgren–Lawrence (K–L) scale) unresponsive to conservative management underwent BMAC injection. The procedure involved bone marrow aspiration from the anterior iliac crest, processing to obtain a concentrate, followed by intra-articular injection. Patients were followed for 24 months, assessing outcomes using the Visual Analog Scale (VAS), International Knee Documentation Committee (IKDC) score, and MOCART 2.0 score.

Results The cohort, with a slight female predominance and predominantly aged 41–50 years, majorly comprised K–L grade III OA patients. BMAC treatment resulted in significant improvements in VAS pain scores, IKDC functional scores, and MOCART 2.0 scores over the 24-month follow-up.

Conclusion BMAC injection provides significant improvement in both pain and functional outcomes at mid-term follow-up in patients with mild-to-moderate OA of the knee. Further high-quality, adequately powered, multi-center, prospective, double-blinded, randomized controlled trials with longer follow-up are necessary to justify the routine clinical use of BMAC for treatment of patients suffering with knee OA.

Keywords Bone marrow aspirate · Bone marrow aspirate concentrate · BMAC · Knee osteoarthritis · Knee · Regenerative medicine

✉ Ashim Gupta
ashim6786@gmail.com

1 Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai, Tamil Nadu 600077, India

2 Department of Biotechnology, School of Engineering and Technology, Sharda University, Greater Noida, Uttar Pradesh 201310, India

3 Clinical Research Associate, Virginia Tech India, Dr MGR Educational and Research Institute, Chennai, Tamil Nadu 600095, India

4 South Texas Orthopaedic Research Institute (STORI Inc.), Laredo, TX 78045, USA

5 Department of Orthopaedics, Government Medical College, Omandurar Government Estate, Chennai, Tamil Nadu 600002, India

6 Department of Orthopaedics, School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh 201306, India

7 Department of Zoology, Kalindi College, University of Delhi, New Delhi 110008, India

8 Regenerative Orthopaedics, Noida, Uttar Pradesh 201301, India

9 Future Biologics, Lawrenceville, GA 30043, USA

10 BioIntegrate, Lawrenceville, GA 30043, USA

Introduction

Osteoarthritis (OA) of the knee is a common and debilitating condition affecting millions worldwide. It is characterized by progressive degeneration of articular cartilage, synovial inflammation, and subchondral bone remodeling, leading to pain, stiffness, and functional impairment [1–3]. Articular cartilage is known to have a low innate healing capacity due to the lack of vasculature and undifferentiated cells, as well as the presence of specialized cells with low mitotic activity [4, 5]. Current treatment modalities for knee OA include pharmacological, nonpharmacological, and surgical interventions, but none of them can restore the lost cartilage or modify the disease course [6–8]. Therefore, there is a growing interest in exploring regenerative therapies that can potentially enhance the repair and regeneration of damaged tissues and improve the quality of life of patients with knee OA [9–12].

One of the promising regenerative therapies for knee OA is bone marrow aspirate concentrate (BMAC), which is a minimally manipulated autologous product derived from bone marrow aspiration [13, 14]. BMAC contains a heterogeneous mixture of cells, including mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), and platelets, as well as various growth factors and cytokines [15–19]. BMAC has been shown to have anti-inflammatory, immunomodulatory, angiogenic, and chondrogenic properties in vitro and animal models [20–22]. Moreover, BMAC can be easily obtained and processed at the point of care using commercially available devices.

Several clinical studies have evaluated the efficacy and safety of BMAC injection for the treatment of knee OA in humans [13, 23–27]. Keeling et al. [28] included 8 studies with a total of 299 knees and reported significant improvements in pain and patient-reported outcomes at short-term to mid-term follow-up following BMAC injection. However, the authors also noted that the level of evidence was low to moderate due to the heterogeneity of study designs, outcome measures, and follow-up periods. We intend to make a significant contribution to the field of knee OA research by providing robust magnetic resonance imaging (MRI) data with a 2-year follow-up period. This empirical evidence, when integrated into the existing body of knowledge, has the potential to elevate the current level of evidence, thereby enhancing the overall quality of research in this domain.

The primary aim of this study was to assess the pain relief by Visual Analog Score (VAS) for the patients who underwent intra-articular injection of BMAC for OA knee whereas the secondary aim was to evaluate the functional improvement via International Knee Documentation Committee (IKDC) score, MOCART 2.0 score at the end of 24 months, and complications following the procedure.

Materials and Methods

This was a prospective, single-center, non-randomized study that was conducted between January 2021 and December 2022 after obtaining institutional ethical committee approval SU/SMS&R/76-A/2021/113. A total of 63 patients with radiographic evidence of Grade II to III (K–L scale) primary OA knee who showed no symptomatic relief from the conservative line of management (non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy, weight loss) for 6 months were included in the study. All patients underwent an MRI of the knee joint before the procedure.

Exclusion criteria included patients with grade I or IV OA knee (K–L scale), severe deformity (>10° coronal/ sagittal plane), concomitant meniscal/ ligament involvement, inflammatory arthritis, rheumatological or other systemic diseases, malignancy, patients on immunosuppressive medication, previous history of knee surgeries or intra-articular injections within last 3 months, post-traumatic arthritis, and infections.

Surgical Procedure

All patients who met the inclusion criteria were counseled for the procedure and informed consent was obtained. All the procedures were performed by a single surgeon. Before the start of surgery, the 13G aspiration needle (Bone Access Needle (Medtronic, Inc) and six 10 ml syringes are flushed with heparin (5000 U/20 ml) and then filled with 1 ml of the heparin solution.

The procedure was carried out under spinal anesthesia for all patients. Parts were prepared and draped maintaining all aseptic precautions. Bone marrow was aspirated from the patient's ipsilateral iliac crest. After performing a small 2 cm incision behind the patient's iliac crest, a 13G needle was introduced using the sharp stylet. Once, the medullary space was accessed, the sharp stylet was exchanged for the blunt stylet with the access needle being advanced to the desired depth. The aspiration cannula was then connected to a 10 ml syringe and bone marrow was aspirated with manipulation in different directions to allow access to untapped bone marrow as shown in Fig. 1. A total of 60 ml of bone marrow was harvested for a single knee.

Following extraction, the aspirate is transferred by hand to sterile tubes which are then processed in a separate room under sterile conditions to isolate the buffy coat through centrifugation. Differential centrifugation (Rotofix 32A centrifuge, 3200 rpm for 15 min and 4800 rpm for 15 min) yielded



Fig. 1 Aspiration of bone marrow from the right iliac crest

around 10–12 ml of BMAC injectate for every 60 ml of bone marrow aspirate.

The BMAC was then transported back to the operating room maintaining utmost sterility. BMAC was then loaded into the pre-washed heparin syringes. The involved knee was then injected with the concentrate using an anterolateral portal with the knee positioned at 90° of flexion without the use of any local anesthetic agent. A dose of 2 million BMAC cells per kilogram of body weight, with a cellular viability rate of 92% in the BMAC injectate, was administered into both knee joints in two equally divided doses via the antero-superolateral portal, as depicted in Fig. 2. The knee joint was passively mobilized throughout its range of motion immediately after the injection to disperse the BMAC injectate throughout the joint. A flow diagram of the procedure is shown in Fig. 3.

Post-operative Protocol

Patients were started on full-weight-bearing mobilization immediately post-surgery. Physical rehabilitation included quadriceps and hamstring strengthening exercises and patients were permitted to do light activities as tolerated. After 6–8 weeks, patients were permitted to resume a full range of activities. All patients were instructed to avoid oral NSAIDs for at least 4 weeks following the procedure since BMAC therapy works by stimulating the body's innate inflammatory healing mechanisms which can be hampered with the use of NSAIDs.



Fig. 2 Intra-articular injection of BMAC via antero-superolateral portal into left knee joint

Outcome Measures

All patients had regular follow-ups at baseline and 6, 12, and 24-month follow-ups with scores being evaluated annually in person via direct examination. Patients were evaluated using a VAS pain score (0–10, with 10 being the most severe); and an IKDC score. The IKDC is a self-administered tool that includes sections on knee symptoms (7 items), knee function (2 items), and sports activities (2 items) with scores ranging from 0 to 100, with 100 representing the highest possible level of function and lowest degree of symptoms. At the final follow-up of 2 years, patients were asked about their overall satisfaction with the procedure based on a five-point Likert scale and if they would recommend the procedure to others. Following the BMAC implantation procedure, a thorough evaluation of the knee joints was conducted through MRI at the 2-year post-implantation mark, aiming to meticulously document cartilage thickness changes and employing the Magnetic Resonance Observation of Cartilage Repair Tissue 2.0 (MOCART 2.0) scoring system, which encompasses seven key components: volume fill (0–20 points), integration into adjacent cartilage (0–15 points), surface of the repair tissue (0–10 points), structure of the repair tissue (0–10

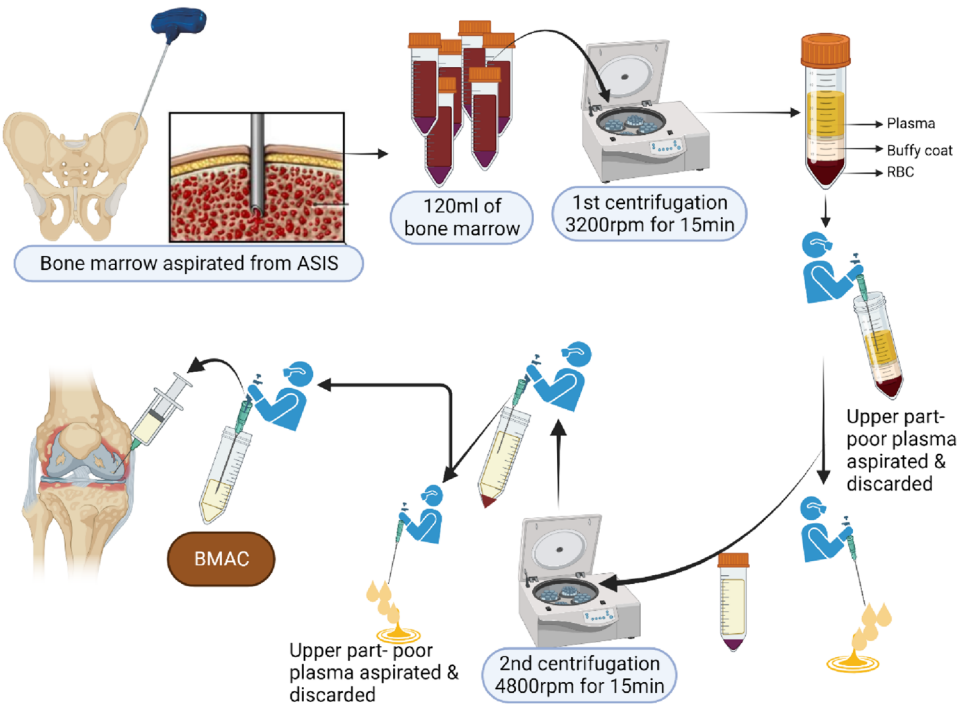


Fig. 3 Schematic representation of BMAC isolation (created with Biorender.com)

points), signal intensity of the repair tissue (0–15 points), bony defects or overgrowth (0–10 points), and subchondral changes (0–20 points), thereby providing a comprehensive assessment of knee cartilage repair quality.

Statistical Analysis

Data normality was evaluated using the Shapiro–Wilk test. Continuous variables were presented as means with standard deviation. Comparison of VAS, IKDC, and MOCART 2.0 parameters at subsequent follow-ups was analyzed using the paired samples *t* test. Data are presented as histograms and a *p* value less than 0.05 was considered significant with a 95% confidence interval.

Results

A total of 72 patients participated in the study, among whom 5 were excluded due to previous history of intra-articular injections to the knee, 2 patients had grade I knee OA, and 2 patients had associated inflammatory arthritis of the knee. A total of 63 patients were eligible for final analysis. Table 1 shows the demographics of the study population. The mean age of the population was 38.42 ± 12.19 years, with the majority of the participants being female ($N = 35$, 55.6%). The patients had an average BMI of 30.19 ± 9.23, with the majority ($N = 26$, 41.3%) classified as having class 1 obesity (30–34.9). All the patients included in the study had knee OA, with 38 (60.3%) classified as grade III and 25 (39.7%) classified as grade II according to the K–L scale. The demographic variables are depicted in Table 1. There was no statistically significant association between age, BMI, or grade of arthritis with pain and functional outcome. None of the patients in the study experienced any complications during the study including donor site morbidity, local reaction around the knee, hematoma, or paraesthesia.

Table 1 Demographic variables of the study population

Parameters	$N = 63$
Age (years)	
31–40	16 (25.4%)
41–50	25 (39.7%)
51–60	12 (19.0%)
61–70	10 (15.9%)
Mean ± SD	38.42 ± 12.19
Sex	
Male	28 (44.4%)
Female	35 (55.6%)
BMI (Kg/m^2)	
18.5–24.9	16 (25.4%)
25.0–29.9	21 (33.3%)
30.0–35.0	26 (41.3%)
Mean BMI	30.19 ± 9.23
Kellgren–Lawrence grading	
II	25 (39.7%)
III	38 (60.3%)

Cellular Characterization

The mean BMAC cellular count was determined to be 45.5 million per mL, with an average BMAC volume of 5.7 mL per joint. Furthermore, the average frequency of CFU-F (colony-forming unit fibroblasts) within BMAC was approximately 0.0021%, equivalent to approximately 1 CFU-F per 50,000 total nucleated cells (TNC). The enrichment factor for various cell types demonstrated a range of 4.1 × to 5.3 × above the baseline. Moreover, the centrifugation-based concentration of BMAC resulted in a reduction of hematocrit volume from an initial measurement of 36.4–25.2%.

VAS Pain Score

The mean pre-operative VAS pain score of the patients was 7 ± 1.2 (mean ± SD). The VAS score showed a gradually declining trend at each subsequent follow-up which was found to be highly significant (Table 2 and Fig. 4). The mean VAS scores at 6, 12, and 24 months were 6.4 ± 0.9, 5.3 ± 2.5, and 2.5 ± 1.7, respectively.

IKDC Score

The mean pre-operative IKDC score of the patients was 24.3 ± 8.4. The IKDC knee function score showed a highly significant improvement at each subsequent follow-up, with the IKDC scores at 6, 12, and 24 months being 44.1 ± 9.5, 58.2 ± 10.8, and 83.9 ± 9.1, respectively (Table 3 and Fig. 5).

Radiological Analysis

A representative case of baseline and 24-month follow-up radiograph of bilateral knee joint showing reduced cartilage thickness who received BMAC injection for OA knee is depicted in Fig. 6A and 6B, respectively. Figure 7A and 7B demonstrates the baseline and 24-month follow-up MRI of the right knee joint who received BMAC injection for OA knee, respectively, which demonstrated improved thickness of cartilage as depicted by MOCART score in Table 4.

MOCART Score

Table 4 presents a comparison of MOCART 2.0 scores over a 24-month follow-up period relative to baseline

Table 2 VAS score at various follow-up time points compared to the baseline

Time point	Mean ± SD	Mean difference	95% CI	Standard error	*p* value compared to baseline
Baseline	7.0 ± 1.2	–	–	–	–
6-month follow-up	6.4 ± 0.9	0.60	0.56 to 0.63	0.019	<0.0001*
12-month follow-up	5.3 ± 2.5	1.70	1.00 to 2.39	0.349	<0.0001*
24-month follow-up	2.5 ± 1.7	4.50	3.97 to 5.02	0.262	<0.0001*

*Indicates statistically significant

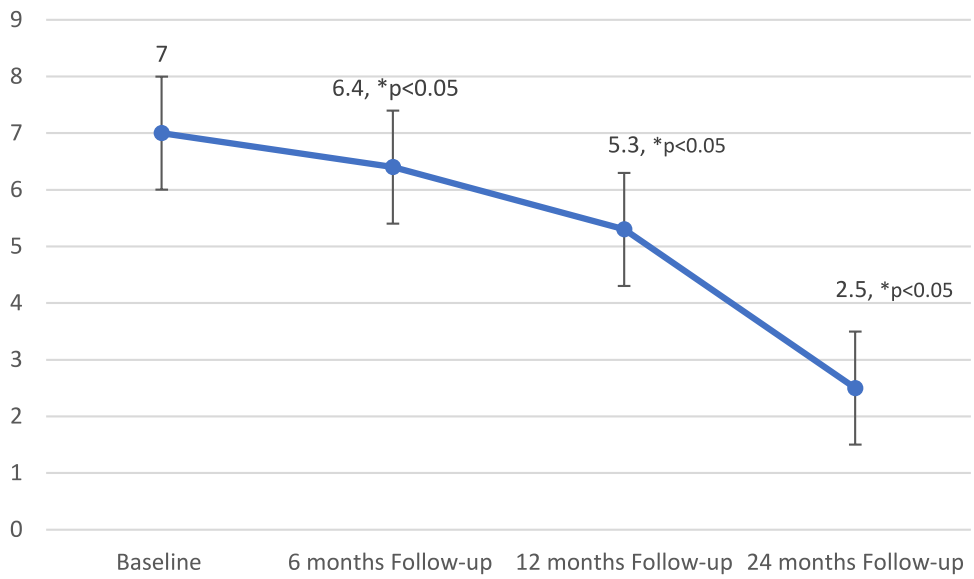


Fig. 4 VAS score at various follow-up time points compared to the baseline. *Represents $p < 0.05$ compared to baseline

Table 3 IKDC score at various follow-up time points compared to the baseline

Time-point	Mean ± SD	Mean difference	95% CI	Standard error	*p* value compared to baseline
Baseline	24.3 ± 8.4	–	–	–	–
6-month follow-up	44.1 ± 9.5	−19.80	−23.99 to −15.60	1.59	<0.0001*
12-month follow-up	58.2 ± 10.8	−33.90	−37.35 to −30.44	1.73	<0.0001*
24-month follow-up	83.9 ± 9.1	−59.60	−62.72 to −56.48	1.56	<0.0001*

*Indicates statistically significant

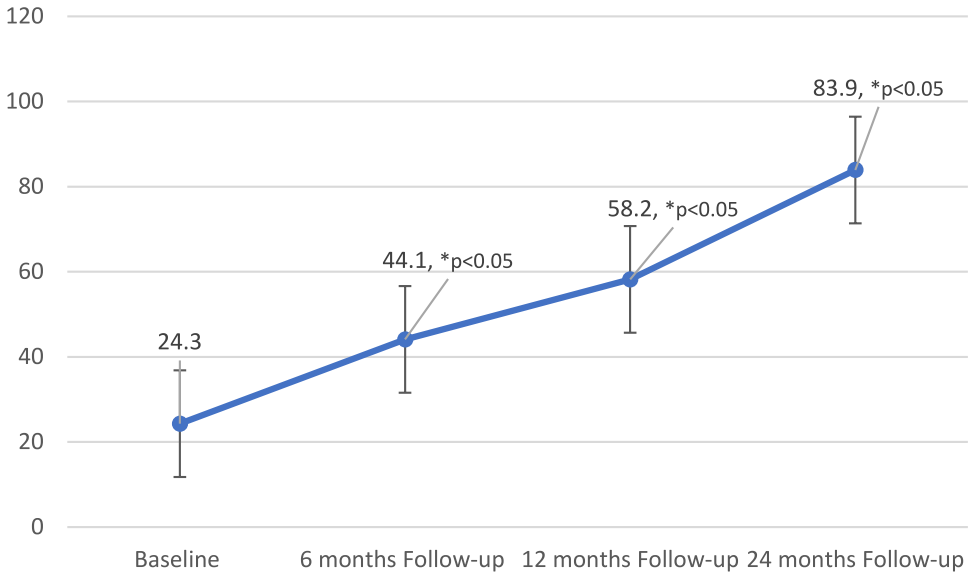


Fig. 5 IKDC score at various follow-up time points compared to the baseline. *Represents $p < 0.05$ compared to baseline

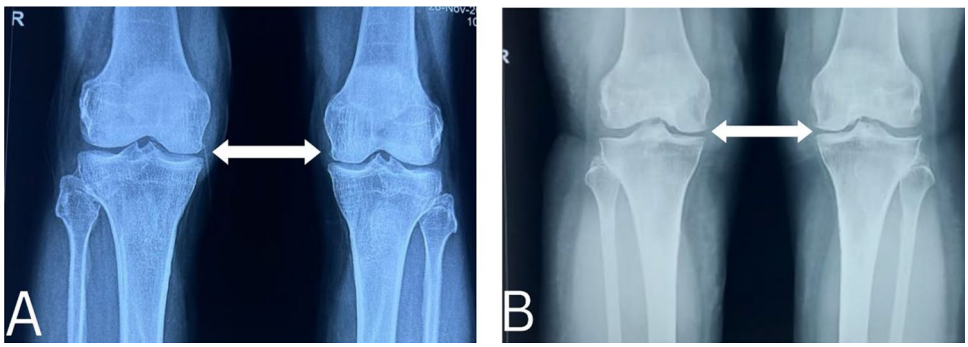


Fig. 6 **A** Pre-procedural radiograph of bilateral knees (AP view on standing position) showing decreased medial joint line in bilateral knees suggestive of KL grade II knee OA and **B** 2-year follow-up radiograph of bilateral knees (AP view on standing position) showing the maintenance of medial joint line in bilateral knees indicating response to BMAC therapy

values. Initially, the baseline MOCART 2.0 score was 54.7 (SD = 7.4). Notably, at the 24-month follow-up, a significant increase was observed, with the mean score reaching 94.3 (SD = 6.1). This represents a substantial mean difference of −39.60 from the baseline, with a precise 95% confidence interval of −41.97 to −37.23, indicating high estimation precision. The standard error for this mean difference was 1.21, reinforcing the reliability of the findings. Crucially, the statistical analysis revealed a highly significant difference compared to baseline ($p < 0.0001$), providing strong evidence for substantial improvement in the MOCART 2.0 score from baseline to the 24-month follow-up.

Patient Satisfaction

The interpretation of patient satisfaction using a five-point Likert scale in this study offers valuable insights into the patients' perceptions of the overall procedure. This scale, typically ranging from 'Strongly Disagree' to 'Strongly Agree', allows for a nuanced understanding of patient sentiments. The finding that 84.2% of patients ($N = 53$) reported

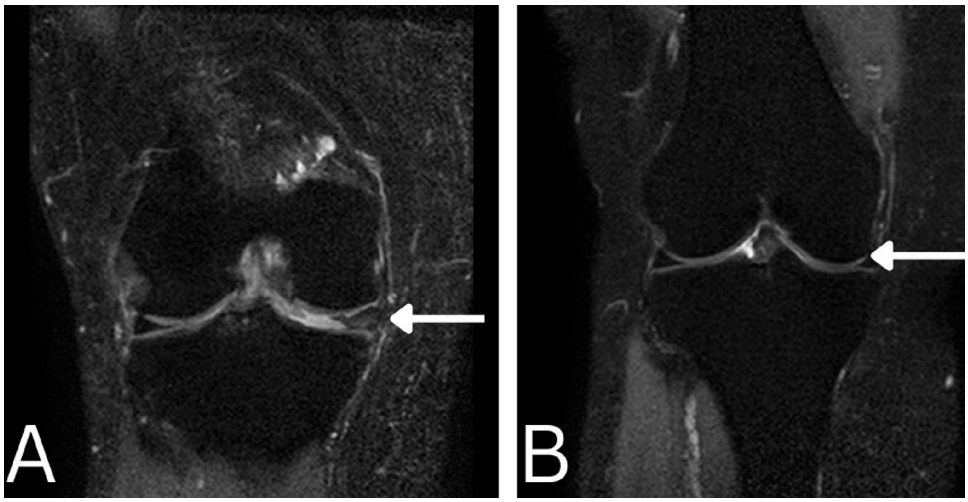


Fig. 7 **A** Pre-procedural T2W MRI (coronal section) showing hyperintensity with thinned out cartilage along the medial femoral condyle suggestive of OA knee and **B** 2-year follow-up T2W MRI (coronal image) showing increased cartilaginous thickness with a relatively maintained cartilaginous signal indicating response to BMAC therapy

Table 4 MOCART 2.0 score at various follow-up time points compared to the baseline

Time point	Mean ± SD	Mean difference	95% CI	Standard error	*p* value compared to baseline
Baseline	54.7 ± 7.4	–	–	–	–
24-month follow-up	94.3 ± 6.1	−39.60	−41.97, −37.23	1.21	<0.0001*

being 'very satisfied' is statistically significant and indicates a positive response toward the procedure. This level of satisfaction, presumably corresponding to the top tier of the Likert scale, suggests that the aspects such as comfort, effectiveness, and communication by medical staff were highly regarded by the patients. Furthermore, the fact that 87.3% of the respondents ($N=55$) would recommend the procedure to others is a crucial metric, serving as a proxy for the procedure's perceived effectiveness and the trust the patients place in it. This willingness to recommend is a strong endorsement and reflects the patients' confidence in the procedure.

Discussion

Orthobiologics has emerged as a rapidly progressive and innovative field in orthopedic practice mainly focusing on regeneration of damaged or diseased tissue, thereby delaying or preventing disease progression [29]. One of the key players in this field is the use of mesenchymal stem cells (MSCs), which have shown tremendous potential in their ability to differentiate into various cell lineages such as chondrocytes, adipocytes, and osteocytes [30, 31]. Their amazing ability to self-renew and favor their local microenvironment to support and nurture regeneration and repair by inhibiting pro-inflammatory cytokines (IL-1, IL-6, TNF-α, and IFN-γ) has piqued the curiosity of many researchers, particularly in the fields of trauma and orthopedic surgery.

Bone marrow consists of hematopoietic and mesenchymal cells, including blood progenitor and stromal cells. BMAC varies in cell concentrations due to processing methods and donor age, complicating the standardization of BMAC processing [32]. Multiple factors have been attributed to influence the quality of the concentrate obtained. BMAC is usually harvested from the iliac crest and rarely from the metaphysis of the distal femur and proximal tibia [33]. There is currently no substantiating evidence indicating a superior advantage of the anterior superior iliac spine (ASIS) over the posterior superior iliac spine (PSIS), or vice versa. There is also controversy regarding the superiority of the BMAC from different sites obtained [34, 35]. Mesenchymal stromal cells (MSCs) from bone marrow and mandible show promise for bone regeneration, due to their high osteogenic potential, although their full clinical potential remains to be explored [36].

Few studies showed that although no difference is found in the phenotype of the cells concerning the site, the iliac crest contained more stem cells compared to other sites [37, 38]. Other factors that influence BMA quality are the age of the patient with older patients showing a reduction in the absolute number of MSCs and also the reduced proliferative and differentiation capacity [39–41]. Finally, the technique of production after harvesting is also shown to influence BMA quality [19, 42]. Typically, the collected bone marrow aspirate (BMA) is subjected to centrifugation directly in the operating room. This centrifugation process serves to

concentrate nucleated cells such as stem cells, monocytes, and lymphocytes, as well as essential proteins like growth factors, cytokines, and chemokines, by removing a significant portion of red blood cells and plasma. Subsequently, the volume of BMAC is reduced to approximately 3–8 ml using a cell separator. While these general steps of BMA centrifugation to obtain BMAC are shared by most procedures, there are multiple commercially available systems designed for producing BMAC [35]. However, due to the lack of standardized production techniques, including variations in BMA starting volumes, centrifuge devices, and other methodological differences, different biological products of BMAC are generated [13, 42, 43]. Consequently, these variations result in different progenitor cell and platelet counts, as well as varying concentrations of growth factors and cytokines. Cell characterization is conducted in this context with the primary objective of guaranteeing the consistent replicability and reproducibility of findings as reported by the authors in this study. Recently, Hernigou et al. [44] published a study showing the clinical efficacy of subchondral autologous bone marrow concentrate in secondary arthritis of the knee and concluded that subchondral BMAC was effective in treating OA knee and had lesser complication rates and post-op pain when compared to TKA. BMAC offers the unique advantage of enabling both the harvesting and subsequent transplantation of mesenchymal stem cells (MSCs) to the afflicted site within a single procedural session. This attribute renders BMAC a particularly viable and secure reservoir of MSCs for the management of knee OA. The growth factors play a crucial role in initiating the migration of stem cells to the site of injury and providing adhesion sites for the migrating stem cells [45].

Our study revealed significant outcomes in terms of pain reduction and functional improvement. The study, with an average participant age of 38.42 years, predominantly featured grade III OA cases and a majority female demographic. It reported notable reductions in the VAS pain scores from a mean of 7 to 2.5, and substantial improvements in IKDC scores, without any reported complications in the 24-month follow-up period. Comparatively, the literature on the efficacy of BMAC in knee OA often includes a more diverse patient population, covering a broader range of ages and severity of OA [23, 24, 26, 28, 46]. Several studies confirm the effectiveness of BMAC in improving pain and patient-reported outcomes, with many reporting significant improvements in pain scores and low incidence of adverse events, thus underscoring the safety of BMAC injections [13, 28, 47].

The potential consequences of BMAC therapy mainly include donor site morbidities (iliac crest) such as hemorrhage (0.05%) which is the most common followed by infection and chronic pain. However, this was not observed in any of the patients in this study [48]. The principal findings derived from this study confirm that the administration of BMAC injections represents a secure and efficacious regenerative therapeutic approach for individuals afflicted with mild-to-moderate knee OA. These conclusions remain following the outcomes reported in earlier systematic reviews and meta-analyses, which have consistently documented comparable results [13, 24, 28, 49, 50].

A notable strength of this study lies in our extensive 24-month follow-up period, during which we conducted comprehensive MRI analysis alongside assessments of functional outcomes. MRI evaluations of cartilage repair have yielded consistent findings with functional outcomes, with conclusive evidence of improved cartilage status. In our study, there was a notable enhancement observed in MOCART 2.0 scores, which encompasses seven key components: volume fill, integration into adjacent cartilage, surface of the repair tissue, structure of the repair tissue, signal intensity of the repair tissue, bony defects or overgrowth, and subchondral changes, over 24 months. This contrasts with the findings of Pintore et al., where MRI did not reveal significant alterations attributable to BMAC treatment within a 12-month timeframe [25]. Nonetheless, it is imperative to acknowledge the inherent limitations of this study. These limitations encompass several aspects, including the absence of objective scoring for MRI findings. Moreover, this article fails to address critical areas that warrant further investigation, such as determining the optimal dosage, timing, and frequency of BMAC injections for knee OA. In addition, the long-term safety and durability of BMAC injections for knee OA, the identification of predictive biomarkers or patient characteristics influencing response to BMAC injections, and the cost-effectiveness and cost-utility analysis of BMAC injections compared to alternative treatments remain unexplored facets in need of further scrutiny. Our study provides comprehensive evidence for the use of BMAC injections for knee OA, showing that they are a safe and effective regenerative therapy for patients with mild-to-moderate knee OA. To establish the routine utilization of BMAC as the preferred orthobiologic intervention for addressing OA of the knee, adequately powered, multi-center, prospective, double-blinded, randomized controlled trials with longer follow-up must be conducted.

Conclusion

Intra-articular BMAC injection is safe and leads to significant reduction in pain, improvement in functional outcomes and cartilage thickness at 2-year follow-up in patients with mild–moderate OA knee. Further high-quality, adequately powered, randomized controlled trials with longer follow-up along with comparative studies to determine efficacy of BMAC compared to other orthobiologics are needed to

establish its efficacy and justify its routine clinical use for the management of knee OA.

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Author Contributions Conceptualization: Jeyaraman M; data collection: Jeyaraman M, Jeyaraman N, and Ranjan R; manuscript writing: Jeyaraman M and Ramasubramanian S; manuscript revision: Gupta A; proof reading: Jeyaraman M, Jha SK, and Gupta A; administration: Jha SK; and supervision: Gupta A.

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Data Availability The data are contained within the manuscript.

Declarations

Conflicts of Interest The authors declare no conflict of interest.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study informed consent is not required.

Institutional Review Board Statement The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of School of Medical Sciences and Research, Sharda University (Ref no. SU/SMS&R/76-A/2021/113).

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