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ORIGINAL ARTICLE

Autologous Bone Marrow Aspiration Concentrate (BMAC) Therapy for Primary Knee Osteoarthritis—An Observational and Dose Escalation Study

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Abstract

Introduction Anti-inflammatory and anti-fibrotic properties maximize the therapeutic potential of bone marrow aspiration concentrate (BMAC) in osteoarthritis (OA) knee. There is a lack of studies to standardize the treatment procedure to make the studies done across various centers comparable to understand the lacunae better and develop further the deficiency in our understanding of BMAC for OA knee. We aimed to assess the degree of pain relief, functional outcome, and cartilage thickness with different doses of BMAC in primary OA knee.

Materials and Methods A single-centered prospective observational study was conducted with 80 patients of OA knee who were divided into 4 groups where group A ($n=20$), group B ($n=20$), group C ($n=20$), and group D ($n=20$) received intra-articular 1, 2, 5 million BMAC cells per kg body weight, and intra-articular saline, respectively. All patients were followed up with Visual Analog Scale (VAS), knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and International Knee Documentation Committee (IKDC) scores both pre and post-procedurally at 1, 3, 6, and 12 months follow-up.

Results The study found no significant differences in demographics or co-morbidities across four participant groups (A, B, C, D). However, clinical outcomes varied markedly: Groups B and C showed significant improvements in pain perception (VAS scores), knee function, and quality of life (KOOS and WOMAC scores), while Group A showed marginal or non-significant changes, and Group D exhibited no significant improvements. These findings suggest that treatments in Groups B and C reached the Minimal Clinically Important Difference, significantly enhancing patient-reported outcomes.

Conclusion A dose of 2 million BMAC cells per kg body weight for knee OA serves as the better regenerative modality of choice in cartilage regeneration. With our dose-escalation study, we would be able to standardize the treatment procedure and enable global comparison of the treatment method across various regions of the world.

Keywords Osteoarthritis · Knee · BMAC · Mesenchymal stromal cells · Dose escalation

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Introduction

Due to the lack of vascularity and undifferentiated cells in the articular cartilage, the spontaneous healing potential following minor trauma and degeneration is limited [1]. Upon damage, it eventually progresses toward a degenerative condition called osteoarthritis (OA) which is a degenerative destructive cartilage disease of the joint with the formation of osteophytes and involvement of changes in the periarticular bone resulting in disability [2, 3]. To our knowledge, no approved treatment method can potentially reverse the disease process of OA or restore the native articular architecture [4]. Despite multiple studies that aim to halt the disease process at the molecular level, there is a void in the development of a practically plausible treatment strategy to revert the disease process [5]. Moreover, from strategies such as microfracture to osteochondral autologous transplantation, there were several surgical interventions aimed at cartilage regeneration [6–8]. However, most of the procedures introduced were only palliative and there is a need for an optimal standardized regenerative treatment method to reverse the disease process of OA.

Of late, there are encouraging results on the utility of bone marrow aspiration concentrate (BMAC) as a promising biological tool with a rich source of pluripotent mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and growth factors which are recently approved by the United States Food and Drug Administration for clinical use [9–11]. Having investigated the BMAC for its anti-inflammatory and immunomodulatory roles, utilization of BMAC for cartilage regeneration has been in clinical practice. Although there were several studies analyzing the use of BMAC in cartilage regeneration in OA Knee, there is a lack of studies to standardize the treatment procedure to make the studies done across various centers comparable to better understand the lacunae and develop further the deficiency in our understanding of BMAC for OA knee [12].

We found across all the comparative studies using BMAC for OA knee to have a limitation mentioning the variability of the procedure protocols across the studies that prevented from deriving a meaningful conclusion across the studies conducted so far on the subject. Moreover, there were several studies analyzing the use of BMAC in cartilage regeneration in OA Knee, there is a lack of studies to standardize the treatment procedure to make the studies done across various centers comparable to better understand the lacunae and develop further on the deficiency in our understanding of BMAC for OA knee [12]. Internationally, there is no literature available on the quantification and standardization of BMAC therapy for OA knee. We aimed to quantify and standardize BMAC therapy in primary OA knee in terms of pain relief and functional outcome before and after injection.

Materials and Methods

After obtaining institutional ethics committee approval [Dr.MGR-ERI/SLMCH/2022/017, dated 07.11.2022] and written informed consent from all the participants, a total of 80 patients [According to Pal et al. [13], the overall prevalence of knee OA was found to be 28.7%] were recruited for the study in the Department of Orthopaedics, Faculty of Medicine, Sri Lalithambigai Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai.

Inclusion Criteria

Patients aged between 40 and 80 years irrespective of sex, patients who are radiologically diagnosed with Kellgren–Lawrence (KL) stage 2 and 3 primary OA knees, and patients not responding to conservative management for more than 3 months were included in the study.

Exclusion Criteria

Patients of both sexes who are <40 years and >80 years, patients with secondary OA knees, knee deformities, and inflammatory arthropathy due to rheumatoid arthritis, and other autoimmune diseases, patients who are radiologically diagnosed with KL stage 1 and 4 OA knees, patients with previous history of intra-articular corticosteroid or hyaluronic acid injection to the knee in the past 3 months, patients with active infection at the site of the procedure, patients with severe deformity (>10° in the coronal or sagittal plane) as assessed by scannogram, and patients with HIV, Hepatitis B or C, septicemia, bleeding disorders, and other coagulation disorders were excluded from the study.

Preparation of BMAC

After explaining the procedure to the patients in vernacular language, BMAC was prepared by a double centrifugation process called differential or density centrifugation technique. A total of 120 ml of bone marrow was aspirated from the anterior iliac crest in a heparinized syringe and transferred into heparinized tubes. Then these tubes were subjected to first centrifugation at 3600 rpm for 15 min. BMAC portion was subjected to a second centrifugation at 4800 rpm for 15 min in plain tubes. The final resultant contains 10–12 ml BMAC injectate (contains BM-MSC). The BMAC was then quantified with a Muse cell flow cytometer for the number of mononuclear cells per ml

and the dosage of BMAC was adjusted accordingly to the group specified for evaluation.

Pre-procedural Protocol

After obtaining a radiograph and MRI of the affected knee joint, the patient was informed regarding the procedure, and active quadriceps exercises were initiated pre-procedurally.

Group Allocation

Participants were randomly allocated to four different groups in a random manner to minimize bias and ensure that each participant has an equal chance of being assigned to any of the four groups. In this case, randomization was used to allocate individuals into 4 groups with 20 participants each, thereby distributing potential confounding factors evenly across the groups and increasing the validity of any subsequent comparisons or analyses.

Intra-procedural Protocol

The study participants were divided into four groups as follows

a) Group A ($n=20$): One dose of BMAC injectate with 1 million mononuclear cells per kilogram body weight was given on day 0 under sterile conditions;
b) Group B ($n=20$): One dose of BMAC injectate with 2 million mononuclear cells per kilogram body weight was given on day 0 under sterile conditions;
c) Group C ($n=20$): One dose of BMAC injectate with 5 million mononuclear cells per kilogram body weight was given on day 0 under sterile conditions; and
d) Group D ($n=20$): One dose of saline injectate was given on day 0 under sterile conditions.

Following the procedure, a sterile dressing was applied and the knee was mobilized passively for equal distribution of injected BMAC into the joint space. The patients were trained for home-based active quadriceps and knee strengthening programs. All the patients were advised to bear weight immediately after BMAC injection and the pain was combated with ice pack application. NSAIDs and painkillers were avoided in all patients.

Post-procedural Protocol

Once BMAC was injected into knee joints for OA, the patients were advised to follow the post-procedural protocol as follows: a) give adequate rest, b) active range of movements of the knee, c) active quadriceps exercises, d) full weight bearing immediately post-procedure, e) regular follow-up radiographs at 1, 3, 6, and 12 months, and f) pre-procedurally and post-procedurally assessments at 1, 3, 6, and 12 months were performed using VAS, KOOS, WOMAC, and IKDC scores, which provide a comprehensive evaluation of the patient's functional status and symptomatology at various time points in our study.

Statistical Analysis

Descriptive statistics were reported as mean ± SD for continuous variables, and frequencies (percentage) for categorical variables. Chi-square was used to find the association between categorical variables. Repeated measure ANOVA was utilized to find the significance within the same group. Data were statistically evaluated with IBM SPSS Statistics for Windows, Version 26.0., IBM Corp., Chicago, Illinois, USA. p value <0.05 was considered as statistically significant.

Results

The study analyzed demographic variables and clinical outcomes of participants across four groups (A, B, C, and D). The demographic analysis showed a varied age distribution with no significant difference across groups, indicated by a Chi-square value of 2.79 (9 degrees of freedom) and a p value of 0.97. The sex distribution was also balanced across the groups, with a Chi-square value of 1.0 (df = 3, $p=0.80$), and the average BMI ranged from 26.23 to 27.34 kg/m^2. The prevalence of co-morbidities like diabetes mellitus, hypertension, and seizures was comparable across groups, with no significant differences noted ($X^2=3.17$, df = 6, $p=0.78$) (Table 1).

The clinical outcome measures varied significantly. VAS scores, reflecting pain perception, showed significant reductions in Groups B and C at all follow-up intervals ($p<0.001$), contrasting with the non-significant changes in Groups A and D ($p=0.277$ and $p=0.74$, respectively) (Table 2 and Fig. 1). The KOOS score indicated substantial improvements in knee function and quality of life in Groups B and C ($p<0.001$), a marginal improvement in Group A ($p=0.056$), and no significant change in Group D ($p=0.54$) (Table 3 and Fig. 2). Similarly, the WOMAC scores demonstrated marked improvements in symptoms of OA knee in Groups B and C ($p<0.001$), but not in Groups A and D ($p=0.15$ and $p=0.19$, respectively) (Table 4 and Fig. 3). The IKDC scores revealed significant post-procedure improvement in Groups B and C ($p<0.001$), while Group A showed a non-significant trend toward deterioration ($p=0.064$), and Group D maintained stable scores ($p=0.26$) (Table 5 and Fig. 4).

The observed changes in VAS, KOOS, WOMAC, and IKDC scores, especially in Groups B and C, indicate that

Table 1 Demographic variables of the study participants

Variables	Group A ($n=20$)	Group B ($n=20$)	Group C ($n=20$)	Group D ($n=20$)	X^2 (df), p
Age (years)					
41–50	8 (40)	7 (35)	6 (30)	5 (25)	
51–60	7 (35)	9 (45)	8 (40)	7 (35)	2.79 (9)
61–70	3 (15)	2 (10)	3 (15)	4 (20)	0.97
71–80	2 (10)	2 (10)	3 (15)	4 (20)	
Sex					
Male	9 (45)	12 (60)	11 (55)	10 (50)	1.0 (3)
Female	11 (55)	8 (40)	9 (45)	10 (50)	0.80
BMI (kg/m^2)	27.18 ± 5.7	26.23 ± 3.4	27.34 ± 4.6	26.84 ± 4.2	0.784
Co-morbidities					
Diabetes mellitus	4 (20)	5 (25)	4 (20)	6 (30)	3.17 (6)
Hypertension	7 (35)	9 (45)	7 (35)	5 (25)	0.78
Seizures	2 (10)	1 (5)	0	1 (5)	
KL grading					
Grade 2	13 (65)	12 (60)	14 (70)	12 (60)	0.59 (3)
Grade 3	7 (35)	8 (40)	6 (30)	8 (40)	0.89
Treatment modality	Intra-articular injection of 1 million BMAC cells per kg body weight	Intra-articular injection of 2 million BMAC cells per kg body weight	Intra-articular injection of 5 million BMAC cells per kg body weight	Intra-articular saline injection	

Table 2 VAS score in various treatment groups

VAS score	Group A ($n=20$)	Group B ($n=20$)	Group C ($n=20$)	Group D ($n=20$)
Pre-procedure	7.3 ± 1.5	6.9 ± 1.1	6.7 ± 1.0	7.5 ± 1.9
1st month	7.2 ± 1.3	6.3 ± 0.8	6.1 ± 0.9	7.6 ± 2.3
3rd month	6.8 ± 2.0	5.2 ± 2.4	5.5 ± 1.2	7.9 ± 1.5
6th month	6.7 ± 1.8	3.6 ± 2.0	4.3 ± 2.1	7.0 ± 2.1
12th month	6.5 ± 2.6	2.4 ± 1.6	2.9 ± 1.7	7.3 ± 1.9
p value	0.277	<0.001	<0.001	0.74

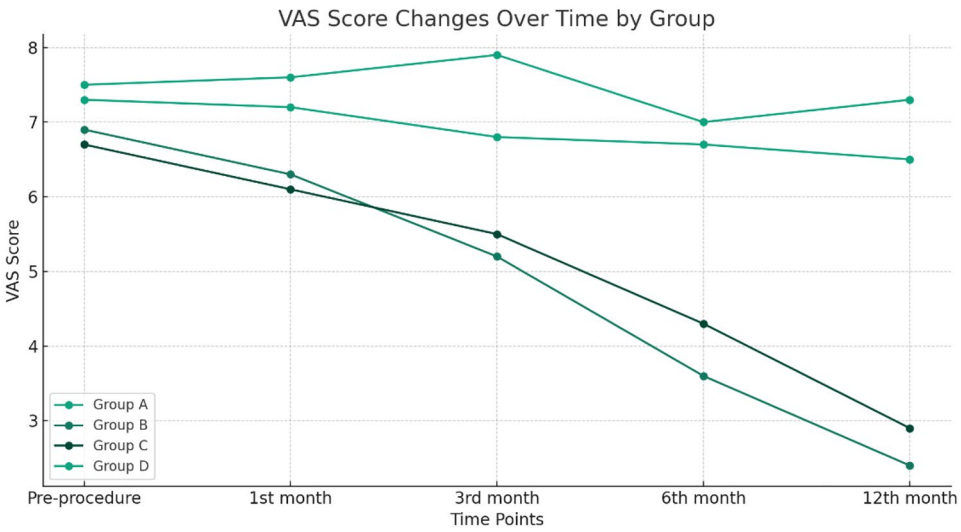


Fig. 1 VAS score in various treatment groups

Table 3 KOOS score in various treatment groups

KOOS score	Group A ($n=20$)	Group B ($n=20$)	Group C ($n=20$)	Group D ($n=20$)
Pre-procedure	38.29 ± 5.24	42.10 ± 10.15	41.20 ± 11.14	39.20 ± 6.24
1st month	39.90 ± 6.10	69.51 ± 10.80	67.60 ± 9.80	38.19 ± 6.20
3rd month	40.16 ± 10.09	72.16 ± 9.40	70.56 ± 10.40	39.26 ± 11.10
6th month	40.20 ± 12.61	75.10 ± 9.65	80.01 ± 11.66	40.12 ± 14.16
12th month	41.90 ± 5.80	79.10 ± 5.24	84.10 ± 6.14	40.09 ± 1.28
p value	0.056	<0.001	<0.001	0.54

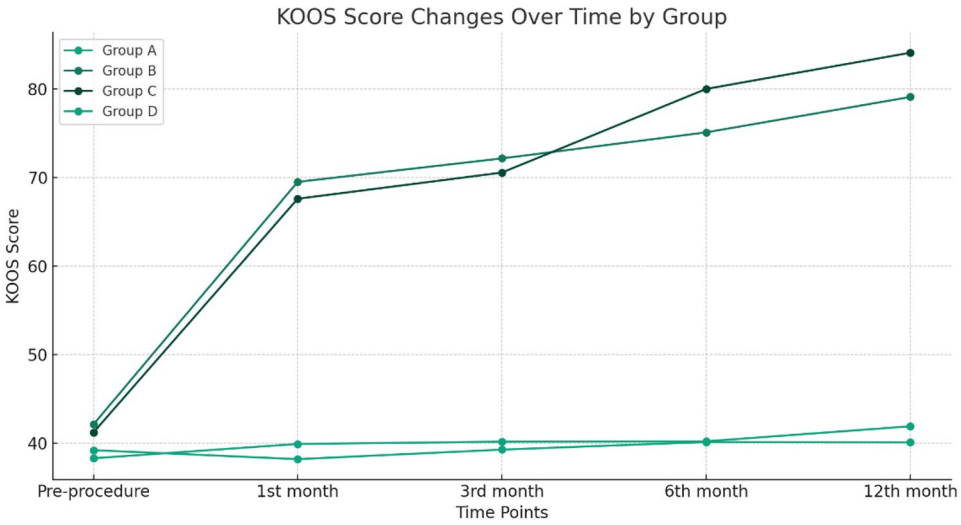


Fig. 2 KOOS score in various treatment groups

Table 4 WOMAC score in various treatment groups

WOMAC score	Group A ($n=20$)	Group B ($n=20$)	Group C ($n=20$)	Group D ($n=20$)
Pre-procedure	52.60 ± 16.12	56.16 ± 19.21	54.26 ± 16.12	53.16 ± 17.21
1st month	53.15 ± 6.17	24.35 ± 10.12	22.15 ± 9.20	53.35 ± 7.11
3rd month	53.14 ± 4.54	13.42 ± 9.54	12.20 ± 7.14	57.14 ± 4.54
6th month	55.35 ± 6.72	9.13 ± 5.27	10.30 ± 4.72	56.53 ± 7.27
12th month	58.62 ± 7.78	7.91 ± 2.30	8.01 ± 3.10	58.62 ± 5.87
p value	0.15	<0.001	<0.001	0.19

the treatments had a clinically meaningful impact on patient-reported outcomes, achieving the Minimal Clinically Important Difference (MCID) at 2 million mononuclear cells per kilogram body weight. This reflects a tangible benefit in patient-reported outcomes following treatment. Pre-procedural and post-procedural of Groups A, B, C, and D are represented in Figs. 5, 6, 7 and 8, respectively.

Discussion

Mesenchymal stromal cells (MSCs), progenitor cells sourced from bone marrow, adipose tissue, synovium, cartilage, and skeletal muscles are most conventionally utilized from bone marrow for clinical purposes [14, 15]. The International Society for Cellular Therapy defines MSCs as plastic adherent cells that express CD-73, −90, and −105 and lack the expression of CD-14, −34, −45, −79, and HLA-DR with trilineage differentiation potential into osteoblasts, chondroblasts, and adipocytes in vitro [16]. The differentiation of the MSCs into specific lineages is mainly based on the specific environment cues of which transforming growth factor-beta has been associated with the cartilage lineage differentiation and remains a cornerstone of cartilage regeneration through MSCs [17]. The molecular mechanisms that govern the development of OA involve an early inflammatory phase involving innate immune cells like natural killer cells or macrophages [18, 19]. The tumor necrosis factor-alpha and IL-1beta help in shifting the cytokine balance toward catabolism resulting in cartilage damage and resorption [20].

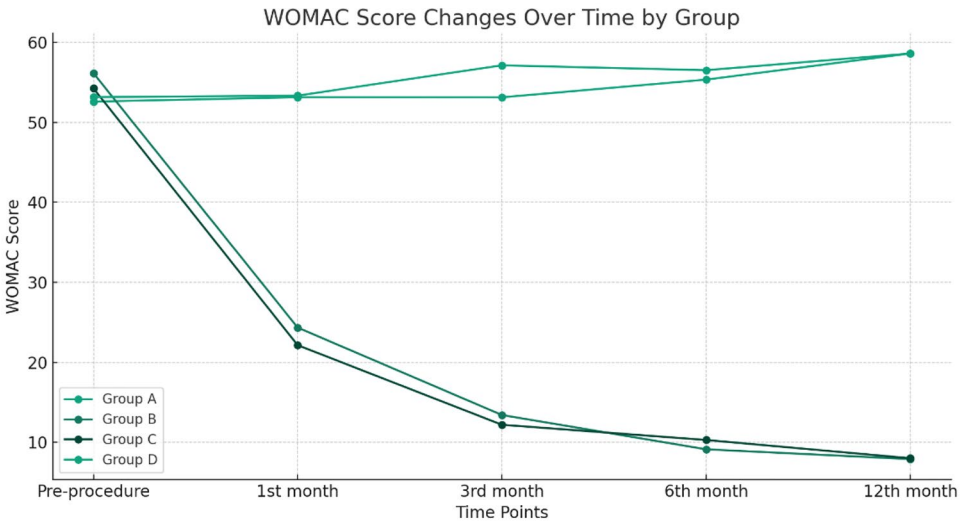


Fig. 3 WOMAC score in various treatment groups

Table 5 IKDC score in various treatment groups

IKDC score	Group A ($n=20$)	Group B ($n=20$)	Group C ($n=20$)	Group D ($n=20$)
Pre-procedure	70.05 ± 12.30	82.90 ± 8.10	79.80 ± 9.01	71.05 ± 7.13
1st month	71.02 ± 4.20	62.13 ± 8.20	60.31 ± 7.02	72.20 ± 7.02
3rd month	73.97 ± 8.30	59.20 ± 9.70	56.02 ± 8.07	75.07 ± 7.80
6th month	74.60 ± 6.34	43.10 ± 9.30	41.04 ± 8.03	74.16 ± 7.03
12th month	77.14 ± 11.20	22.30 ± 6.50	23.20 ± 7.05	75.30 ± 6.50
p value	0.064	<0.001	<0.001	0.26

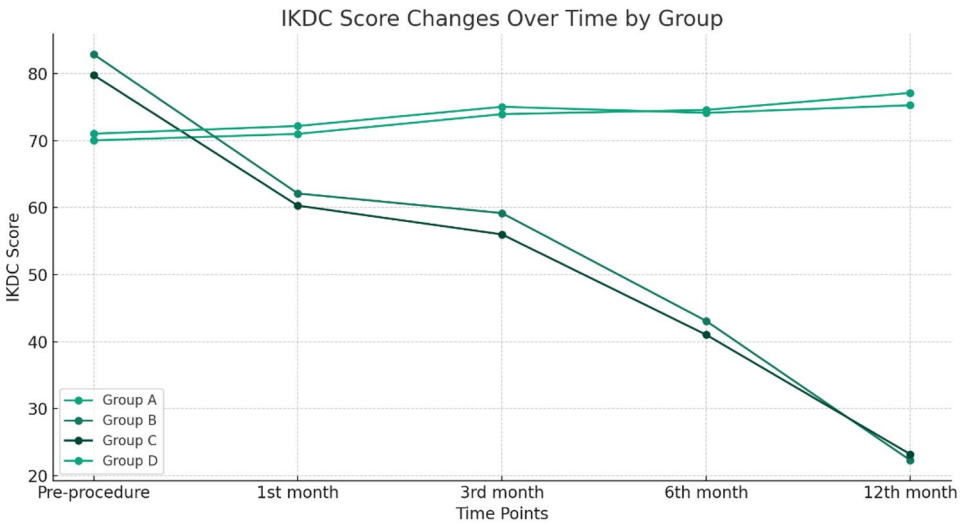


Fig. 4 IKDC score in various treatment groups

Along with the proinflammatory cytokines such as IL-1 and reduction in the growth factors such as TGF-beta, with activated matrix metalloproteinases, chondrocyte senescence is noticed at the molecular level [19]. We are evolving ourselves in the understanding of how BMAC helps in restoring this balance. The MSCs in the BMAC will be a potential factor that drives the cells toward cartilage repair. Moreover, the nucleated cells in the BMAC provide a paracrine effect with their growth factors and cytokines in them to promote tissue healing and immunomodulation. MSCs possess immunosuppressive effects on inflammatory cells such as dendritic cells, macrophages, natural killer cells, and T and B lymphocytes [18]. Hence, they have anti-inflammatory and anti-fibrotic properties to maximize the therapeutic potential of BMAC

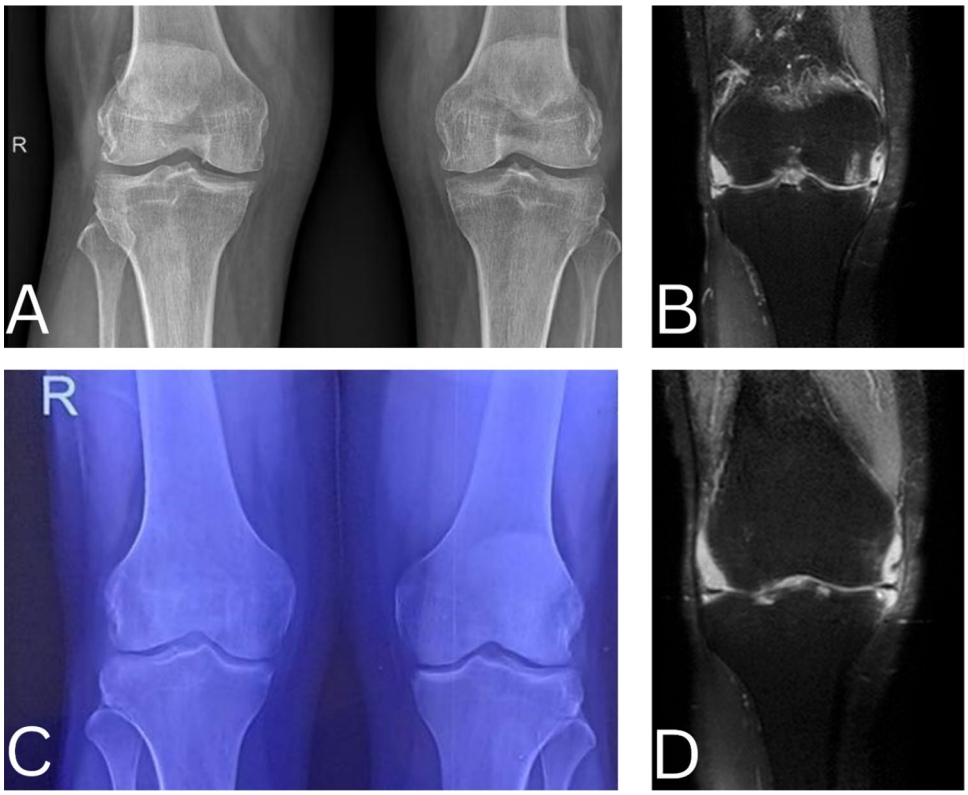


Fig. 5 **A** Pre-procedural radiograph of bilateral knees (AP view on standing position) showing decreased medial joint line in bilateral knees suggestive of KL grade II knee OA; **B** pre-procedural T2W MRI (coronal section) showing hyperintensity with thinned out cartilage along the medial femoral condyle suggestive of OA knee; **C** 1-year follow-up radiograph of bilateral knees (AP view on standing position) showing no improvement in medial joint line space in bilateral knees; and **D** 1-year follow-up T2W MRI (coronal image) showing no improvement in cartilaginous signals indicating no response to BMAC therapy

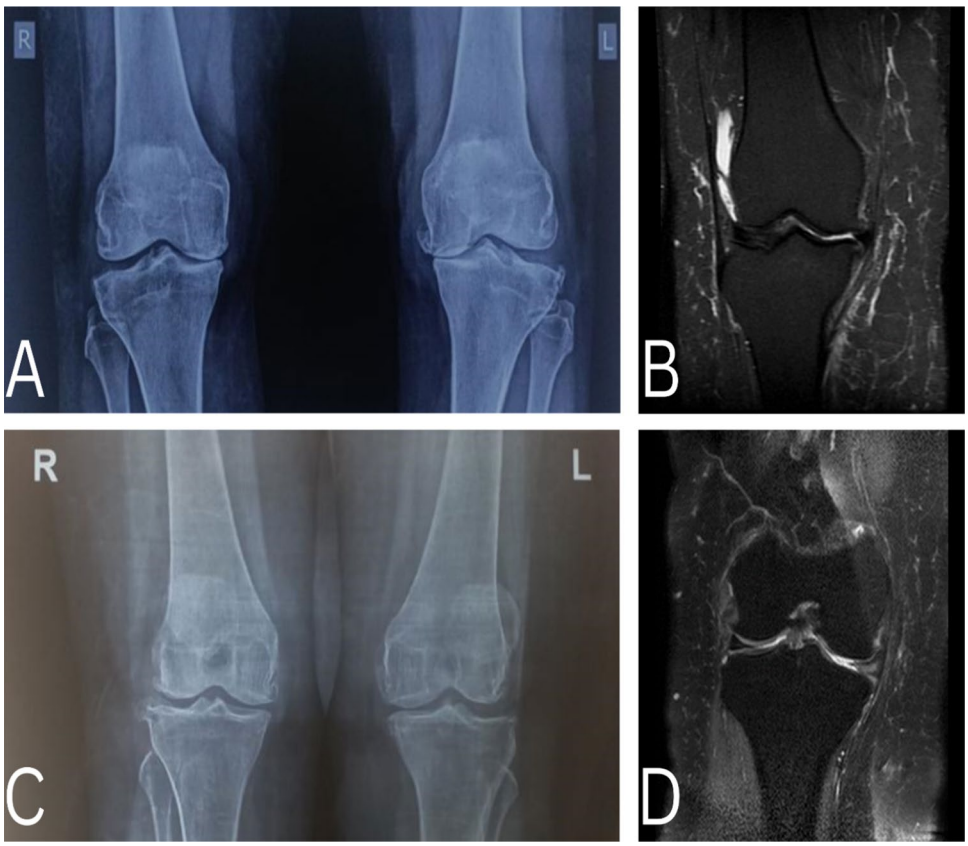


Fig. 6 **A** Pre-procedural radiograph of bilateral knees (AP view on standing position) showing decreased medial joint line in bilateral knees suggestive of KL grade II knee OA; **B** pre-procedural T2W MRI (coronal section) showing hyperintensity with thinned out cartilage along the medial femoral condyle suggestive of OA knee; **C** 1-year follow-up radiograph of bilateral knees (AP view on standing position) showing improvement in medial joint line space in bilateral knees; and **D** 1-year follow-up T2W MRI (coronal image) showing improvement in cartilaginous signals indicating response to BMAC therapy

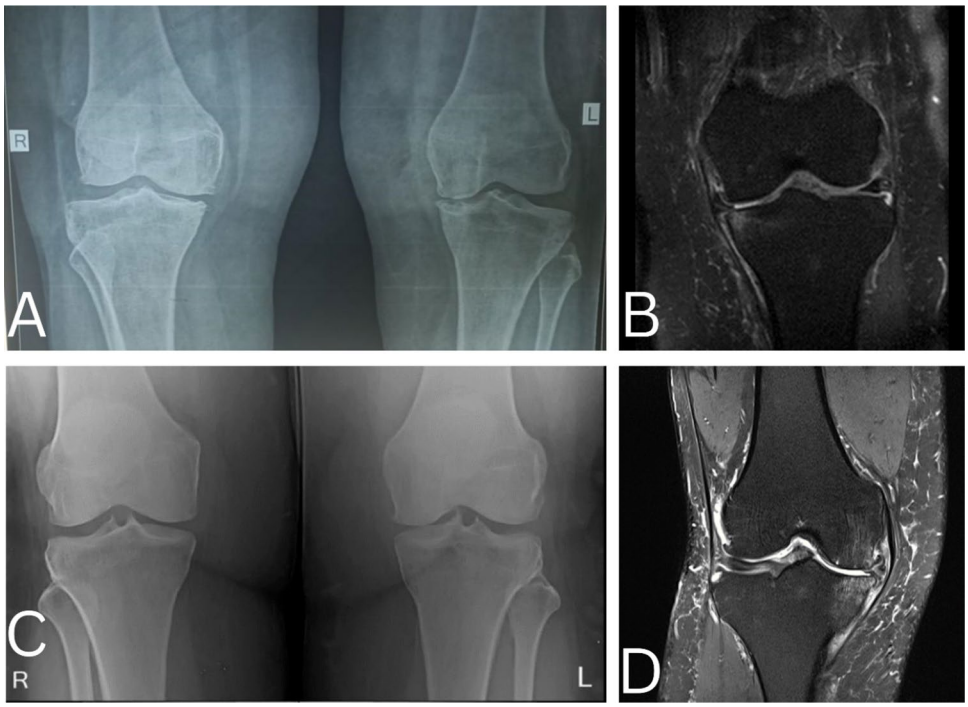


Fig. 7 **A** Pre-procedural radiograph of bilateral knees (AP view on standing position) showing decreased medial joint line in bilateral knees suggestive of KL grade II knee OA; **B** pre-procedural T2W MRI (coronal section) showing hyperintensity with thinned out cartilage along the medial femoral condyle suggestive of OA knee; **C** 1-year follow-up radiograph of bilateral knees (AP view on standing position) showing improvement in medial joint line space in bilateral knees; and **D** 1-year follow-up T2W MRI (coronal image) showing increased improvement in cartilaginous signals indicating response to BMAC therapy

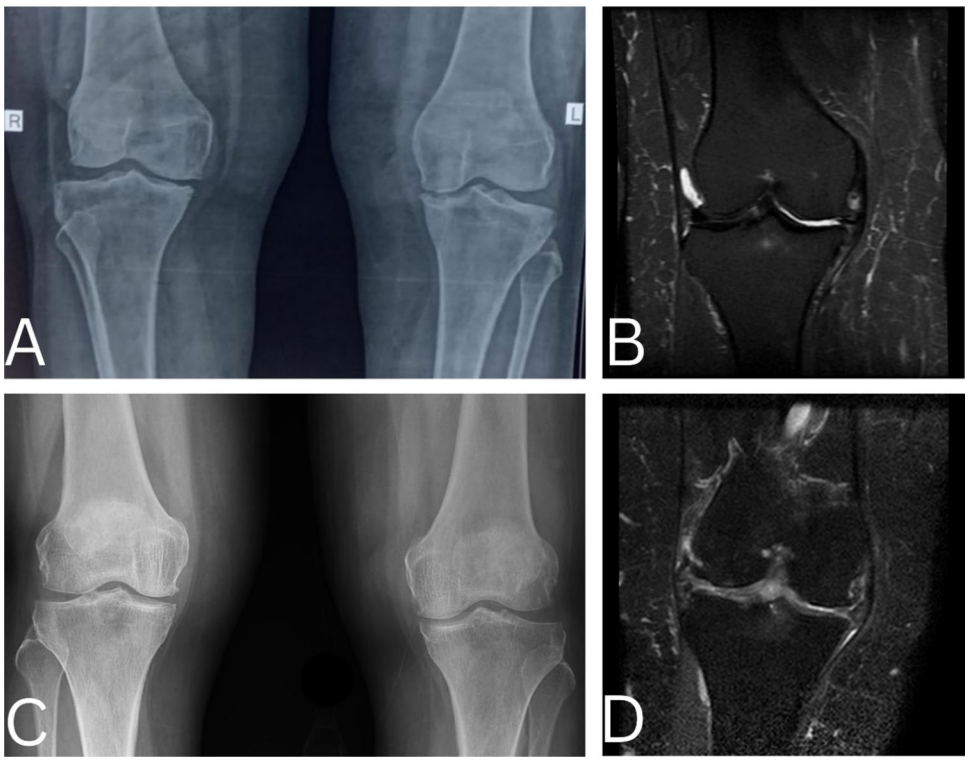


Fig. 8 **A** Pre-procedural radiograph of bilateral knees (AP view on standing position) showing decreased medial joint line in bilateral knees suggestive of KL grade II knee OA; **B** pre-procedural T2W MRI (coronal section) showing hyperintensity with thinned out cartilage along the medial femoral condyle suggestive of OA knee; **C** 1-year follow-up radiograph of bilateral knees (AP view on standing position) showing no improvement in medial joint line space in bilateral knees; and **D** 1-year follow-up T2W MRI (coronal image) showing no improvement in cartilaginous signals, indicating no response to saline injection

in OA knee. Apart from the MSCs, the other growth factors and progenitor cells in the BMAC would help in establishing the micromolecular homeostasis that is crucial in restoring the chemical balance of the pathological milieu that exists in OA knee [21].

Cavallo et al., in their systematic review, concluded that BMAC for OA knee has shown promising results on effectiveness and safety clinical studies in the literature [22]. However, they found the knowledge to be still rudimentary. They suggested further studies in BMAC to optimize their

usage with future studies. In another network meta-analysis of the interventions for OA knee [12], it was noted that in the studies with BMAC despite demonstrating potential benefits, there exists a wide credibility interval making it impossible to draw definitive conclusions. Hence, studies to standardize and quantify the procedure would be the ideal way to tighten confidence in the results of the studies on BMAC for OA knee.

The study showed significant knee OA management with BMAC, consistent with typical OA demographics. Uniform distribution of demographic and clinical variables across groups lent credibility to the findings. Higher BMAC doses led to greater improvements in VAS, KOOS, WOMAC, and IKDC scores, indicating dose-dependent efficacy. Optimal outcomes were achieved at 2 million mononuclear cells/kg, highlighting the significance of cell concentration in cell-based therapies for OA.

In evaluating the efficacy of BMAC in cartilage regeneration for OA knee, our research highlights several key findings. The primary study concluded that Stempeucel®, a form of allogenic pooled bone marrow-derived MSC (BM-MSC), was safe across all tested doses, yet its pain reduction efficacy was not statistically significant compared to placebo at the lower dose of 25 million cells, suggesting dose dependency in therapeutic outcomes [23]. Comparative analyses further revealed adipose tissue-derived mesenchymal stem cells (AD-MSC) to exhibit superior safety and efficacy over BM-MSC, indicating the potential of alternative MSC sources in knee OA management [14, 24]. Furthermore, autologous MSC sources were found to be more effective than allogeneic sources, emphasizing the importance of source selection in MSC-based therapies [25]. Muthu et al. suggested that the culture expansion of MSCs may not be a critical factor in achieving optimal outcomes for cartilage regeneration, advocating for the use of uncultured autologous MSCs [26]. In terms of dosage, a specific group in the Muthu et al. analysis exhibited significant improvements in pain and functional outcomes, leading to the recommendation of an MSC cell count of 5–10 million cells for enhanced therapeutic benefits which concurs with the current study [27]. Moreover, current methods of MSC delivery, such as PRP and HA, did not show superiority over direct delivery, indicating the need for exploration of more advanced delivery vehicles like composite bioscaffolds [28].

Our study, centering on the efficacy of BMAC in knee OA, utilized a controlled trial approach with varied BMAC cell concentrations across patient groups. The concept of dose–response optimization in the BMC study aligns with our findings of dose-dependent efficacy in BMAC treatment for knee OA. These insights into dose-escalation methodologies could be crucial for future research in BMAC treatments for OA [29]. In terms of methodology and outcome measures, our study's focus on quantitative assessments such as VAS, KOOS, WOMAC, and IKDC scores is more aligned with the comprehensive review provided by Cavallo et al. [22], which synthesizes various studies on BMAC in OA treatment, highlighting the need for methodological rigor and comparable outcomes to those we measured. Both our study and Cavallo et al. emphasize improvements in pain and function, supporting the potential of BMAC in OA treatment. Concerning efficacy and dose response, our study's demonstration of a dose-dependent improvement in knee OA treatment echoes the importance of dose optimization highlighted by Cavallo et al. [21]. Cavallo et al. [22], in particular, corroborate our findings by suggesting benefits from higher BMAC doses or multiple injections. Comparative effectiveness and safety are central themes in our study, where we noted significant clinical and functional improvement, and a strong safety and effectiveness profile for BMAC in knee OA, although it also indicates that BMAC does not consistently show superiority over other treatments [22].

Despite the standardization of the treatment procedure based on rigorous clinical studies, the universal application of the standardized protocol is another key step to make the treatment comparable. Hence, validation studies on the developed protocol would take the way forward in the implementation of the developed protocol of BMAC for OA knee. Although stem-cell-based therapies are being prevalently investigated for various orthopedic ailments that were once thought to have no solution on their own, appropriate standardized treatment methods would always ensure obtaining similar benefits across its utility globally. Hence, the scope for further research in MSCs in OA relies on validation of the current study results for universal acceptance, standardized protocols for allogenic preparation, and randomized controlled trials to be conducted on BMAC in OA knees.

The generalizability of this study is potentially limited due to several factors. With only 80 participants, the sample size is relatively small for a clinical study, raising concerns about the applicability of the findings to a broader population. The age and sex distribution further narrow this applicability; the study excludes patients under 40 and over 80 years and displays a female preponderance, which may not accurately represent all demographics with knee OA. Conducted in a single center, the findings of this study might not extend to different geographic or healthcare settings. Furthermore, the exclusion of patients with conditions such as secondary OA, knee deformities, or inflammatory arthropathy limits the finding's relevance to these groups. The investigation's focus on specific dosages of BMAC also restricts the applicability to other dosages or treatment types. The short-term follow-up of this study up to 12 months fails to assess longer-term outcomes and potential side effects. The lack of detailed blinding procedures and a true placebo control in Group D could introduce bias. In addition, the reliance on subjective scoring systems like VAS, KOOS,

WOMAC, and IKDC might be influenced by patient perception and reporting bias. Lastly, potential uncontrolled confounding variables, such as lifestyle factors or concurrent treatments, could have impacted the results, further complicating the interpretation of the study findings.

While the dose-escalation design is informative for understanding the safety and efficacy profile at different doses, it may introduce complexities in the interpretation of results. The optimal dosage might not be definitively identified, and varying doses could lead to mixed or inconclusive outcomes. The study population may exhibit diverse characteristics in terms of age, severity of OA, and other relevant factors. This heterogeneity can introduce variability in treatment responses and complicate the interpretation of results. The results of this study contribute to the growing body of evidence supporting the use of BMAC in OA treatment, as seen in recent systematic reviews and meta-analyses. They highlight the potential of BMAC as a promising intervention, particularly at higher cell concentrations, in improving pain and functional outcomes in knee OA. However, the wide credibility intervals noted in previous studies necessitate further research to standardize and quantify the procedure, ensuring more definitive conclusions and wider acceptance of this treatment modality.

Conclusion

Our observational and dose-escalation study has demonstrated that autologous BMAC therapy exhibits dose-dependent efficacy in the treatment of primary knee OA. Specifically, administering 2 million BMAC cells per kilogram of body weight emerged as the optimal dosage, significantly enhancing patient-reported outcomes, including pain relief, functional improvement, and cartilage regeneration. These findings not only contribute to the refinement and standardization of BMAC treatment protocols but also facilitate a global benchmark for comparison, enriching the collective understanding of the therapeutic potential of BMAC in knee OA management. It is imperative to corroborate these results through larger, multicenter trials to establish a universally endorsed therapeutic guideline for BMAC application in OA knee treatment.

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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.

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