

Safety and Efficacy of BMAC and Adipose-Derived MSCs Treatment in Combination for Knee Osteoarthritis

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1. Abstract

1.1. Background: Knee osteoarthritis (KOA) is one of the most widespread degenerative diseases that lead to pain and disability. Oral NSAIDs and Intra-articular corticosteroid injections are usually used to relieve symptoms in patients with knee osteoarthritis. In this study, we assessed the safety and efficacy of the combination of autologous adipose-derived mesenchymal stem cells (AD-MSC) that is mechanically treated with a stromal vascular fraction (SVF) and bone marrow aspirate concentrate (BMAC) injections on pain reduction and improvement of functioning in patients with KOA. The aim was to gain more information as there is a lack of research on combinational orthobiologic treatment.

1.2. Methods: 302 knee joints of patients aged between 40 and 85 years with KOA, grade 3-4 of the Kellgren–Lawrence scale were administered with a single intra-articular injection of BMAC+AD-MSC combination. These patients were evaluated before and 12 months after BMAC +AD-MSC treatment using the Visual Analog Scale (VAS) and Oxford Knee Score (OKS).

1.3. Results: After 12 months of follow-up, both VAS and OKS scores improved significantly in the BMAC +AD-MSC group from baseline after the injection ($P < 0.05$). No acute pain flares, infections, or other adverse complications were reported during this period.

1.4. Conclusion: A combination of BMC and AD-MSC was safe

and effective in improving patient-reported outcomes in patients with moderate-to-severe KOA for the entire duration of 12 months.

2. Introduction

Knee osteoarthritis (KOA) is one of the most widespread chronic progressive joint disorders that involves the steady deterioration of the articular cartilage followed by the degeneration of ligaments and menisci, pain, stiffness, and loss of joint function [1]. However, none of the available treatments reverse or repair the degenerative nature of the disease [2]. Hence, there has been significant interest in injections classified as regenerative. Recently, mesenchymal progenitor cells (MPCs), or mesenchymal stem cells (MSCs), extracted from adipose tissue, umbilical cord blood, or bone marrow, have been examined as potential therapeutic options to treat knee osteoarthritis as they can differentiate into various tissue types and self-renew [3,4]. The paracrine activity of these stem cells facilitate anti-inflammatory, anti-fibrotic, anti-apoptotic, mitogenic, angiogenic, immunomodulatory, and wound healing properties [5]. These mesenchymal stem cells could stimulate new cartilage-like cells in vitro [6], enhance repair, regenerate cartilage, and promote type II collagen production, unlike direct cell engraftment and differentiation [7]. Clinical studies of intra-articular injection of bone marrow aspirate concentrate (BMACs) into the knee have demonstrated reduction of pain and improved function with utmost safety and reliability [8-27]. Adipose-de-

rived mesenchymal stem cells (AD-MSC) including mechanically treated stromal vascular fraction (SVF) could potentially treat multiple disease processes through restoration and revival of acute and chronically damaged tissues [9,10,24-26]. Recent studies on animals and humans have shown the efficacy of adipose-derived mesenchymal stem cells, including mechanically treated stromal vascular fraction, to decrease inflammation and pain and increase the range of motion (ROM) in joints [2]. Thus, the injections of bone marrow aspirate concentrate (BMAC) and adipose-derived mesenchymal stem cells (AD-MSCs) prove safer and more productive to treat KOA for a short duration of 6-24 months without any adverse complications [13]. To date, the majority of studies focus on either use of BMAC or SVF. However, no clinical study is available on the combinational treatment involving AD-MSCs and BMAC. Hence, the primary objective of this study was to assess the efficacy of BMC and AD-MSCs in combination for knee OA after a single injection, with validated patient-reported outcomes.

3. Methodology

3.1. Study Design

The current research was an interventional study involving an intra-articular injection of BMAC and AD-MSCs in combination among patients with osteoarthritic knees. The duration of the study was from July 2019 to March 2021. These patients were then followed up to determine the efficacy of the combinational treatment (BMAC + AD-MSCs) regarding pain and monitoring adverse events, if any. For this study, the researchers selected the participants from patients with knee pain who were referred to the Medica Stem Cells clinic in the UK and Ireland. Every patient was explained about the benefits, side effects and success rate of the treatment. Study procedures were performed after signed consent from each patient. Similarly, all patients were equally recommended on lifestyle modifications and appropriate exercises for knee osteoarthritis (standard and basic treatments). All complications were carefully followed.

3.2. Study Inclusion/Exclusion Criteria

The inclusion criteria of this study were males and females, aged 40 to 85 years, grade 3 and 4 (moderate to severe) of the Kellgren–Lawrence scale in X-ray/MRI scan within the past 3 months, with a symptom duration of more than 6 months. Visual Analogue Scale of more than three, absence of any pathologic conditions around the knee such as bursitis or cellulitis, having tried a regimen of systemic anti-inflammatory medicines and physical therapy or injections (corticosteroids or viscosupplements), and willingness to participate in the study.

Exclusion criteria include any patient parameters falling outside of the inclusion criteria, any current oral or parenteral steroid, ongoing cancer treatment such as chemotherapy, genetic disorder, history of knee arthroplasty. Some of the other criteria include pregnancy or breastfeeding; the presence of peripheral neuropathy, active radiculopathy, or myopathy in lower limbs; severe hepat-

ic, gastrointestinal, respiratory, renal, cerebral, and cardiovascular diseases; any condition with bleeding tendency; any severe local infection were excluded.

4. Sample Preparation

4.1. BMAC

Bone marrow was harvested with the help of a multiport bone marrow aspiration needle extracted from the posterior superior iliac crest. The total quantity of bone marrow harvested was 60 cc for one knee and 100-120 cc for treating both knees. With the help of the manufacturer's preparation and processing protocol, bone marrow aspirate concentrate (BMAC) was prepared to utilize the Arthrex Angel centrifugation system. (Arthrex, Inc. <https://www.arthrex.com/orthobiologics/arthrex-angel-system>) The final quantity of BMAC utilized differed from 5 cc to 7 cc per affected knee joint.

4.2. AD-MSCs

For the production of the adipose-derived mesenchymal stem cells (AD-MSCs) stromal vascular fraction (SVF), the Adipose Tissue Harvesting Kit in combination with BMAC end product was used. - <https://www.arthrex.com/orthobiologics/autologous-conditioned-plasma>. 160 ml of tumescence solution was penetrated the target area for the liposuction procedure. This target region was an abdominal wall. After waiting for 15 minutes, around 30 ml of adipose tissue was harvested into two ACP double syringes in the equal proportion of 15 ml each with the help of the harvesting cannula from the Adipose Tissue Harvesting Kit. These ACP double syringes were then centrifuged at 2500 rpm in the appropriate centrifuge Rotofix 32A for 4 minutes. This centrifugation step result in a separation of the lipoaspirate into three layers. The oil and aqueous fractions were eliminated using the double syringe by leaving only the fat graft behind. This fat graft was poured through the swooshing device at least 30 times to dissociate the adipocytes mechanically. Second centrifugation for 4 minutes at 2,500 rpm was carried out; the separated oil was eliminated, leaving behind the SVF (cell pellet) in the ACP Double Syringe itself. Consequently, ACP SVF, was prepared by re-suspending the SVF cell pellet in BMAC.

5. Intervention

All patients confirmed the cessation of NSAIDs at least five days before the procedure. Before injecting, the affected knee joint site was infiltrated with a dilute solution of .00125% lidocaine provided/INGa significant anaesthetic effect on local soft tissues. With the help of ultrasound guidance, intra-articular injections of the combination of BMAC+AD-MSCs were given precisely into the affected joint. The patients were also instructed to avoid oral NSAIDs four to six weeks after the procedure. The patient was also advised to avoid high impact activity for two weeks.

6. Outcomes

All patients were evaluated before and 12 months after treatment by the Visual Analogue Scale (VAS) and Oxford Knee Scale

(OKS) questionnaires. VAS assesses pain intensity with 10 degrees, starting from 0 (no pain) to 10 (most possible pain). 11 OKS estimates the overall function of the patient’s affected region. It includes 12 items with five scores, ranging from 0 to 4 (none: 4, very mild: 3, mild: 2, moderate: 1, and severe: 0); the score of 0 points represents the worst function, and the score of 4 points refers to the most outstanding performance. The most important demographic criteria were age and sex. Both BMAC and AD-MSC procedures were performed to find a significant improvement in knee joint pain and function.

7. Possibility of Adverse Events

While performing both BMAC and AD-MSC procedures, the patients were informed about the possibility of complications that include pain at the injection site, bruising, allergy, infection, stiffness, itching, nausea/vomiting, dizziness, bleeding, temporary increase in blood sugar level, and nerve injury.

8. Statistical Analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). The pre-and post-treatment scores after 12 months were considered using the Paired t-test. A value of probability value $p < 0.05$ was considered statistically significant.

9. Result

We assessed 400 patients with knee osteoarthritis pain who were the candidates to participate in our study. Ninety patients had at least one exclusion criterion: kidney disorder, cancer, and genetic disorder, so they were omitted. Eight patients declined to participate. The remaining patients (n=302) were finally administered with the combinational treatment (BMAC+AD-MSCs). Mean age was 60 years, ranging from 19 to 85 years, and there were 165 (54.64%) males and 137 (45.36%) females, 186 right knees, and 116 left knees (Table 1). The degree of the degenerative arthritis was evaluated to be grade III-IV by K-L grade (Kellgren–Lawrence grading scale) on standing anteroposterior (AP) view. 132 knees were evaluated as K–L grade III, and 170 knees were evaluated as K–L grade IV, respectively. The results are summarized in Table 2. Before the treatment, there was no significant difference in age, sex (Table 1), VAS, and OKS scores (Table 2). After 12 months of follow-up, the VAS score showed 82% improvement in males and 75% in females. Similarly, the OKS score showed 79% improvement in males and females. The data analysis revealed the improvement of the OKS score and the reduction of the VAS score after 12 months of follow-up (value < 0.05) (Table 3, Figure 1 & 2).

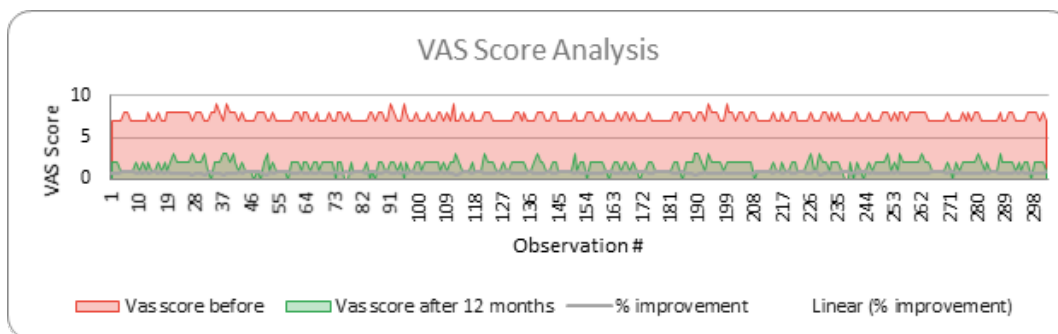


Figure 1: VAS Score Analysis (Before v/s After 12 months of BMAC+AD-MSCs treatment).

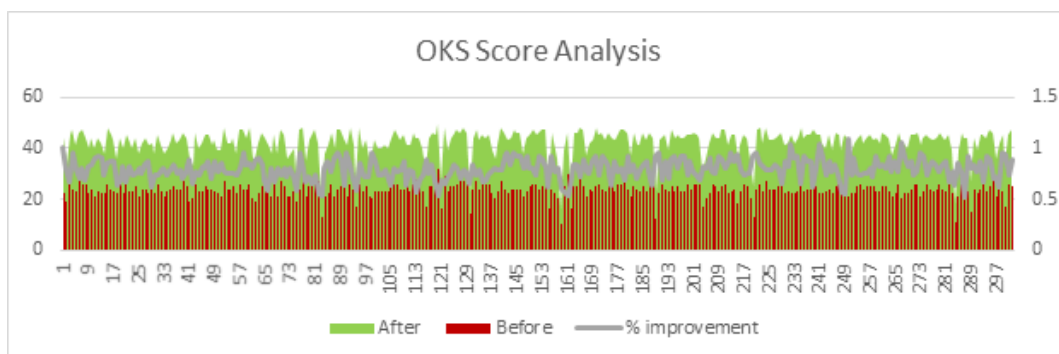


Figure 2: OKS Score Analysis (Before v/s After 12 months of BMAC+AD-MSCs treatment).

Table 1: Baseline characteristics of patients.

Sex	BMAC+AD-MSCs group
	Males 165 (54.64%); Females 137 (45.36%) K–L grade II (132 knees); K–L grade III (170 knees)
Age, mean ± SD	60 ± 8.63

Table 2: Average % improvement in VAS and OKS scores.

Scores	BMAC+ AD-MSCs (after 12 months of treatment)	
	Male	Female
VAS	82%	75%
OKS	79%	79%

Table 3: Average % improvement in VAS and OKS scores.

Scores	BMAC+AD-MSCs(P-value <0.05)	
	Pre-treatment	Post-treatment (after 12 months)
VAS, mean ± SD	8.2±1.38	2.1±1.1
OKS, mean ± SD	23.69±11.1	42.41±7.8

10. Discussion

To our knowledge, this was the first direct novel insight on the efficacy of the combinational treatment that involves BMAC and AD-MSC, including mechanically treated SVF against knee OA. Novelty of this study highlights a significant improvement in clinical outcomes of VAS and OKS scores for the AD-MSCs and BMAC groups 12 months after the injection. This study confirmed the mode of action of regenerative medicine, which involved a flow of events over time leading to an immunomodulatory effect that can lead to tissue remodelling. The anti-inflammatory effect and the improvement in knee pain, function, and cartilage quality may be associated with the soluble growth factors produced by the mesenchymal stem cells [14]. There are established facts about the ability of BMAC to culture or differentiate was, often referred to as stem cells, with the potential of secreting a higher volume of potentially beneficial chemokines and soluble growth bioactive proteins. However, its clinical superiority was found to be theoretical. Although the full clinical potential of BMAC was unclear, its clinical case series have shown promise for the treatment of OA [16-17], thereby recommending the role of BMAC in open implantation for cartilage repair [19-22]. Similar to the effect of AD-MSCs, improved function and reduced pain were observed in patients treated with a bone marrow concentrate protocol regardless of cellular dose [23]. The stromal vascular fraction (SVF) extracted from adipose tissues was a heterogeneous cell population that included a mesenchymal stem cell (6.7%) compartment, an endothelial precursor cell compartment (2%), and a monocyte/macrophage compartment (10%), among others [28]. These adipose-derived mesenchymal stem cells have been shown to exhibit anti-fibrotic and immunomodulatory properties, promote proliferation and chondrogenic differentiation in co-culture through the secretion of growth factors, and protect cells from oxidative stress and apoptosis [29]. They exhibit protective and rejuvenating properties and remain plentiful in supply as they are easily derived from human lipoaspirate samples. Autologous adipose-derived mesenchymal stem cells were proven to be safe without any rejection risk. Hence, it could be a new potential therapy for de-

creasing pain for knee osteoarthritis conditions without adverse events [2,30-31]. A single dose of BMAC or AD-MSCs injections as standalone treatments into the knee joint of patients with knee joints resulted in significant improvement in symptoms for 12-month follow-up. However, AD-MSCs injection proved to be more effective than BMAC in reducing knee pain, which is a crucial finding to date [36]. The extraction of adipose tissues through standard liposuction procedure under local anaesthesia was found to have about 500–2500 times more mesenchymal stem cells when compared with the same volume of bone marrow cells [32]. Additionally, the number of stem cells present in the bone marrow would be reduced with age, while the pool of stem cells in adipose tissue would remain stable throughout life. Compared to bone marrow-derived cells, adipose tissue-derived cells were found to be genetically more stable, with longer telomere length, lower senescence ratio, and more proliferative and differentiation capability [33-34]. In general, the combinational treatment involving BMAC and AD-MSCs was considered a fairly simple procedure that could be easily completed in an outpatient setting. Currently, many studies are in progress to determine the lasting durability of these procedures and probable alterations to get comparatively better results. In this study, only the preliminary data was revealed recommending the safety and long-term efficacy of a cost-effective outpatient procedure of combinational administration of AD-MSC and BMAC in the knee.

11. Study Limitations

The limitations of the present study include the lack of objective assessment of the interventional outcomes and the lack of a placebo/control group. Earlier studies have revealed a remarkable placebo effect while evaluating the effects of biologics [35]. There was an added criticism about the missing factor of a comparative arm of steroids or HA, which would have significantly expanded this study's real-world applicability. There was no comparison of BMAC + AD-MSCs combinational treatment outcomes for various KL grades. No MRI assessment was performed to quantify the regeneration in cartilage following the treatment as our priority was clinical change as imaging assessment may disagree with clin-

ical outcomes [36]. To date, there has been a lack of high-quality research studies on the combination of BMAC and SVFs, for more than two years with various trial settings for knee osteoarthritis treatment [13].

12. Future Investigations

The duration of follow-up of the current study was only one year. However, the current cohort study could be continued for the second and third years, thereby reporting the outcomes of symptoms and radiological investigations aimed at cartilage thickness in the following research paper. Future studies aim to compare BMAC + AD-MSCs combinational treatment with corticosteroids, hyaluronic acid injections, platelet-rich plasma, placebo, only BMAC, and only AD-MSCs.

13. Conclusion

This study demonstrated that the combination of AD-MSCs and BMAC was an effective and well-tolerated treatment method to reduce pain and improve function significantly in patients with moderate to severe knee arthritis for nearly 12 months. The results of the current study were established based on subjective findings. Further detailed research should be conducted to assess their effect with different methods, long-term follow-up and objective findings.

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