

Original Research Article

Functional outcomes of bone marrow aspirate concentrate application in osteoarthritis of the knee

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ABSTRACT

Background: Osteoarthritis (OA) of the knee is a very common musculoskeletal disorder. Although total knee replacement is a suitable option in the treatment of severe OA, it has some limitations when performed in the early stage and early age. Bone marrow aspirate concentrate (BMAC), which is rich in mesenchymal stem cells, is promising due to its potentially regenerative and symptomatic effects in many disorders of the musculoskeletal system. This study aims to investigate the efficacy of BMAC in terms of functional recovery in OA of the knee joint.

Methods: Total of 52 patients with unilateral symptomatic knee OA but no inflammatory disease, advanced malalignment or instability were enrolled in this study. Bone marrow aspirate was collected from the iliac crest in one session, prepared using a manufactured kit and the patients received intra-articular injections of this BMAC. The mean age of the patients was 59.2±7.4 and the mean follow-up period was 22.1±3.6 months. Functional outcomes of the patients were evaluated using Modified Cincinnati and Tegner Lysholm scoring systems.

Results: It was observed that both Lysholm and Cincinnati scores of the patients were statistically significantly higher throughout the follow-up period as compared to the period before the procedure (p=0.0001). There was no statistically significant difference in Lysholm and Cincinnati ratings between gender, side and body mass index groups throughout the follow-up period (p >0.05). It was found that the results of the patients with Kellgren-Lawrence Grade 4 severe joint arthrosis were statistically significantly lower (p <0.05).

Conclusions: Considering the functional outcomes of the patients up to two years, it was observed that the application of concentrated bone marrow aspirate provided functional recovery in arthrosis of the knee joint.

Keywords: Bone marrow aspirate concentrate, Degenerative joint disease, Knee osteoarthritis, Stem cells

INTRODUCTION

Joint arthrosis and its most common type osteoarthritis are among the most prevalent disorders of the musculoskeletal system.¹ Osteoarthritis of the knee is a painful, chronic and progressive disease characterized by synovial pathologies and degenerative changes in cartilage and subchondral bone.² Symptomatic knee

arthrosis is seen in more than 10% of the individuals over the age of 60.³

Treatment options in the early phase of osteoarthritis such as NSAIDs, glucosamine, hyaluronic acid, and steroids are used in order to relieve symptoms rather than biological joint restoration or biomechanical arrangement purposes. Despite the developments in conservative

treatment approaches, these methods cannot be used to stop the progression of the disease.^{4,5}

In case the conservative treatment methods fail, one of the best treatment methods for advanced arthrosis of the knee is total knee replacement.⁶ Biomechanical solutions have provided significant benefit within the last 50 years with the use of more sensitive instruments for joint implantation. However, problems with the implant such as wear and loosening and in parallel, the presence of recurring surgical risks that increase morbidity are well known. Therefore, great expectations almost in all medical fields are focused on regenerative medicine today. It is anticipated that this new branch of medicine could alter the course of chronic diseases and provide regeneration of fatigued and failed organ systems in various cases.⁷ With the increasing interest in regenerative medicine, the focus is placed on the use of stem cells and especially mesenchymal stem cells (MSCs) for cartilage regeneration. Although mesenchymal stem cells can be applied by stromal vascular fraction or different culturing processes, mesenchymal stem cells are now directly collected from the areas that are rich in these cells in the body without culturing and applied after concentrating the cells rather than using the mentioned techniques, as they are expensive and have various challenges.^{8,9}

The efficacy of bone marrow aspirate concentrate (BMAC), which is one of these methods, in osteoarthritis of the knee has been demonstrated in many studies.¹⁰⁻¹⁶ It is known that BMAC is rich in mesenchymal stem cells, hematopoietic stem cells, endothelial progenitor cells and platelets. This study aims to investigate the efficacy of bone marrow aspirate concentrate in terms of functional recovery in osteoarthritis of the knee joint.

METHODS

The patients who received a Bone Marrow Aspirate Concentrate (BMAC) injection for the treatment of symptomatic unilateral arthrosis of the knee joint between January 2015 and March 2017 were enrolled in this study.

Exclusion criteria

- Patients with knee instability, severe malalignment, flexion contracture over 10 degrees,
- Hematologic disorder and inflammatory arthritis such as ankylosing spondylitis and rheumatoid arthritis,
- An underlying disease such as immune deficiency, septicemia, malignancy and active infection
- And symptomatic complaints in both knees.

The mean age of the 52 patients who fulfilled the inclusion criteria and were enrolled in the study was 59.2±7.4. There were 35 (67.3%) female and 17 (32.7%) male patients. The Kellgren-Lawrence scale was used for

the grading of the knee joint arthrosis in patients that were included in the study. Kellgren-Lawrence grade I patients according to the weight-bearing X-ray images were excluded from the study. Among the patients included in the study, 13 (25%) had grade II, 28 (53.8%) had grade III, and 11 (21.2%) had grade IV arthrosis.

BMAC injection procedure

The patients were placed in supine position, the iliac wing was covered with a sterile drape under operating room conditions and a local anesthetic was administered on the Spina Iliaca Anterior Superior (SIAS). 60cc of bone marrow was aspirated using a bone marrow biopsy needle. A manufactured BMAC centrifuge system was used to prepare the bone marrow aspirate concentrate in accordance with the manufacturer's protocol (Figure 1). Final volume of the employed BMAC was between 5 and 7cc for the knee joint. The obtained concentrate was injected into the knee joint from the anterolateral aspect when the knee was in flexion following suitable sterilization.

Functional outcomes of the patients were evaluated using Modified Cincinnati and Tegner-Lysholm rating systems right before the procedure and at months 6, 12, and 24 after the procedure. In addition to the overall evaluation of the patients' functional status according to follow-up periods, analysis according to variables such as gender, side, body mass index and degree of arthrosis was also conducted.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS software (Version 17.0, SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were described by mean±standard deviation ($p>0.05$ in Kolmogorov-Smirnov test or Shapiro-Wilk test ($n<30$), and the continuous variables that were not normally distributed were described by median values. Comparisons between the groups were performed using Student T test or One way ANOVA for normally distributed data. Pre-post data analysis was performed using the Paired T test and Repeated Measures Analysis. The level of statistical significance was accepted as $p < 0.05$.

RESULTS

Distribution of the patients according to clinical characteristics such as demographics, stage and side of knee arthrosis, and follow-up periods is provided in Table 1. The mean follow-up period was 22.1±3.6 months. The mean body mass index of the patients included in the study was 28.1±3.5. Reviewing the Lysholm and Cincinnati scores of the patients throughout the follow-up period, it was observed that both scores were statistically significantly higher in all follow-ups as compared to the period before the procedure. However, these scores

exhibited a statistically significant drop in follow-ups after month 12.

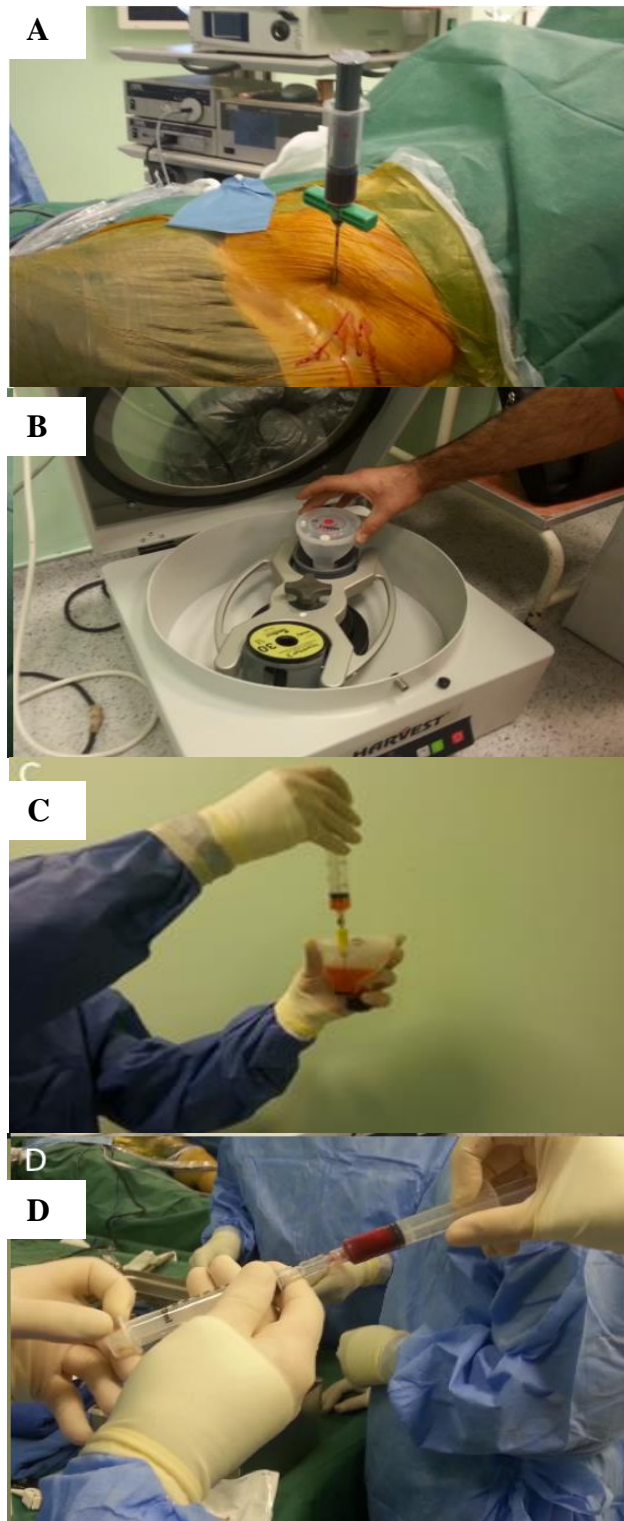


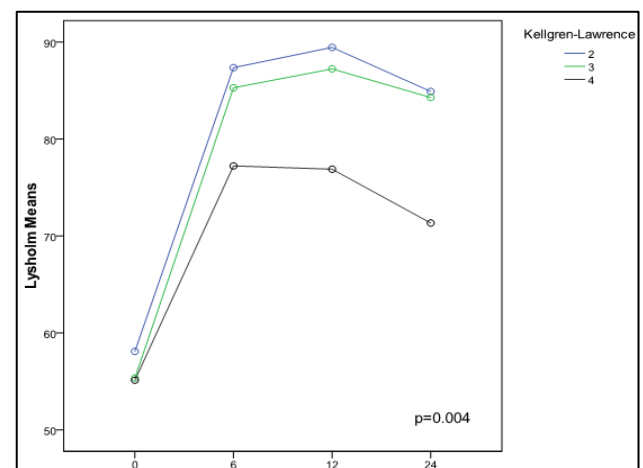
Figure 1: Bone marrow aspirate concentrate preparation. (A): Aspiration through the iliac wing SIAS, (B): centrifuging after placement in the produced kits, (C): withdrawing the amount to be injected into the injector, (D); withdrawing 5-7cc of concentrated bone marrow aspirate into the final sterile injector before injection.

Results of the statistical comparison of Lysholm measurements in time are as follows: ppreop and 6m. postop= 0.0001; ppreop and 12m. postop= 0.0001; ppreop and 24m. postop= 0.0001, p 6m. postop and 12m. postop= 0.002; p 6m. postop and 24m. postop= 0.002, p 12m. postop and 24 m. postop= 0.0001. Results of the statistical comparison of Cincinnati measurements in time are as follows; ppreop and 6m. postop= 0.0001; ppreop and 12m. postop= 0.0001; ppreop and 24m. postop= 0.0001, p 6m. postop and 12m. postop= 0.309; p 6m. postop and 24m. postop= 0.0001, p 12m postop and 24m. postop= 0.0001.

Table 1: Baseline patient demographics.

Characteristics	Study group (N=52)*
Age, year	59.2±7.4 (44-72)
BMI	28.1±3.5 (21-37)
Gender	
Female	35 (67.3%)
Male	17 (32.7%)
Side	
Right	33 (63.5%)
Left	19 (36.5%)
Kellgren-Lawrence grade	
2	13 (25%)
3	28 (53.8%)
4	11 (21.2%)
BMI	
≤30	39 (75%)
>30	13 (25%)

Data are reported as mean±standard deviation (range) for continuous variables and number (%) for discrete variables. N: number of patients, BMI: body mass index



The change in Lysholm scores in time when the patients are grouped according to the Kellgren-Lawrence (KL) grade. It was found that the functional scores of the patients with KL Grade 4 arthrosis was statistically significantly lower (p=0.004). In the graph, the horizontal axis represents follow-up periods in months and the vertical axis represents the scores. (2:Grade 2, 3:Grade 3, 4:Grade 4).

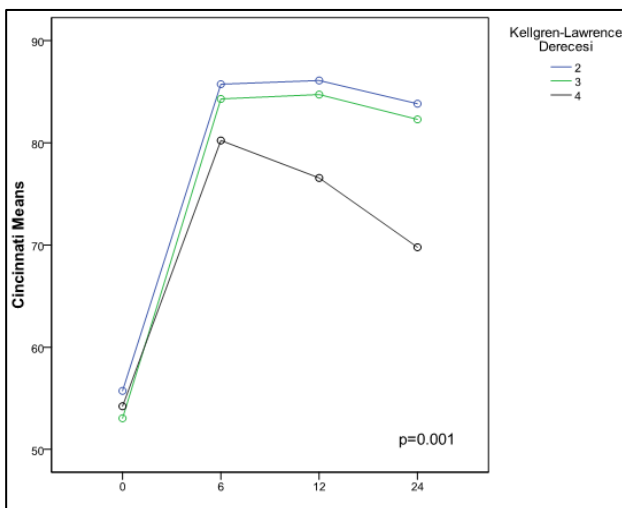
Figure 2: Change in Lysholm functional scores.

There was no statistically significant difference in Lysholm and Cincinnati ratings in time between gender, side and BMI subgroups throughout the follow-up period ($p > 0.05$). There was a statistically significant difference between the time-dependent change in the functional scores and the Kellgren-Lawrence Grade during the follow-up period.

Table 2: The change in the functional scores of patients between the preoperative period and at postoperative months 6, 12 and 24, and the statistical analysis of the change according to the preoperative baseline value throughout the follow-up period.

Scores	N	Mean±SD	Min-Max	P values
Lysholm scores				
Preoperative	52	56.6±7.3	38-68	b
Postoperative month 6	52	84.5±5.9	60-92	0.0001
Postoperative month 12	52	86.2±6.5	68-95	0.0001
Postoperative month 24	41	81.6±8.5	56-92	0.0001
Cincinnati scores				
Preoperative	52	54.7±6.7	36-68	b
Postoperative month 6	52	84.3±4.7	66-92	0.0001
Postoperative month 12	52	83.7±5.3	70-92	0.0001
Postoperative month 24	41	79.9±8.6	54-90	0.0001

N: number of patients, SD: standard deviation, min: minimum, max: maximum, b: baseline.



The change in Cincinnati scores in time when the patients are grouped according to the Kellgren-Lawrence grade. It was found that the functional scores of the patients with KL Grade 4 arthrosis was statistically significantly lower ($p=0.001$). In the graph, the horizontal axis represents follow-up periods in months and the vertical axis represents the scores. (2:Grade 2, 3:Grade 3, 4:Grade 4).

Figure 3: Change in Cincinnati functional scores.

As seen in Figure 2 and 3, both Lysholm and Cincinnati functional scores of Kellgren-Lawrence Grade 4 patients were statistically significantly lower ($p < 0.05$) when compared to Grade 2 and 3 patients. The mean change in the functional scores of patients in time is provided in Table 2. The change in scores in time when the patients are grouped according to the Kellgren-Lawrence grade is provided in Figure 2 and 3.

DISCUSSION

Osteoarthritis is a very prevalent disorder that negatively affects the daily life activities of millions of people globally. Although total knee arthroplasty is one of the most important treatment options for severe arthrosis in the elderly, the treatment options for joint arthrosis in the middle-aged population is very limited. This study shows the efficacy of bone marrow aspirate concentrate application as a treatment option for knee arthrosis before arthroplasty.

Despite the advancements in technology and sensitive implantation instruments, complications of total knee replacement such as loosening and infection that shorten the lifespan of prostheses and necessitate further surgery push people into searching for different treatment options especially for arthrosis seen at early ages. Administration of NSAIDs, glucosamine, hyaluronic acid, and corticosteroids are included in the conservative treatment methods for arthrosis of the knee joint other than prosthesis. Arthroscopic debridement of articular cartilage followed by microfracture application or cell-based surgical procedures such as autologous chondrocyte implantation is also among the surgical alternatives for cartilage lesions. However, studies have demonstrated that these biological procedures are effective in non-degenerative focal cartilage lesions seen at early ages.¹⁷⁻¹⁹

Various studies that investigate the efficacy of bone marrow aspirate rich in mesenchymal stem cells in arthrosis of the knee joint have demonstrated that intra-articular injection into the knee enhanced patient functions and was successful in eliminating the pain.¹⁰⁻¹⁶ In a case series, Centeno et al, investigated the results of 840 applications that included only BMAC application as well as adipose graft in combination with BMAC application, and found that both applications provided functional improvement without any difference between the groups.¹⁰

In a similar study, Kim et al, applied adipose tissue in combination with BMAC on 75 knees of 41 patients, and reported a decrease in visual analogue scale (VAS) scores, and improvement in International Knee Documentation Committee (IKDC), SF-36 health score, knee and osteoarthritis outcome score (KOOS) and Lysholm Knee Questionnaire functional scores.¹³ There is only one prospective, single blind, placebo-controlled trial that investigates the efficacy of BMAC application.

In this study by Shapiro et al, they injected BMAC in one knee and saline in the other knee of 25 patients with bilateral knee arthrosis and compared the results of the two knees.¹⁶

It was reported that OARSI Intermittent and Constant osteoarthritis pain and VAS pain scores of the patients were decreased throughout the 6-month follow-up period, however this decrease was not statistically significant different and it was observed in both knees. The surprising result that BMAC and saline injections provided similar results was reported to be possibly associated with the short follow-up period and the hypothesis on pain pathways as the similar results were obtained from the other knee of the same patient.

In present study, it was found that both Lysholm and Cincinnati scores of Kellgren-Lawrence stage 4 patients were worse than the scores of grade 2 and 3 patients ($p < 0.05$). Similar to the results of this study, Centeno et al, and Kim et al, showed that intra-articular administration of BMAC provided better functional recovery and pain relief in patients with early stage knee arthrosis in comparison to the patients with advanced arthrosis.^{10,13}

One of the most important limitations of this study was that there was no control group. There is a need for randomized controlled studies with longer follow-up periods and higher number of patients. On the other hand, the case series that consists of patients with isolated knee arthrosis in accordance with the inclusion and exclusion criteria is one of the strengths of present study.

CONCLUSION

Considering the 2-year functional outcomes of the patients, it was observed that the application of bone marrow aspirate concentrate provided functional recovery in arthrosis of the knee joint. Further studies are necessary in order to determine the effectiveness of applications and long-term functional outcomes in advanced arthrosis of the knee.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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