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Autologous bone marrow aspirate concentrate injection for the treatment of osteoarthritis: a randomized controlled trial, Ibn-Sina Hospital

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Abstract

Osteoarthritis (OA) is a progressive condition causing symptomatic arthritis in males and females over 45 years, manifested by pain and loss of joint function. The regenerative therapy carry a new insight for treating many orthopedic and sports problems with minimally invasive procedures to treat osteoarthritis. The bone marrow aspirate concentrate is a possible biological treatment for symptomatic osteoarthritis and chondral defects. Consequently, this study aims to investigate the impact of injection of autologous bone marrow aspirate in the treatment of symptomatic knee osteoarthritis, in addition to assess safety, pain, and functional changes. The current study comprised a randomized controlled trial (RCT) to assess the efficacy of autologous bone marrow aspirate concentrate in the treatment of symptomatic knee OA in 30 patients with 55 joints. Two injections were used within 2 months apart. The current results showed a marked drop in the WOMAC score in the intervention arm before and after the injection compared to the control (P-value=0.0001). In conclusion, an improvement of pain

and knee function was seen after bone marrow mesenchymal cell injection. The authors recommend extending the following study and treating more patients with knee osteoarthritis with mesenchymal stem cells.
Keywords: bone marrow aspirate concentrate, knee, Osteoarthritis, Treatment.

Introduction

It is a well-known fact that Osteoarthritis (OA) is a progressive condition that causes symptomatic arthritis in 10% of males and 18% of females over 45 years old. It is characterized by hyaline cartilage deterioration manifested by pain and loss of joint function. AO is increasing in prevalence and is considered the fourth leading cause of disability. OA increases to 80% in the population over 65 years old (1). The primary treatment modality is symptomatic. The drugs used in OA have limited success with many side effects. While, knee arthroplasty carries the risk of 20% complications and loss of function after 12 months (1, 2). Regenerative and biological methods offer new insight into treating many orthopedic and sports problems. They provide new, non-surgical, minimally invasive procedures to treat osteoarthritis. Bone marrow aspirate concentrate is a possible biological treatment for symptomatic osteoarthritis and chondral defects (3). Bone marrow aspirate is usually taken from the iliac bones. After centrifugation, a small cellular volume can be obtained, which has around 1/10000-1/100000 mesenchymal stem cell progenitors per mononuclear cell (4). Also, platelet concentration increases with growth factors and cytokines like platelet-derived growth factor, transforming factor, vascular endothelial growth factor, etc.(5). Compared to platelet-rich plasma, bone marrow aspirate has a higher concentration of several growth factors and cytokines involved in angiogenesis, chondrocyte metabolism, stem cell homing, and anti-inflammatory activity (6). The other important point is that the autologous, homologous use of bone marrow aspirate complies with FDA regulations as minimal manipulation cell-based therapy (7). Based on published clinical trial outcomes, MSC therapy appears safe. In a formal systematic review and meta-analysis of trials involving intravascular administration of autologous or allogeneic expanded MSC therapies (totaling over 1000 participants), no significant adverse events except transient fever were identified. A systematic review of clinical trials using intra-articular autologous expanded MSC therapies with a mean follow-up of 21 months and assessing 844 procedures showed no association with adverse events, including infection, malignancy, or death (8). A review of the literature showed scarce publications regarding intra-articular autologous expanded MSC therapies in OA in Iraq. Therefore, this study was designed as a randomized controlled trial (RCT) that aimed to assess the efficacy of autologous bone marrow aspirate concentrate bone marrow aspirate concentrate (BMAC) of 1.8 X 10^{9} median cellular content in treating symptomatic knee OA in a total of 30 patients and 55 joints using 2 injections, 2 months apart. Additionally, it intended to determine the potential of BMAC therapy to achieve disease modification in knee osteoarthritis to assess pain, function, and disease modification.

Patients and methods

A randomized controlled trial was done at Ibn-Sina Training Hospital in Baghdad. According to the Helsinki Declaration, all participants completed written informed consent and ethical approval. The study is double armed centered clinical trial registered (NCT05193877)www.clinicaltrials.gov

The trial design consists of 60 participants randomly and equally allocated to the control and treatment groups by simple random sampling. Participants were not blinded to their treatment allocation. The control group received conventional conservative management only. The intervention group received (2 injections) intra-articular injections of (4cc) per joint at (8 -12 weeks intervals).

Inclusion criteria

- Radiological diagnosis of Osteoarthritis according to Kellgren-Lawrence Criteria.
- A qualified radiologist determined the radiological grading of Osteoarthritis of the knee.
- Primary Osteoarthritis is not responsive to conventional treatment and physiotherapy.
- A minimum pain score of 5 on an 11-point numerical scale.
- Age >50 years

Exclusion criteria

- Pregnancy and breastfeeding.
- Knee symptoms due to other conditions like tumors or referred pain from the lumbar spine.
- MRI confirmed the displaced meniscal tear
- MRI confirmed Grade IV chondral loss.
- Previous knee surgery within the last 12 months.
- Previous intra-articular injectable therapies within the last 6 months
- History of severe systemic illness.
- Active neoplasm under treatment in the last 12 months-
- Health conditions, including known allergies to local
- Bleeding tendency.

Intervention

A 4 milliliter of bone marrow aspirates concentrate from 50 ml bone marrow aspirate after centrifugation.

Evaluation of total nucleated count and viability

Depending on the individual case, bone marrow aspiration is done under local or general anesthesia. Around 50 ml of bone marrow is aspirated from the posterior iliac crest after proper sterilization using a bone marrow aspiration needle (size according to the patient) and collected in ACD (acid citrate dextrose) syringes. Mononuclear cells (MNCs) are obtained by centrifugation (seawon Korea kit). The isolated MNCs are checked for viability manually and confirmed on automated cell count machine.
The separated MNCs are administered intra-articularly under ultrasound guidance immediately after centrifugation.

Outcome measure

The Womac scales were used as the primary outcome measure, which includes a severity scale from 0 to 4 for the three main variables: pain (5 items), stiffness (2 items), and functional limitation (17 items).

Statistical analysis

The raw data is summarized and presented in an appropriate table. The statistical analysis was carried out using SPSS (statistical package for social science) software version 25.

Results

Sample size and sampling technique

Conventional treatment, which includes analgesics, local steroids, or biologic agents, is usually short-lived.

Ninety-five patients were assessed to be included in this study, and 60 were allocated for a procedure. Thirty in intervention and thirty controls had been treated and screened for 12 months. The mean age for all participants was 56.0, standard deviation= 6.1, and ranged from (45-70). Our sample consisted of 17 (28.3%) males and 43 (71.7%) females.

Table.1 illustrates the mean age for males and females. There was no significant statistical difference in the mean age of cases and control groups (Independent sample T-test).

Table. 1: Mean age and standard deviation for males and females. (Independent sample T-test, α=0.05)

Gender	Number	Mean age	Standard deviation	P-value
Male	17	56.2	6.7	0.8
Female	43	55.9	5.9	

Most of our patients (58.3%) were between 51-60 years, (25.0%) were between 41-50 years, and only (16.7%) were between 61-70. Females were more in all age groups (Figure. 1) (Figure. 2)

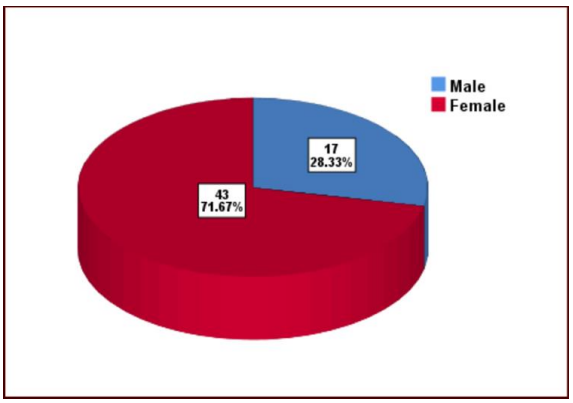

Figure. 1: Shows the distribution of the patients according to the gender

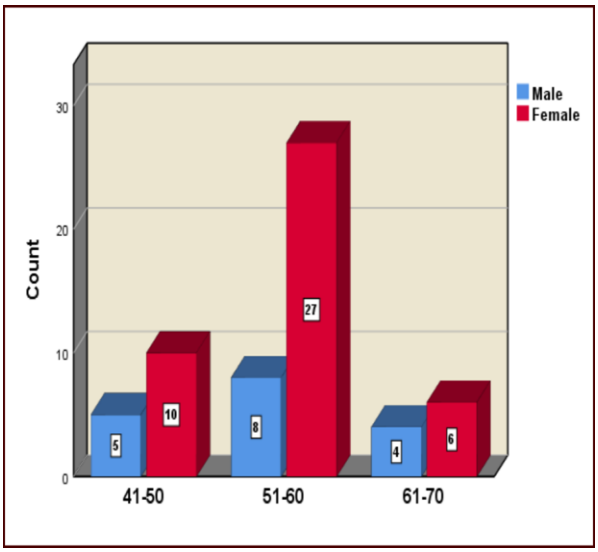

Figure. 2: Shows distribution of Male and female patients according to age groups

Also, the gender distribution among the two groups is demonstrated in (Table 2) there was no significant statistical difference in genders between intervention and control groups.

Table. 2: Gender distribution for intervention and control groups. (Pearson Chi-square test, α=0.05)

Gender	Control	Active	P value
Male	8	9	0.5
Female	22	21	
Total	30	30	

Regarding the occupations of our participants, most of them (55%) were housewives; the rest were distributed among other occupations as illustrated in (Figure. 3). Total active arm 30 patients with 55 knee joints.

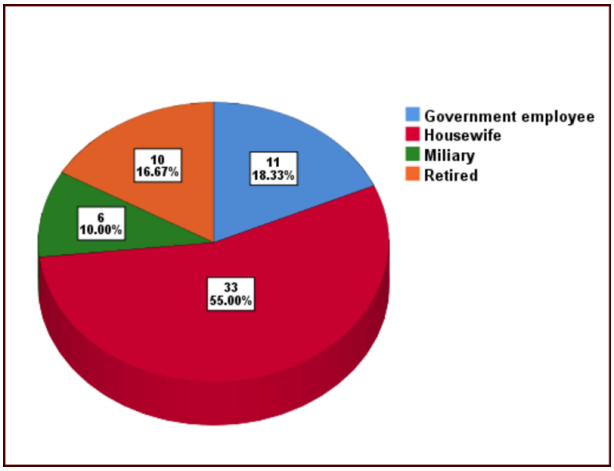

Figure. 3: Shows the occupation distribution among study participants. (n=60)

The grading (Kellgren-Lawrence Criteria) of our patients was from one to three, and the majority had grade II in the intervention and control group as illustrated in (Figure. 4).

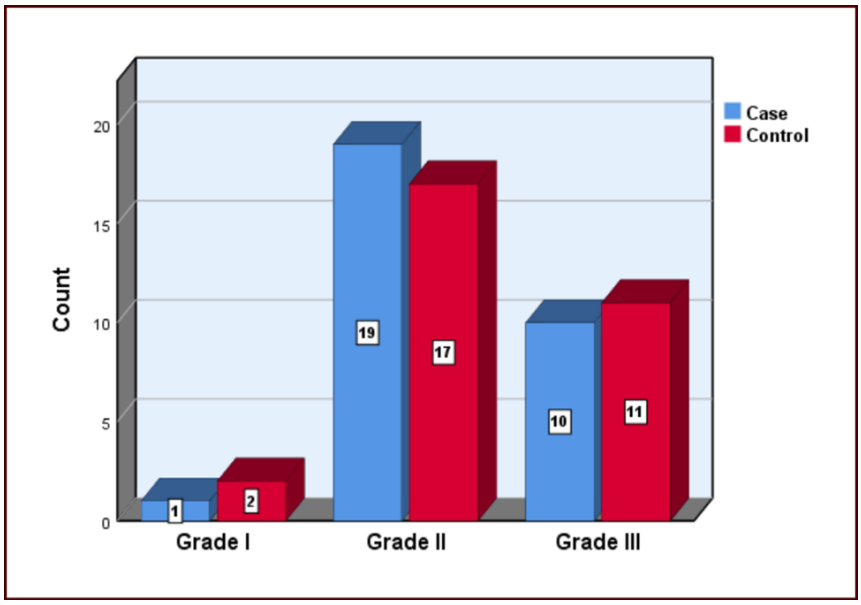

Figure 4: Shows the grading distribution among intervention and control groups

WOMAC score was measured for all participants before the intervention, after twelve months of the procedure for cases, and after medical treatment for control. The mean and standard deviation for each group are illustrated in (Table. 3); there is a significant statistical difference when using (paired sample T-test). The decrease in the WOMAC scale in the intervention group was significantly more than in the control group.

Table.3: Womac scale before and after treatment

Arm	number	Womac before	Womac after	Standard deviation	p-value
Intervention	30	69.6	29.0	15.4	0.0001
Control	30	54.4	42.1	17.1	

Table.4: bone marrow mononuclear cell count and viability

Cellular count /product	Number cell/product	Viability
Minimum	1.4x10 7	75%
Maximum	1.8 x 10 9	99%

Discussion

The standard classic treatments for osteoarthritis include analgesic drugs, physiotherapy with all modalities, surgical correction, and arthroplasty (1). The new biologic and regenerative medicine techniques include platelet-rich plasma(PRP), exosomes, growth factors, bone marrow aspirate concentrate(BMAC), adipose-derived stem cells(ADSC), and expanded mesenchymal stem cells from different sources. The injection methods

included intraarticular, subchondral, arthroscope, and 3D bioprinting. Previous studies showed that bone marrow aspirate concentrate injection effectively improved pain and patient-reported outcomes in knee OA at short- to midterm follow-up. (9, 10, 11). Recent large meta-analysis studies using bone marrow aspirate concentrate in controlled clinical trials showed that pain and joint function improved after using single or multiple intraarticular bone marrow aspirate injections. Each participant achieved the baseline and follow-up surveys. The questionnaire, which is called Emory Quality of Life (EQOL), comprised the knee injury and osteoarthritis outcome score (KOOS), in addition to the Visual Analog scale (VAS) for pain. The response and results of the follow-up were compared with baseline data for all participants and between significant improvements in EQOL, VAS, and all KOO parameters. These data demonstrate significant improvement in pain and function with BMAC injections in patients with symptomatic knee osteoarthritis. (12, 13, 14, 15). The current study showed a marked drop in the WOMAC score in the intervention arm before and after the injection compared to the control group, as shown in Figure. 4 and Table. 3 (P-value=0.0001). The definite proof for cartilage regeneration includes histopathological evidence of cartilage formation and radiological evidence by plain X-ray and magnetic resonance imaging. These are currently evident in animal studies and few clinical human trials using modern regenerative medicine techniques. In the current study, 12 months follow-up did not show marked improvement in radiological staging of knee osteoarthritis. Relevant pain and knee function improvement after bone marrow mesenchymal cell injection is documented with level 1 clinical evidence as concluded from a meta-analysis of 33 clinical studies with 724 patients. Also, two systematic reviews, one of them showed level 1 clinical evidence reviewing 17 clinical trials that include 767 patients with knee osteoarthritis treated with mesenchymal stem cells showed marked clinical and functional improvement (16, 17, 18). The current clinical trial confirmed, after 12 months of follow-up, the safety and efficacy of intra-articular bone marrow aspirate concentrate injection targeting treatment of early osteoarthritis, as shown in Table. 3 and Figure. 4, the total treated cases were 30 with 55 joints, two interventions were done 8-12 weeks apart, the mean cellular content was 1.8 x 10^9 mononuclear cells per 4 ml product injected to one joint the total joints injected in this study were 55 knee joints. The WOMAC score showed a significant statistical difference compared to the control group, which only used analgesics (p=0001).

Conclusions

Based on current evidence, the results of the current study suggest that MSC therapy effectively relieves pain and improves function in patients with Knee OA. It is also safe and has an excellent impact as a clinical therapy for patients with knee OA. However, before MSC therapy is applied in clinical practice, safety and efficacy must be evaluated using a more rigorous, more significant sample size validation. In addition, radiological and pathological proof should be ascertained.

DECLARATIONS

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Competing interests statement

No conflict of interest related with the publishing of this article.

Ethics statement

The author approved that this research follows the journal's Attach Ethic Approval guidelines as appeared on the journal's author guidelines page.

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