

Bone marrow stem cell therapy (bmscs) in treatment of osteoarthritis, a preliminary case series study

Abstract

Background: Osteoarthritis (OA) is a total joint disease with a hallmark of cartilage degenerative process, involving the immune system, producing local inflammatory reactions, mainly pro-inflammatory cytokines and metalloproteinases. No treatment still available to improve or reverse the disease process. Stem cell therapy opened new horizons for treatment of many incurable diseases. Among autologous somatic stem cells, bone marrow-derived mesenchymal stem cells (BMSCs) are widely used to repair mesenchymal tissues (bone and cartilage), Autologous BMSCs are thought to be safe with limited immunogenicity and disease transmission and effective because of their multi-lineage potential, immunosuppressive activities, so they attract attentions and encourage clinical use.

Aim: This study aimed to examine the effect of BMSCs transplantation on the clinical profile of OA of the knee joint using WOMAC Osteoarthritis Index. Our project was approved by the Hargeisa International Hospital (HIH), Medical Sciences Research Committee and Ethical Committee.

Patients and Methods: Forty patients with knee osteoarthritis were selected for this study, all of them were subjected to chondroprotective drugs and paracetamol 500 mg twice a day. Twenty patients of them undergo BMSCs (group I), and the other 20 patients act as a control group (group II). In group I, females represent 90% and ages ranged from 49 to 85 years, with mean + SD of 58+8, while in group II females represent 85% and ages ranged from 50 to 83 years, with mean + SD of 57+9. The two groups had mild to severe knee OA. After a signing a written consent, 20 to 30 ML of bone marrow was taken from upper medial tibial bone (2 cm above and medial to tibial tuberosity) and heparinized by 2000 IU of crystalline heparin, to prevent clotting and taking in consideration all safety measures including aseptic and antiseptic technique, 10 ml of bone marrow was injected in each knee of each patient.

Results: BMSCs was associated with significant clinical improvement, where mean total WOMAC score at 2, 4 and 6 months of patients post injection in group I showed significant improvement statistically ($p=0.015$, $p=0.011$ and $p=0.03$) in Pain, Stiffness, and Physical function of the patients joints respectively.

Conclusion: The use of BMSC in the treatment of osteoarthritis appears to have therapeutic value in patients with mild to severe OA of the knee as determined by responses from the WOMAC scale of osteoarthritis assessment.

Keywords: Mesenchymal stem cells, Osteoarthritis knee, WOMAC score, HAQDI, Regenerative therapy

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Abdou Ellabban

Professor of rheumatology, Minia University, Egypt

Correspondence: Abdou Ellabban, Professor of rheumatology, Minia University, Egypt, and Hargeisa International Hospital (HIH), Somaliland Email ellabbanabdou@gmail.com

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Introduction

Osteoarthritis of the knee is the most common form of arthritis that cause pain, stiffness, and decreased function, and one of leading causes of disability among non institutionalized adults.¹ It represent the most common joint disease in middle aged and older people and is among the most frequent and symptomatic health problems for this age demographic,² and characterized by the degeneration of the articular cartilage, leading to loss of matrix, fibrillation, formation of fissures, and ultimately the complete loss of the cartilage surface.³ To date, the common treatment focuses on alleviating the pain and thus allows the patient to move and reduces morbidity.⁴ More recently, pharmacological treatment with drugs such as chondroitin sulfate, even though they cannot reduce the symptoms quickly, has proven to have some structure-modifying effects on the disease area in the long term.⁵ Surgical methods used for repair of articular cartilage lesions

include autologous chondrocytes transplantation, micro fracture, and mosaicplasty. These techniques are, however, limited to the repair of focal defects and consequently we lack a reparative technique for the more global/diffuse pathology of OA.⁶ Stem cell therapy opened new horizons for treatment of many incurable diseases. Mesenchymal stem cells (MSCs) due to their multi-lineage potential, immunosuppressive activities, limited immunogenicity and relative ease of growth in culture, have attracted attentions for clinical use.⁷ Direct intra-articular injection of BMSCs would offer great advantages if it could be translated into clinical practice with the simplicity and ease of the injection that could provide better treatment opportunities, especially for the elderly with co-morbidity.⁸ Therefore, we conducted this preliminary case series study to assess the safety and the efficacy of intra-articular injection of autologous stem cells derived from bone marrow in patients with knee osteoarthritis.

Patients and methods

Forty patients with knee osteoarthritis were selected for this study; all of them were subjected to chondroprotective drugs and paracetamol 500 mg twice a day. Twenty patients of them undergo BMSCs (group I), and the other 20 patients act as a control group (group II). In group I, females represent 90% and ages ranged from 49 to 85 years, with mean + SD of 58+8, while in group II, females represent 85% and ages ranged from 50 to 83 years, with mean + SD of 57+9. The two groups had mild to severe knee OA. After a signing a written consent, 20 to 30 ML of bone marrow was taken from upper medial tibial bone (2 cm above and medial to tibial tuberosity) and heparinized by 2000 IU of crystalline heparin, to prevent clotting and taking in consideration all safety measures including aseptic and antiseptic technique, 10 ml of bone marrow was injected in each knee of each patient.

Clinical evaluation was assessed through physical examination and the validated WOMAC indices.⁹ performed prior to the treatment and at 2, 4 and 6 months post treatment.

Statistical analysis

The statistical analyses were performed with SPSS (SPSS Inc., Chicago, IL, USA) where the Comparisons of the VAS, and WOMAC scores between patients groups were made using the Mann-Whitney test as it is the most suitable descriptive and non-parametric test. A p value of less than 0.05 between groups was considered significant.

Results

This study included 40 patients treated between January 2016 and July 2016, at Hargeisa International Hospital (HIH), 5 male and 35 female divided into two groups, each group 20 patients (mean age in group I [treatment group] 58 ± 8 years and in group II [control group] 57 ± 9 years) who were diagnosed with Kellgren and Lawrence grades II to IV knee osteoarthritis. All selected patients had been poorly responsive to conservative treatment (physical and medical) for at least 6 months. No serious side effects occurred during 6 months of follow-up post treatment, apart from transient mild local pain and discomfort in the injected knee during the first 1 to 4 days occurred infrequently (10 % of patients) and was managed with increasing dose of paracetamol. Table 1 summarizes the Baseline characteristics of osteoarthritis participant's patients groups and disability indexes.

Table 1 Baseline characteristics of osteoarthritis participant's patients groups

Patients Characteristics	BMSCs (n = 20) Mean (SD)	Control (n = 20) Mean (SD)
Women, no. (%)	18 (90%)	17 (85%)
Age (years)	58 (8)	57 (9)
Body-mass index (kg/m ²)	37.1 (6.5)	36.7 (5.4)
Bone mineral density (g/cm ²)	1.023 (0.1)	1.065 (0.121)
Plasma glucose (mmol/L)	5.3 (1.2)	5.5 (0.5)
C-reactive protein (mg/L)	2.6 (2.3; 6.4)	3.2 (2.2; 6.8)
Health assessment questionnaire, score	0.9 (0.3; 0.8)	1.06 (0.2; 0.6)
WOMAC Index		
Total index (mm)	937.3 (446.5)	864.4 (564.5)
Pain (mm)	186.0 (74.0)	168.4 (113.6)
Function (mm)	683.7 (344.0)	582.1 (376.5)
Stiffness (mm)	76.3 (44.0)	73.5 (53.4)

We used The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) that is a measurement system for clinical assessment of knee OA assessing pain (5 questions,

0-20 points), stiffness (2 questions, 0-8 points) and joint functionality (17 questions, 0-68 points) Table 2.¹⁰ The initial mean value of Total WOMAC index (mm) was 937.3 and 864.4 in group I and 2 respectively, with the functional limitation dominating over pain then stiffness. Compared with the basal WOMAC score variables levels, improvement after BMSCs was significant, in the Pain, Stiffness, and Physical function of the patient's joints respectively. Mean total WOMAC score at 0 to 6 month follow-up were (p=0.015, p= 0.011 and p=0.03) in the Pain, Stiffness, and Physical functioning of the patients joints respectively are show in Table 3.

Table 2 Summarizes the clinical characteristics of the studied osteoarthritis patients groups after 6 months of follow-up

Patients Characteristics	BMSCs (group I) (n = 20) Mean (SD)	Control (group II) (n = 20) Mean (SD)
Women, no. (%)	18 (90%)	17 (85%)
Age (years)	59 (2)	58 (4)
Body-mass index (kg/m ²)	37.1 (6.5)	36.7 (5.4)
Bone mineral density (g/cm ²)	1.054 (0.110)	1.096 (0.166)
Plasma glucose (mmol/L)	5.6 (1.2)	5.4 (0.8)
C-reactive protein (mg/L)	3.4 (2.4; 6.2)	3.6 (2.1; 7.6)
Health assessment questionnaire, (HAQ score)	0.49 (0.2; 0.9)	01.02 (0.3; 0.5)
WOMAC Index		
Total index (mm)	602.8 (377.4)	749.2 (492.1)
Pain (mm)	89 (57.1)	170.5 (115.7)
Function (mm)	431.2 (294.4)	496.5 (324.6)
Stiffness (mm)	34.1 (43.8)	64.9 (47.8)

Table 3 Change in WOMAC index (clinical outcome) and HAQ score from baseline to 6 months in knee OA patients on stem cell therapy and control

Change in WOMAC Index	BMSCs (n = 20) Mean (SD)	Control (n = 20) Mean (SD)	P value
HAQ score	0.49	1.02	0.001
Δ Total index (mm)	-334.5 (69.1)	-115.2 (72.4)	0.005
Δ Pain (mm)	-97.0 (16.9)	-29.7 (19.6)	0.015
Δ Function (mm)	-252.5 (49.6)	-85.6 (51.9)	0.03
Δ Stiffness (mm)	-42.5 (7.2)	-10.2 (7.4)	0.011

Discussion

Osteoarthritis is a progressive disorder of the joints caused by gradual loss of articular cartilage, which naturally possesses a limited regenerative capacity. In the present study, the potential therapeutic value of intra-articular injection of bone marrow mesenchymal stem cells (BMSCs) has been evaluated for six months in 20 osteoarthritic patients and 20 controls. During this 6 months follow-up period - comparison of the change in WOMAC index (clinical outcome) and HAQ from baseline to six months post- bone marrow stem cell injection displayed improvement in WOMAC clinical parameters including pain and stiffness and functional ability in addition to improvement in Health Assessment Questionnaire (HAQ score), this is in consistent with the proof-of-concept trial reached its predetermined primary outcomes, that is, intra-articular injection of BMSCs into osteoarthritic knee was not associated with apparent adverse events, but improved function of the knee measured with WOMAC over 6 months of follow-up. Patients in the high-dose group demonstrated significantly improved WOMAC score with a clinically meaningful pain reduction which is approximately 30% from the baseline.^{9,11} Similarly *et al.*¹² in 2015 stated that the use of allogeneic bone marrow MSCs in symptomatic osteoarthritis that was unresponsive to conservative management, has resulted in both pain and functional improvement and significant improvements in cartilage

quality on T2 MRI cartilage mapping at 12 months in comparison to controls.¹²

Haq score interpretation

The total HAQ score reduced significantly in the osteoarthritis treated group with BMSCs than the control group where the HAQ score means was 0.49 and 1.02 in the two groups respectively with $p < 0.001$. As the total HAQ score is between 0-3.0, and increasing scores indicate worse functioning with 0 indicating no functional impairment and 3 indicating complete impairment. Analyzing nearly 9,000 patients with RA, those identified as independent had a mean \pm SD HAQ score of 0.38 ± 0.45 . Similarly, those very satisfied with their health had a score of 0.42 ± 0.53 .¹³ The pro-inflammatory cytokines involved in the destruction of hyaline cartilage and development of degenerative osteoarthritis has also highlighted the potential of MSCs as a disease modifying agent due to their immunomodulatory/anti-inflammatory properties.¹³ An ability to migrate to sites of injury, inhibit pro-inflammatory pathways and promote tissue repair through release of anabolic cytokines and direct differentiation into an array of specialized connective tissue cells, has led to renewed focus on MSCs in the area of regenerative medicine.¹⁴ We believe that the outcomes obtained from this case series study support the research studies suggesting that intra-articular injection of bone marrow stem cells play an important role in the therapeutic approach of OA.

Conclusion

The use of BMSCs in the treatment of osteoarthritis appears to have therapeutic value in patients with mild to severe OA of the knee as determined by responses from the WOMAC scale and HAQDI score of osteoarthritis assessment.

Acknowledgments

None.

Conflicts of interest

None.

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