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Effect of administration of mesenchymal stem cells on cartilage recovery and knee function in patients with Knee Osteoarthritis

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ABSTRACT

Background: Osteoarthritis (OA) is a chronic joint disease characterized by degenerative changes of articular cartilage and secondary bone hyperplasia. Because articular cartilage has a specific structure, such as the absence of blood vessels and the low rate of chondrocyte transformation in the cartilage matrix, treatment presents several clinical challenges. So, the aim of study was to evaluate the effect of mesenchymal stem cell administration on cartilage repair and knee function in patients with knee osteoarthritis. *Materials & Methods:* In this randomized clinical trial, 20 patients with knee osteoarthritis in Imam Hussein Hospital in 2017 were selected and randomly divided to the experimental and control groups. Functional improvement (According to WOMAC), pain relief (according to VAS), and meniscus degeneration (according to MRI) were determined and compared between the studied groups. *Results:* Functional improvement (According to WOMAC) (P= 0.034), pain relief (according to VAS) (P= 0.049), and meniscus degeneration (P= 0.02) were significantly better in the experimental group than the control. *Conclusions:* According to the obtained results, it can be concluded that administration of mesenchyme stem cells has an acceptable effectiveness on cartilage recovery, knee function, and pain relief in patient with knee osteoarthritis.

Keywords: Stem cells; Knee; Osteoarthritis, MSCs, cartilage, meniscus.

1. INTRODUCTION

Osteoarthritis (OA) or arthritis is a degenerative rheumatic diseases which is characterized by the mechanical and enzymatic degradation of the extracellular matrix and thereby degeneration of articular cartilage (Man and Mologhianu, 2014 and Poitras et al., 2007). In this disease, the immune system function causes local inflammation and tissue destruction by producing pro-inflammatory cytokines and metalloproteinase enzymes (Davatchi et al., 2011). Being the most common articular disease, prevalence of OA is even more than that of cardiovascular diseases and diabetes (Brouwer et al., 2006). OA usually affects one-third of adults and its prevalence increases with age (Bjordal et al., 2007) and weight (Poitras et al., 2007). Studies have shown that knee OA occurs in 13-30% of people aged over 65 and it is one of the common causes of disability in adults.It has also been shown that OA will be the fourth debilitating disease by 2020 (Baker K et al., 2007 and Wang AT et al., 2019). Treatment of knee osteoarthritis includes pain reduction and correction of deformities in the knee. High tibial osteotomy surgery, arthroplasty, and arthrodesis are also other treatments used in advanced cases of the disease, although they are followed by high risks and complications (Chuang et al., 2007 and Heidari, 2011). Drug therapy such as the use of NSAID's itself can interfere with the synthesis of articular cartilage and generally have a lot of complications (Steinmeyer et al., 2018). Although intra-articular administration may relieve pain for a while, they must be constantly repeated which can have their own side effects (Jones et al., 2019).

Although it is possible to treat internal osteoarthritis with surgery, but it should be noted that in many cases surgery is not suitable for various reasons such as old age. In addition, the surgeries that aim to transfer the body load to somewhere out of the knee would pose many problems in arthroplasty surgery in the future (Sutton and Holloway, 2013). Therefore, it can be concluded that currently there is no scientifically-proved definite and proper treatment for knee osteoarthritis. The cartilaginous parts and meniscuses, due to their important roles, are constantly vulnerable to damage and erosion and any damage to them would finally lead to articular injuries and osteoarthritis (Angele et al., 2008). Currently, recent advances have highlighted the potential of stem cell-based therapy in the treatment of OA patients. Today, it has been well shown that, in proper conditions, stem cells can change into various types of cells such as osteogenic or chondrogenic cells (Evans, 2013 and Harrell CR et al., 2019). Among stem cells, due to their differentiation capacity in chondrocytes and immune system features, mesenchymal stem cells (MSCs) have been studied as new therapeutic drugs in OA stem cells. Simple acquisition, rapid proliferation, preservation of differentiation potential after repeated passages in vitro, partial immunologic rejection, efficient transplantation and long-term coexistence in the host are key features of MSC that make their therapeutic use possible in OA (Maryam et al., 2019 and Maryam et al., 2017).

Various studies have been performed on the effect of MSCs stem cells on osteoarthritis, for example the results of a review study by Wolfstadt *et al.* (2015) in Canada revealed that although administration of mesenchymal cells for the treatment of knee osteoarthritis has shown good efficacy in animal samples, yet there is no consensus about its effectiveness in humans and further studies are needed in this regard (Wolfstadt et al., 2015). In an intervention study conducted by Jo *et al.* (2014) in South Korea, 18 patients with knee osteoarthritis were studied and it was observed that administration of stem cells in these patients resulted in significant improvement in WOMAC score and existing imaging findings and also significant reduction in cartilaginous degeneration (Jo et al., 2014). Uth *et al.* (2014) stated that administration of stem cells, as a novel method, has a good effectiveness in the treatment of knee osteoarthritis and its side effects are negligible. Improvement in the process of cartilage genesis in the affected joints was mentioned as the mechanism of this treatment (Uth and Trifonov, 2014). Considering the above, feasibility studies for

reconstruction of damaged cartilage and meniscus in OA patients seems necessary. Because our information on this issue is limited and most previous studied have been conducted in laboratories, the present paper aims to study the effect of mesenchymal cells administration on the regeneration of meniscuses in patients with knee osteoarthritis.

2. MATERIALS & METHODS

Study population

A clinical trial was conducted on 20 patients, aged 40-60, with knee osteoarthritis grade III and II in Imam Hussein Hospitals, Iran in 2017. Osteoarthritis in the subjects was confirmed by radiography and MRI. Patients with an articular cartilage lesion in the knee caused by trauma or osteochondritis dissecans of the knee were enrolled in this study and they were divided into experimental and control groups. Patients in the control group were not treated with MSCs. Exclusion criteria were previous surgical treatment for anterior and/or posterior cruciate ligament reconstruction, cancer, pregnancy, deviation of the knee, knee inflammatory diseases such as RA, previous traumatic knee injury, and autoimmune diseases. In the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsink and the process of trial was fully explained to the subjects and then their consensus was given in writing.

Bone marrow MSCs preparation

At one stage, 80 cc fat was suctioned from the abdominal fat of the subjects and was sent to Cleanroom for extraction of mesenchymal stem cells. After culturing the cells, when the mesenchymal stem cells reached 50 million and were free of any infection, they were administered into the knee of subjects from the super-lateral portable. The next day, administration was done for active room and full weight-bearing subjects. Then, the subjects were returned to their routine life and asked to avoid taking any painkillers or anti-inflammatories and physiotherapy.

Evaluation of patients

Subjects were examined for signs of inflammation once. Pain change trend and activity of them were recorded in VAS and WOMAC scores. After 6 months, this was repeated again and an AP and lateral standing radiography was prepared. VAS and WOMAC scores obtained after 6 months were compared with the initial figures. Additionally, variations in radiographies were recorded in order to find that whether mesenchymal stem cells are effective in the improvement of the knee cartilage regeneration and pain relief or not.

Statistical analysis

Data analysis was performed using SPSS 18 software. Frequency and frequency percentage for qualitative variables and mean and standard deviation for quantitative variables were calculated. The results were interpreted at a significance level of 0.05.

Ethical considerations

This article has been approved with code M430.SUMS by the Ethics Committee of Semnan University of Medical Sciences.

3. RESULTS

A total of 40 subjects participated in this study who were equally divided into two groups of experimental and control. Mean and standard deviation of age in the control and experimental groups were equal to 49.1±6.9 and 50.6±7.1, respectively. Number of men and women was equal to 6 (30%) and 14 (70%) in the control group and 8 (40%) and 12 (60%) in the experimental group. There was no significant difference between experimental and control groups in terms of age and gender (P>0.05). Table 1 shows the frequency distribution of improvement in the function of the subjects in both studied groups. Based on WOMAC scores, improvement in the function of subjects in the experimental group was significantly higher than the control (P=0.034).

Table 1 Frequency distribution of improvement in the function of the subjects in both studied groups

WOMAC Improvement				
Group	<25% (N/%)	26-50% (N/%)	51-75% (N/%)	>75% (N/%)
Control	2(10)	7(35)	11(55)	0(0)
Experimental	0(0)	3(15)	12(600	5(25)

Table 2 presents the frequency distribution of VAS improvement in both studied groups. Based on VAS scores, pain relief improvement in the experimental group was significantly higher than the control (P=0.049).

Table 2 Frequency distribution of VAS improvement in both studied groups

VAS Improvement				
Group	<25% (N/%)	26-50%(N/%)	51-75%(N/%)	>75%(N/%)
Control	1(5)	9(45)	6(30)	4(20)
Experimental	0(0)	2(10)	12(60)	6(0)

The frequency distribution of meniscus degeneration improvement in both studied groups is given in Table 3 and figure 1-3. Based on MRI results, meniscus degeneration improvement in the experimental group was significantly higher than the control (P=0.02).

Table 3 Frequency distribution of meniscus degeneration improvement in both studied groups

Meniscus Degeneration			
Group	Improved (N/%)	No change (N/%)	Worsened (N/%)
Control	1(5)	12(60)	7(35)
Experimental	11(55)	7(35)	2(10)

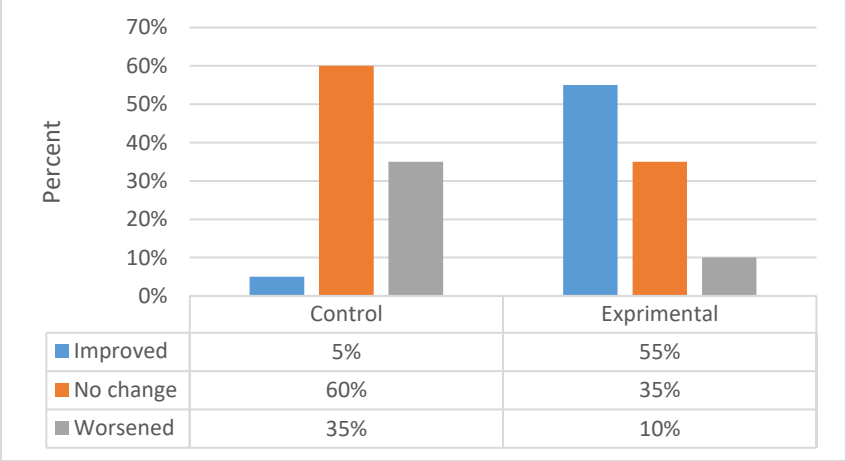

Figure 1 Frequency distribution of meniscus degeneration improvement

Figure 2 MRI images of OA patients before Intervention

Figure 3 MRI images of OA patients after Intervention

4. DISCUSSION

OA is a degenerative and inflammatory joint disease (Maryam et al., 2019). Articular cartilage lesions in the knee can cause pain and swelling, and increase the risk of osteoarthritis (Hashimoto et al., 2019). Traditional pharmacological treatments, non-pharmacological treatments and surgical procedures can only offer symptomatic benefits, whereas the damaged cartilages currently cannot be effectively repaired. With the advance in regenerative medicine, MSCs have emerged as an alternative cellular therapy for the treatment of knee OA (Maryam et al., 2019). Because of their ability to differentiate into various types, immunosuppressant activities, limited stimulation of the immune system, and easy culture, mesenchymal stem cells could have broad applications (Wang et al., 2018). Conduction of studies on the feasibility of rebuilding the damaged and worn meniscuses seems necessary, since our information on this issue is limited and most previous studied have been conducted in laboratories. Hence, the present paper aimed to study the effect of mesenchymal cells administration on the degeneration of meniscuses in patients with knee osteoarthritis.

Our results showed that improvement in the function of patients in terms of WOMAC was significantly higher in the experimental group than the control. The experimental group also showed a significantly better improvement in pain relief based on VAS. In addition, meniscus degeneration based on MRI result was again significantly better in the experimental group than the control. Various researches have been done on the mechanism of MSC in the treatment of OA. One of the important therapeutic mechanisms of MSCs is its immunomodulatory effects against OA. Inflammatory factors can activate MSCs, then MSCs secrete PGE2, IDO, NO and other factors and can subsequently suppress immune cells directly or indirectly. Moreover, recent researches have enhanced our knowledge of paracrine signaling by MSCs by secreting biologically active molecules that may be more important than differentiated cells in stimulating repair responses, thus effectively increasing the range of therapeutic applications of MSCs (Kong et al., 2017). A study has shown that mature chondrocytes and secretion of cytokines can enhance the differentiation of mesenchymal stem cells into chondrocytes. Meanwhile, cytokines secreted by MSCs can also elevate chondrocyte proliferation and ECM matrix synthesis, which can cause bone and cartilage repair (Mamidi et al., 2016). Barry et al. also suggested that endogenous MSCs help maintain healthy tissue by acting as a reservoir for cell repair or as immune preservatives to reduce inflammation. However, they stated that paracrine signaling by MSCs may be more important than differentiation in stimulating repair responses. In other words, MSC does not specifically work to replace damaged cartilage, but rather coordinates and strengthens this repair response (Barry and Murphy, 2013).

Clinical outcome and efficacy of MSC therapies are mainly measured by qualitative tests and questionnaires including the use of; the Visual Analogue Scale (VAS), Knee injury and Osteoarthritis Outcome Scores (KOOS), The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and International Knee Documentation Committee Questionnaire (IKDC) (Hudetz et al., 2017). Many preclinical studies have investigated the use of MSCs from different sources for the treatment if knee OA. In a study by Jo *et al.* (2014) observed a significant reduction in WOMAC score, pain (VAS core), and cartilage repair (MRI). They also found that the greater the number of stem cells administration is, the higher recovery the results would show (Jo et al., 2014). The same result was found in the present study, but the amount of administered stem cells as an effective factor was not measured due to the limitations. Also, in the study conducted by Orozco *et al.* (2013) on 12 patients with knee osteoarthritis who had not responded to

other treatments, functional recovery was observed in 65-78% of patients and the quality of knee cartilage significantly improved (Orozco et al., 2013). This confirms the findings of the present study. Emadeldin *et al.* (2012) conducted a one-year trial on the treatment with stem cells administration in 6 patients with knee osteoarthritis. Their results indicated that cartilaginous degeneration, according to MRI method, showed a significant decrease. In addition, improve functional trend and reduced pain were also observed in patients (Emadedin et al., 2012). Although duration of trial was shorter in the present study (6 months), these positive effects were found. In review study by Gupta *et al.* (2012), it was revealed that stem cells administration not only slows down the process of cartilaginous degeneration in patients with knee osteoarthritis but also causes the recovery of damaged knee cartilages, functional recovery, and pain relief (Gupta et al., 2012). These results are consistent with the findings of the present study.

In another study Dovatchi et al. reviewed the original report of intra-articular injection of autologous bone marrow-derived MSCs in patients with knee OA. They reported a 5-year follow-up study with 3 patients. In thier study, the beneficial effect of injectable MSCs began to decrease after 6 months and relatively good functional recovery and motor range but intensified pain in 3 patients were observed after administration. However, clinical outcomes at 5 years were still better than baseline, and there were no patients undergoing knee arthroplasty. In the present study, overall recovery in different items was relatively good. Wakitani et al. used autologous human culture and expanded bone marrow-derived MSCs to repair cartilage defects in the osteoarthritic knees. Their results showed that patients treated with bone marrow stem cells had higher arthroscopic and histological scores than the control group, while no significant clinical progress. This study demonstrated the potential of using MSC treatment for cartilage repair and reduction of arthritis symptoms through the immunomodulatory effects of MSCs (Wakitani et al., 2002).

Generally, without effective treatment, OA is an important clinical strain in our elderly. The development of regenerative drugs and innovative stem cell technologies is a unique opportunity to treat the disease. Although the use of MSCs in articular repair has been well established, there is still excitement about MSCs being used to treat OA. Despite the early concerns of many researchers about mesenchymal stem cell therapy, the results of this clinical trial and other research indicate that MSCs are relatively safe for intravascular and intra-articular injection. Finally, although this study shows promising therapeutic effects, their long-term therapeutic effects should be further investigated. Furthermore, it is recommended that further studies to be carried out on more number of patients in order to confirm the findings of the present study. Additionally, comparison of effectiveness of mesenchymal stem cells administration with other therapeutic methods in the treatment of knee osteoarthritis can be an interesting area of research for future studies.

5. CONCLUSION

According to the obtained results, it can be concluded that administration of mesenchymal stem cells has an acceptable effectiveness on cartilage recovery, knee function, and pain relief in patient with knee osteoarthritis. Therefore, this treatment can be recommended in this group of patients and also further research with a higher sample size is recommended.

List of abbreviations

OA:	Osteoarthritis
WOMAC:	Western Ontario and McMaster Universities Osteoarthritis Index
VAS:	Visual analogue scale
MSCs:	Mesenchymal stem cells
NSAIDs:	Nonsteroidal anti-inflammatory drugs
MRI:	Magnetic resonance imaging
PGE2:	Prostaglandin E2
IDO:	Indoleamine 2,3-dioxygenase
NO:	Nitric oxide
ECM:	Extracellular matrix
IKDC:	International Knee Documentation Committee Questionnaire

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Conflicts of Interest:
The authors declare no conflict of interest.

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