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Role of bone marrow-derived mesenchymal stem cells in treatment avascular necrosis of femoral head

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Abstract

Avascular necrosis (AVN) of the femoral head (FH) is a debilitating and painful disease with multiple etiologic risk factors head shows an increasing tendency and most commonly affects younger or middle-aged adults. Fifty patients (55 hips) with stage I, II or III avascular necrosis of femoral head were treated by autologous Bone marrow-derived mesenchymal stem cells injection. The patients were followed up clinically and radiologically for a minimum of 2 years at baseline, three, six, 12, and 24 months. The functional outcome was assessed in terms of Harris hip score, and disease progression was assessed radiologically by comparing the preoperative and follow-up MRI at the end of 2 years. On 2-year follow-up, there was considerable improvement in the hip function as measured by the Harris hip score ($p = 0.041$). On MRI, there was a decrease in the size of the lesion in group A ($p = 0.03$). Our findings showed that autologous Bone marrow-derived mesenchymal stem cells in avascular necrosis of femoral head is a safe and effective procedure and has better outcome.

Keywords: Avascular necrosis; Stem cell therapy; Bone marrow-derived mesenchymal stem cells

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Introduction

Avascular necrosis (AVN) of the femoral head (FH) is a debilitating and painful disease with multiple etiologic risk factors head shows an increasing tendency and most commonly affects younger or middle-aged adults. It is estimated that approximately 30 million patients suffer from (AVN) around the world [1]. The mainly causative factors for AVN are idiopathic, trauma, use of glucocorticoids, alcohol abuse, hemoglobinopathy Gaucher's disease and coagulopathies [2].

Disease progression commonly leads to collapse of the affected FH and ultimately, development of osteoarthritis [3]. As a result, there has been an increased focus on early interventions for AVN, aimed at preservation of the native articulation [4]. Core decompression (CD) is currently the most widely accepted treatment for early-stage AVN of the FH; however, due to limited efficacy, its use has been debated [5].

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The development of safe, cost-effective, and potentially minimally invasive joint preserving treatments for early stage (precollapse) AVN merits further investigation [6].

Classification Systems

Multiple classification systems have been developed for AVN, most commonly used systems: Ficat and Arlet, University of Pennsylvania/Steinberg, Association Research Circulation Osseous (ARCO), and the Japanese Orthopaedic Association [7]. The Ficat and Arlet classification system was first developed in the 1960s and is based on clinical symptoms, radiographic findings, and uptake on bone scan [8]. It is the most used classification system as well as the most straightforward but does not account for size or location of the osteonecrotic lesion, which are now considered important factors predicting treatment outcomes [9].

Stage 0 is preclinical, with no findings on imaging expect for reduced uptake on bone scan. Stage I is preradiographic, with clinical symptoms and increased uptake on bone scan. Stage II involves sclerotic or cystic changes on radiographs without femoral head flattening or crescent sign. Stage III involves the radiographic crescent sign with preserved joint space, whereas stage IV is defined as femoral head flattening and arthritic changes of the hip joint [10].

The University of Pennsylvania/Steinberg classification system was developed in the 1980s and incorporates MRI findings as well as size and articular involvement of the osteonecrotic lesion [11]. As with the Ficat and Arlet system, stage 0 is normal or nondiagnostic imaging. Stage I is normal radiographs with abnormal MRI and/or bone scan, with a subclassification of A, B, or C based on the percentage of femoral head affected by the lesion [12].

Stage II involves cystic or sclerotic changes in the femoral head, also subclassified by percentage of femoral head involved. Stage III involves a crescent sign without flattening of the femoral head, subclassified by percentage of articular surface involvement. Stage IV involves flattening of the femoral head that is subclassified by percentage of femoral head surface involvement and millimeters of depression [13].

Stage V involves joint-space narrowing or acetabular changes, subclassified into mild, moderate, and severe. Stage VI is defined as advanced degenerative radiographic changes [14]. The ARCO classification system was developed in the early 1990s based on the University of Pennsylvania system but with additional 4 subclassifications to reflect location of the lesion, percentage of femoral head involvement, length of crescent, and percentage of collapse [15]. There are 5 total stages:

- 0 (normal imaging findings)
- I (positive findings on bone scan or MRI)
- II (abnormal radiographic findings with sclerotic and/or cystic changes with abnormal MRI, CT, and/or bone scan findings)

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Patients and methods

The study was conducted in two centers fifty patients (55 hips) with stage I, II or III avascular necrosis of femoral head were treated by autologous Bone marrow-derived mesenchymal stem cells injection.

Patients were assessed at baseline, three, six, 12, and 24 months. Patients' assessments of pain included a visual analogue scale (VAS) from 0 mm (no pain) to 100 mm (severe pain). Symptoms were also assessed by the subscales A and B (both dedicated to the hip status) of the WOMAC score. In the case of hip bilateral involvement, patients were asked to complete a separate questionnaire for each hip.

During each visit, safety was assessed by recording adverse events and serious adverse events. The decision to possibly turn to THR when the treatment had been insufficient in controlling pain and/or disability, was discussed with the patient at the end of each assessment session. The final decision was taken according to the patient's own wishes.

Radiological evaluation

Anteroposterior and frog leg view weight-bearing radiographs and an MRI study were taken at baseline, three, six, 12, 18, and 24 months. Radiological progression of AVN was measured by reference to the ARCO staging [16-18] figure 1. For location and quantification of ON lesion, the ARCO subclassifications were used. The surface collapse extension was, after selection of the most prominent view, expressed as a percentage of the entire articular surface: A = < 15% involvement, B = 15–30% involvement, C = > 30% involvement. The dome depression was expressed as A = a depression of less than 2 mm, B = 2–4 mm, and C = more than 4 mm. A single reader, unaware of the treatment assignments, analyzed all radiographs and MRI.

Statistical methods

Continuous variables were assessed using the Student's t-test and categorical variables were compared using the Fisher's exact test. Correlation between MRI changes was made with Spearman's rank correlation coefficient. Survivorship free from conversion to THA, any procedure, and femoral head collapse was made using the Kaplan-Meier method at the 2-year postoperative time points. Because this was a preliminary study and to capture all hips for failure in patients with bilateral disease, each hip was analyzed independently. Statistical significance was set at a p value of < 0.05.

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Results

Number	Initial AVN class	AVN etiology	Treatment protocol
534	ARCO 1-2	steroid	Concentrated BMMNC
50	ARCO 1-2	ethanol	Concentrated BMMNC
24	ARCO 1-2	idiopathic	Concentrated BMMNC
51	ARCO 1-2	trauma	Concentrated BMMNC
97	ARCO 1C-2C	more than one etiology	Concentrated BMMNC

ARCO = Association Research Circulation Osseous classification

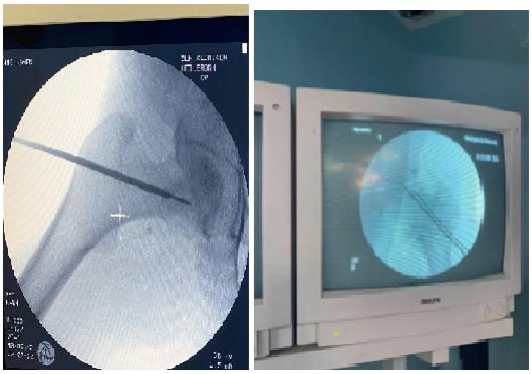

Figure 1.
Fluoroscopy screen for AVN.

This retrospectively study the electronic medical records and imaging of a consecutive series of patients who were treated by the supervising consultant for AVN of the femoral head over a two-year period.

Patients included had AVN of one or both hips that was graded to be stage I or II by the Ficat classification. All patients were treated with bone marrow-derived mesenchymal stem cells implantation from the iliac crest. Overall, 55 hips in 50 patients were included in the study. Demographic information on age, gender, body mass index and the etiology of AVN was collected and is shown in Table 1.

Staging of AVN as per the Ficat classification was determined by preoperative radiographs and magnetic resonance imaging (MRI). Patient's visual analogue pain scores (VAS) were recorded pre- and postoperatively on a scale of 0–10, with 10 being the worst pain. From the operative record, any concurrent procedure, including contralateral THA, subchondroplasty procedure,

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and hip arthroscopy, was noted. Statistical analysis of the data was performed using the Student's t-test.

Table 1.

Demographic information on age, gender, body mass index and the etiology of AVN

Demographics		
Age (years)	18–25	1 (5%)
	26–35	12 (63%)
	36–45	4 (21%)
	46–55	1 (5%)
	56–65	1 (5%)
Gender	Male	10 (53%)
	Female	9 (47%)
BMI	22–26	10 (53%)
	27–30	7 (36%)
	31–35	2 (11%)
Etiology		
Steroid use		19%
Alcohol		28%
Idiopathic		50%
Post-traumatic		9%
Symptom progression		
<30 days		12%
>30 days		88%
Comorbidities		
Hypertension		28%
Diabetes mellitus		26%
Metastatic CA		16%
Atrial fibrillation		8%

Data expressed as *n* (%) unless otherwise indicated.

Discussion

Avascular necrosis (AVN) of the femoral head is a progressive disease that is characterized by interruption of blood supply, necrosis of subchondral bone, and the eventual bone collapse of the femoral head, resulting in severe hip pain and dysfunction mainly in young patients [19]. Although total hip arthroplasty (THA) is the most effective treatment for patients with AVN in the terminal stages, the outcomes of THA in young adults or active populations are often not excellent, with a high failure rate caused by loosening of the prosthetic, excessive wear of

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polyethylene inserts, and peri-prosthetic infection [20]. Therefore, hip-preserving treatments for AVN has become a challenge in young patients.

Stem cells have been shown to have the ability to self-renew and to differentiate into multiple cell types [21]. Mesenchymal stem cells (MSCs) are one of the most frequently used stem cell subsets, which are widely distributed in various tissues, such as bone marrow, peripheral blood, fat, umbilical cord, etc. [22]. MSCs can differentiate into osteoblasts and endothelial cells to affect bone repair and angiogenesis [23] and can produce growth factors to promote the blood supply to necrotic regions by paracrine effects [24].

the pathogenesis of AVN is considered to be related to bone marrow-derived mesenchymal stem cells (BMSCs), including cell apoptosis, decrease in cell numbers, and decline in osteogenic differentiation potential [25]. Thus, stem cell therapy has become one of the hip-preserving alternatives for AVN.

It has been nearly 20 years since the first report of stem cell therapy for AVN [26]. With the rapid development of cell biotechnology and tissue engineering, stem cell therapy has shown promising results in the treatment of AVN. However, there still are many unresolved problems and challenges in stem cell therapy for AVN stemming from the lack of standardized procedures, optimal accumulation of cells, and systematic security assessment [27].

A variety of new therapeutic methods are derived from the classical core decompression combined with BMSCs transplantation. Platelet-rich plasma (PRP) is a platelet concentrate obtained after autologous blood centrifugation [28]. It contains a large number of growth factors and proteins. Martin used a minimally invasive decompression technique, then injected autologous BMSCs and PRP into the area of AVN.

As a result of other studies, 78% (60/77) of patients experienced significant pain relief and halted the progression of disease, and only 21% ultimately requiring total hip replacement [29]. In addition, BMSCs can be easily transfected with foreign genes and expressed them stability. BMSCs transfected with the target gene can be seeded with carriers of different materials and then implanted into the necrotic area of the femoral head for the treatment of AVN [30].

The combination of biotechnology, tissue engineering and gene transfection technology provides a new way for the treatment of AVN. Data published reported that in a rabbit model of AVN induced by core decompression and delivery of liquid nitrogen into the femoral head, implantation of BMSCs seeded bio-derived bone materials combined with recombinant bone morphogenetic protein 2 (rhBMP-2) into the femoral head resulted in normal bone repair, suggesting that transplantation of BMSCs transfected with the rhBMP-2 gene is an effective way to treat AVN [20].

Other researchers published data used expanded BMSCs in combination with biologically active scaffolds to repair bone defects and found that this method promoted the growth of new bone in the defect area, suggesting that BMSCs has the ability to repair bone defects. This method provides a new idea for the treatment of bone defects of end stage AVN [21]. In addition, the emergence of more new technologies such as nanotechnology and 3D printing

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technology has enriched the traditional treatment methods, and it may provide more and better choices for the treatment of femoral head necrosis [28].

Previous studies have shown a decreased concentration of BmMSCs in the proximal femur of patients with ON; as such, the addition of BmMSC, which contains osteogenic and angiogenic progenitor cells, was thought to be able to heal the avascular, necrotic regions of the femoral head [29].

Augmenting hip decompression with BmMSC was first described in 2002 after which multiple prospective randomized and retrospective studies comparing core decompression with decompression augmented with BmMSC have reported success with more patients in the BmMSC arm able to avoid THA [30].

The outcome of treatment is mixed with series also failing to demonstrate better results in the cell therapy arm, also Previous studies have not evaluated the combination of PRP and BmMSC [5]. The preliminary results of this prospective cohort study are comparable to previous reports in terms of hip preservation [9] and highlight the risk factors for progression in this group of patients with corticosteroid-induced on such as a high initial Kerboul angle and low BmMSC count and function [31].

The modified Kerboul angle has been shown to be associated with collapse of the femoral head in patients with ON. That study separated the patients into “low risk” and “high risk” for collapse based on the preoperative grade and randomized to nonoperative treatment or core decompression alone [32]. There was no difference in outcome between the operative and nonoperative groups and among the high-risk (modified Kerboul Grade 3 and 4) patients, 100% of patients collapsed, whereas only 29% of the low-risk patients (modified Kerboul Grade 1 and 2) progressed to collapse [33].

The results of our study are similar with 80% of patients classified as “high risk” undergoing an additional surgical procedure (THA or repeat decompression); however, no low-risk patients progressed to collapse. This study supports randomized trials showing an improvement in femoral head involvement after hip decompression augmented with cell therapy [34]. Further follow-up and repeat MRI at later intervals may show further improvements in femoral head involvement and are needed to determine whether the initial healing continues or halts.

Conclusion

AVN is a progressive disease with complex etiology and unclear pathogenesis and lacks optimal treatment, especially for young patients. With the development of biotechnology, stem cell therapy in AVN has become the focus of current research. This data summarized the current trends in Bone marrow-derived mesenchymal stem cells in AVN - for clinical application and showed that an increasing number of studies have confirmed the effectiveness of stem cell therapy in AVN.

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Competing interests

The authors declare no conflict of interest.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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