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Functional Outcome of Autologous Bone Marrow Concentrate Implantation in Osteonecrosis of Femoral Head: A Two Year Follow-up Study

Venus Khanna[1], **Madhan Jeyaraman**[2], **Shashank Goel**[3] **and Manish Khanna**[3*]

[1]*Department of Pathology, Hind Institute of Medical Sciences, Atria, Sitapur, India*

[2]*Department of Orthopaedics, School of Medical Sciences and Research, Sharda University, Delhi-NCR, India*

[3]*Department of Orthopaedics, Hind Institute of Medical Sciences, Safedabad, Barabanki, India*

[*]**Corresponding author:** Manish Khanna, Vastu Khand, Gomti Nagar, Uttar Pradesh, India, Tel: +91 83106 00785; E-mail: manishvenus@rediffmail.com

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Abstract

Background: Osteonecrosis of the femoral head is a progressive disease that generally affects patients in the third through fifth decades of life, if left untreated; it may lead to complete deterioration of the hip joint. The management of osteonecrosis of the femoral head differs with the stage of the disease and the activity. In this study, we tried to analyse clinically, radiologically and statistically the hips which received autologous bone marrow concentrate implantation along with core decompression.

Materials and methods: An observational study was conducted at department of Orthopaedics, Hind Institute of Medical Sciences, Safedabad, Barabanki, Uttar Pradesh from October 2015 to August 2018. The patients with radiological confirmation of stage I, II or early III without collapse of osteonecrosis of femoral head were treated with core decompression and autologous bone marrow concentrate implantation. All patients were assessed clinically and radiologically for duration of 2 years.

Results: A total of 10 patients and 13 hips were analysed with follow up period of 2 years to analyze the functional recovery with modified Harris hip score. We observed excellent results (mHHS ≥ 90) in 9 (69.2%) hips, good results (mHHS 80-89) in 2 (15.4%) hips, no improvement in 1 hip (7.7%) and 1 hip (7.7%) worsened at the end of 24 months. Radiographically, the hips showed no significant changes at the end of 6 months and increased sclerosis and mild hypertrophy at the margins of the femoral head at the end of 12 months. At 24 months, in 7 cases the femoral head slightly hypertrophied at the margins and assuming a slight 'Umbrella' shaped appearance. We reported no significant increase in pain in these seven hips after one year. The correlation analysis with Pearson's correlation coefficient (r) was 0.81 which show highly positive correlation between BMAC and avascular necrosis of head of femur. There was a statistical significant difference between BMAC and avascular necrosis of head of femur ($p<0.001$) at the end of 2 year follow up.

Conclusion: We conclude that autologous bone marrow concentrate implantation has a definitive and positive role towards the regeneration of head of femur in stage I, II and early III without collapse of osteonecrosis of femoral head.

Keywords: Osteonecrosis femoral head; Core decompression; Autologous bone marrow concentrate

Introduction

Osteonecrosis of the femoral head is a progressive disease that generally affects patients in the third through fifth decades of life; if left untreated, it may lead to complete deterioration of the hip joint [1]. Several theories on the pathogenesis of osteonecrosis have been proposed. Hypotheses include direct cellular toxicity, coagulopathic states, hyperlipidaemia with fat emboli, vascular interruptions or abnormalities, and elevated bone marrow pressure [2]. None of these theories can fully explain the entire pathology. Most patients with the above-mentioned risk factors never develop osteonecrosis, and many patients without identifiable risk factors may acquire the disease.

The collapse of the necrotic region of the femoral head results in loss in joint congruity thus there occur degenerative changes in hip joint. Usually the etiology of AVN is associated with multiple factors especially in younger individuals. Idiopathic osteonecrosis are those cases where the cause cannot be find out (and it account to be approximate 20%).

Risk factors like long term used of corticosteroids in various medical conditions, long term consumption of alcohol in excess, smoking are well established cause contributing to AVN.2 Recently, have been seen that organ transplantation such as Liver, renal, heart and infection with human immunodeficiency virus are the conditions where chances of development of AVN are there [3-5]. Not only these various auto immune diseases, condition like Gauchers disease, trauma especially dislocation hip, fracture neck femur are conditions where osteonecrosis of hip (unilateral/bilateral) is a common outcome seen [3].

Although several studies of various treatment modalities have been reported during the past decade, osteonecrosis of the femoral head remains a therapeutic challenge. Reports have described that 70% to 90% of osteonecrosis of the femoral head will collapse within a five year period, and consequently undergo arthroplasty suggesting that conservative treatment procedures should be instituted early. However, till date, no prophylactic management has been completely successful. Because of the young age of many of these patients, hip replacement cannot be expected to last the patient's lifetime and therefore attempts should be made to save the femoral head prior to collapse with the use of less invasive procedures. So far, the efficacy of joint preserving surgeries like core decompression for early stage osteonecrosis has been variable and is still controversial [6].

The pathogenesis of osteonecrosis is still unclear but it can be seen as a vascular and bone disease. On one hand, the function of the capillaries serving as a conduit for the stem cells and bone cells needed in the bone remodeling unit and providing blood supply could be altered by emboli or thrombosis [7]. On the other hand, mesenchymal stem cells and osteoblasts that could potentially induce bone formation have been shown to be decreased in number and activity. Moreover, osteocytes and bone lining cells in the necrotic lesion and the proximal femur undergo apoptosis. This altered bone remodeling can be responsible for three different events in the pathogenesis of osteonecrosis; the appearance of osteonecrosis itself, the insufficient bone repair that occurs after osteonecrosis and its evolution to the subchondral fracture [8-9]. Such pathophysiological approaches used in managing AVN hip by placing bone marrow concentrate in the necrotic head region have raised a lot of clinical interest in recent times.

We have previously experienced in many cases poor outcome from the core decompression technique as described by Ficat et al done alone so we at our medical institute had started adding up bone marrow concentrate in the core decompressed site form Oct 2015. By August 2016, 13 patients (17 hips) had been operated on with this technique. Out of these 13 patients, 10 patients or 13 hips are the basis of the current study.

Materials and Methods

Study design

This observational study was being initiated at dept of Orthopaedics, Hind Institute of Medical Sciences, Safedabad, Barabanki, and Uttar Pradesh from October 2015 to August 2018. Ethical approval was being obtained as per ICMR guidelines (Helsinki Declaration of 1975, as revised in 2008) for the study. Patients were considered eligible for enrolling in the study if they were symptomatic, above 18 years of age, with radiological confirmation of stage I, II or early III without collapse (according to Ficat and Arlet Classification) osteonecrosis of femoral head which were further confirmed by MRI scan. Those patients were selected who have no previous history of any invasive/minimally invasive procedures done in the involved hip, who were further mentally alert as well and medically fit also for the surgery. All of these patients were operated from October 2015 to August 2016.

The selected patients were also subjected to thorough pre-surgical clinical, functional and radiological assessment according to routine protocol for the surgical management of osteonecrosis head of femur. We had also obtained informed written consent from the patients after explaining the procedure and the risks. Patients having age above 60 years, traumatic etiology, Ficat and Arlet stage late III (with collapse of head) and above, patients with any active infection, malignant disease during the past 5 years, mentally unsound patients, patients with neuro-vascular involvement were excluded from the study. We have further excluded those patients who were also lost during follow up in two years.

Patientships were subjected to core decompression plus autologous bone marrow cell concentrate implantation and were further followed up for next 2 years to assess the functional outcome and any related complications. Post-operatively all the patients were kept non weight bearing for five to six weeks, partial weight bearing for the next two to three weeks and then full weight bearing was being allowed at seven to eight weeks post operatively. Primary outcome were measured in all these cases based on comparison between pre-operative and post-operative Modified Harris Hip Score (mHHS) and hip radiographs were further taken at interval of 6 months, 12 months and 24 months.

Operative technique

Marrow aspiration: Posterior superior iliac spine which is the most favourable site for aspiration was being used under spinal anaesthesia for aspirating bone marrow. Jamshedi needle was being inserted into the spongy bone of PSIS, a 20 ml of disposable plastic syringe was being further connected to it and then bone marrow was aspirated. To reduce the degree of dilution with peripheral blood small fractions of bone marrow was being aspirated each time. Aspirated bone marrow is then collected in the sterile plastic blood bags. With same skin opening several perforations are being made into the iliac crest for aspiration of the bone marrow from multiple sites [10-12].

Bone marrow concentration: The Cold Centifuge is being used for concentrating aspirated bone marrow for separating the mononuclear cell (MNC) layer containing the stemcells. The aspirated bone marrow is centrifuged at 1200 rpm for about 10 mins. Thus a 150 ml bone marrow aspirate is reduced to approximately 8 ml of MNC cocktail. The quantification of cell population in the MNC cocktail by Flowcytometry was done and finally this ready suspension was poured into a syringe for reinjection [10-12].

Core decompression and implanting the bone marrow concentrate: After placing patient on fracture table with image intensifier in position, the core decompression was being done (with a percutaneous approach or open method depending upon the case and the site, size of lesion. The instrument used during surgery where the same as used in conventional core decompression procedure. The position of the necrotic lesions was checked using C arm. The MNC cocktail obtained in a syringe was poured on bone-graft to soak the graft and these soaked bone grafts were placed in the core decompressed site. The remaining concentrate is also later injected into the decompressed site using a small trocar. Wound is closed with regular dressings done in post-operative periods.

Statistical Analysis

The descriptive statistics were reported as mean (SD) for continuous variables, frequencies (percentage) for categorical variables. Data were statistically evaluated with IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Chicago, IL. The chi square test was performed to assess the association between AVN of head of femur and BMAC. Pearson correlation coefficient was performed to observe the correlation between AVN of head of femur and BMAC.

Results

A total of 13 patients and 17 hips with osteonecrosis of head of femur underwent core decompression and bone marrow concentrate implantation. Out of 13 patients 3 were lost in follow-up, hence, total of 10 patients and 13 hips were included in the study with follow up period of 2 years to analyze the functional recovery. The age of patients ranged from 25-49 years with mean (± SE) 39.17 ± 1.71 years. There were 3 (30.00%) females and 7 (70.00%) males. Out of 10 patients, 7 (70.00%) had unilateral involvement and 3 (30.00%) had bilateral involvement. The etiology of most of the patients were idiopathic in 6 patients (60.00%) followed by history of steroid intake in 3 patients (30.00%), and prolong alcohol intake history in 1 patient (10.00%). In our study out of 13 hips, we observed that 3 (23.10%) hips were in stage I, 7 (53.80%) were in stage II and 3 (23.10%) were in stage III (early) according to Ficat and Arlet staging.

The significant pain relief were reported in 11 hips (84.6%), 1 (7.7%) hip reported little or no pain relief, while 1 hip (7.7%) progressed to stage IV and was treated with total hip arthroplasty at a later stage. In our present study, we observed that all the patients had pre-op mHHS<70 (poor) with mean score of 67.22 ± 2.79. Further, we obtained excellent results (mHHS ≥ 90) in 9 (69.2%) hips, good results (mHHS 80-89) in 2 (15.4%) hips, no improvement in 1 hip (7.7%) and 1 hip (7.7%) worsened at the end of 24 months. The two hips without any improvement/worsening were observed to be of stage III. The mean mHHS at the follow-ups were tabulated below in Table 1. No significant complications in any patients were observed.

Period	Mean mHHS ± SE (n=13)	p value
Pre-op	61.22 ± 2.79	1.627
6 months	81.56 ± 1.12	<0.001
12 months	89.56 ± 1.12	<0.001
24 months	91.06 ±1.01	<0.001

Table 1: Functional assessment of AVN hips who received core decompression with BMAC.

Radiographically, the hips that showed improvement in mHHS, there seems to be no significant changes at the end of 6 months but the joint space was maintained and the patients improved symptomatically. At the end of 12 months there was increased sclerosis and mild hypertrophy at the margins of the femoral head with the joint still being congruent and joint space maintained. At 24 months, in seven cases the femoral head slightly hypertrophied at the margins and assuming a slight 'Umbrella' like look (but the joint space and the congruency was still maintained). There was no significant finding of any increased in pain in these seven hips after one year (Figures 1-3).

The correlation analysis with Pearson's correlation coefficient (r) was 0.81 which show highly positive correlation between BMAC and avascular necrosis of head of femur. There was a statistical significant difference between BMAC and avascular necrosis of head of femur ($p<0.001$) at the end of 6, 12 and 24 months follow up (Figures 1-3).

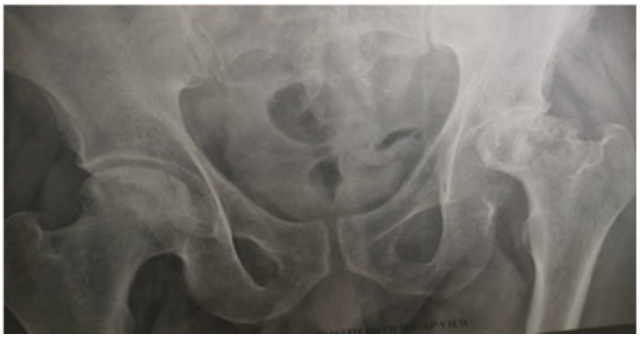

Figure 1: Radiograph of pelvis with bilateral hips with grade 1 AVN in right hip and grade 2 AVN in left hip.

Discussion

Bone Marrow Aspirate Concentrate (BMAC) is a potential minimally invasive regenerative and therapeutic procedure that uses patient's bone marrow cells to initiate healing for various orthopedic conditions including delayed union and non-union, avascular necrosis, osteoarthritis, tendinopathies and cartilage injuries [13]. Bone marrow obtained by iliac crest aspiration is a common source for harvesting mesenchymal stem cells, other progenitor cells, and associated cytokine/growth factors [14,15].

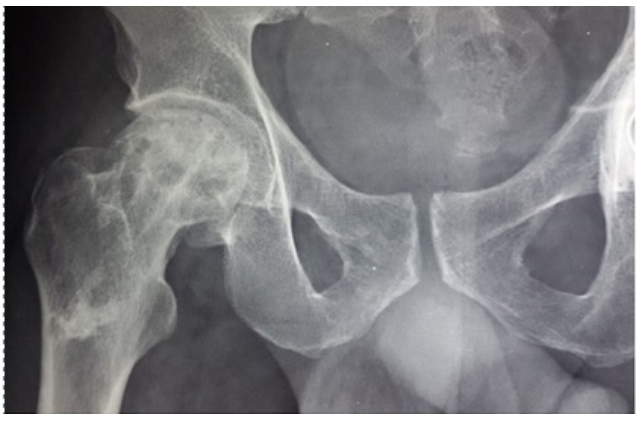

Figure 2: Post operative radiograph of right hip showing partial osteointegration after injecting bone marrow aspirate at 12 months.

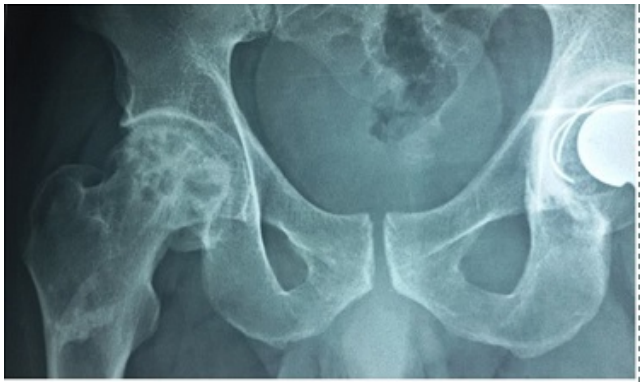

Figure 3: Post operative radiograph of right hip showing complete osteointegration after injecting bone marrow aspirate at 24 months.

Mesenchymal stem cells (MSCs) are immature, natural, resident, pluripotent cells of bone marrow with the properties of self-renewal, differentiative and proliferative capacity. MSCs have their intrinsic ability for repair and regeneration or indirect through their immunomodulatory and paracrine effects [16]. Bone marrow-derived mononuclear cells elicit angiogenesis and hence significantly enhancing blood flow to the pathological site and inherently delivering the core components, such as growth factors and cytokines that play a vital role in the normal healing process [17].

After density gradient centrifugation, progenitor cells (0.001% to 0.01%) account for a small population within the bone marrow [18-20]. High concentrations of growth factors such as Platelet-Derived Growth Factor (PDGF), transforming growth factor-β (TGF-β), Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF) and Bone Morphogenetic Proteins (BMP) 2 and 7, which are reported to have anabolic and anti-inflammatory effects, are present in BMAC [21,22]. BMAC has a considerable concentration of interleukin-1 receptor antagonist (IL-1RA) which inhibits IL-1 catabolism and hence responsible for the symptomatic pain relief with this biologic approach [23,24].

Hernigou et al. studied the role of core decompression and autologous bone marrow grafting with 342 patients (534 hips) with avascular osteonecrosis at early stages (Stages I and II). The functional outcome was determined by the changes in the Harris hip score. Total hip replacement was necessary in 94 hips among the 534 hips operated before collapse (Stages I and II). A total of 440 patients who did not require total hip arthroplasty had a mean Harris hip score of 70 and 88 points pre and post-operatively. A total of 69 hips with stage I osteonecrosis of the femoral head demonstrated total resolution of osteonecrosis based on preoperative and postoperative MRI studies. They commented that radiographs did not show any changes on hips which received BMAC [25].

Pepke et al. conducted a trial of 25 hips could not detect a benefit from the additional injection of bone marrow concentrate with regard to bone regeneration and clinical outcome in the short term. They reported that further studies of BMAC properties with a larger sample size and longer follow-up are needed to better validate our results and possibly modify our procedure [26]. Gangji *et al* presented the results of a randomized and prospective clinical trial of ARCO I-II patients treated with core decompression only vs. core decompression with autologous bone marrow application. They described an increased head survival rate in the BMAC group. The limitation of this study was a short follow-up period (two years) and small number of patients in both study groups. The small study population is a result of the prospective design and very restrictive inclusion criteria of FHN patients [27].

Sen et al. reported increased hip survival with BMAC but without any noticeable differences on imaging between the 2 groups on 51 patients with stage I and II AVN hips. They reported that patients with post-traumatic AVN had better outcomes than those with nontraumatic AVN [28]. Zhao et al compared the results of 51 hips that underwent core decompression and 53 hips that underwent core decompression augmented with bone marrow. Higher Harris Hip Scores were reported in the bone marrow group at the end of follow-up, and significantly fewer patients from the bone marrow group required total hip replacement or fibular vascularized graft [29]. Lieberman et al used autologous bone morphogenetic proteins to augment core decompression in 15 patients. Their results were good in 12 cases at final follow-up and 3 patients underwent a total hip arthroplasty, all of whom had at least two-thirds of the femoral head affected before decompression. Lieberman et al. concluded that success was dependent on the necrotic femoral head weight-bearing area involved [30].

In our study, a total of 10 patients with 13 hips were analyzed with follow up period of 2 years to analyze the functional recovery with modified Harris hip score. We observed excellent results (mHHS ≥ 90) in 9 (69.2%) hips, good results (mHHS 80-89) in 2 (15.4%) hips, no improvement in 1 hip (7.7%) and 1 hip (7.7%) worsened at the end of 24 months. Radiographically, the hips showed no significant changes at the end of 6 months and increased sclerosis and mild hypertrophy at the margins of the femoral head at the end of 12 months. At 24 months, in 7 cases the femoral head slightly hypertrophied at the margins and assuming a slight 'Umbrella' shaped appearance. We reported no significant increase in pain in these seven hips after one year. Core decompression already decreases intra-osseous pressure with temporarily increasing the vascularity and the addition of bone marrow concentrate provides the added angiogenesis thus augmenting neo bone formation.

The correlation analysis with Pearson's correlation coefficient (r) was 0.81 which show highly positive correlation between BMAC and avascular necrosis of head of femur. There was a statistical significant difference between BMAC and avascular necrosis of head of femur ($p<0.001$) at the end of 6, 12 and 24 months follow up.

Limitations

Smaller sample size (n=10 with 13 hips)

Smaller follow up time frame (2 years)

The amount of BMAC and the number of bone marrow mesenchymal stem cells to treat AVN of head of femur have to be standardized Randomized controlled trial have to be considered.

Conclusion

Autologous bone marrow concentrate have the potential to self-renew, undertake clonal expansion, and differentiate into osteoblastic lineage. BMAC has been used in bone, cartilage and tendon injuries with encouraging results. The combination of core decompression and

injection of BMAC into the necrotic lesion provides satisfactory results in patients with stage I, II and early III without collapse of osteonecrosis of femoral head and can lead to complete resolution of the necrotic lesion. The procedure is simple, with a low complication rate and the patients are allowed to weight bear as tolerated allowing them an early return to function and activities of daily living. The future potential of cell characterization in order to determine the optimum cell for repair/regeneration of various tissue types also needs to be explored.

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