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Etiopathogenesis and Stem Cell Treatment Outcomes in Avascular Necrosis of the Femoral Head: A Review of 50 Cases

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Authors' contributions

This work was carried out in collaboration between all authors. Author PVM designed the study, protocol and edited the manuscripts. Author SS managed literature searches, wrote the first draft of the manuscript and subsequent edits. Authors ABJ and SCP collected and reviewed patient data. Author AD was in-charge of laboratory processing of patient samples. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aim: Avascular necrosis (AVN) is a progressive condition characterized by a vascular insult to the bone, which can lead to collapse of the bone and subsequent degenerative changes. Vascular impairment that results in AVN may occur due to compression of blood vessels that may be due to trauma, immunosuppressive medications or idiopathic etiology. The aim of this review was to identify the prevalence of AVN based on age, sex and causative factors. This review also aimed to analyze the outcome of autologous mesenchymal stem cell therapy in patients suffering from avascular necrosis of femoral head.
Methods: 50 cases of avascular necrosis who had undergone autologous mesenchymal stem cell therapy were included in the study. Demographic and etiologic categorization was done based on

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data obtained from case history of patients. Outcome following cell based therapy was done based on Harris Hip Score and radiographic tests (X-ray, MRI).

Results and Conclusion: Based on findings in this review, prolonged steroid medication was found to be the prime causative factor for non-traumatic AVN of femoral head. Autologous cell based therapy has been shown to be effective in arresting progression of the condition. Analysis showed statistically significant outcomes with respect to parameters of pain, joint function and range of motion following cell based therapy. This minimally invasive procedure is effective in management of all stages of the condition and aids in preservation/regeneration of joint structure.

Keywords: Avascular necrosis; etiologic factors; mesenchymal stem cells; platelet rich plasma; autologous.

1. INTRODUCTION

Avascular necrosis (AVN) is a progressive orthopedic condition that is caused due to obstruction of vascular supply to the bone. Ischemia results in the death of marrow and osteocytes and subsequent collapse of the necrotic segment [1].

Avascular necrosis, also known as Osteonecrosis of the femoral head was first described in 1738 by Alexander Munro [2]. In approximately 1835, Cruveilhier depicted femoral head morphologic changes secondary to interruption of blood flow following trauma [3]. Articular surfaces of the joint are more frequently involved due to smaller diameter of terminal blood vessels as well as absence of collateral vascular supply [4].

In early stages, the condition may be asymptomatic and gradual restriction of movements occurs over time. The progression of AVN is related to the stage and extent of the necrotic lesion at the time of the diagnosis [5]. Joint deterioration tends to develop within two-three years of initial diagnosis, thus compromising prognostic value. A significant percentage of total hip arthroplasties performed annually are due to avascular necrosis of the femoral head.

AVN commonly affects individuals in the age group of 30-40 years with males being affected three times more commonly than females. Bilateral hip joint involvement is noticed in approximately 75% cases [6].

1.1 Etiopathogenesis

Vascular impairment that results in AVN may occur due to intra- and extraluminal compression of blood vessels caused by external pressure or trauma. Traumatic injury resulting in fracture or dislocation of the femoral head may interrupt the major vascular supply to the hip joint. Absence of collateral blood supply impairs normal reparative process thereby preventing bone remodeling and subsequently results in degenerative changes in the joint [7].

Nitrogen bubbles, as seen in decompression sickness/Caisson disease, are also known to occlude blood vessels thus resulting in necrosis of the affected region. Vessel infarction may also occur due to other causes such as arteriosclerotic, hypercoagulability and hypofibrinolytic conditions etc. Common non-traumatic causes include corticosteroid use, alcohol abuse, autoimmune conditions such as systemic lupus erythematosus, radiation exposure, hyperlipidemic conditions etc.

A dose-response relationship exists between alcohol consumption and development of AVN. Alcohol has been shown to induce proliferation and differentiation of adipose cells. This in turn leads to formation of fat emboli which may contribute to stasis of blood flow and development of AVN [8]. Similarly, prolonged course of steroid medication has also been shown to be associated with fatty conversion in bone marrow. Steroids induce hyperlipidaemia, oxidative stress and changes in venous endothelial cells which contribute to venous stasis, increased intraosseous pressure and ultimately bone necrosis [9,10].

Irrespective of the cause of AVN, diminished resistance of the affected bone is noticed which, in turn, determines secondary vascular impairement at the capillary level. Bone remodeling alterations may induce defects in healing of bony microfractures, subsequently leading to subchondral fractures and ultimately AVN [11].

2. ROLE OF STEM CELLS IN MANAGEMENT OF AVASCULAR NECROSIS OF FEMORAL HEAD

Mesenchymal stem cells (MSCs) have the capacity for self renewal and differentiation into various tissues. These cells also possess the property of transdifferentiation, which is the ability of one type of cell to differentiate into another cell type based on the environment. The role of adult stem cells in the human body is to participate in organ homeostasis, wound healing etc. In context of AVN, mesenchymal stem cells can differentiate into osteogenic lineage cells, thereby enabling bone repair [12]. Additionally, bone marrow derived stromal cells are also known to secrete pro-angiogenic cytokines. These cytokines result in increased neo-angiogenesis and facilitate further osteogenesis [13].

The purpose of this review article was to categorize patients suffering from avascular necrosis of the femoral head based on age, sex and causative factors. This review also aimed to analyze the outcome of autologous mesenchymal stem cell therapy in patients suffering from avascular necrosis of the femoral head.

3. MATERIALS AND METHODS

3.1 Study Population

50 cases of avascular necrosis treated with autologous mesenchymal stem cell therapy between Aug 2012 and September 2016 were randomly included in the study. The patients were categorized based on age of onset, cause and presentation of AVN.

Patients had undergone 3-4 sessions of autologous mesenchymal stem cell therapy (MSC) along with platelet concentrate (Platelet Rich Plasma-PRP) therapy. Source of autologous MSCs and PRP was from the bone marrow, adipose tissue and peripheral blood. Approximately, 100-150 mL of bone marrow from iliac crest, 50-100 mL adipose tissue from gluteal region and 50 mL peripheral blood from cubital vein were obtained. Aspiration and transplantation of therapeutically effective dose calculation was based on grade of the disease and body mass index of the patient. 500-5000 x 10^6 bone marrow derived MSCs, 1600-400 x 10^6 adipose-derived stromal vascular fraction and 1.5 x 10^6 platelet concentrate was transplanted in the affected area. Intraarticular transplant of cells was done using a modification of the technique by Wettstein and Dienst. This approach allowed access to the peripheral compartment of the hip joint via proximal anterolateral portal and was done under radiographic guidance [14]. Intravenously, cells were infused via the cubital vein.

Assessment of treatment outcome was done clinically using Harris Hip Score. Radiological assessment was done using X-ray and MRI prior to and 1 year following treatment.

4. RESULTS

Of the 50 patients reviewed in this study, 39 male patients between the ages 21-40 years suffered from AVN, with 70% having bilateral involvement of femoral head. Sixteen males out of 21 had developed AVN due to steroid use, while 5 cases were attributed to long-term alcohol consumption. In females, steroid medication indicated for systemic conditions was found to be the common cause of AVN. Tables 1 and 2 depicts the data of patients evaluated in this study. Subjects affected with AVN due to steroid use presented with higher severity of the condition (Grade III/IV) based on Ficat and Arlet classification.

Table 3 shows patient data on outcome of cell based therapy. 11 patients failed to follow-up for radiological assessment after the first year of cell based therapy. In the first year, 46 patients showed improvement with respect to clinical parameters of pain and range of motion. 2 patients did not show any improvement in symptoms while 2 did not return for treatment after the first session. MRI assessment after 1 year of therapy showed no progression of AVN in 35 patients, while 2 patients showed deterioration by one grade (as per Ficat and Arlet classification).

Table 1. Age and sex based categorization of patients suffering from AVN of femoral head

Age	Number of patients	
		Females: 11
<20 years	1	
21-30 years	18	Males: 39
31-40 years	22	
>41 years	9	

Mann Whitney U test was used to statistically analyze pre- and post treatment parameters of pain, joint function, range of motion and MRI changes (Tables 4, 5 and 6).

Table 2. Etiology based categorization of patients suffering from AVN of femoral head

Cause	Number of patients	Presentation
Steroid induced	21 (16 males, 5 females)	4 unilateral/ 17 bilateral
Traumatic	17 (15 males, 2 females)	10 unilateral/ 7 bilateral
Alcohol induced/Idiopathic	12 (9 males, 3 females)	1 unilateral/ 11 bilateral

Table 3. Outcome after cell based therapy

Outcome	Number of patients
Clinical and radiological improvement	35
Clinical improvement alone (No radiographic data)	11
Radiological deterioration	2
No data	2

Table 4. Pre treatment patient data

	Pain	Joint function	Range of motion	MRI
N	50	50	50	50
Mean	3.840	2.660	4.840	2.860
Standard deviation	0.792	0.658	0.976	0.729

Fig. 1a and 1b shows MRI of 2 cases (representative purpose) showing no progression of AVN one year post cell based therapy.

Table 5. Post treatment patient data

	Pain	Joint function	Range of motion	MRI
N	48	48	48	37
Mean	2.167	1.979	5.583	3.000
Standard deviation	0.834	0.252	0.539	0.667

Table 6. Mann Whitney U analysis: Pre and Post cell based therapy

	Pain	Joint function	Range of motion	MRI
U	2194.000	1893.500	689.000	823.500
P value (two-tailed)	<0.0001	<0.0001	<0.0001	0.344

Clinical results achieved were maintained in all patients as confirmed by telephone conversation based on Harris Hip Score. Fig. 2 depicts statistical representation of Harris Hip Score parameters of the 50 cases studied.

5. DISCUSSION

AVN of the femoral head is a debilitating disease that usually leads to osteoarthritis of the hip joint in relatively young adults. The condition shows inter-individual variation with respect to progression and the natural history of the condition plays a major role in predicting prognosis. The extent and the location of the lesion involving the femoral head also determines the prognosis of AVN. Studies have stated the overall collapse rate of AVN (hips) as 78% within 2 years. Lesions involving the lateral one third of the weight bearing area or diffuse femoral head involvement had more than 90% chance of collapse [15,16].

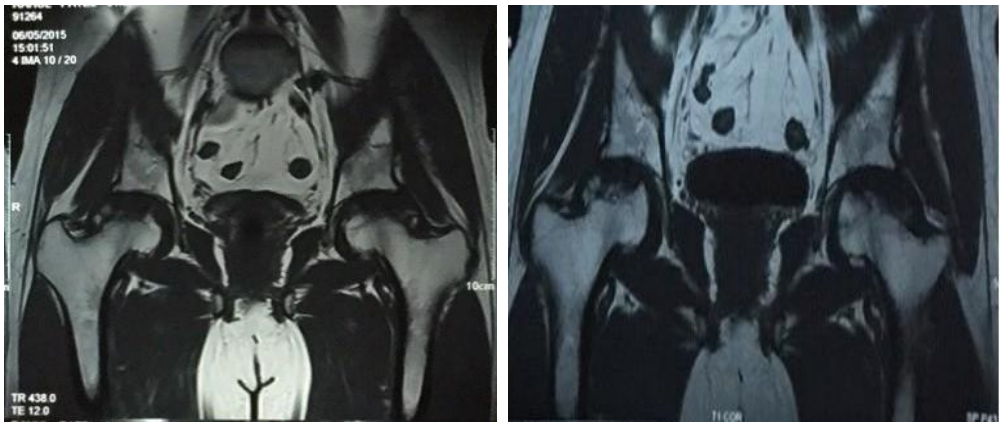

Fig. 1a. Patient 1- Pre and Post cell based therapy

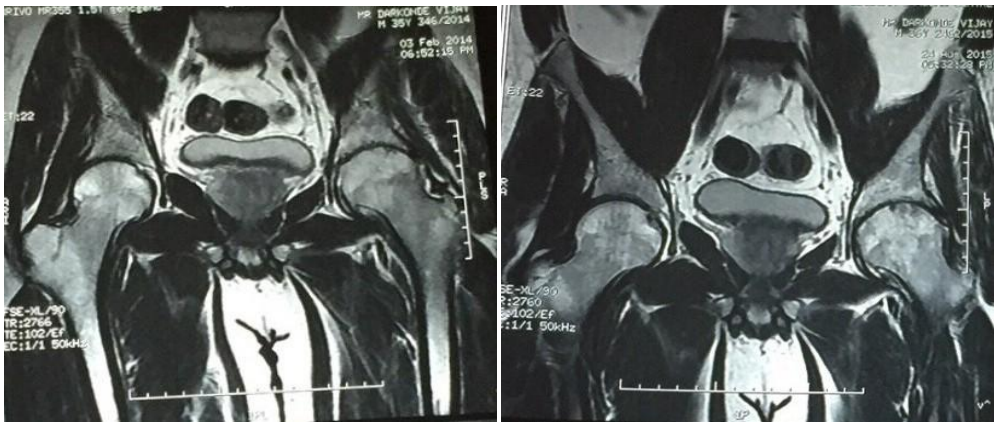

Fig. 1b. Patient 2-Pre and Post cell based therapy

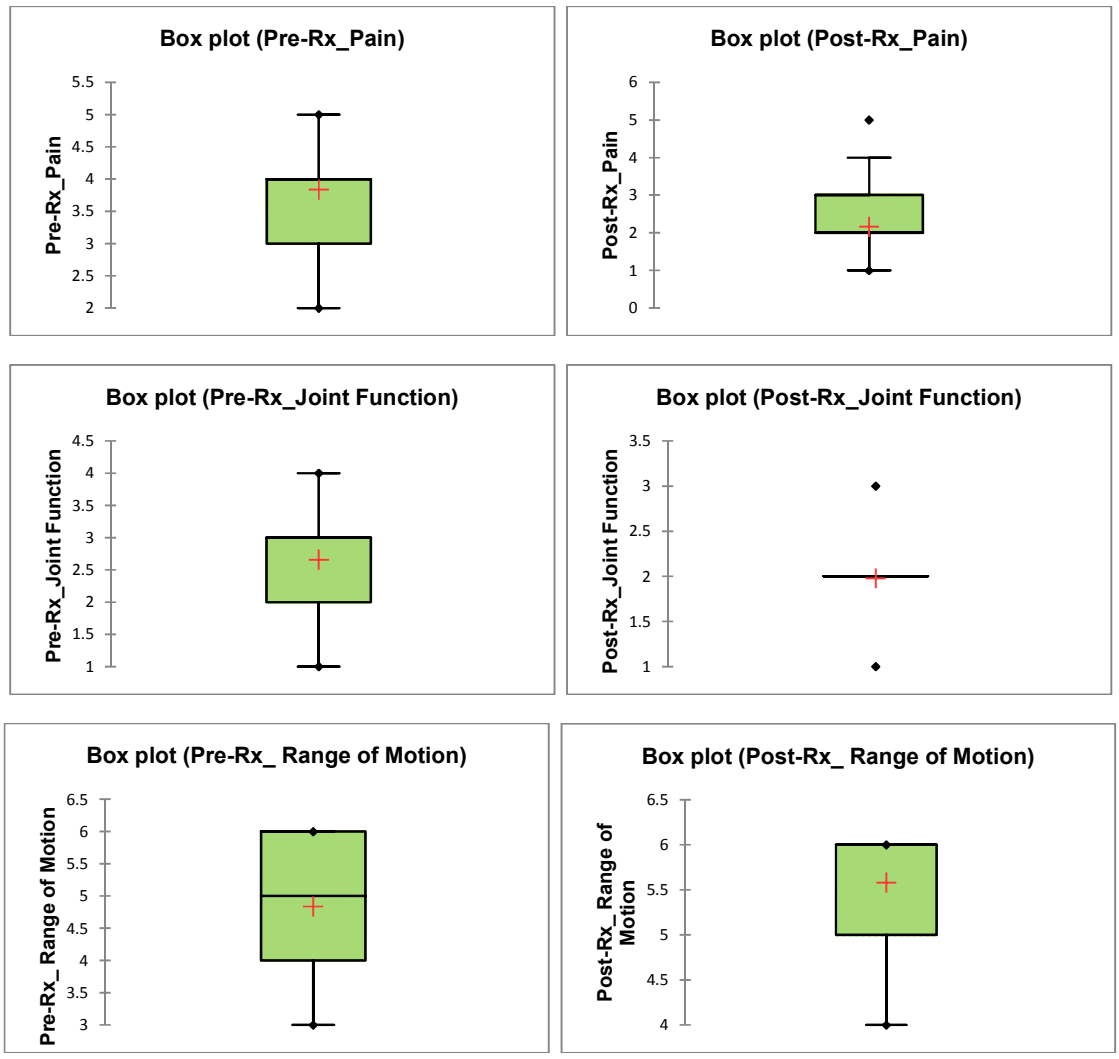

Fig. 2. Harris Hip Score: Assessment of pain, joint function, range of motion: Pre and Post cell based therapy

Data from various studies support a “multiple hit” theory, which refers to accumulated tissue stress from various insults initiating the disease process. Tissue stress may be a result of intraosseous hypertension, emboli and/or extravascular compression [17,18]. In the present study, long-term steroid medication for systemic conditions such as systemic lupus erythematosus, acute lymphoblastic leukaemia, thrombocytopenic purpura, asthma and cosmetic dermatological conditions was found to be the most common non traumatic cause of AVN (42%) in both male and female subjects. Male predilection observed in occurrence of AVN was attributed to binge alcohol consumption, trauma (commonly due to two-wheeler road traffic accidents) as well as prolonged steroid medication. Our findings are supported by those from other studies which state ≥ 3: 1 male-female prevalence of AVN [19,20]. Nonetheless, it must be noted that the frequency of AVN in female population due to the above mentioned causative factors is also increasing owing to lifestyle changes.

Conventionally, treatment of early stage AVN is accomplished by use of pharmacological agents such as bisphosphonates, statins, anti-inflammatory and pain relieving medications. Pre-collapse stages of AVN of femoral head may be treated by core decompression to reduce pain and preserve joint structure and function, and may be supplemented with the use of bone grafts. The goal of this procedure is to reduce pressure within the dead bone by restoring vascular supply [21,22]. The inherent disadvantage of core decompression is that it provides temporary effectiveness only in early stages and may result in further weakening of osteoporotic bone structure. In our study, 7 patients had undergone core decompression procedure with limited/no improvement in symptoms and showed continued progression of AVN.

Osteotomy, pedicle grafts have also been studied, with no significant success, in management of AVN of the femoral head. Total hip replacement is advised in advanced stages of joint collapse. Statistics report 90-95% limited longevity of 10 years following hip replacement (Data from the American Academy of Orthopaedic Surgeons). Implantation of prosthesis does not provide complete range of movements and requires caution to be observed in order to prevent complications. Considering the early age of onset of AVN, repeated surgeries may be indicated depending upon prognosis and implant survival. Open surgical modalities may also be associated with complications such as infection, dislocation of prosthesis, nerve and blood vessel related complications, systemic complications etc.

Impaired bone remodeling in AVN is associated with microcirculation disturbances and reduced osteogenic differentiation capacity of mesenchymal cells in the affected area [23]. As previously mentioned, bone marrow derived MSCs are capable of osteogenic differentiation. Additionally, MSCs derived from adipose tissue have been shown to support formation of new vascular networks through self assembly of transplanted cells and endothelial progenitor cells [24]. Several studies have demonstrated the positive effect of mesenchymal stem cell therapy in AVN [25,26]. In a study done by Gangji et al., autologous bone marrow cells when transplanted into femoral heads showed significant reduction in joint deterioration [27]. Centeno et al. [28], reported regeneration of hip bones when treated with autologous bone marrow-derived stem cells.

The treatment protocol employed in this study used autologous bone marrow and adipose derived MSCs. Platelet rich plasma, which is a rich source of growth factors such as VEGF, FGF etc., was also administered as a supportive and scaffolding base for MSCs. In AVN, the necrotic foci induces release of signaling molecules, in which specific receptors or ligands expressed in injured tissues play an important role. Mesenchymal stem cells are capable of adhering to vascular endothelial cells-which express variety of adhesion molecules- and reaching the site of ischemia [29]. Mesenchymal stem cells can not only migrate into the femoral head, but also remain in the region for a relatively long time. The treatment resulted in arrest of progression of AVN in 35 cases with reduction in joint effusion and other inflammatory parameters. This improvement, although not statistically significant, is considered positive as the condition in its natural course is progressive and is not associated with reversal of radiological parameters.

Assessment of clinical parameters was done based on Harris Hip Score components. Statistically significant improvement in parameters of pain, joint function and range of motion was observed and the results of therapy are being maintained over a period 3-4 years. Approximately 92% patients reported reduction in

pain intensity from marked/moderate to slight/no pain following cell based therapy. Deterioration noticed in 2 patients was attributed to co-existing systemic complications of chronic kidney disease and systemic lupus erythematosus. As previously explained, pain in AVN develops gradually and increases in intensity as the condition progresses, leading to difficulty in performing activities of daily living. Pain medications may have temporary effectiveness but long-term use may be associated with side effects. Pain may be a result of various causes with inflammation being one of the most common etiologic factors. Mesenchymal stem cells are capable of attenuating the inflammatory milieu, thereby aiding in pain management. Clinically, pain reduction is associated with improvement in ability to perform activities of daily living. In our study population, limitation in range of motion was observed chiefly with respect to hip flexion, abduction and adduction. Advanced grades of AVN generally involve collapse of the articular cortex, fragmentation, mottled trabecular pattern, subchondral cysts, and/or subchondral fracture. These lead to impaired joint function and painful movements. Studies have reported arrest in progression and occasional reduction in size of necrotic lesion in the femoral head along with attenuation of surrounding inflammatory activity, the result of which is gradual improvement in joint movements [30]. In the present study, subjects were advised use of walker/crutches for 3 weeks following cell based therapy. This was to facilitate bone healing as well as pain management by decreasing the load on the joint that results due to weight bearing movements. Improvement in range of motion parameters by >90% was observed, the results of which are being maintained by regular physiotherapy exercises. Improved range of motion facilitated subjects to walk longer distances without support and pain, bend and sit comfortably for extended periods of time. The importance of maintaining range of motion also lies in prevention of further joint degeneration. Mobilizing the joint aids in vascularization of healing areas, thereby, improving muscle strength and joint function.

The route of administration of cells also plays an important role in the degree of improvement achieved. Intraarticular route of administration chosen in the protocol was to achieve higher concentration of cells in the localized area. Intravenous administration of cells has been shown to result in directional migration of the cells to femoral heads to survive in the necrotic environment [31]. Nevertheless, further studies should be done to study the migratory and homing properties of stem cells in order to formulate more specific treatment protocols.

On basis of previously reported studies and from findings in this study, it can be demonstrated that autologous mesenchymal stem cell therapy may aid in regeneration of medullary bone, results of which are maintained over long periods of time. Mesenchymal stem cells also bring about concomitant neovascularization which supports regeneration of necrotic and newly formed tissues. Multi-differentiation potential, immune-modulatory and paracrine mechanisms of MSCs aid in tissue regeneration, therefore are an effective and attractive treatment alternative to conventional therapeutic modalities.

6. CONCLUSION

Long term immunosuppressive medication continues to remain the prime causative agent for non traumatic AVN of femoral head. Autologous mesenchymal stem cell therapy is a safe and effective therapeutic modality that arrests the progression of avascular necrosis of the femoral head irrespective of the etiologic factor. This minimally invasive procedure is effective in management of all stages of the condition and ensures preservation/regeneration of joint structure. Larger, multicentre trials with long term follow up (min. 5 years) must be undertaken to support the findings of this study proving the efficacy of cell based therapy in AVN of the femoral head.

CONSENT AND ETHICAL APPROVAL

Informed consent was obtained from all patients prior to cell based therapy as per standard format adopted at our institution.

The standard treatment protocol for AVN of femoral head has been approved by the Western Institutional Review Board (WIRB).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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