

Minimally Invasive, Regenerative Approach for Treatment of Avascular Necrosis of Femoral Head: A Case Report

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Abstract

Vascular insult to bone may result in Avascular Necrosis, which is a progressive condition that ultimately leads to collapse of bone and secondary arthritic changes in the joint. The condition may be a result of trauma, immunosuppressive medications or idiopathic etiology. Prolonged or short-term high dose steroid medication has been described as the prime cause of non-traumatic Avascular Necrosis (AVN). AVN is managed conventionally by pharmacological agents to relieve symptoms or through surgical procedures such as core decompression, joint replacement etc. Early age of onset and limited long-term efficacy of invasive surgical modalities with probability of infections and other complications raise the need for newer safe and effective therapeutic modalities. Regenerative medicine and cell based therapy, is a novel therapeutic approach that utilizes the innate regenerative capacity of cells and the natural healing potential of the body in treatment of various health conditions. On basis of this concept of regenerating human cells, tissues and organs, this case report highlights positive outcomes of cell based therapy in a case of Avascular Necrosis of the femoral head. A minimally invasive approach in harvesting and transplantation of mesenchymal stem cells and growth factors derived from bone marrow, adipose tissue and peripheral blood has been described.

Keywords: Avascular Necrosis, Mesenchymal Stem Cells, Steroids, Platelet Rich Plasma

Introduction

The first description of Avascular necrosis (AVN), also known as Osteonecrosis of the femoral head was in 1738 by Alexander Munro [1]. Later studies, such as one done by Cruveilhier around 1835, depicted femoral head morphologic changes secondary to interruption of blood flow following trauma [2]. Articular surfaces of the joint that have smaller diameter of terminal blood vessels with no collateral vascular supply are more frequently involved in Avascular Necrosis [3].

Early stages of AVN are generally asymptomatic and restriction of movements occurs over time. Progression of the condition is related to the extent of necrotic lesion at the time of initial diagnosis [4]. Regardless of the stage of AVN during diagnosis, studies have reported joint deterioration within two-three years which compromises the prognostic value, thus highlighting the importance of early diagnosis and intervention.

Conventional management of AVN includes pharmacological treatment using anti-inflammatory medications, bisphosphonates etc. to reduce symptoms while more advanced stages are advised prosthetic joint replacement surgery [5]. Early, pre-collapse stages of AVN of the femoral head may be treated by core decompression to reduce pain and preserve joint structure and function. The procedure may be supplemented with use of bone grafts. The goal of core decompression is to reduce intraosseous pressure created due to necrotic tissue thereby aiming to restore vascular supply. However, the inherent disadvantage of the procedure, apart from being invasive and temporarily effective only in early stages, is that core decompression does not halt progression of AVN and may result in further weakening of osteoporotic bone structure [6]. Prosthetic joint replacement is advised in advanced stages of AVN, however, statistics report 90–95% limited longevity of 10 years following the procedure (Data from the American Academy of Orthopaedic Surgeons). Additionally, implantation of prosthesis does not provide complete range of movements and requires caution to be observed in order to prevent complications. Invasive surgical modalities may also be associated with complications such as infection, dislocation of prosthesis, nerve and blood vessel related complications, systemic complications etc.

Due to early age of onset of the condition and limited long-term efficacy of surgical interventions, the need of the hour is newer therapeutic modalities. Regenerative medicine, cell based therapy, gene therapy etc. are showing promise in management of various health conditions. This case report describes a minimally invasive, novel therapeutic approach in management of an advanced grade of Avascular Necrosis of bilateral femoral heads.

Consent and Ethical Approval

Informed consent was obtained from the patient 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) and DCGI approved Institutional Ethical committee of the hospital.

Case history

A thirty seven years old male patient presented with complains of pain in both left and right thighs and hip joints. The patient initially had pain on walking and climbing stairs, which gradually progressed to pain while getting up from sitting position.

Pre-treatment: STAGE III	Post treatment: STAGE II
A serpiginous low signal area is seen in subchondral location in the right as well as left femoral heads	Geographic shaped altered signal intensities in bilateral femoral heads at superior aspect
Crescent sign is seen involving medial and central portion of both femoral heads with 50% involvement	-
Minimal collapse of femoral head seen	Erosions seen at articular margin of bilateral acetabulum at superior aspect
Bilateral hip joint effusion. Edema in neck of femur	Marrow edema in bilateral head and neck region

Table 1: MRI taken prior to and one year post cell based therapy.

Hip joint: Range of Motion	Pre-treatment	6 months Post Treatment		1 year Post treatment			
		Right	Left	Right	Left	Right	Left
Flexion	80	70	90	90	120	120	
Abduction	30	35	40	40	45	45	
Adduction	30	30	40	40	45	45	
External Rotation	40	30	45	35	45	45	

Table 2: Physiotherapy evaluation of ranges of motion (in degree) done prior to, at 6th month and one year post treatment.

The patient's occupation involved strenuous activity which he was unable to perform due to pain and stiffness. Medical history revealed that he suffered from dengue before two years during which he was in coma for four days due to dengue shock syndrome with encephalitis. He underwent treatment with steroids during his course at the hospital following which he recovered completely. Six months later, the patient developed pain in left thigh which interfered with his ability to lift his leg and walk comfortably. Approximately a month and half later, he had pain in right leg which further led to inability in performing activities of daily living. After investigations the patient was diagnosed with Avascular Necrosis (AVN) of bilateral femoral heads. As per Ficat and Arlet classification of AVN of femoral head, the stage was designated as III, which denotes collapse and flattening of joint structure [7] (Table 1).

Treatment

Autologous cell based therapy was advised to the patient over a period of one year. The patient underwent three sessions of treatment at the 1st, 3rd and 6th months following initial consultation (Table 2). A standard cell based therapy protocol as followed at our center for avascular necrosis was adopted. The procedure involved aspiration and transplantation of mesenchymal stem cells and growth factors derived from bone marrow, adipose tissue and peripheral blood. 100–150 ml bone marrow cells were harvested from iliac crest while 50–100 ml adipose tissue was taken from gluteal region. Approximately 50 ml peripheral blood was aspirated from cubital vein. The blood was

Transplantation of therapeutically effective dose of 500–1500 x 10⁶ bone marrow derived mononuclear cells, 400–1600 x 10⁶ adipose-derived stromal vascular fraction and 1.5 x 10⁶ platelet concentrate was done via intra-articular and intravenous routes [6,8]. Two to three milliliters bone marrow derived mononuclear cells were injected into the intra-articular space in the affected joint under radiological C-Arm guidance using a spinal needle. This was followed by a waiting period of 3–4 minutes to ensure adequate spreading of cells. 1–2 ml of adipose-derived cells was then transplanted in a similar manner. After 3–4 minutes, activated PRP was injected into the joint space which would serve as a scaffold and source of growth factors for transplanted cells. The procedure was repeated during each session of treatment. Patient was advised rehabilitation wherein physiotherapy exercises to strengthen specific muscle groups were demonstrated.

Discussion

Avascular necrosis is a condition that results due to interruption of vascular supply to the joint, which usually leads to secondary osteoarthritic changes in relatively young adults. Trauma, alcohol consumption and steroid use have been implicated as common factors in causation of AVN. In the present case, the most probable cause for AVN is high steroid dose administered over a short period of time.

Harris Hip Score	Pre-treatment	Six months Post-treatment	One year Post-treatment
Pain	20 (Moderate pain, some limitation of ordinary activity/work)	40 (Slight, Occasional)	40 (Slight, Occasional)
Limp	8 (Slight)	8 (Slight)	11 (None)
Support	11 (None)	11 (None)	11 (None)
Distance walked	8 (Six blocks)	8 (Six blocks)	11 (Unlimited)
Sitting	3 (On high chair)	5 (Comfortably in ordinary chair)	5 (Comfortably in ordinary chair)
Enter public transportation	1 (Yes)	1 (Yes)	1 (Yes)
Stairs	1 (In any manner)	2 (Normally using railing)	2 (Normally using railing)
Puts on shoes and socks	0 (Unable)	2 (With difficulty)	4 (With ease)
Deformity	Nil	Nil	Nil
Total Score (including range of motion score)	56 (Poor)	77 (Fair)	90 (Excellent)

Table 3: Harris Hip Score— Comparison of changes in clinical parameters prior to and one year post treatment.

Steroids have been shown to induce fatty conversion in bone marrow. Hyperlipidemia, oxidative stress and resultant changes in vascular endothelial cells due to steroid medication contribute to venous stasis, increased intraosseous pressure and ultimately bone necrosis [10,11].

Results

Table 3 presents pre- and post-treatment comparison in clinical parameters of pain, joint function and deformity (Figures 1 & 2). Harris Hip score, which is a clinician based outcome measure, was used as a standard scale to evaluate changes in clinical parameters which includes pain and functional domains [9]. The patient experienced reduction in pain within a month following treatment. With regular physiotherapy, improvement in ranges of motion was noticed. In approximately six months following treatment, the patient was able to bend forward and climb stairs more comfortably. After a year of treatment, dramatic improvement was observed with respect to pain and ability to walk long distances. The findings of this study are in sync with those of our previous studies, wherein consistent improvement was noticed in assessed parameters.

Discussion

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The treatment protocol employed in this study used autologous bone marrow and adipose derived mononuclear and mesenchymal stem cells (MSC). Studies have shown that bone marrow derived mesenchymal stem cells are capable of osteogenic differentiation. As an example, Gangji, et al. transplanted autologous bone marrow cells into femoral heads and observed

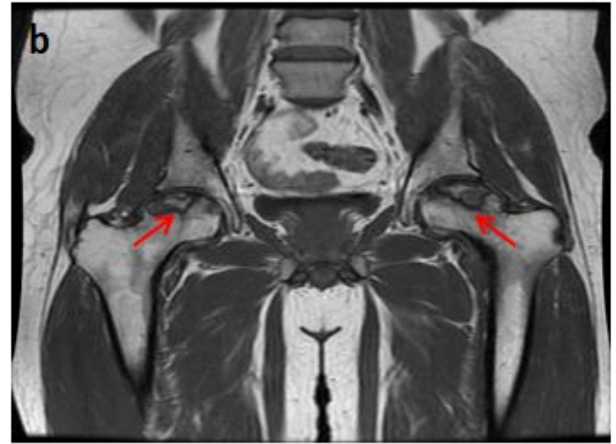
significant reduction in joint deterioration [12]. Similarly, Centeno, et al. reported regeneration of hip bones when treated with autologous bone marrow-derived stem cells [13]. Bone marrow derived mononuclear cells also possess endothelial cell fraction that can facilitate angiogenesis which aids in neovascularization of necrotic tissue in avascular necrosis.

In this study, we have also used adipose derived stem cells as they have been shown to have higher number of stromal cell population (MSCs) compared to bone marrow. Cells derived from adipose tissue have been shown to regenerate medullary bone [14]. Additionally, adipose derived mesenchymal stem cells have been shown to support formation of new vascular networks through self assembly of transplanted cells and endothelial progenitor cells [15]. Also, necrotic fragments of tissue require stromal and growth factor support which is provided by stromal vascular fraction of adipose tissue. The above mentioned and other paracrine properties of MSCs derived from bone marrow and adipose tissue sources have been shown to induce positive changes in cases of AVN. In a previous study done by our team with cell based therapy in 50 cases of avascular necrosis, improvement in clinical parameters was observed in 46 patients, the results of which have been maintained for over 3–4 years. The study also showed positive results in radiological parameters that prevented patients from undergoing total hip replacement [6]. MSCs are capable of adhering to vascular endothelial cells-which express variety of adhesion molecules- and reaching the site of necrosis. MSCs are not only capable of migrating into the femoral head but are also known to remain in the region for a relatively long time [16]. Additionally, MSCs are known to synthesize different growth factors, chemokines which result in local regenerative response [17]. The results of the present study are in consensus with those reported in other studies that demonstrate medullary bone repair and neovascularization that supports regeneration of necrotic and newly formed tissues [6].

Additionally, Platelet Rich Plasma derived from peripheral blood, which is a rich source of growth factors such as VEGF, FGF etc., was also administered lastly, as a supportive and scaffolding base for MSCs. The result of the combination therapy of mesenchymal stem cells and growth factors resulted in alleviation

T1 Coronal

Pre-treatment



Post-treatment

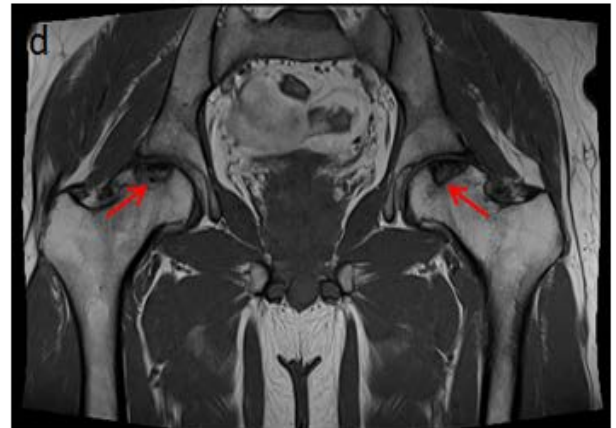
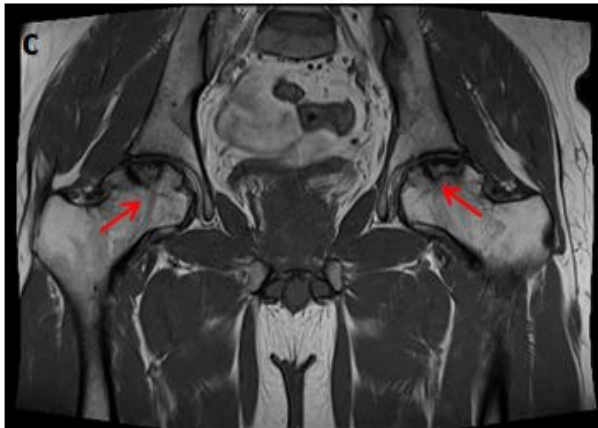
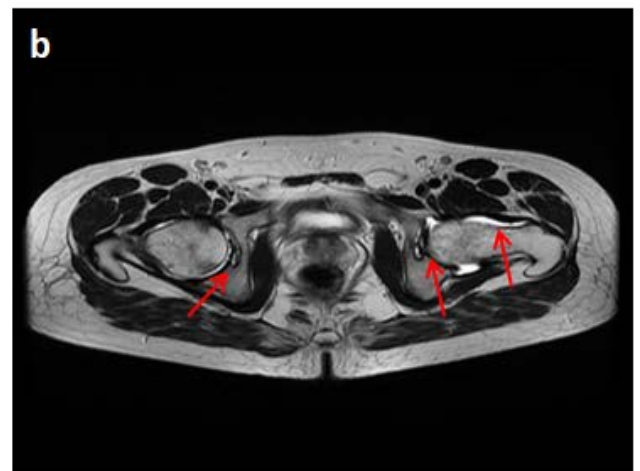


Figure 1 a-d: changes in MRI taken before and one year after treatment with cell based therapy. T1 Coronal slice of bilateral hip joint. A & B: Pre-treatment—Low intensity signal observed in subchondral location of femoral heads bilaterally. Crescent sign involving 50% of the articular surface denoting Stage 3 AVN. Evidence of minimal collapse of femoral head. C & D: Post treatment—Reduction in extent of necrotic lesion observed, erosions at articular margin of acetabulum.

T2 Axial

Pre-treatment



Post-treatment

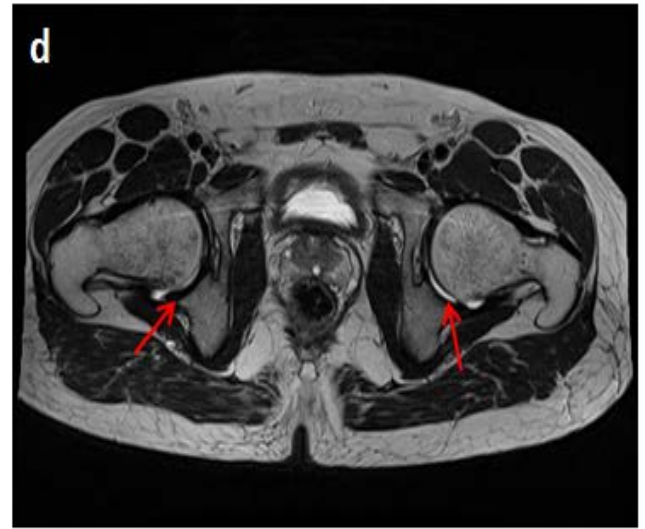
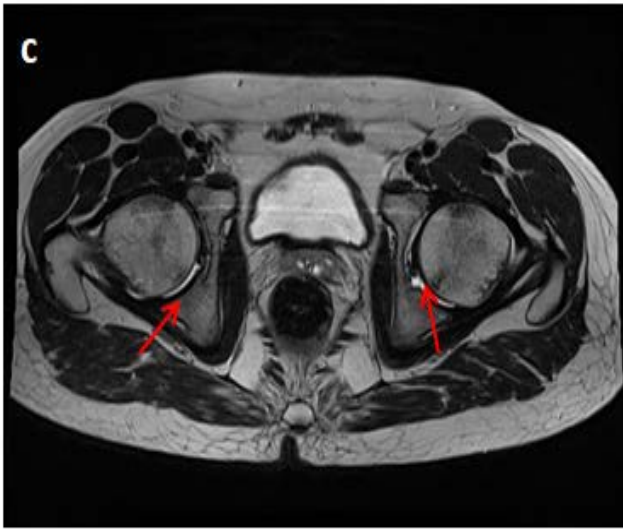
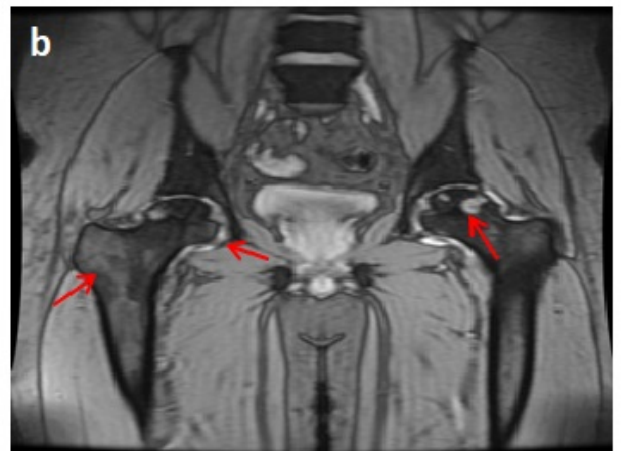
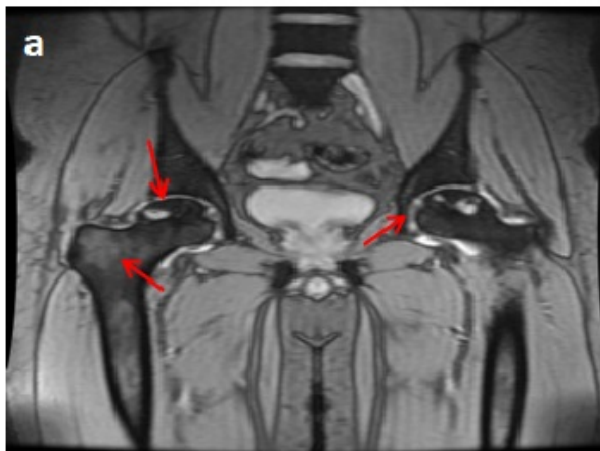


Figure 2 A-D: T2 Axial slice. A & B: Pre-treatment—Bilateral hip joint effusion with edema in neck of femur. C & D: Post treatment—Notice reduction in extent of edema and joint effusion.

STIR Coronal

Pre-treatment



Post-treatment

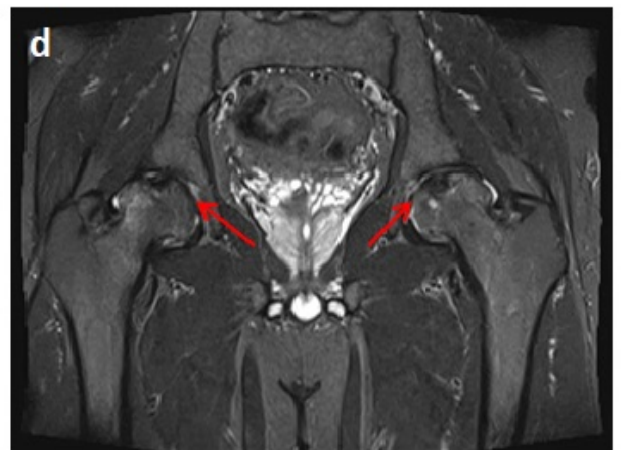


Figure 3 A-D: STIR Coronal Slice. A & B: Pre-treatment– Fat Suppression STIR imaging shows increased signal in bilateral femoral head and neck denoting edema and effusion. C & d: Post treatment—Notice the reduction in edema and joint effusion.

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