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ORIGINAL ARTICLE

Efficacy of Autologous Adult Live-Cultured Osteoblast (AALCO) Implantation in Avascular Necrosis of the Femoral Head: A Mid-Term Outcome Analysis

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Abstract

Introduction Avascular Necrosis (AVN) of the femoral head, a condition characterized by the interruption of blood supply leading to bone tissue death, presents significant therapeutic challenges. Recent advancements in orthobiologics, including the use of Autologous Adult Live-Cultured Osteoblasts (AALCO), combined with core decompression, offer a novel approach for managing AVN. This study assesses the efficacy of this treatment modality in improving functional outcomes and hindering disease progression.

Materials and methods This retrospective observational study encompassed 30 patients treated between 2020 and 2023 for idiopathic AVN of the femoral head, grades I to III, who had not responded to conservative treatment. Patients were excluded based on specific criteria including age, secondary AVN causes, and certain health conditions. The treatment involved a two-stage surgical procedure under spinal anesthesia with OSSGROW® for AALCO generation. Post-operative care emphasized early mobilization, DVT prevention, and avoidance of NSAIDs. Outcome measures were evaluated using the Visual Analog Scale (VAS) for pain, modified Harris Hip Score, and annual MRI imaging for up to 36 months.

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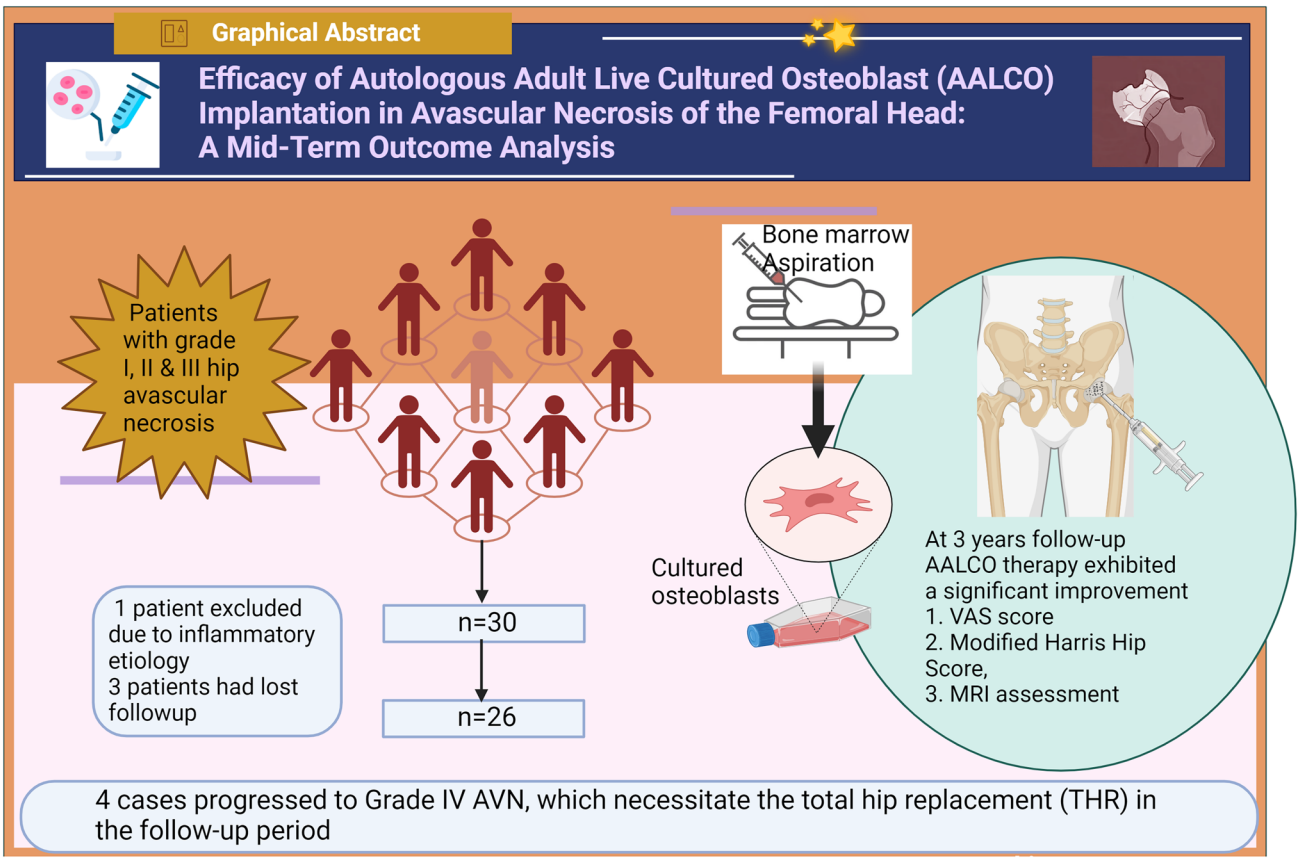
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Results Among 26 patients (41 hips) completing the study, statistically significant improvements in pain and hip functionality were documented, alongside positive radiological signs of osteogenesis in the majority of cases. However, four instances required advancement to total hip replacement due to disease progression.

Conclusion The combination of core decompression and AALCO implantation shows promise as an effective treatment for AVN of the femoral head, with notable improvements in functional and radiological outcomes. This study supports the potential of orthobiologic approaches in AVN treatment, warranting further investigation through comprehensive randomized controlled trials.

Graphical Abstract



Keywords Avascular necrosis · Femoral head · Osteoblast · Progenitor cells

Introduction

Avascular Necrosis (AVN) of the femoral head, also known as osteonecrosis, occurs due to a disruption in blood flow to the proximal femur [1]. The annual incidence of this condition is estimated to be between 10,000 and 20,000 cases, with variations depending on geographic location [2]. The causes behind AVN are diverse, including both traumatic injuries, such as fractures and dislocations, and non-traumatic origins like excessive alcohol consumption, prolonged use of steroids, blood clotting disorders, and genetic predispositions [3]. Recent studies indicate that COVID-19 infection might result in a long-term consequence called AVN of the femoral head. Acute post-COVID AVN has been identified as another aspect of long-term COVID-19 by Agarwala et al. [4]. The femoral head's blood supply is delicate, and microvascular damage can lead to decreased blood supply and avascular necrosis [5]. Additionally, studies have shown that the frequency of AVN of the femoral head is higher in Indian patients undergoing total hip arthroplasty as compared to the Western population [6].

Currently, AVN of the femoral head presents a challenging condition with no definitive cure. Treatment options include non-surgical methods, such as medication with lipid-lowering agents, anticoagulants, vasoactive drugs, and bisphosphonates, alongside non-pharmacological interventions

like extracorporeal shockwave therapy, pulsed electromagnetic therapy, and hyperbaric oxygen therapy. Surgical alternatives range from core decompression to total hip replacement, with traditional core decompression being a widely recognized method for reducing intraosseous pressure by drilling holes into the femoral head [2, 7, 8].

The advent of orthobiologicals, such as platelet-rich plasma (PRP) [9–11], bone marrow aspirate concentrate (BMAC) implantation [12–14], stromal vascular fraction (SVF) implantation [15], and autologous adult cultured osteoblast (AALCO) implantation [16, 17] combined with core decompression, introduces an innovative approach within the field of orthobiologics, potentially offering a new solution for treating osteonecrosis of the femoral head [18, 19]. BMAC is a minimally manipulated autologous product derived from bone marrow aspiration, comprising a complex mixture of mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), and platelets, along with an array of growth factors and cytokines. Its potential for therapeutic application is supported by observed anti-inflammatory, immunomodulatory, angiogenic, and chondrogenic effects in both in vitro studies and animal models. Significantly, research has demonstrated a reduction in MSC quantities within the bone marrow and stroma of femoral heads affected by AVN, highlighting the potential efficacy of AALCO and BMAC in treating this disease [16, 20].

This study aims to assess the mid-term functional outcomes in patients treated with core decompression and Autologous Adult Live-Cultured Osteoblasts (AALCOs) implantation for AVN of the femoral head, with a follow-up period of at least 3 years. Secondary objectives include evaluating the safety, side effect profile, patient satisfaction, and radiological disease progression of the procedure.

Materials and Methods

Study Design and Patient Selection

A retrospective observational study of 30 patients who underwent autologous cultured osteoblast implantation for the management of avascular necrosis of the femoral head was carried out between 2020 and 2023 after obtaining approval from the institutional ethical committee [T/IM-NF/Ortho/23/190] dated 26.03.2024.

Inclusion Criteria

The study included patients above the age of 18 years presenting with idiopathic AVN of the femoral head, classified between grades I to III according to the modified Ficat and Arlet classification, who failed a conservative line of management (pharmaceutical therapy and physical therapy) for 6 months and presented with persistent pain and disability. All patients who had completed a minimum follow-up of 3 years were included.

Exclusion Criteria

Patients who were under 18 years of age, had secondary AVN due to other causes including alcohol, smoking, and steroid intake; had active neoplastic disease, BMI above 35, had a previous history of surgery or trauma to the affected hip joint, had signs of active infection or inflammation over the joint, had inflammatory arthritis, or tested positive for HIV, HbsAg, HCV, or VDRL and patients not willing for the procedure were excluded from the study.

Surgical Procedure

AALCO implantation is a two-stage procedure. Both of these are performed under spinal anesthesia. OSSGROW® (Regrow Biosciences Pvt Ltd., Mumbai, India) is an FDA-approved commercial technique that produces AALCO from bone marrow aspirate.

- Stage 1: In the first stage, 12 ml of bone marrow is aspirated from the patient's iliac crest maintaining all aseptic precautions. This aspirate is subsequently forwarded to Regrow Biosciences laboratory for the ex vivo cultivation of mesenchymal stem cells (MSCs), which are induced toward osteoblastic lineage until the third passage, resulting in the generation of AALCO, comprising 48 million cells.
- Stage 2: The finished product containing a highly potent homogenous population of AALCO [48 million autologous adult live cultured osteoblasts] is obtained from the laboratory 3–4 weeks after the first stage. The patient is then taken to OT and routine core decompression is done under fluoroscopic guidance; followed by the curettage of necrotic bone and tissue with lavage using normal saline (Fig. 1). Finally, the implantation of the cultured cells is done using a gel TISSEELKit (Baxter, U.S.) at the site of osteonecrosis under fluoroscopic guidance (Fig. 2).

Post-Operative Protocol

Post-surgery, all patients were allowed to commence weight-bearing as tolerated and began mobilization immediately. The physiotherapy program included exercises aimed at strengthening the abductor muscles, quadriceps, and hamstrings, with subjects encouraged to partake in light activities as tolerated. After 6–8 weeks, subjects

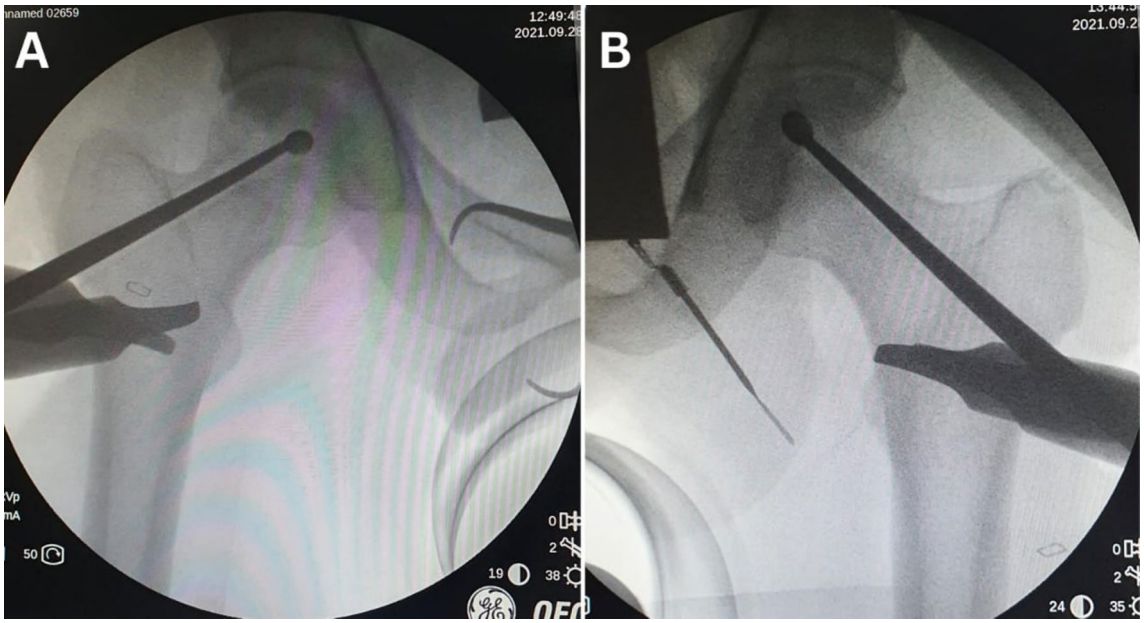


Fig. 1 Intra-operative images showing the core decompression of necrotic area in the **A** right and **B** left femoral head

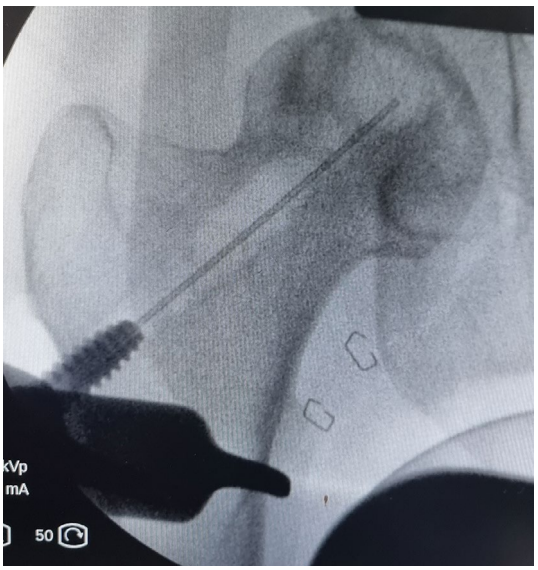


Fig. 2 Placement of autologous adult live cultured osteoblasts using a gel TISSEELKit at the site of osteonecrosis under fluoroscopic guidance

were allowed to resume full activities. Prophylactic Oral Apixaban 2.5 mg, administered twice daily for 2 weeks, was prescribed to mitigate the risk of deep vein thrombosis (DVT). Subjects were advised against the intake of oral non-steroidal anti-inflammatory drugs for a minimum of 4 weeks post-procedure to prevent interference with the therapeutic mechanisms of AALCO therapy, which relies on the body's innate inflammatory healing response.

Outcome Assessment

Subjects underwent assessment pre-operatively and at subsequent follow-ups at 1, 3, 6, 12, 24, and 36 months. Functional outcomes were quantified at each serial follow-up utilizing the Visual Analog Scale (VAS) for pain and the modified Harris hip score. Radiological assessment was done using annual MRI imaging which was employed to monitor radiological improvement of the disease. Any procedure-related issues that occurred throughout the follow-up were documented, as were any patients who required further intervention due to disease progression.

Statistical Analysis

The statistical analysis was performed utilizing SPSS Version 26, IBM Corp, Chicago, IL, USA. Data normality was assessed using the Shapiro–Wilk test. Continuous variables were represented as means with standard deviations, whereas categorical variables were expressed in terms of frequencies and proportions. The evaluation of statistical significance between cohorts was conducted through parametric tests, with *t*-tests applied for continuous variables and chi-square tests for categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 30 patients were eligible for the trial among whom 1 was excluded due to inflammatory etiology and 3 patients were lost to follow-up. A total of 26 patients (41 hips) were eligible for final evaluation who had completed a minimum follow-up of 3 years (Fig. 3). The demographic variables of the study participants are depicted in Table 1.

Functional Outcomes

Functional outcomes were assessed with visual analog score and modified Harris hip scores at baseline and 1st-, 3rd-, 6th-, 12th-, 24th-, and 36th-month follow-ups. A statistically significant difference was observed with VAS ($p < 0.001$) and modified Harris hip scores ($p < 0.001$) at baseline and 36th-month follow-up (Table 2).

Radiological Outcomes

Radiological outcomes were determined through Magnetic Resonance Imaging (MRI) assessments conducted after the study period. The MRI findings at the 36-month follow-up mark revealed significant osteogenesis at the site of AALCO implantation in 22 out of the 26 evaluated patients. This osteogenic activity is indicative of successful bone remodeling and integration of the implant with the host bone tissue. Furthermore, the radiological outcomes were paralleled by a noteworthy reduction in pain levels and a decreased dependency on walking support among the participants. These findings underscore the potential of AALCO implantation as a viable therapeutic intervention for enhancing bone regeneration and functional recovery in patients with hip dysfunctions. A representation case of bilateral AVN treated with AALCO implantation is depicted in Figs. 4 and 5.

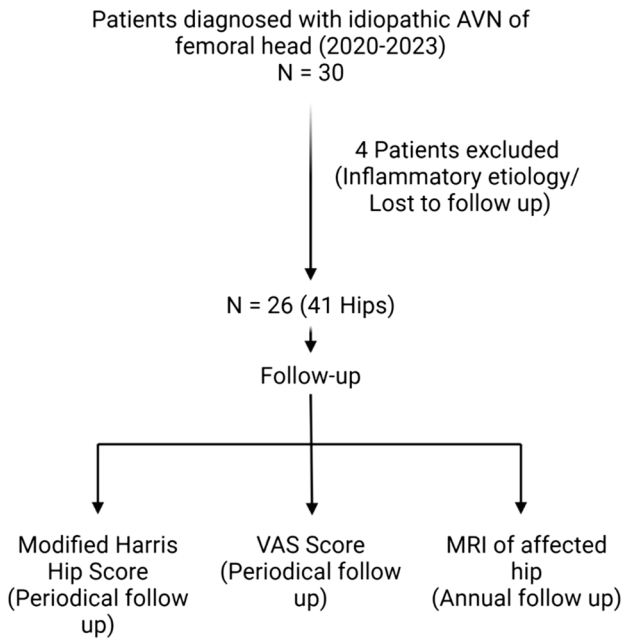


Fig. 3 Schematic representation of patient recruitment and follow-up in the study duration

Table 1 Demographics variables of the study participants

Demographic parameters	$N = 26$ (41 hips)	Percentage
Age (years)		
21–35	5	19.25
36–50	12	46.15
51–65	6	23.07
66–80	3	11.53
Sex		
Male	18	69.23
Female	8	30.77
Obesity		
Grade 1	18	69.23
Grade 2	6	23.07
Grade 3	2	7.70
Laterality		
Bilateral	15	73.17
Right	6	14.78
Left	5	12.05
Modified Ficat Arlet classification		
Grade 1	7 hips	17.07
Grade 2a	19 hips	46.34
Grade 2b	10 hips	24.39
Grade 3	5 hips	12.20

Complications

Despite the promising outcomes, the study identified complications in a subset of the patient population. Specifically,

Table 2 Assessment of functional outcomes at various time frames

Time frame	Visual analog scores	Modified Harris Hip Scores
Baseline	9.00 ± 0.00	46.12 ± 3.68
1st-month follow-up	7.65 ± 0.35	51.60 ± 9.65
3rd-month follow-up	6.45 ± 0.26	68.21 ± 6.32
6th-month follow-up	5.17 ± 0.14	73.85 ± 4.44
12th-month follow-up	4.25 ± 0.78	82.40 ± 4.83
24th-month follow-up	3.55 ± 0.51	88.60 ± 5.06
36th-month follow-up	3.01 ± 0.03	89.23 ± 2.19
p-value	< 0.001	< 0.001

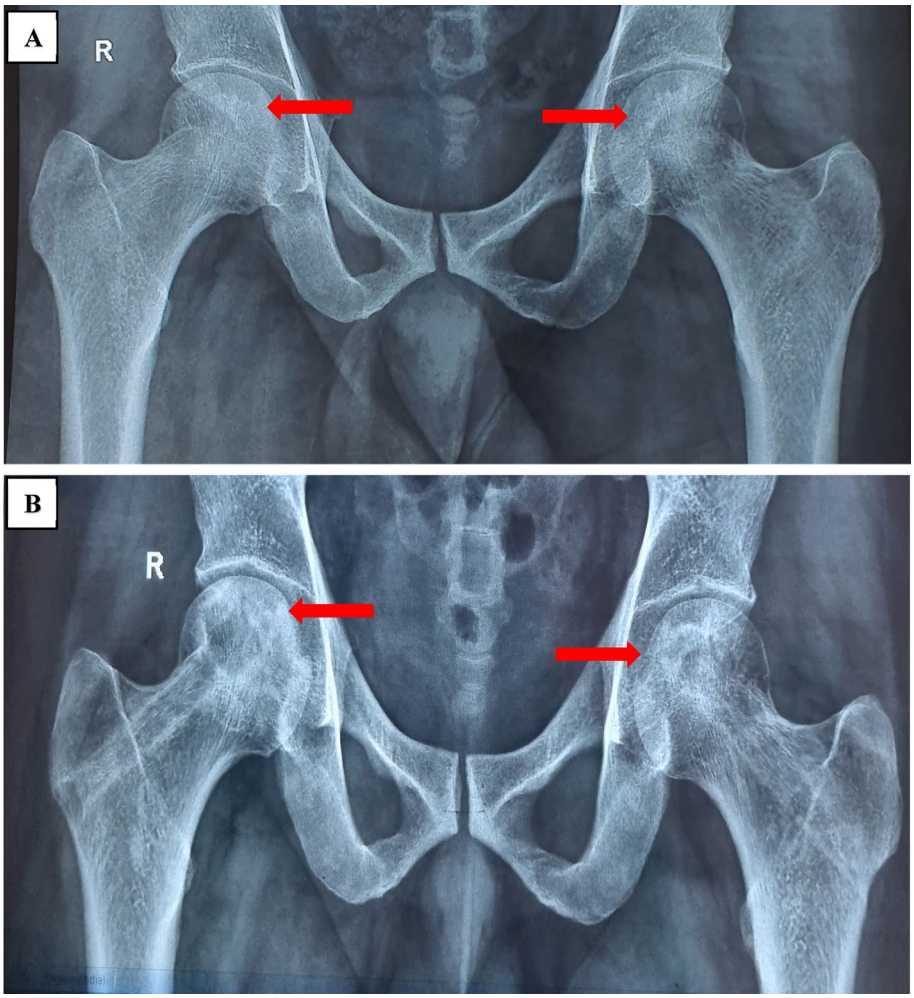


Fig. 4 Plain radiograph of pelvis with bilateral hips showing **A** avascular necrosis of bilateral femoral heads and **B** improved osteogenesis at the necrotic area with the evidence of core decompression over bilateral femoral heads at 36th-month follow-up

4 cases exhibited progression to a more severe condition, advancing to Modified Ficat Arlet classification of Grade IV. This progression was characterized by exacerbated hip degeneration, necessitating the surgical intervention of total hip replacement (THR). The advancement to Grade IV and the subsequent requirement for THR in these patients highlights a critical aspect of postoperative management and the need for rigorous follow-up protocols. It underscores the variability in individual responses to AALCO implantation and the importance of identifying potential predictors of adverse outcomes. The complications observed prompt further investigation into the factors contributing to the progression of hip degeneration post-implantation and underscore the need for a personalized approach in the management of patients undergoing such therapeutic interventions.

Discussion

Our clinical study demonstrated considerable clinical effectiveness in patients undergoing core decompression accompanied by Autologous Adult Live-Cultured Osteoblasts (AALCO) at mid-term evaluations. Notably, these patients exhibited statistically significant enhancements in both functional and radiological parameters, with the majority expressing high levels of satisfaction with the outcomes of the procedure.

The traditional approach of core decompression as a standalone treatment has diminished in popularity, with evidence suggesting that approximately 50% of patients may progress to a state of clinical failure following this

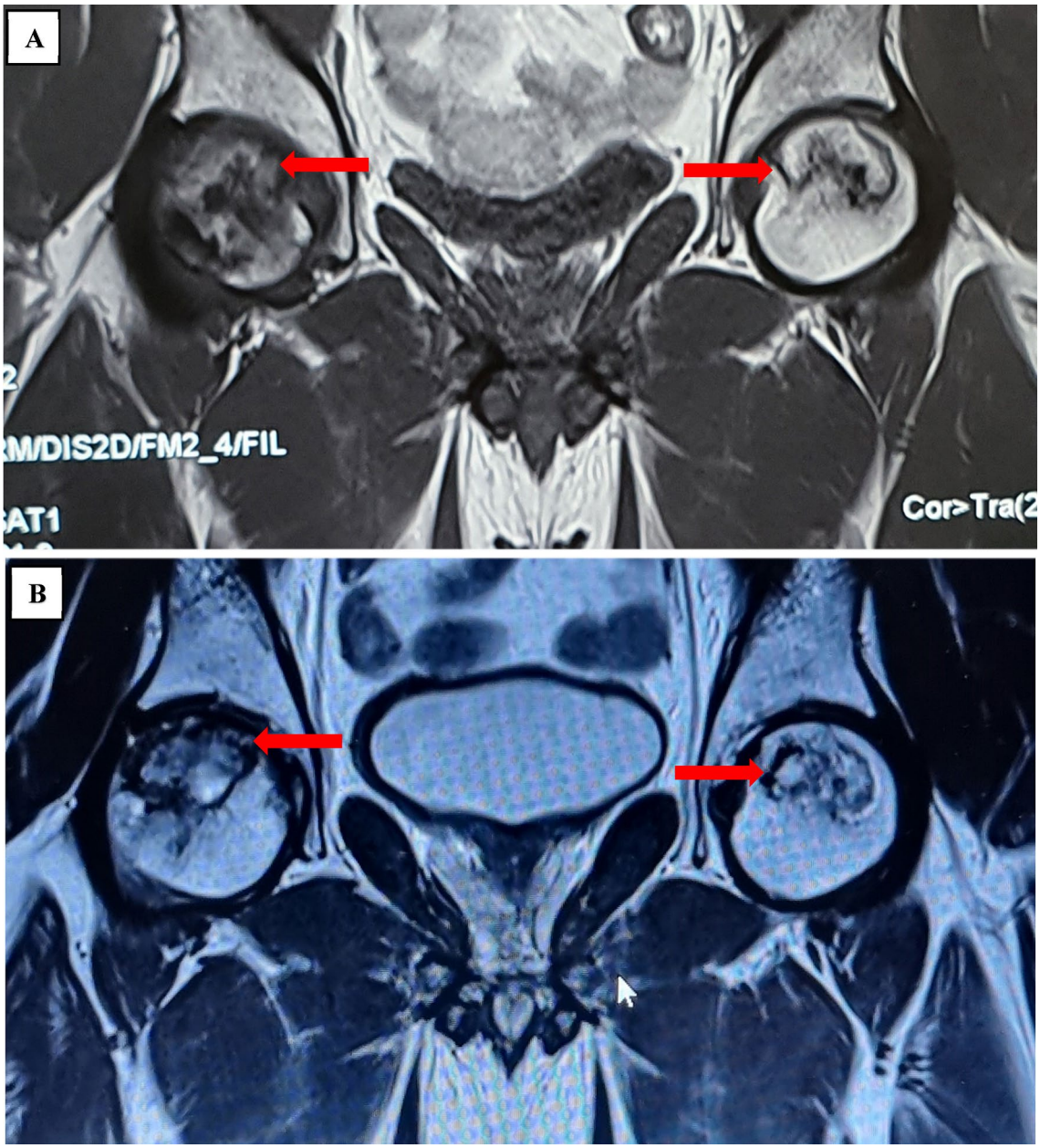


Fig. 5 **A** Pre-operative MRI of the pelvis with bilateral hips showing grade 2b avascular necrosis of bilateral femoral heads and **B** 36th-month follow-up MRI of the pelvis with bilateral hips showing improved osteogenesis at the necrotic area of femoral head without altering the contour of femoral heads by halting the disease progression

method [12]. Consequently, the integration of adjunct therapies, such as MSCs, BMAC, SVF, and AALCO, has gained traction. These advanced therapeutic strategies have not only demonstrated the potential to defer the necessity for total hip replacement (THR) in roughly 70% of affected individuals but have also provided indications of halting or even reversing the progression of the disease [16, 20, 21].

The application of stem cell therapy in medical treatments raised concerns due to potential complications, such as rejection and risk of tumor formation. However, this was found to be associated with the use of allogenic stem cells [22, 23]. Recent research has highlighted autologous stem cell therapy as a considerably safer option, demonstrating a minimal risk of adverse effects over the long term [24, 25]. This shift toward autologous stem cells has significantly altered the therapeutic landscape, offering a more promising outlook for patients.

In the context of avascular necrosis (AVN), the integration of autologous stem cell therapy has been particularly

noteworthy. Research conducted by Xu and colleagues has shown that combining core decompression with the transplantation of autologous marrow stem cells not only enhances efficacy in the early stages of AVN but also markedly decreases the necessity for total hip arthroplasty (THA) conversion compared to core decompression alone.

Furthermore, the progression to THA, which could escalate to 75% due to the natural advancement of AVN, has been shown to decrease significantly with the advent of biologicals. Utilization of BMAC has reduced this conversion rate to approximately 47%, and the introduction of Autologous Adult Live-Cultured Osteoblasts (AALCO) has further lowered these figures to around 20%, according to findings by Hauzeur et al. [26]. According to Gangji et al., transplantation of osteoblast cells in patients with AVN of the femoral head is more effective than implantation of BMAC in delaying the progression to subchondral fracture of the femoral head and reducing pain associated with AVN of the femoral head [18].

Comparative analysis between each of the orthobiological remains exceedingly rare within the existing body of literature. However, a case report by Shankar et al., which represents a unique instance of direct comparison between BMAC and AALCO therapies in the same patient, offers valuable insights. This report details a 5-year longitudinal follow-up of a 44-year-old male patient who underwent core decompression with BMAC implantation on one hip and AALCO implantation on the other, aimed at treating idiopathic avascular necrosis (AVN) of the femoral head. While clinical improvements were observed on both sides, the hip receiving AALCO treatment exhibited markedly superior outcomes in terms of pain reduction and hip function (assessed through the Harris hip score) at corresponding intervals of follow-up. Moreover, while radiological assessments revealed disease progression on the BMAC-treated side, the hip treated with AALCO showed no signs of disease advancement, even at the final follow-up of 6 years [27]. This evidence underscores the potential advantages of AALCO implantation over BMAC in managing AVN of the femoral head, highlighting its role in enhancing patient outcomes and possibly altering the disease's natural history in a favorable direction.

Although BMAC and AALCO implantation are based on the same principles, (i.e.) osteoprogenitor cells present in bone marrow are crucial for stimulating new bone growth; a notable drawback of BMAC is its composition of diverse BM cells, making it less specific in action. Studies have indicated that osteoblasts, particularly those characterized by high levels of bone alkaline phosphatase, possess a markedly enhanced capacity for bone regeneration [28]. In in vitro, induction of alkaline phosphatase levels predicts in vivo bone-forming capacity of human bone marrow stromal cells. This distinction underscores the superior effectiveness of AALCO therapy in promoting bone repair and regeneration.

Employing AALCOs implantation for AVN treatment represents an innovative approach in regenerative medicine focused on osteogenesis, leveraging the capabilities of differentiated osteoblast cells. This method's strength lies in the precise regulation of cell quantity and quality, enhancing the uniformity and reliability of therapeutic outcomes. Conversely, the use of AALCOs incurs high production costs, attributable to the need for specialized equipment, advanced technical expertise, a highly skilled surgical team, and doubtful efficacy in stage 3. This requirement for specific resources and knowledge underscores a critical barrier to the widespread adoption of AALCO-based treatments, despite their potential for more controlled and consistent therapeutic effects [29, 30]. The clinical studies of AALCO for AVN femoral head are summarized in Table 3.

The main limitations of this study include the small sample size, lack of a comparative group, and failure to evaluate other secondary causes of AVN. Additionally, location and size of the avascular lesion were not taken into consideration. Further, large-scale prospective RCTs are needed to evaluate the long-term efficacy and safety of AALCO implantation for AVN.

Conclusions

Core decompression combined with AALCO implantation is a feasible, secure, and cost-effective treatment strategy for individuals with modified Ficat and Arlet Grade I–III AVN of the femoral head. This technique has demonstrated good functional outcomes and high levels of patient satisfaction, with a minimum follow-up period 3 years, during which no complications were observed nor progression of the disease. To corroborate these results, additional extensive, randomized controlled trials with longer follow-up durations are warranted.

Table 3 Summary of clinical studies of AALCO for AVN femoral head

Author (year)	Type of study	No of participants	Key findings	Significance
Kim et al. [31] (2008)	Case report	1 patient (2 hips)	5-year follow-up radiographs and MRI showed evidence of remodeling as well as maintenance of the right femoral head, but the left femoral head showed slight irregularity, sclerotic changes, and osteophyte formation	AALCO is effective in AVN femoral head
Palekar et al. [32] (2021)	Case series	15 patients	Hip joints were preserved structurally by regaining the joint biomechanics after osteoblast implantation	Use of autologous osteoblast cell implant is recommended in early AVN femoral head
Palekar et al. [16] (2021)	Retrospective study	64 patients (101 hips)	AALCO treatment could delay total hip arthroplasty for 71.3% of hips; Improved in 71.1% of patients in the early stage (Grades I and II) versus 58% in the late stage (Grades III and IV) of osteonecrosis	AALCO halted the progression of osteonecrosis, preserved the natural hip, and eliminated the need for hip replacement surgeries
Sadat-Ali et al. [33] (2022)	Prospective study	63 patients	2-year follow-up MRI revealed new bone formation and amelioration of the avascular lesions	AALCO transplantation embarked the greater potential in the healing of AVN femoral heads
Agarwal et al. [17] (2023)	Case series	6 patients (6 hips)	Significant improvement in their quality of life and activity of daily living after AALCO implantation; The necrotic area of the femoral head did not evolve in the size of the lesions	AALCO implantation results in pain reduction and improvement in hip function in AVN of the femoral head due to sickle cell anemia
Shankar et al. [27] (2023)	Case report	1 patient (1 hip)	6-year MRI follow-up of left hip transplanted with AALCO remains viable along with maintenance of contour of femoral head when compared with right hip transplanted with undifferentiated BMAC cocktail	AALCO transplantation remains the effective biological option for AVN femoral head
Present study	Prospective study	26 patients (41 hips)	3-year MRI follow-up demonstrated osteogenesis at the site of AALCO implantation for 22 patients, whereas 4 cases advanced to grade IV and resulted in the need for total hip replacement	Core decompression with AALCO implantation holds a viable treatment option for grade I to III AVN femoral head

Data availability All data is contained within the manuscript.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All India Institute of Medical Sciences, Bhubaneswar—T/IM-NF/Ortho/23/190 dated 26.03.2024.

Informed Consent For this type of study, informed consent is not required.

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