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CORE DECOMPRESSION IN OSTEONECROSIS OF THE FEMORAL HEAD: WHERE DO WE STAND TODAY?

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Abstract

Early diagnosis and treatment with hip preservation procedures is the goal of osteonecrosis hip. Core decompression (CD) of the femoral head is a cost-effective procedure that reduces the intraosseous pressure, promotes neoangiogenesis, and enhances new bone formation. The need for the conversion of the total hip arthroplasty in the early-stage osteonecrosis hip is around 38% after an average follow-up of 26 months. The current techniques of CD involve multiple drilling (3 mm Steinmann pin) or drilling with large diameter reamers (5.0–7.2 mm) and numerous cellular and noncellular orthobiologic product instillations into the core tracks. The augmented CD with bone marrow aspirate concentrate (BMAC) or bone-marrow-derived mixed connective tissue progenitor's cells instillation has consistently shown superior outcomes in early-stage osteonecrosis of the femoral head (ONFH; Ficat stage I and II and Association Research Circulation Osseous [ARCO] stage I and II). However, to date, no conclusive evidence supporting other orthobiologic products (platelet-rich plasma, bone morphogenetic protein, and tantalum) in ONFH is shown.

Keywords: *Core decompression*, *osteonecrosis*, *AVN*; *Hip joint*; *Stem cells*; *Cell therapy*; *PRP*

INTRODUCTION

Osteonecrosis of the femoral head (ONFH) is a painful and disabling condition of the hip joint in young individuals. The blood supply to the femoral head is disrupted in this condition leading to subsequent death and repair of the bone cells. During this process, the mechanical loading on the femoral head causes deformation and arthritis of the hip joint.[1] If the natural course of the disease pursues, more than 80% of patients will end up with hip arthritis.[1–3] Total hip arthroplasty (THA) remains the only viable option when the joint becomes arthritic. However, THA is not a durable option for these young individuals. Therefore, early diagnosis and treatment with hip preservation procedures should be the goal. Literature supports early intervention in the femoral head to restore vascularity before it collapses.[1,4]

Core decompression (CD) is an effective procedure that reduces the intraosseous pressure in the femoral head, augments the neoangiogenesis around the decompression tracks, enhances new bone formation, and delays the progression of osteoarthritis.[4] However, there is no standardized technique for performing CD in ONFH.[5] Undoubtedly, the technique

and the patient selection criteria for the procedure have improved over time. Marker et al. compared the CD technique in ONFH patients who were operated on before 1992 with those operated between 1992 and 2007.[6] They reported that 41% of patients required secondary hip procedure in the pre-1992 patient cohort compared with 30% after 1992.

Recently, CD is barely performed as an isolated procedure. Numerous additional therapies into the core track have considerably improved the outcome.[7–12] Cell therapy and other noncellular orthobiologic products provide better pain relief, functional outcome, and hip survivorship.[7–13] However, the lack of uniformity among the studies, variable etiology, and inclusion of different grades of disease makes the interpretation difficult. This review will focus on isolated CD and augmented CD techniques in ONFH.

WORKING PRINCIPLE OF CD

The pathophysiology of nontraumatic osteonecrosis (chronic alcoholism, steroid intake, hemoglobinopathies, etc.) involves thromboembolic occlusion of intraosseous vessels and extravascular compression leading to the diminished blood supply to the femoral head.[1,14] The two main pathogenesis of ONFH are raised intraosseous pressure because of venous congestion and diminished arterial supply because of secondary compression or primary occlusion because of the underlying etiology. CD removes a core of bone from the femoral head and thus decreases intraosseous pressure and pain. The neoangiogenesis through the core tract and neo-bone formation by creeping substitution further augments the healing process.[15,16] However, the pathogenesis of steroid induced ONFH, which involves bone marrow adipogenesis and fat cell hypertrophy, is not restricted even after CD. So, its efficacy in steroid-induced ONFH is theoretically minimal.[16,17] The vascular disruption in traumatic ONFH also makes the patient unsuitable for CD.[18] However, many traumatic and steroid-induced ONFH have been included in the clinical studies without segregated outcomes.

BASIC SCIENCE PROOF OF CONCEPT

Numerous preclinical studies have proven the beneficial effect of CD in ONFH.[19–21] Wang et al. reported increased blood flow into the femoral head following CD in a rabbit model of steroid-associated ONFH.[20] Maruyama et al. also observed an increase in bone mineral density and bone volume fraction in the femoral head in the CD group compared with the control group. Histological analysis revealed significantly increased alkaline phosphatase and CD31 positive cells in males after CD treatment. However, the number of empty lacunae in the surrounding trabecular bone was significantly higher in the CD group. They concluded that CD improved the morphological properties but did not improve the mechanical strength in the femoral head in the early-stage ONFH and suggested the need for additional biological and mechanical strategies to improve the outcome of early-stage steroid-associated ONFH.[21]

Preclinical studies on cell therapies in ONFH have shown better results compared with the isolated CD.[22–24] Wu et al. reported increased migration of mesenchymal stem cells to the necrotic area after administration of the cultured stem cells and Danshen (a Chinese herbal product) into the femoral artery of a rabbit model. There was an upregulated expression of the chemokines MCP-1 and SDF-1. Danshen combined with MSCs also promoted revascularization by increasing the expression of VEGF and bone morphogenetic protein (BMP)-2 in the femoral head, enhancing reossification and revascularization.[22] In an animal model (rabbit), Fan et al. reported that low oxygen tension (2%) with simultaneous bone marrow-derived mesenchymal stem cells implantation showed increased proliferation and osteogenic potential. The low-oxygen treated stem cells have added advantage of the decreased adipogenic potential.[25] A recent animal study on allogenic peripheral blood-derived mesenchymal stem cells reported upregulation of BMP-2 and downregulation of peroxisome proliferator-activated receptor-gamma mRNA. Additionally, bone density and bone trabeculae tended to increase gradually.[26] Several other preclinical and preliminary clinical

studies have demonstrated excellent repairing ability of autologous bone marrow mesenchymal stem cells when seeded with bone matrix scaffold, beta-tricalcium phosphate, or bio-derived bone materials combined with recombinant human BMP (rhBMP)-2. These cells-mixed scaffolds were implanted directly into the core tract.[27–30]

In an interesting clinical study on traumatic ONFH, Xu et al. reported lower miR-224-3p levels in exosomes after bone marrow-derived mesenchymal stem cells implantation, and angiogenesis promotion of the necrotic femoral head by upregulating FIP200.[24] It seems the cultured expanded mesenchymal stem cells have the potential to revert vascularity even in traumatic ONFH. Few other research developments have focused on improving the proliferation of selective osteoblastic lineage of mesenchymal stem cells. Researchers have also found that moderate-intensity extracorporeal shock wave therapy augments the mesenchymal stem cells proliferation, induces the conversion of mesenchymal stem cells into osteoblasts, and inhibits differentiation of stem cells into adipocytes.[31] Similarly, co-transplantation of adipose tissue and bone marrow-derived stem cells have better healing potentials.[32]

THE IDEAL CANDIDATE FOR CD

Although CD was considered an effective procedure in early-stage ONFH, the evaluation of CD in ONFH of various etiologies, stages, and classifications in the studies makes it challenging to interpret the result. However, the research by Marker et al. reported that one of the predictors of a better outcome in patients of the post-1992 hip cohort was the inclusion of lesser numbers of Ficat stage III disease.[6]

The long-term outcome of CD seems promising in a selective group of patients.[10–33] Fairbank et al. evaluated ONFH patients in both pre- and postcollapse stages (n = 128 hips). After a 10-year follow-up, the hip survival rates in Ficat stages I–III of disease were 96%, 74%, and 35%, respectively.[33]

Few studies focused on the location of the lesion in addition to the disease stage.[7,34] Yoon and their associates found more numbers of conversion THA following CD in Ficat stage II or III disease (5 out of 17 hips) than those of stage I after a mean follow-up of 61 months.[34] They reported increased failure with larger-sized lesions (>30% of the femoral head) and laterally or centrally located lesions. Considering all the factors, the ideal candidate for CD in ONFH is a precollapse stage with lesion size < 15% and Kerboul angle $< 200^0$, Ficat stage I or II, ARCO I or II, and Steinberg stage I, II or III.[1,7,10,35]

CONSENSUS ON THE TECHNIQUE OF CD

Until 2004, the standard technique of CD was the removal of 8–10 mm wide osseous core from the femoral head centering over the lesion.[1,10,36,37] The risks for subtrochanteric fracture, delayed weight-bearing following the procedure, and catastrophic joint damage because of inadvertent penetration of such a wide drill bit mandated the surgeons to think of better alternatives.[1] Kim et al. in 2004 presented the technique of multiple drilling in the ARCO annual meeting.[36] Subsequently, Mont et al., in their first study described multiple drilling with a tiny diameter drill bit (3.2 mm drill bit).[37] They recommended 2–3 tracks into the lesion with a 3 mm Steinmann pin. They achieved 80% success (Harris hips score of < 70 and no secondary procedures) in Ficat stage I disease (n = 30) with the small core tracks. Subsequently, many comparative studies on the standard CD and small diameter multiple drilling reported equivalent outcomes in pain relief, hip functional outcome, and hip survivorship.[38–41] In a cadaveric study, Brown et al. reported that CD with a small diameter bore and multiple drilling techniques withstood significantly greater load before failure than the single large bore technique after adjustment for bone mineral density ($P < 0.05$).[42] They reported a larger core of bone removal with the single bore technique using 8 mm compared with the 3 mm multiple drilling techniques ($P < 0.001$). The multiple small bore technique removes less bone, thereby potentially leading to a higher load to failure after CD in early ONFH. To conclude, multiple tiny drilling using a 3 mm Steinman pin poses all the advantages of wide-bore CD but with fewer complications.

THE AUGMENTED CD IS MORE EFFICACIOUS THAN ISOLATED CD

The isolated CD is no longer the treatment of ONFH, but surgeons augment the healing process with numerous additional treatments to the core track. A recent meta-analysis on isolated CD in ONFH reported that CD provides short-term clinical improvement and pain relief in most cases.[5] The hip-survivorship rate was also not rewarding; the pooled outcome of 1135 hips with nearly 80% early-stage ONFH showed 38% conversion THA within an average span of 26 months. The review failed to determine the effectiveness of isolated CD in ONFH irrespective of stage and etiology.

AUGMENTED CD

The augmented CD involves the following procedures: bone grafting, cell therapy, noncellular orthobiologic products instillation, and numerous mechanical device insertion for structural support. Since the introduction of cell therapies into the ONFH, the number of studies on isolated CD has decreased. Most of the recent studies suggest that CD with bone marrow-derived cell therapies have a better outcome than isolated CD procedure[43–50] (Figures 1–3). Apart from patient selection, all authors have stressed the qualitative value of the mixed connective tissue progenitor cells for preventing treatment failure. The number of mesenchymal stem cells (MSCs) in 1 cm^3 of a normal femoral head was found to be 700 ± 264 MSCs per cm^3. With an average femoral head volume of 50 cm^3, approximately 35,000 MSCs would be the critical number of MSCs needed to re-establish the number of MSCs as in the normal femoral head.[51,52] Hernigou et al. reported that implantation of more than 2 million mononuclear cells per mL of the necrotic foci is necessary for a successful outcome from a bone marrow-derived MSC therapy.[51,52] The treatment outcome in ONFH can be evaluated in three directions: clinical outcome, radiological outcome, and hip survivorship. The most important aspects of improvement for the surgeon and patients are clinical improvement and hip survivorship.

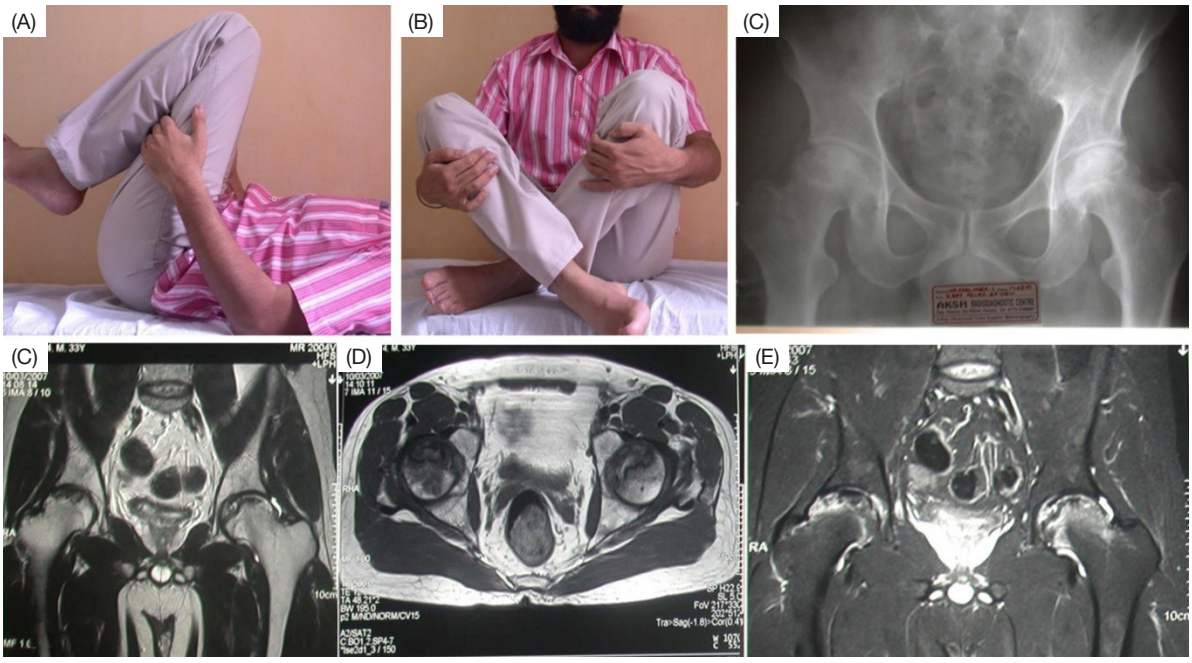

Figure 1. Idiopathic bilateral ONFH in a 33-year-old male (A–F) with functional limitations and radiographic stage 2 ONFH (Ficat and Arlet).

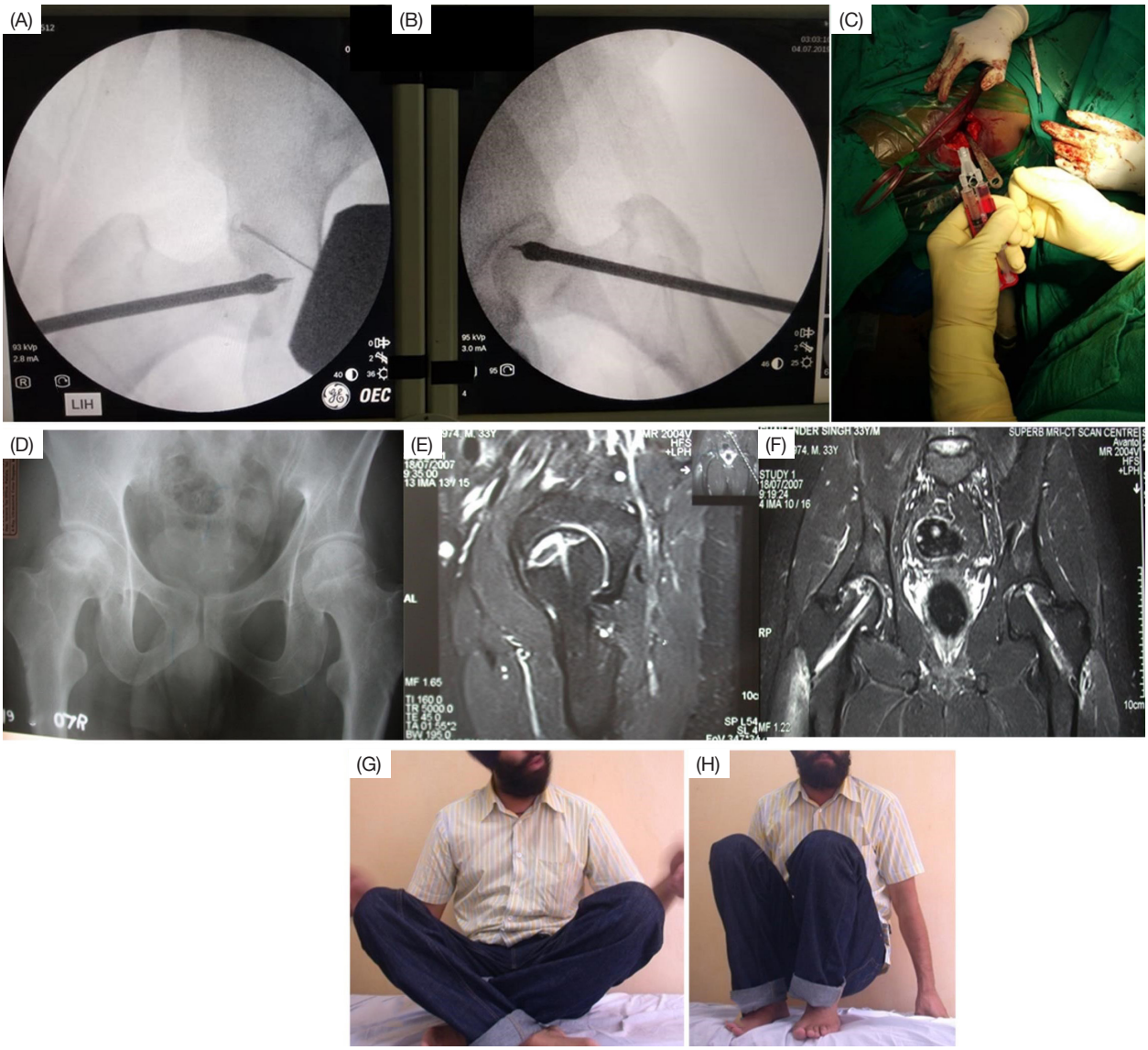

Figure 2. Core decompression (A, B) followed by bone marrow aspirate concentrateimplantation in both the hip joints (C). Imaging after 6 months of stem cells implantation shows partial resolution of the lesion (D, E, F). Clinical outcomes improved (G, H).

Bone grafting

Numerous types of bone graft (cancellous bone, solid cortical, or fibular graft) have been used in the core tracks. The study by Wei and Ge reported hip survivorship of 81% after 2 years after CD and non-vascularized bone grafting (n = 223 hips) in ARCO stage II and III ONFH.[53] The functional score of the hip (HHS) also increased from 61 to 86. Few other studies supported the use of bone graft in the core track and extended their indications of CD to the moderate grades ONFH (early collapse, ARCO II, III).[54,55]

Cell therapies

Bone marrow-derived cytotherapy

The levels of osteoprogenitor cells in the proximal femur are low in ONFH; thereby, the healing capacity is inadequate.[51,52] Bone marrow aspirate

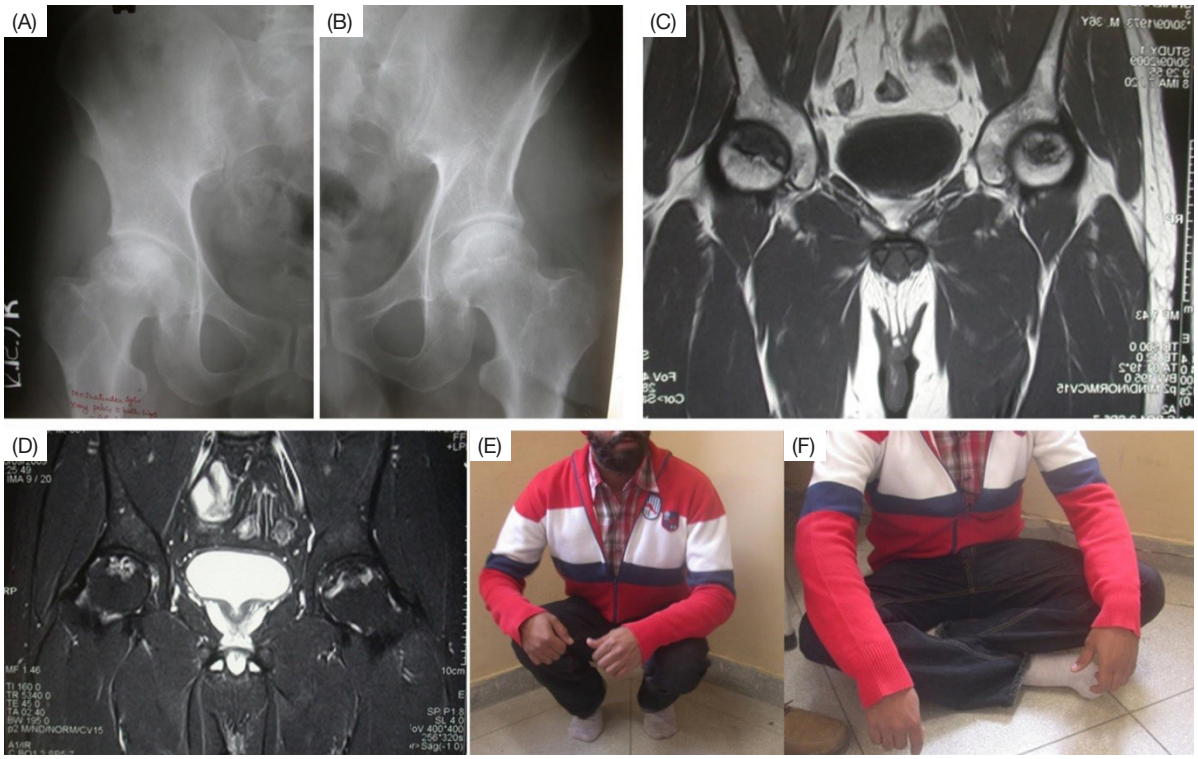

Figure 3. After 4-years of core decompression and stem cells instillation, the radiological and clinical improvements are clearly visible (A–E).

concentrate (BMAC) or mixed connective tissue progenitor cells instillation after CD regenerates the osteogenic cells and induce vasculogenesis, and thus helps in preserving the femoral head.

A recent meta-analysis of seven randomized controlled trials (n = 579 patients) reported that CD with bone marrow-derived cell therapies showed a significant reduction of pain (mean difference [MD] of visual analog scale [VAS] was 12.88) and conversion THA (odds ratio –0.14) compared with isolated CD.[50] The findings of this meta-analysis were relevant as both groups were comparable in this analysis. There were 265 and 263 hips in the isolated CD and augmented CD groups, respectively. Both the groups had comparability with age, gender, drill diameter, etiology, and stage of OFNH.[50] Wang et al. had similar observations in their meta-analysis of 14 randomized controlled trials.[11]

The meta-analysis by Zhang et al. compared the outcomes of CD and CD with bone marrow MSC translplantation.[46] Of 16 articles with 583 hips in the bone marrow MSC and 468 hips in the CD groups, the authors observed lower hip pain score (VAS; MD = 10.88; P = 0.003) and higher functional score (HHS; MD = 5.59; P = 0.01) in the bone marrow MSC group at 2-year follow-up. The progression of the disease stage was observed in 138 and 202 patients in the bone marrow MSC and CD groups, respectively (P = 0.0002). About 22.5% of patients in the bone marrow MSC group and 42.3% in the CD group needed conversion THA (P = 0.001).

A systematic review (level II evidence) of overlapping meta-analyses on the cell therapy in ONFH reported that bone marrow-derived mesenchymal stem cell therapy had consistently shown better efficacy than an isolated CD concerning pain relief, functional outcome, and hip survivorship.[48] The only systematic review by Andronic et al. contradicted the above statement by reporting a lack of conclusive evidence towards the beneficial effects

of biological augmentation in CD for nontraumatic ONFH.[56] However, this review should be interpreted with caution as the outcomes are based on very few studies with the inclusion of different modalities of orthobiogic treatment. The level of evidence of the included studies in this review is also low (level III).[55]

A study from France reported better hip-survivorship with augmented CD (autologous bone graft, stem cells, platelet-rich plasma (PRP), and BMP-2) at 2- and 10-year follow-up (10-year survival of 58.1% vs. 57.9%, P = 0.0082) after adjusting for preoperative characteristics (Kerboull angle and Ficat stage).[7] The risk for femoral head collapse and conversion THA was greater in patients with >30% necrosis volume on magnetic resonance imaging quantification and Kerboull angle of >60 degrees.

PRP

The platelet component of blood contains numerous bioactive proteins and growth factors (transforming growth factor β [TGF-β], platelet-derived growth factor [PDGF], fibroblast GF [FGF], endothelial GF [EGF], and vascular EGF [VEGF]) stored in the α-granules. These growth factors are released when the platelets are activated, showing stimulation of neoangiogenesis, chemotactic effect on MSC, and the proliferation of osteoblastic precursors.[9] Although the regenerative potential of PRP has been evaluated in many chronic degenerative conditions of the musculoskeletal system, its applicability in ONFH is relatively new. Aggarwal et al. compared isolated CD and PRP with CD in age and sex-matched early ONFH patients. There was a significantly better pain relief, functional score, and Harris Hip Score in the PRP group after an average follow-up of 64.3 months.[57] There was no progression in any patient of ARCO stage 1 disease. However, 24% disease progression was noted in stage 2 in the PRP group and 43% in the isolated CD group. The hip survivorship from THA was significantly higher in the PRP group compared with isolated CD (92% vs. 78%, P = 0.01).[57] Few other studies have also documented better outcomes following PRP augmented CD.[9,58] However, with limited evidence, routine use of PRP in ONFH remains inconclusive.

Noncellular orthobiologic products instillation

BMP

BMPs stimulate the proliferation and differentiation of MSCs and thus help in bone remodeling. BMP-2 and BMP-7 have been used in a few studies on a limited number of patients.[1,10] Martinot et al. reviewed 92 cases where they evaluated the outcome of isolated CD, augmented bone marrow injection, and augmented BMP-7 with bone marrow injection in ONFH.[7] At 10 years, the hip survivorship was significantly better in the BMP group compared with the CD group (hazard ratio [HR], 0.356), but no significant difference between CD and bone marrow groups was noted (HR, 0.567). The cost and non-availability of BMP are major issues at this moment. It needs further research to evaluate the efficacy of BMP in ONFH.

Structural support

Tantalum rod

Porous tantalum rod insertion after CD provides structural support and prevents collapse.[1,10] In a prospective study, Veillette et al. evaluated the outcome of tantalum rods in 54 patients (60 hips). The overall survival rates of the hip were 91.8%, 81.7%, and 68.1% after 1 year, 2 years, and 4 years, respectively.[59] In patients with no chronic systemic diseases, the survivorship increased to 92% at 4 years.[59] The increased cost, prolonged surgical time, and retrieval difficulty during conversion THA are the major problems of this technique.[1] With a small patient cohort, there is no firm evidence in support of porous tantalum rod use in early ONFH.

Combined treatment

Numerous cocktail regimens with CD have been studied preliminarily. In a pilot study, Kang et al. reported 91% and 62% hip survivorship following CD and alendronate treatment in stage II and III ONFH (modified Ficat and Arlet stage II and III) after a minimum of 4 years.[60] The isolated CD group had hip survivorship of 79% and 46%, respectively. The author concluded that CD combined with systemic alendronate administration could reduce pain and delay the progression of early-stage ONFH.[60] Similarly, combined treatment with hyperbaric oxygen and extracorporeal shock wave therapy has

shown benefits.[1,10,45] These cocktail regimens need further research for application into clinical practice.

FEASIBILITY OF CD AS A ROUTINE PROCEDURE

CD is an inexpensive and most cost-effective proce-dure. However, the augmented CD with cellular and noncellular additive therapies is expensive and not widely available. It is one of the major limitations of the broad applicability of augmented CD in early ONFH despite knowing its superiority over standard CD. Even the CD technique has shown no detrimen-tal effect on future THA, and with the introduction of multiple drilling techniques, the risk for joint penetration and subtrochanteric fracture has been minimized.[61] In a network meta-analysis of random-ized controlled trials, Yu et al. reported that CD and cytotherapy are the most successful hip preservation procedures among all available techniques for early and intermediate-grade ONFH.[45] The CD (prefer-ably augmented CD) is most appropriate for early ONFH (Ficat grade I, II/ Steinberg grade I, II, and IIIA/ARCO grade I, II), where the lesion is located medially with the size of <15% of the femoral head and subtending a Kerboul angle of <200 degrees. However, the intermediate grade ONFH (Ficat stage III/Steinberg grade IIIB-C, or IV/ARCO III) can show some benefits after augmented CD.

CONCLUSION

The augmented CD technique has a better outcome compared with CD alone. The bone marrow-derived cell therapies (level-2 evidence) have persistently superior results in clinical improvement, radiological improvement, and conversion-THA among different additive procedures. The regulations on this technique may be waived off for its routine use as a treatment modality in early ONFH. There is no conclusive evidence supporting other orthobiologic products (PRP, BMP, or tantalum) in ONFH. Future research on the treatment of ONFH should be directed towards etiology-specific and disease severity grade-specific studies.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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