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Hip Preservation Techniques: The Use of Biologics to Improve Outcomes

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The use of biologic adjuvants in orthopedic injuries continues to expand along with the comprehension of the healing and regeneration mechanisms of tissues. Biological treatments represent a potentially attractive option for a number of hip disorders and include a variety of cell therapies and blood derived products, such as mesenchymal stem cells, bone marrow aspirate concentrate, matrix-induced autologous chondrocyte implantation, platelet rich plasma and others. Clinical studies have reported promising results and emerging basic studies have provided a clearer understanding of the underlying mechanisms of action of biologics in orthopedics. However, crucial questions remain regarding their indications, limitations, and overall efficacy. This review focuses on the current state of the use of biologics to improve outcomes in hip preservation surgery.

KEYWORDS hip, femoroacetabular impingement, arthroscopy, preservation surgery, orthobiologics

Introduction

Hip joint preservation surgery has seen extraordinary progress over the past few decades. Today, hip preservation surgeries include the treatment of pre-arthritic disorders such as femoroacetabular impingement syndrome (FAIS) and developmental dysplasia of the hip (DDH); treatment of sequelae of childhood disorders such as Perthes disease and slipped capital femoral epiphysis (SCFE); and the treatment of osteonecrosis of the femoral head (ONFH). Evolving techniques and technology, careful patient selection, advances in imaging modalities and better comprehension of hip anatomy and biomechanics are some of the factors that have been contributing to the success of hip preservation surgery.

Likewise, biological treatments for hip disorders have experienced a significant growth in recent years[1]. The use of biologics in orthopedics aims to improve healing and regeneration of damaged tissues, as well as potentially reduce recovery time for patients. Biologics described for hip disorders include a variety of cell therapies and blood derived products. As biological strategies become increasingly used in the clinical practice, research on these strategies has also increased. We present an overview of the current state of the use of biologics in hip preservation surgery.

Mesenchymal Stem Cells (MSCs)

Stem cells are undifferentiated cells that are able to proliferate, release immune regulators and growth factors, and differentiate into specialized cell types.[2] Stem cells can be divided into mesenchymal stem cells (MSCs), induced pluripotent stem cells and embryonic stem cells.[1] MSCs are the most common type used in orthopedics due to ease of harvesting, their ability to differentiate into tissues of interest for the surgeon, as well as the lack of ethical issues and absence of

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oncogenic potential compared to embryonic stem cells or induced pluripotent stem cells, respectively.[1,2] MSCs can be obtained from multiple sites including umbilical cord, placenta, periosteum, synovial tissue, muscular tissue, adipose tissue and bone marrow[2]. However, the site of extraction can influence not only the final concentration of MSCs, but also their differentiation capabilities, with adipose-derived MSCs presenting a reduced chondrogenic capacity compared to bone-marrow derived MSCs.[3] Stem cell treatment requires isolation of the stem cells and additional seeding and expansion in the laboratory for 4 to 6 weeks, obtaining up to 200 million cells per milliliter. There is evidence that a higher number of stem cells results in improved outcomes, but the optimal dose and number of injections remains unclear.[3]

The use of MSCs in the management of hip osteoarthritis (OA) has been described. Mardones and Larrain[4] reported a case series of 7 patients with hip OA treated with laboratory-expanded autologous MSCs (20×10^6 cells) obtained from bone marrow aspirate. The MSCs were injected into the patients' hips under fluoroscopic control. The authors reported that the Vail-10 score and modified Harris Hip Score (HHS) showed significant improvement at 3 and 6 months for all patients; it is important to highlight, however, the very short-term follow-up period and the small number of patients evaluated in this series.

The use of MSCs has also been described as an augmentation for FAIS surgery. Mardones et al[5] retrospectively reviewed the outcomes of 29 hips that had undergone hip arthroscopy plus laboratory-expanded autologous bone marrow MSCs injections for FAIS and focal chondral defect treatment, with a mean follow-up of 24 months. Each patient received 3 intra-articular injections of 20×10^6 cells, 1 per week, 4 to 6 weeks post-operative, under radioscopic guidance. The patients were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), modified HHS and visual analogue score (VAS) for pain. All patient-reported outcomes measures showed significant improvement from baseline to final follow-up. No major complications were observed, but 4 hips (13%) required a total hip arthroplasty (THA) at the median of 9 months post-intervention. The authors concluded that the combined therapy (hip arthroscopy plus expanded autologous bone marrow MSCs) may improve the functional scores in patients with FAIS and chondral injuries. The lack of a control group, however, did not allow the assessment of a presumed advantage of the use of MSCs as an augmentation, in comparison to hip arthroscopy alone.

Two randomized controlled trials evaluated the role of MSCs in the treatment of ONFH. Zhao et al[6] studied 93 patients (97 hips) with pre-collapse ONFH (ARCO stage 1 or 2) randomly assigned to core decompression treatment or MSCs treatment. Each hip in the MSCs group received femoral head implantation of 2×10^6 laboratory-expanded autologous bone marrow MSCs. Five years after treatment, only 2 of the 53 MSCs-treated hips (3.8%) progressed and required additional surgery (vascularized bone grafting); in the core decompression group, however, 10 of the 44 hips (22.7%) progressed and required additional surgery (vascularized bone grafting or THA). No major complications were observed in any of the groups. The authors concluded that MSCs implantation is safe and effective in delaying or avoiding collapse of the femoral head in patients with ONFH. Sen et al[7] randomly assigned 40 patients (51 hips) with ARCO stage 1 or 2 ONFH into 2 treatment groups (core decompression alone or core decompression followed by MSCs implantation). Outcomes between groups were compared using the HHS and Kaplan-Meier survival analysis at 1-year and 2-year follow-ups. The authors reported that both the HHS and mean hip survival were significantly better in the group treated with core decompression followed by MSCs implantation. Although the findings of these studies are promising, their interpretation is limited due to the small number of patients included.

Bone Marrow Aspirate Concentrate (BMAC)

Bone marrow aspirate concentrate (BMAC) is composed of a mixture of cellular elements, including MSCs, white blood cells, red blood cells, as well as cytokines and growth factors that may contribute to its anti-inflammatory and anabolic effects.[8] Studies suggest that only 0.001% to 0.01% of BMAC are MSCs[3].

BMAC has been used for hip preservation surgery in patients with ONFH, with mixed results reported. Hernigou and Beaujean[9] prospectively studied 189 hips with ONFH (Steinberg stage I to stage IV) treated with core decompression plus BMAC injection. The authors reported that only 9 (6.2%) of the 145 stage I and II hips progressed to THA at a mean follow-up of 7 years, compared to 25 (56.8%) of the 44 stage III and IV hips; the authors concluded that the procedure was effective in treating patients with earlier stages of ONFH. Tomaru et al[10] retrospectively assessed 44 patients with idiopathic ONFH (ARCO stage 1 to stage 4) treated with core decompression plus BMAC injection, and found a 34% conversion rate to THA at a 10-year follow-up period. The authors concluded that the overall result was not satisfactory, but the procedure could be considered as one of the alternatives for joint-preserving treatment of ONFH. Cruz-Pardos et al[11] studied 60 hips with pre-collapse stage ONFH (Ficat stage I and II) treated either with core decompression alone or core decompression followed by BMAC injection and reported that rate of femoral head collapse and post-operative Merlé D'Aubigne and Postel hip score were similar between groups at a mean follow-up of 45 months. Hauzeur et al[12] studied 46 hips with non-traumatic ONFH (ARCO stage 3) treated either with core decompression plus saline injection or core decompression plus BMAC injection and reported no differences between the groups for patient reported outcomes, radiological evolution and need for THA at a 24-month follow-up. Pepke et al[13] conducted a prospective randomized trial evaluating 24 consecutive patients with ONFH (ARCO stage 2) treated either with core decompression alone or core decompression plus BMAC injection and

reported no difference in the VAS for pain, HHS, head survival rate and radiological outcomes at a 24-month follow-up. Mishima et al[14] reported a case series of 14 patients (22 hips) with ONFH at the pre-collapse or collapse stages treated with a combined therapy consisting of core decompression plus BMAC injection, followed by 6 months of continuous low-intensity pulsed ultrasound; at a mean follow-up of 26 months, the VAS for pain and Japanese Orthopedic Association (JOA) hip score improved in all patients and none required a THA. The authors concluded that their approach was safe and efficacious as a joint-preserving procedure for patients with ONFH. A recent systematic review by Piuzzi et al[15] on BMAC therapy for ONFH found significant heterogeneity in the studies regarding etiology, stage of the disease, lesion size, cell sourcing and assessment of outcomes, concluding that more evidence is needed to produce a standardized technique and clinical recommendation.

BMAC has been investigated for the treatment of OA in a number of joints, with few studies reporting the effects on the hip. Rodriguez-Fontan et al[16] treated a series of 15 osteoarthritic hips (Tönnis grade 1 and 2) with BMAC. The authors evaluated the clinical outcomes using the WOMAC score and reported a significant improvement for 11 hips (73.3%) after injection; additionally, no significant difference was found between the 6-month follow-up and the mean latest (13.2 months) follow-up scores.

The use of BMAC has also been described as an augmentation for FAIS surgery. Rivera et al[17] compared the outcomes of 40 patients with FAIS that underwent hip arthroscopy surgery plus BMAC injection to a control group of 40 patients with the same characteristics, but operated without BMAC therapy. The authors reported significant differences between groups at 12 and 24 months of follow-up, with lower VAS scores and higher iHOT-33 and modified HHS scores in the study group and concluded that the use of BMAC in arthroscopic treatment of FAIS reduces pain levels and improve functionality compared to hip arthroscopy alone.

Matrix-Induced Autologous Chondrocyte Implantation (MACI) and Autologous Matrix-Induced Chondrogenesis (AMIC)

Matrix-induced autologous chondrocyte implantation (MACI) was recently described for treatment of chondral defects of the hip and is performed by a 2-stage procedure, i.e., the biopsy of the patient's cartilage at the area surrounding the pulvinar or at femoral head-neck junction for chondrocyte culture, expansion and seeding onto a biocompatible scaffold, which is later implanted into the chondral defect.[3,18]

The autologous matrix-induced chondrogenesis (AMIC) technique is a single-step procedure based on performing microfractures at the chondral defect area, followed by the implantation of a resorbable collagen membrane to cover this area and held in situ the bone marrow progenitor cells that would lead to a differentiation process towards cartilage-like tissue.[18] Usual indications for the treatment of chondral defects of the hip with MACI or AMIC are Outerbridge grade III or IV lesions with size between 2 and 4 cm^2 in patients 50 years old or younger, with an uncompromised joint space (radiological Tönnis grade < 2).[18,19]

Few studies reported the clinical outcomes of these techniques on the hip. Thier et al[20] evaluated 29 patients with acetabular full-thickness cartilage defects treated arthroscopically with MACI. The authors reported that all evaluated patient-reported outcomes scores (iHOT33, EQ-5D, NAHS) showed an increase in activity level, quality of life and reduction of pain at an average follow-up of 19 months. Fontana et al[21] conducted a controlled retrospective study of 30 patients affected by post-traumatic hip chondropathy. Fifteen patients were treated arthroscopically with MACI whereas the other 15 underwent arthroscopic debridement of the chondral lesion. The 2 groups were similar in sex, age, location and degree of the chondral lesion. After a mean follow-up of 74 months, the authors found that HHS values were significantly higher for patients treated with MACI compared to patients treated with debridement alone. Fontana and De Girolamo[22] conducted a retrospective analysis of a consecutive series of 147 patients with acetabular chondral lesions measuring between 2 to 8 cm^2, comparing the clinical outcomes of patients treated with AMIC to those treated with microfracture. The authors reported that modified HHS in both groups was significantly improved at 6 months and 1 year after treatment, but during the subsequent 4 years the outcomes in the microfracture group slowly deteriorated, whilst the results in the AMIC group remained stable; another significant finding of the study was a higher complication rate in the patients treated with microfracture, with 7.8% of the patients requiring conversion to THA, compared with none in the AMIC group. Finally, Mancini and Fontana[23] compared the clinical outcomes of 57 consecutive patients treated with the MACI or AMIC techniques for acetabular chondral defects secondary to FAIS. The authors noted that modified HHS continued to improve up to 3 years post-op and remained stable until 5 years post-op without differences between the groups, concluding that AMIC technique provide the same beneficial effects as the 2-stage MACI, with reduced total treatment time and morbidity.

Platelet-Rich Plasma (PRP)

Platelet rich plasma (PRP) consists of a sample of plasma with a 2fold or more increase in platelet concentration above baseline levels.[24] PRP can potentially enhance healing by the delivery of various cytokines and growth factors contained in platelets, including platelet-derived growth factor (PDGF), transforming growth factor ß (TGF- ß), vascular endothelial growth factor (VEGF) and connective tissue growth factor (CTGF).[25] Clinical use of PRP has been described for the treatment of a wide range of musculoskeletal conditions, such as degenerative and traumatic knee cartilage lesions, acute muscle injuries, ligament injuries, rotator cuff injuries,

meniscal disorders, and tendinopathies. Likewise, PRP has been increasingly used in hip preservation surgery.

The outcomes of PRP vs hyaluronic acid (HA) for the management of hip early OA has been studied in randomized controlled trials, with mixed results reported. Battaglia et al[26] studied 100 patients with chronic unilateral hip OA (Kellgren-Lawrence grades 2 to 4) randomly assigned to receive PRP or HA via intra-articular ultrasound-guided injections and reported an overall improvement in VAS and HHS at 1-month, 3-month and 1-year follow-ups compared to baseline, with no differences between PRP and HA. Dallari et al[27] compared the efficacy of PRP, HA or a combination of both (PRP + HA) in 111 hip OA patients (Kellgren-Lawrence grades 1 to 4) and assessed the outcomes using the VAS and WOMAC scores at 2, 6 and 12 months after treatment. The authors reported that at all follow-ups, the PRP group presented the lowest VAS scores; furthermore, the WOMAC scores of the PRP group was significantly better compared to the other groups at 2- and 6-month follow-ups. The authors concluded that PRP injections offer a clinical improvement without relevant side effects and the addition of HA to PRP did not lead to a significant improvement in pain symptoms. Di Sante et al[28] compared the efficacy of PRP vs HA in 43 patients with unilateral hip OA (Kellgren-Lawrence grades 2 and 3), using pain reduction as measured by VAS as primary outcome. The authors reported that PRP-treated group presented a decrease in the VAS score at the 4-week follow-up, but not at the 4-month follow-up; in the HA group, however, a decrease in the VAS score was detected at the 4-month follow-up. The authors concluded that PRP had an immediate effect on pain that was not maintained over time. Finally, Doria et al[29] compared the clinical efficacy of PRP vs HA for early OA of the hip in 80 patients, evaluating the WOMAC, HHS and VAS scores at baseline, 6 months and 1 year after treatment. The authors found a significant improvement for all outcome measures without difference between groups, and recommended that PRP should not be used as first-line treatment for hip OA.

The use of PRP for augmentation of core decompression of ONFH has been recently described[30] and 1 study evaluated the outcomes of a mixture of BMAC and PRP for the treatment of ONFH.[31] The authors injected a combination of BMAC (12 mL) and PRP (6 mL) into the femoral head immediately after core decompression in 35 hips with pre-collapse ONFH. At a mean follow-up of 3 years, the survivorship free from THA and free from femoral head collapse was 84% and 93%, respectively, and the mean HHS improved from 57 points before surgery to 85 points at most recent follow-up. Despite the promising results, the clinical value of PRP for ONFH is limited due to low number of patients evaluated and short-term follow-up period.

The effect of PRP as augmentation for arthroscopic FAIS and labral surgery was evaluated in 3 randomized controlled trials. LaFrance et al[32] compared the efficacy of PRP to that of 0.9% normal saline injection and describe improvement in all patient-reported outcome measures throughout the follow-up period (12 months), with no difference between the groups. The authors concluded that intra-articular PRP injection after FAIS surgery did not improve the clinical outcomes. Rafols et al[33] compared PRP injection and no injection and found some differences in the outcomes between the groups, with the patients in the PRP group presenting lower VAS scores only on the second day after surgery and a lower incidence of joint effusion at the 6-month follow-up, while modified HHS and labral integration on magnetic resonance imaging showed no differences between the groups at any follow-up point. The authors concluded that PRP injection after FAIS surgery may have a benefit regarding postoperative inflammation, but the long-term clinical benefit is still unclear. Redmond et al[34] evaluated the efficacy of PRP injection compared to bupivacaine injection. Surgeries included either arthroscopic labral repair or debridement and the authors reported that the PRP group demonstrated a lower modified HHS and a higher VAS score than the bupivacaine group 2 years after surgery, but the reason for these findings could not be identified.

The challenge when trying to critically evaluate data from studies on the clinical use of PRP is the variability that exists in its composition and preparation.[35] Various formulations of PRP exist, with leukocyte-rich (LR-PRP) and leukocyte-poor (LP-PRP) being used in the literature. As indications for treatment of hip disorders with PRP continue to evolve, it will be necessary to define the ideal concentration of platelets and any other elements such as leukocytes, as well as the number of injections for each condition.[36]

Hyperacute Serum (HAS)

Hyperacute serum (HAS) is a blood derived product designed to avoid the complex preparation process required by activated and overconcentrated plasma derivatives, such as PRP. HAS is free of platelets, fibrin, cells, and anticoagulants, representing the extracellular matrix milieu immediately after an injury and blood clotting, and its preparation protocol is designed to be as close to the physiological activation of blood upon injury as technically possible.[37,38]

We are not aware of any clinical study using HAS in hip preservation surgery, but an in vitro study demonstrated that HAS restored cell proliferation capacity and rescued viable cell number in osteoarthritic subchondral bone from human femoral heads.[38] Furthermore, in another study HAS presented a better cell proliferative effect on MSCs, osteoblasts and osteoarthritic chondrocytes compared to PRP.[39] Although the potential clinical use of HAS appears promising, further basic and clinical research is required to provide evidence of its effectiveness.

Conclusion

The use of biologics in hip preservation surgery is rapidly evolving. While basic science supports the healing and regeneration of damaged tissues with the use of biologics described herein, the clinical results are still under debate. A large proportion of clinical research on this topic is composed by

studies without a comparison group, limited number of subjects and short-term follow-up, providing overall a low level of evidence. More high-quality research is necessary to establish solid conclusions and determine the ideal indications and limitations of the biological strategies described in this review.

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