CURRENT CONCEPTS REVIEW

Orthobiologics: Current role in Orthopedic Surgery and Traumatology

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Abstract

Orthobiologics are organic and synthetic materials that help in the cure of musculo-skeletal problems and are utilized in Orthopaedic Surgery, both in and out of the surgical theater, to augment the possibilities of curing bone and soft tissue lesions. Taking into account that their effect is frequently multifactorial and, in some occasions not entirely comprehended, together with the insufficient clinical information, orthobiologics should be scrupulously assessed against other secure and clinically accepted options. The fundamental orthobiologics today ready for use in Orthopedic Surgery are the following: osseous hollow fillers, extracellular matrix (ECM) substances, platelet-rich plasma (PRP), bone morphogenetic protein-2 (BMP-2), bone marrow aspirate (BMA), bone marrow aspirate concentrate (BMAC), and mesenchymal stem cells (MSCs). It is predictable that in the time to come we will have more secure and more efficacious orthobiologics. Meanwhile, it is paramount that orthopedic surgeons have appropriate information of contemporary orthobiologics (biological adjuvants) so that they can utilize them correctly.

Level of evidence: III

Keywords: Bone void fillers, BMA, BMAC, BMP-2, ECM products, MSCs, Orthobiologics, PRP

Introduction

According to Rodeo and Bedi, the term "orthobiologics" covers various techniques, from the injection of platelet-rich plasma (PRP) to the compilation and injection of stem cells arisen from bone marrow, amnios, or fat tissue (1).

The scientific basis for the current utilization of orthobiologics is their potential to ameliorate symptoms and probably to increase the chances of healing of tissues with little intrinsic healing ability such as cartilage, tendons, ligaments, bone, muscle and meniscus (1-4).

Although the basic science of orthobiologics suggests that they have great potential to ameliorate the healing of the aforementioned tissues, there is currently little clinical data to back up their utilization in the management of musculoskeletal problems. Besides, the orthopedic industry is marketing various orthobiologics whose clinical efficacy has not yet been proven. Finally, the lack of information on their risks, manufacturing methods and possible outcomes is currently a cause for concern (5,6).

For all these reasons, it is essential to have a good understanding of how orthobiologics work and their safety and efficacy. Treatments with orthobiologics must be well indicated and prepared in a precise and sterile way to reduce the peril of possible infections and other complications.

In this article, we review the current role of orthobiologics in Orthopedic Surgery.

Orthobiologics for bone healing

The orthobiologics today usable for osseous healing are bone grafting, cell-based therapies, PRP and growth factors (GFs) (7). Orthobiologics are frequently utilized to ameliorate the biology of osseous healing, particularly in cases of atrophic nonunion. Today, autologous bone grafting is the gold standard, as it has

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the three fundamental characteristics that facilitate osseous healing: osteoconduction, osteoinduction, and osteogenesis. However, we cannot forget that there are co-morbidities related to obtaining an autologous graft. Currently, the use of bone marrow aspirate concentrate (BMAC) alone or in combination with demineralized bone matrix (DBM), recombinant human bone morphogenetic proteins and PRP have demonstrated to be efficacious tools that can help orthopedic surgeons to solve fracture nonunions (7).

Bone grafts

Autologous bone graft

Autologous iliac crest bone graft (ICBG) is the gold standard for osseous consolidation problems (8). This is because it contains the cortical bone structure together with the osseous-consolidating characteristics of cancellous bone autograft (9). Nonetheless, the possible morbidity of the autologous ICBG extraction technique has given rise to the appearance of optional bone autograft extraction techniques, such as the reamer-irrigator-aspirator (10).

Irrespective of the technique utilized to get autologous bone grafting or the site from which it is obtained, bone autografting endures an effective tool for osseous consolidation, particularly in the context of nonunion and revision surgeries, where osseous consolidation is needed more than void filling (11).

Osseous allograft and DBM (demineralized bone matrix)

Allografts are often utilized as hole fillers and structural struts. The osteoconductive characteristics of the cancellous bone allograft permit it to be integrated into the host osseous tissue and also serve as a void filler; however, the structural characteristics of the cortical allograft permit it to be utilized when physical support is needed, such as for raising the articular surface in tibial plateau fractures. Morselized and cancellous allografts are freeze-dried cancellous bone chips with analogous osteoconductive characteristcs to cancellous autograft, which are often utilized to fill osseous defects, such as those created after cyst curettage or those that occur in large depressed articular fractures. These allograft cancellous chips have biomechanical characteristics alike to those of metaphyseal osseous tissue in that they can give some mechanical support in compression (12).

Cortical and osteochondral allografts are more structurally sound and are frequently utilized as cortical struts in trauma or for limb salvage surgical techniques in oncology. They are often used in realignment osteotomies (i.e., high tibial osteotomy, distal femoral osteotomy), mosaicplasties for big osteochondral defects, or bone/joint augmentation in reconstructions of the glenoid cavity of the shoulder. DBM is an osteoconductive and osteoinductive bone graft replacement, which consists of bone allograft with inorganic materials extracted. The osseoinductive potential of DBM is due to the fact that it contains BMP and vascular endothelial growth factor (VEGF) (13).

The first investigations, conducted more than 20 years ago in the treatment of animal and human fractures, demonstrated the effectiveness of DBM compared to autologous grafting (14,15). This efficacy was later supported by Desai et al, who stated that DBM might be superior to bone morphogenetic protein 2 (BMP-2) in the management of tibial nonunions when used in conjunction with BMAC (16).

In another study, Lareau et al analysed 25 Jones fractures of the 5th metatarsal, the majority of which were managed with screw fixation supplemented with BMAC and DBM in National Football League (NFL) players. The percentage of return to play was 100%, with a mean in-season return to play of about 9 weeks (17).

Bone graft replacements

There are currently several synthetic substitutes based on calcium salts, which attempt to imitate the osteoconductive characteristics of bone grafting. These are calcium sulphate, calcium phosphate, tricalcium phosphate and coral hydroxyapatite. These osteoconductive options are frequently utilized as void fillers in large segmental defects. In addition, in cases of infection, they can be mixed with antibiotics. They can also be combined with biologically active osteoinductive and osteogenic substrates such as BMAC, PRP or BMP. There are several alternatives for synthetic bone graft substitutes, all having a comparable compressive strength to cancellous bone, with the exception of calcium phosphate, which has a compressive strength of up to 10 times that of cancellous bone and an inferior resorption rate than other synthetic replacements (18).

Cell therapies

Bone marrow aspirate concentrate (BMAC)

The utilization of BMAC in osseous healing has yielded positive outcomes; in fact, it is still used in management of atrophic nonunions. Hernigou et al have published an 88% consolidation percentage in atrophic nonunions managed with percutaneous BMAC injection alone (19). Desai et al, using a combination of DBM and BMAC in atrophic nonunions of the tibia, found an 86% consolidation rate at 4.5 months (16). Even though the indications for the utilization of BMAC in the management of acute fractures are not yet well known, Schottel and Warner have used it to supplement fracture fixation while using allografts (20).

Adipose-derived mesnchymal stem cells (ADMSCs)

Despite extensive preclinical studies on the use of adipose tissue derived mesenchymal stem cells (ADSc), at this point there are no reported clinical trial results in the utilization of ADSc for bone healing. Nevertheless, there are several ongoing studies from which we may extract some knowledge in the near future (21,22).

Platelet-rich-plasma (PRP)

PRP has provided satisfactory outcomes on bone consolidation problems. In one publication, injection of PRP into the atrophic nonunion zone of long bones led to a percentage of union of 87% at 4 months (23). A study comparing PRP with exchange of intramedullary (IM)

nailing for long bone nonunions led to a 93% binding percentage in the PRP group versus an 80% binding rate in the exchange IM nailing group (24). The above reports indicate the promising role that PRP appears to have in bone healing, although it is obvious that more research is needed to confirm this.

Osteoinductive growth factors and proteins
Bone morphogenetic protein (BMPs)

Jones et al showed that in the management of tibial diaphysis fractures with broad osseous reduction the results when using recombinant human bone morphogenetic protein 2 (rhBMP-2) in combination with allograft cancellous chips were comparable to those of the isolated autograft use (25). Another study got 100% consolidation in a group of 45 individuals with atrophic nonaseptic nonunion using a combination of rhBMP-7 and autograft (26).

Although the literature has demonstrated the powerful inductive potential of BMPs, their utilization in bone consolidation problems (atrophic non-unions) has declined with respect to other orthobiologics. This is related to their high price and the possible complications associated with their use, among which are heterotopic osseous formation (particularly due to the tendency of liquid BMPs to leak into encircling soft tissues), the unlikely potential for carcinogenesis, renal and hepatic failure, and compartment syndrome (11,18,27,28).

Platelet-derived growth factor (PDGF)

Currently, local utilization of PDGF in bone consolidation appears secure. However, forthcoming larger-scale clinical trials are required to confirm its potential clinical benefit. In fact, at present, there is no PDGF agent that has been specifically approved for use in fracture healing.

Parathyroid hormone (PTH)

In a comparative investigation reported by Aspenberg et al, 102 postmenopausal women with fractures of the distal radius managed with closed reduction were analyzed. A group of women who were given daily injections of 20 mg of recombinant human PTH (rhPTH) in addition to closed reduction were compared with a control group (with placebo injections in addition to closed reduction). Fracture consolidation time in individuals manageed with daily injections of 20 mg rhPTH was significantly shorter than in the control group (29).

In another report, Almirol et al observed a significant increase in bone formation biomarkers (N-terminal procollagen type 1 peptide and osteocalcin) in premenopausal women with lower extremity stress fractures managed with 20 mg rhPTH every 24 hours compared with a placebo control cohort (30).

Micro ribonucleic acids (MicroRNAs)

Hadjiargyrou and Komatsu have published that microRNAs (miRNAs), small non-coding RNAs, may be key regulatory molecules for fracture repair (31). Although a number of miRNA-based therapeutics have lately got into clinical trials, there are not yet studies designed for skeletal applications.

In short, concerning the function of orthobiologics in osseous consolidation and their ability to successfully promote it, even in difficult situations, has been demonstrated. Although the role of these orthobiologics needs to be further investigated with high quality clinical trials before they become the standard of care, their future in bone healing seems promising.

Orthobiologics in the management of articular cartilage defects and osteoarthritis

Articular cartilage defects

Focal chondral defects of the knee are frequent and commonly cause pain, dysfunction and, many times, degeneration of the joint and eventually osteoarthritis (OA) (32). Due to the deficiencies of prevailing therapies, biologic augmentation for the mamagement of focal cartilage defects is currently a topic of great interest. In focal chondral defects, orthobiologics can be used clinically as a solitary surgical technique, or as an augmentation to cartilage reparation surgery.

The most commonly utilized orthobiologics for cartilage defects are BMAC, adipose-derived mesenchymal stem cells (ADSc), PRP, and micronized allogeneic cartilage (MAC) (32). Osteochondral autografts and allografts are utilized to reestablish the natural architecture of the articulation (33).

Autografts are utilized in individuals with full thickness osteochondral injuries of less than 2.5 cm2, as well as in the management of individuals in whom other cartilage restoration techniques have failed (34).

For defects greater than 4 cm2, osteochondral allograft (OCA) is usually the surgical technique of preference. Frank et al encountered a substantial amelioration in result scores at 5 years of follow-up after using OCA, although they also noted a reoperation rate of 32% (35).

Levy et al reported a reoperation percentage of 47% at 10 years. Besides, at 7.2 years on average, 24% of the knees had a poor outcome. The prognostic factors for failure of OCA were two or more precedent surgical procedures on the operated knee and a patient age greater than 30 years at the time of surgery (36).

Some orthobiologics are now used as an augmentation in the course of the surgical management of focal chondral knee defects. These include BMAC, MAC matrix (BioCartilage), PRP, hyaluronic acid (HA), various scaffolds, GFs and cytokine modulation (32).

Osteoarthritis

The predominant orthobiological treatments for OA used today are HA, PRP, BMAC and ADSc (37). In general, taking into account the absence of high level evidence reports, the function of orthobiologics in the management of OA and articular cartilage focal defects endures unclear. Nevertheless, the majority of the existing reports on orthobiologics have found a good safety profile.

Available research seems to support augmenting microfractures with orthobiologics. Thus, cartilage healing can be improved, its quality increased and better clinical results obtained. As pressure increases on orthopedic surgeons to find alternative minimally

invasive techniques for the management of OA and articular cartilage focal defects, orthobiologics seem to be a possibility. However, more and better clinical investigation is required to clarify the function of orthobiologics in the treatment of focal and diffuse injuries of the articular cartilage. It is essential to clarify for each specific clinical problem what type of orthobiologics should be used, how often and in what quantity (37).

Orthobiologics for ligament repair and reconstruction

There are currently several orthobiologics that can be used as adjuvants in the repair or reconstruction of ligament injuries (38).

Anterior cruciate ligament (ACL) of the knee

Ameliorations in tissue engineering and regenerative medicine technology have led to biological augmentation with GFs, PRP, MSCs, and bio-scaffolds being used increasingly in ACL repairs and reconstructions, however, there is no sound clinical confirmation yet to back up its possible benefits. One publication stated that the function of PRP in ACL repair/reconstruction remains debatable and is only related to ameliorated graft maturation over time; PRP was not found to have beneficial effects on bone graft integration, preclusion of osseous tunnel widening and short-run clinical outcomes (39).

Isolated medial collateral ligament (MCL) of the knee

There is currently little information concerning the potential benefits of PRP in knee MCL lesions. A level IV evidence-based study evaluated the use of the PRP in a soccer player with an isolated grade II MCL injury (40). This patient underwent conservative management with many PRP injections and rehabilitation. The individual returned to play 18 days later, with very good functional outcome and no symptoms. However, imaging studies demonstrated incomplete healing of the ligament. Finally, at 16 months of follow-up, there was no relapse of the lesion or other adverse events. The clinical case mentioned above demonstrates that the PRP may have some beneficial role in the conservative treatment of MCL lesions. However, more clinical studies need to be done to fully define the value of the PRP in MCL lesions.

Ulnar collateral ligament (UCL) of the elbow

Some authors have utilized biological adjuncts for nonsurgical management of partial UCL elbow tears with encouraging outcomes (41,42). In a publication on overhead-throwing athletes, Podesta et al observed that following a single injection of PRP, 88% of patients with partial UCL tears returned to normal play levels at 3 months. Along with satisfactory functionality, that study also mentioned a reduced medial elbow joint space on valgus loading (41). Another report, which analyzed 44 competitive baseball players, found that after an injection of PRP associated with a return-to-play rehabilitation program, 73% of patients had good to excellent outcomes (42).

Although no clinical studies have been published as yet regarding the conservative treatment of complete UCL lesions with MSCs or scaffolds, the growing reputation of these techniques in the management of shoulder and knee lesions suggests that MSCs and scaffolds will be valuable in the future management of UCL lesions of the elbow (43).

Orthobiologics in the management of knee meniscus pathology

According to Chirichella et al, direct meniscus repair endures an alternative in young, healthy individuals with tears near the more vascular periphery of the meniscus, although it is not a good option for individuals who do not meet the above-mentioned requirements (44).

Although there are currently few publications on the use of orthobiologics in the management of meniscal tears, recent investigation has suggested that the utilization of PRP, MSCs or microfragmented adipose tissue (MFAT) might stimulate healing of the meniscus. Vangsness et al published good clinical and radiological outcomes after the use of allogenic human mesenchymal stem cells after partial meniscectomy (45).

Orthobiologics alone or in combination with other surgical procedures such as meniscal repair, replacement, or trephination, could be justified in the future as long as it is used in well-designed studies.

Orthobiologics for the elbow

Lateral epicondylitis

Although leukocyte-rich PRP (PRP-LR) has been widely used recently in the treatment of elbow tendinopathies, especially in lateral epicondylitis, there is a clear absence of information in the literature to back up its utilization. Good long-term results have been published with the utilization of biologic augmentation with PRP-LR in individuals with lateral epicondylitis when compared to corticosteroid injections. However, further investigation is required to establish the ideal formulation and administration of PRP injections, and further high-quality investigations are needed to generate definitive information (46).

Medial epicondylitis

Medial epicondylitis is alike lateral epicondylitis but invoolving the insertion of the flexor tendon into the medial epicondyle. In contrast to lateral epicondylitis, there are hardly any studies that have investigated the efficacy of PRP in cases of medial epicondylitis (46).

Ulnar collateral ligament (UCL) lesions

Although there is some evidence to suggest that leukocyte-poor PRP (PRP-LP) may improve outcomes in athletes' UCL partial injuries, the great variability of lesion intensity, level of play and PRP preparation and administration does not allow definitive clinical recommendations to be made (46).

Distal biceps tendinopathy

In distal biceps tendinopathy the use of PRP has provided promising but not conclusive results. Further research is therefore needed. This will require the use of

appropriate control groups to determine the appropriate preparation of PRPs to be used and the optimal patient population in which to indicate it (46).

Orthobiologics for the hip region

Orthobiological treatments such as PRP, mesenchymal stem cells (MSCs) and amniotic injectables are increasingly used in the management of three hip problems: hip OA, gluteal tendinopathy, and proximal hamstring tendinopathy. In spite of an absence of solid proof of their efficacy, their current results are promising, especially those of PRP (47).

There is today an absence of information to back up the utilization of MSCs or amniotic injectables in the above-mentioned hip problems. Even though reported case series indicate that MSCs and amniotic injectables are secure in the short run, there is no information on their long-run security. Therefore evidence supporting the use of MSCs and amniotic injectables for hip problems is lacking. It is essential to define the optimal cell environment and formulation of each orthobiological therapy for specific pathologies and specific subgroups of individuals. To definitively determine the efficacy of orthobiologics in hip problems, multicenter randomized controlled trials (RCTs) with adequate power and using validated outcome measures are needed.

Orthobiologics for elective fusion and nonunions of the foot and ankle

Achieving fusion in foot and ankle bone procedures can sometimes be a problem. In fact, many individuals have comorbidities that diminish bone consolidation percentages (48). In addition, the limited space and the elevated weightbearing demand placed on fusion areas make the option of osseous graft, bone graft replacement, or orthobiologic agent of great significance. Although autologous bone graft endures the gold standard, the availability and absence of donor area morbidity offered by synthetic bone grafts, allografts, and orthobiologics, including GFs and MSCs, has led to their frequent use as augments. Sun et al have lately reported a meta-analysis on the radiologic and clinical effectiveness of recombinant human platelet-derived growth factor-BB in foot and ankle fusion (49).

Orthobiologics in minimally invasive lumbar arthrodesis

Minimally invasive (MI) spine surgery is increasingly used to reduce surgical time, avert adverse events related to open surgery and to reduce costs. In addition, the selection of appropriate implant material for lumbar MI fusion procedures remains critical (50). Today we have various orthobiologics such as autologous and allogeneic bone graft, bone marrow aspirate (BMA), DBM, ceramic and GFs. The perfect biological implant should be effortlessly moldable, osteoconductive, osseoinductive and resorbable. Ideally, the grafts should be radiolucent and traceable to permit radiographic evaluation of the fusion and its clinical correlation.

Table 1 summarizes the main orthobiologics currently used in Orthopedic Surgery and Traumatology [Table 1].

Table 1. Main orthobiologics currently used in Orthopedic Surgery and Traumatology

IN SKELETAL FRACTURES
Bone autograft
Bone allograft
Demineralized bone matrix (DBM)
Bone graft substitutes
Bone marrow aspirate concentrate (BMAC)
Platelet-rich plasma (PRP)
Bone morphogenetic proteins (BMPs)
Platelet-derived growth factor (PDGF)
Parathyroid hormone (PTH)
MicroRNAs
IN FOCAL CARTILAGE DEFECTS
Bone marrow aspirate concentrate (BMAC)
Adipose-derived mesenchymal stem cells (ADMSCS)
Platelet-rich plasma (PRP)
Micronized allogeneic cartilage (MAC)
IN OSTEOARTHRITIS
Hyaluronic acid (HA)
Platelet-rich plasma (PRP)
Bone marrow aspirate concentrate (BMAC)
Adipose-derived mesenchymal stem cells (ADMSCs)
IN LIGAMENT REPAIR AND RECONSTRUCTION
Hyaluronic acid (HA)
Growth factors (GFs) therapy
Platelet-rich plasma (PRP)
Bone marrow aspirate concentrate (BMAC)

Some orthobiologics, such as the PRP and MSCs, show promise for relieving pain and improving the healing of certain tendon, ligament and joint problems. However, the existing publications on PRP and MSCs do not support their use, i.e. they do not confirm their ability to regenerate tissue, nor do they clarify what their indications are. The uncritical utilization of orthobiologics and/or the absence of precise rules for their tissue processing and delivery could put the health and security of individuals at risk. Therefore, better evidence investigations are required to define the best indications and applications of orthobiologics. In addition to being safe, they should

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