JPMER

10.5005/jp-journals-10028-1280

REVIEW ARTICLE

Orthobiologics in Spine

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ABSTRACT

Orthobiologics are the biologically derived materials from the body to promote the repair and regeneration of muculoskeletal tissues. Orthobiologics has got special attention in recent past and become the focus of study of researchers in various traumatic and nontraumatic spinal pathologies. Efforts were made to develop materials capable of bone formation and which encourage healing of fractures. When they are used in higher concentrations than normally present in the body, they can potentially help speed up the healing process. The substances which are considered to be orthobiologics are: bone grafts, autologous blood, autologous conditioned serum (ACS), platelet-rich plasma (PRP), growth factors, and stem cells.

Various clinical and animal studies have shown variable results. This review gives an outline regarding the currently available clinical information and application of orthobiologics in various spinal pathologies for therapeutic use.

Keywords: Autologous conditioned serum, Bone graft, Bone morphogenic, Orthobiologics, Platelet-rich plasma, Spine.

How to cite this article: Rajnish RK, Kumar V, Dhatt SS. Orthobiologics in Spine. J Postgrad Med Edu Res 2018;52(2):83-87.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Orthobiologics are the biologically derived materials from the body, which are engineered to promote the repair or regeneration of musculoskeletal tissue.[1] Efforts were made to develop materials capable of bone formation and encourage healing of fractures, nonunion, and repairing defects of various traumatic and non-traumatic conditions of skeletal system. When they are used in concentrations many times the normal, they can potentially help speed up the healing processes.[1]

The substances which are considered as orthobiologics are: bone grafts, autologous blood, ACS, PRP, growth factors, and stem cells.[1]

This review summarizes the up-to-date scientific and clinical information known about the various orthobiologic materials currently available for therapeutic use in spinal cord pathologies and guiding the clinician regarding the ever-expanding application of orthobiologic materials and technologies to patients with spinal injuries and various pathologies related to the spinal cord.

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BONE GRAFT AND BONE GRAFT SUBSTITUTES

Biology of Spinal Fusion

Achieving a solid fusion is the goal of long-term clinical success in patients undergoing spinal fusion. The spinal fusion requires bone-graft or bone graft substitute at the fusion site to help solid fusion. The decorticated host bony bed is the primary source of new blood supply to revascularize and support the bone graft. In addition to that, surrounding tissues including muscle, fascia, and subcutaneous fat also contribute, though to a lesser extent. The necrotic graft bed in cases of irradiated tumor bed, trauma, and surgically intervened or infected tissues may hamper the healing and successful fusion. In addition, systemic and metabolic bone diseases may decrease the osteoprogenitor cells, as well as the osteoblastic function may interfere with spinal fusion.[2] Other factors which interfere with bone graft are physical barriers such as use of bone cement, and implants used to augment spinal fusion. These, when placed between graft and recipient host bed, may prevent successful revascularization and cellular influx.

Augmentation of Healing in the Spine

The most common indications for spinal fusion are either instability of a spinal segment produced due to spinal pathology or produced as a part of surgery or a spinal deformity that is at risk for progression. Majority of fusions are performed to treat degenerative disorders, the most common site being the lumbar spine.

Although spinal fusion is commonly attempted, nonunion is reported to occur in 5 to 45% of patients.[3-6] This may be a clinically disturbing statistic which makes spine fusion an ideal site for testing bone graft augmentation or other augmentation devices.

The rationale for testing bone augmentation in spine fusion is the reality that there is frequently an inadequate supply of autogenous bone graft for performing multilevel spinal fusion. The morbidity associated with iliac crest bone graft harvest is as high as 30%, with the most frequent complications being chronic pain at donor site, fracture, hematoma formation, infection, and increased operative time and costs.[7-10]

Most commonly, autologous bone graft is harvested from the iliac crest. However, its limited availability and related morbidity have prompted the development of bone graft substitutes.

The three essential properties of bone graft essential for its optimal functions are: (1) Osteoconductive matrix, which provide a three- dimensional scaffold and direction to the repair process, (2) Osteoinductive property, which induces pluripotent cells to differentiate into bone-forming cells, and (3) Osteogenic stem cells, which are capable of differentiating and facilitating the bone formation.

An ideal bone graft material is autogenous bone graft.[11,12] Cortical, cancellous, or cortico-cancellous bone can be harvested from one or more skeletal sites of human body and can be used at the defect site within the same patient. The autogenous bone contains osteoblasts and endosteal osteoprogenitor cells, which are capable of synthesizing a new bone.

Growth factors contained within the donor graft induce local cells to penetrate the graft's three-dimensional matrix of bone.

The use of bone and processed bone products harvested from cadavers has provided an additional source of graft material, but these are not completely safe and are associated with an additional risk of transmitting bacterial or viral pathogens to the graft recipient. However, the modern-day processing technique of allograft bone reduces the risk of transmission of pathogens, but at the cost of biological activity and strength of the graft tissue.

In the current era of increasing complex reconstructive spine surgeries, the demand for safe, reliable, and effective adjuncts to effect osseous healing also has gone steeply high. For the same reasons, various bone graft materials have been introduced as bone graft substitutes or complements to conventional bone grafts.[11]

Synthetic Bone Graft Substitutes

There are several advantages associated with the use of synthetic bone graft substitutes.[12] These can be manufactured and provided in unlimited supply and can be stored for use on demand without the morbidity associated with that of autologous graft donor site. This makes these bone graft substitutes a promising alternative to autografts and allografts. These materials are biocompatible and neither trigger an immunogenic reaction to the host, nor carry the risk of the transmission of an infectious pathogen to the recipient. These materials can be used alone or in combination with autogenous or allogenic bone grafts or other orthobiologics.

Synthetic graft substitutes are composed of calcium sulfate, calcium phosphate, hydroxyapatite, collagen, or an engineered heat-sensitive copolymer. These materials vary in their osteoconductivity, osteoinductivity, and biomechanical characteristics.

All commercially available synthetic bone graft substitutes have only osteoconductive property,[12] which provides a three-dimensional scaffold matrix to facilitate the in-growth of a blood vessel and the subsequent bone formation by the host tissue. Most of these materials are calcium phosphate ceramics, which are manufactured under conditions of high temperature and pressure.

These ceramic materials are inert substances which undergo a very slow chemical resorption in the human body. Before their dissolution within the defect, these scaffolds facilitate the bone formation. As these synthetic materials are resorbed, they are replaced by host cancellous bone to achieve osseous healing.

Although these materials are marketed as being biologically compatible and structurally similar to human bone, their long-term effects and true safety to humans are not yet fully known. Therefore, the level of evidence is insufficient to support a clinical recommendation at this time.

Demineralized Bone Matrix

The demineralized bone matrix (DBM) has osteoconductive as well as osteoinductive properties, which are derived from the processed cortical bone. It contains predominantly type I collagen of DBM by volume and provides the osteoconductive scaffold for osseous in growth. The organic phase of cortical bone contains numerous glycoproteins that are released from within the mineral phase during decalcification. This group of native, low-molecular-weight glycoproteins, which includes fibroblast growth factor, insulin-like growth factor, platelet-derived growth factor, transforming growth factor βand, most importantly, bone morphogenetic proteins (BMPs), is responsible for the osteoinductive activity of DBM.

The effects of DBM were demonstrated in a clinical trial evaluating the rates of healing for posterolateral spine fusion.[13] There was no significant difference in the rate of healing when the DBM combined in a two-to-one ratio with autologous iliac crest as composite graft and iliac crest graft alone were compared in a prospective, randomized multicenter study of 120 patients. However, the use of this composite grafting technique would reduce the volume of autologous bone graft necessary to achieve fusion by 75%.[13]

The DBM has also been suggested as a delivery system for bone marrow or bone growth factors for osseous healing.[11] However, the level of evidence is insufficient to support these clinical recommendations at this time.

Bone Morphogenetic Proteins

In the current clinical practice, BMP have shown as a promising and powerful tool in molecular-based

musculoskeletal repair.[14] These proteins were initially identified as regulatory factors that have tremendous tissue-forming properties.

Sixteen different human BMPs have been recognized as members of the transforming growth factor-beta super-family. This super-family encompasses a large number of growth and differentiation factors that regulate embryonic development and maintain tissue homeostasis.

Bone morphogenetic proteins 2-7 and BMP-9 are only a subset of BMPs that possess independent osteoinductive activity. Of these, only BMP 2 and BMP 7 have been developed for clinical use. The ongoing investigation on these BMPs continues to advance our knowledge of bone physiology and holds tremendous clinical potential as well.

Mechanism of Action of BMP

Earlier, it was considered that BMPs elucidate the chemical and cellular mechanisms governing osteoinduction.[15] These proteins bind to receptors on the membrane of mesenchymal stem cells to trigger an intracellular signaling pathway. This cascade of events led to either the expression or inhibition of genes that regulate the proliferation, differentiation, and metabolic activity of the stem cells. These stem cells transform into tissue-specific progenitor cells that participate in the synthesis of extracellular matrix, musculoskeletal tissue formation, and growth.

The dose of BMP necessary to stimulate bone formation in humans is 10 to 1,000 times higher, and the dose–response curve is much steeper than those observed in animal models because of tighter regulatory mechanisms and more rapid clearance of BMP. The tremendous cost incurred to yield osteoinduction with a BMP in the clinical setting has spurred the development of means to deliver and sustain the presence of BMP in the local environment.

The BMP is being tested for its utility in spinal fusion because of its osteoinductive properties. The BMP is synthesized either from human or bovine bone or through recombinant DNA technology. The BMP is a multifunctional cytokine which plays several critical functions in osteogenesis by promoting differentiation of mesenchymal stem cells into osteochondrogenic cells and regulates proliferation, matrix synthesis, and apoptosis of various cells, such as osteoblasts, chondrocytes, and vascular endothelial cells. Different types of BMPs have specific functions.[16]

Bone morphogenetic protein-2 has received the FDA approval for use in anterior lumbar interbody fusion in titanium cylindrical cages. The use of BMP in any other type of spine fusion has not been approved and would therefore, constitute off-label use of this product.

In the year 2002, the FDA approved the use of BMP-2 as an adjunct in anterior lumbar spinal fusions.[17] The BMP is also currently FDA-approved for use in the revision posterolateral lumbar fusion. Since its approval, there are multiple reports of major conflicts of interest and complications associated with involving clinical investigators. Recently, the FDA released a cautionary letter recommending against BMP-2 usage in anterior cervical fusions, as it can cause massive soft tissue swelling, which may lead to postoperative compromise and restriction of the patient's airway. Heterotopic ossification, osteolysis, seroma/hematoma, infection, arachnoiditis, increased neurological deficits (myelopathy, radiculopathy), retrograde ejaculation, and even cancer are the documented complications with the BMP usage in spinal fusion.[18]

AUTOLOGOUS CONDITIONED SERUM

Autologous conditioned serum is a rich source of anti-inflammatory cytokines like IL-4, IL-10, IL-13, and IL-1Ra, and have a high concentration of growth factors e.g., fibroblast growth factor (FGF-2), hepatocyte growth factor, and transforming growth factor (TGF-β1).[19] IL-1Ra is an antagonist to IL-1, which is a biochemical "sensitizer" of nerve roots in radiculopathy.[20] Hence, epidural perineural injection of ACS is considered to be a promising treatment option for the cervical and lumbar radiculopathy.[21,22]

Platelet-rich Plasma

Platelet-rich plasma is the plasma fraction of autologous blood with a platelet concentration of about four to five times above the base line.[23]

Degranulation of platelets releases various growth factors, such as platelet derived growth factor, TGF-β, which enhances bone healing by promoting mesenchymal stem cells and osteoblast proliferation.[24,25]

The autologous growth factor concentrate (AGF) is prepared from the ultra- centrifugation of platelets. It has been reported that AGF may enhance new bone formation in lumbar spine fusion.[26] However, Weiner et al. did not report any improvement in posterolateral spinal fusion rate with AGF.[27] Hee et al[28] demonstrated that AGF did not improve the spinal fusion rate in spinal lumbar interbody fusion. Furthermore, Carreon et al[29] demonstrated that platelet gel, when added to autograft, failed to enhance the fusion rate in posterolateral fusion to that of an autograft control.

The PRP has been used for intervertebral discs disease, for facet joint diseases, and for radiculopathies. A large number of studies on PRP in the field of orthopedics and sports medicine have been focused on tendon injuries including patellar tendinosis, lateral epicondylitis, Achilles tendinopathy, osteoarthritis, plantar fasciitis, anterior

cruciate ligament, and rotator cuff arthroscopic repair.[22] However, very few studies are available on the use of PRP in lumbar epidural space, but considering its vast potential, safety and encouraging results, it was decided to use it as a modality for pain relief in such patients as an alternative to steroids.

Orthobiologics for Spine: Where Do We Stand Now

There is progressively positive increase in the trend of use of orthobiologics over the past 10 years. At present, we are witnessing an increasing shift in focus and trend on the use of orthobiologics in spine surgeries. This shift is, in all probability, because of the increased knowledge and awareness along with a potential, primary, positive output of the orthobiologics usage.

The fundamental question that is always considered is does it work, and if so, how much does it cost? Fetching ample amount of orthobiologics was difficult in the past However, the use of BMP in recent times for spinal fusion has sorely increased.

The surgeon should be aware of the potential complications associated with the use of particular orthobiologics to avoid major complications. Complications associated in early years of BMP use in cervical spine, such as swelling and problems of breathing and swallowing, could have been avoided. Orthobiologics is a delicate tender science that needs to be thoroughly understood and carefully tendered before judicious and cautious application on human subjects.

The surgeons should be very well aware about the potential complications and untoward events and sequence associated with the use of individual orthobiologics to avoid major setbacks for the patient and clinics, if any.

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