Evidence-based Approach to Bone Grafting Options in the Lumbar Spine

a report by

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We have recently witnessed a rapid expansion of commercially available bone grafting options that have primarily been introduced for use in the lumbar spine in addition or as an alternative to iliac crest bone graft (ICBG). Arguably, these options can shorten operative times by obviating the need for iliac crest bone grafting, while also decreasing the subsequent morbidity associated with harvesting crest graft or just increasing bone graft volume. Nonetheless, before widespread clinical use we should critically evaluate the burden of scientific proof for each product in terms of:

- the level of available pre-clinical data;
- the level of clinical evidence in humans; and
- the fusion environment or location tested.

Specifically, what was the animal model used to claim osteoinductivity? Was it simply a rat ectopic assay or a non-human primate model? Are there any human data available? If so, is it from a randomized clinical trial (RCT) compared with ICBG with strict independent grading of the fusion mass, such as a thin-section computed tomography (CT) scan or plain radiographic evaluation by the authors? Finally, what is the fusion mass environment—human posterolateral lumbar fusion in adults or posterior spinal fusion in adolescent idiopathic scoliosis? More specifically, a posterolateral lumbar fusion is the most challenging primary fusion environment; it should therefore be evident that pre-clinical efficacy alone in a lower order animal will not translate to equivalent efficacy in the human. Just the same, pre-clinical lack of evidence or fusion inhibition will ensure failure in human use.

Today, there are over 170 available ‘bone grafting options’ or formulations on file with the US Food and Drug Administration (FDA). This presents an often confusing landscape where the marketing surrounding such products plays a pivotal role in the transmission of information to the surgeon. Consequently, a rigorous approach to product analysis is necessary for the surgeon to make clinically relevant and cost-effective decisions.

Bone Grafting Terminology

Definitions

Although somewhat repetitive and mundane, a proper understanding of available bone grafting options still hinges on an understanding of the basic definitions of osteoinductivity and osteoconductivity. Simply put, osteoinduction means the ability to induce new bone formation. This is accomplished through the recruitment and differentiation of mesenchymal stem cells to an osteoblast lineage of cells, or through the differentiation of pre-osteoblasts to osteoblasts. Originally refined by Marshall Urist as the ability to form de novo bone in a rat ectopic model (submuscular pouch), proof of efficacy in higher order animals, specifically non-human primates or humans, is absolutely necessary. Currently, the only commercially available products that have been proven to possess osteoinductive properties are the bone morphogenic proteins (BMPs) and allograft demineralized bone matrix (DBM). The relative osteoinductivity of these categories and available products should also be considered, as the differentiation between weakly osteoinductive and strongly osteoinductive products is very important.

On the other hand, osteoconduction means the formation of a matrix or scaffold for new bone formation. In practice, osteoconductive products primarily increase bone graft volume and thus are considered to be graft extenders. DBMs are bone graft extenders and, as noted above, have very slight osteoinductive ability, therefore could be considered to be bone graft enhancers. However, they cannot be used independently in the posterolateral lumbar spine to provide reliable results as they do not induce the formation of new bone. For instance, the osteoinductive capability of DBM is on the magnitude of 10^-6 or less than BMPs. Furthermore, significant DBM lot and manufacturer variability of osteoinductivity has been reported by several authors.

Bone Grafting Functions

A second important concept is the purported purpose of the bone graft product. In other words, what is the intended product function or role? A popular method of categorizing clinical utility has been to group available products as bone graft extenders, enhancers, or substitutes. By definition, a bone graft extender increases the overall volume of autograft bone available, but does not increase the efficacy or osteoinductivity of the harvested graft. There are numerous commercially available products; however, a common example of this is the ceramics, such as calcium
Morphogenic Proteins

Osteoinductive Bone Graft Substitutes—Bone Morphogenic Proteins

rhBMP-2

There are currently two available osteoinductive bone graft substitutes on the market: rhBMP-2 (Infuse, Medtronic, Memphis, TN) and rhBMP-7 (OP-1, Stryker, Allendale, NJ). The mechanism of action of these drugs—chemotaxis, mitogenesis, and differentiation of cells—is similar. The major difference in these products is in the type of cell that they can induce to differentiate. Specifically, rhBMP-2 acts on the mesenchymal stem cell and pre-osteoblast to differentiate into osteoblasts, which then form bone, while rhBMP-7 acts only on the pre-osteoblast (see Figure 1). Further, dosing of the two drugs is different, as rhBMP-2 is currently dosed at 1.5mg/cc (12mg for a large kit), while rhBMP-7 is dosed at 0.88mg/cc (4.4mg per kit). Additionally, rhBMP-7 is prepared with γ irradiation, which renders 30% of the rhBMP-7 inactive, therefore effectively decreasing the drug availability and effect. Both BMPs require a carrier matrix in clinical use.

Pre-clinical and clinical evidence of efficacy for rhBMP-2 is abundant. Boden and co-authors first reported a 100% fusion rate in a small study of 11 patients undergoing an anterior lumbar interbody fusion (ALIF) on an absorbable collagen sponge (ACS). Following this, Burkus et al. demonstrated a 94.5% fusion rate with rhBMP-2 in a tapered titanium spacer compared with a 88.7% fusion rate in the control group (ICBG). In a composite analysis of several studies, the authors reported superiority of rhBMP-2 over iliac crest bone graft in terms of fusion rate, post-operative pain, and blood loss. Similarly, Haid and co-authors reported a 92.3% fusion rate with rhBMP-2 after a single-level posterior lumbar interbody fusion (PLIF) compared with 77.8% fusion rate in the control group (ICBG). Other authors reported similar success after ALIF with rhBMP-2 and a femoral ring allograft; however, subsequent studies have cautioned against the use of rhBMP-2 with femoral ring allografts due to the potential for settling. Additionally, other authors have proven equal or better fusion rates with rhBMP-2 via a transforaminal lumbar interbody fusion TLIF (see Figure 2).

For the posterolateral spine, Boden et al. reported a 100% fusion rate in 20 patients receiving 40mg/level in a ‘fahita’ configuration compared with a 40% fusion rate in the control group (ICBG). More recently, Luhrmann and co-authors reported a 93% posterolateral fusion rate for rhBMP-2 in adult spinal deformity, and a 96% anterior fusion rate. Glassman and colleagues studied rhBMP-2 at 2.0mg/cc on a compressive resistant matrix (15% hydroxyapatite/85% β-tricalcium phosphate) in the posterolateral gutter (40mg/level), again finding superiority over the control group (ICBG). Furthermore, in this study rhBMP-2 was able to overcome the inhibitory effect of smoking on spinal fusion and achieve a fusion rate equal to ICBG in non-smokers. The main factor yet to be determined will be the necessary dose and concentration of rhBMP-2 in various clinical settings and healing environments. One caution that remains is the use of rhBMP-2 with various other osteoconductive ceramics, since rhBMP-2 upregulates not only osteoblasts but also osteoclasts, and the increased osteoclast activity will likely resorb the matrix too quickly; this leads to compromised fusion rates.

In a systematic review of all bone graft substitutes, Resnick and co-authors found rhBMP-2 to be a viable alternative to autograft for interbody fusion procedures and posterior lumbar fusions. These same authors found little, if any, medical evidence to support the use of other biologic agents at the present time.

rhBMP-7

The pre-clinical and clinical evidence for the use of rhBMP-7 is sparser. In a sheep model, Cunningham et al. showed rhBMP-7 to be equivalent to ICBG inside an interbody spacer. Magin and co-authors found similar results in sheep following an instrumented anterior spinal fusion without a spacer.
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The INFUSE® Bone Graft/Interbody Fusion Device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy or patients undergoing treatment for a malignancy, in patients who are skeletally immature, in pregnant women, or in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy.

Antibody formation to rhBMP-2 or its influence on fetal development has not been assessed. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

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Superior results were found in a sheep TLIF model when hydroxyapatite (HA) was used as a carrier. However, in a small series of thoracolumbar burst fractures, rhBMP-7 was not found to produce enough bone to provide early structural support. No other anterior interbody studies are available and a prospective randomized trial has not been undertaken.

Similar positive results have been found in lower animal posterolateral fusion models. Specifically, Grauer et al. found a 100% fusion rate in rabbits versus a 63% fusion rate in control (ICBG). Similar positive results were found in separate pseudarthrosis and nicotine rabbit studies. The clinical success of rhBMP-7 has not been as positive. In a small series, Johnsson and co-authors found six out of 10 patients treated with rhBMP-7 fused compared with eight out of 10 in the control group (ICBG). Vaccaro and co-authors have reported on a small series of un-instrumented degenerative spondylolisthesis patients, initially reporting a 55% fusion rate with 75% ‘clinical success’ on early follow-up, but only a 42% fusion rate at two-year follow-up. In Resnick’s systematic review, sufficient clinical evidence to recommend the use of rhBMP-7 had not been found at that time.

Deminerlized Bone Matrix
DBM is commercially produced by removing the mineral content from donor bone. After processing, the remaining collagen content is then mixed with a variety of carriers designed to provide various handling characteristics. As such, multiple studies have shown that a very small amount of osteoinductive BMP activity exists in formulation. Additionally, significant lot and product variability is present, but at best DBMs have less than 10⁻⁶ the osteoinductive activity of the BMPs.

Consequently, this presents some confusion within the market. For instance, rhBMP (Isotis Orthobiologics, Irvine, CA) is simply a DBM product with minimal osteoinductive activity and, thus, it should not be confused with the osteoinductive BMPs. Pre-clinical studies have shown some osteoinduction in a rat model for some commercially available DBM (Grafton, Osteotech, Eatontown, NJ), while at the same time showing little to no osteoinductivity in other products. In a non-human primate model, Grafton was added to iliac crest bone graft (bone graft extender) and shown to produce fusion in two out of four animals with Grafton flex and three out of four with Grafton matrix. However, there are no non-human primate or human clinical trials proving efficacy as a bone graft substitute, and therefore DBMs should only be used as bone graft extenders. As noted earlier, it is also generally recommended that extenders should not increase total graft volume by more than 25%, as this would necessarily decrease effective autograft osteoinductivity.

Ceramics
Ceramics are non-metallic mineral salts that are formed at high temperatures by sintering. Among the available ceramics are calcium sulfate, tricalcium phosphate, hydroxyapatite, and others. There are also available combinations of these products. They have not proven to provide any osteoinductive properties themselves and therefore
they are not an effective stand-alone bone graft substitute. Further, each of these products is resorbed at highly different rates within the body, and thus a clear understanding of these individual properties is required. For instance, calcium sulfate (plaster of Paris) is generally resorbed in 4–6 weeks. It has been shown to have promise in an ovine interbody fusion model, but has not been proven efficacious in human trials.24 Due to its quick resorption, it is also not an ideal scaffold for a posterolateral fusion, which commonly takes six months to mature. Consequently, clinical use should be tempered to these properties.

Tricalcium phosphates (TCPs) are biocompatible ceramics that are also available. Again, these are osteoconductive scaffolds that can be used as bone graft extenders or in combination with BMPs. In a small series (seven patients), pure β-TCP was found to be effective as a bone graft extender when used with allograft and peripheral blood, and in a larger series (50 patients) as a bone graft extender with autograft.23,24

HA has also been variably used as a bone void filler (back fill for iliac crest bone graft) or as a bone graft extender. It is resorbed very slowly by giant cells, while providing interconnected pores, which promote vascular and bony ingrowth. Use in the lumbar spine is limited to its role as a bone graft extender.

Various attempts at populating these products with blood derivatives or BMPs have also been marketed. For instance, Healis (hydroxyapatite (1%)–collagen, Depuy, Raynam, MA) originally showed promise in a posterolateral rabbit fusion model, but subsequent studies have shown no efficacy.23,24 There are no clinical studies proving efficacy to date. Similarly, platelet-rich plasma (PRP) were initially touted as potential substitutes; however, several clinical studies have shown these products to be inactive.25

Current Recommendations
A thorough understanding of bone grafting terms and the pre-clinical and clinical level of evidence for osteoinductive capability is necessary in the proper selection of bone grafting alternatives. It should also be recognized that pre-clinical efficacy does not necessarily equate to success in higher order animals. In addition, DBM is a popular bone graft extender, with little to no osteoinductive capability. Ceramics such as calcium phosphate and hydroxyapatite can also be used as bone graft extenders, but these should be used with caution in conjunction with rhBMP-2. Few studies are currently available to recommend routine use of rhBMP-7 in lumbar fusions. Finally, rhBMP-2 appears to have a higher fusion rate for both ALIF/TLIF and posterolateral applications, but proper selection of concentration, dose, and carriers appears to be critical.

Disclosure
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