Review Article

An evaluation of biomaterials and osteobiologics for arthrodesis achievement in spine surgery

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Abstract: An increasing variety of orthobiologic materials, including autologous and allogeneic bone graft, bone marrow aspirate, demineralized bone matrix, ceramics, and growth factors are available to the spine surgeon. Although autologous bone graft remains the gold standard material, concerns for failure in achieving fusion have prompted evaluation of current and new biologic materials. As such, this review attempts to summarize the available biologic materials with their pertinent characteristics, advantages, disadvantages, and primary uses.

Keywords: Biologics; biomaterials; spine surgery; autograft; allograft

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Introduction

An estimated 300,000 patients in the United States undergo spinal fusion procedures annually for a variety of spinal pathologies in the context of trauma, deformity, and degenerative conditions (1,2). The goal of arthrodesis or fusion is to induce bony bridging between two or more adjacent vertebrae to eliminate motion between the segments (3,4). For this purpose, instrumentation such as pedicle screws, rods, hooks, or interbody devices may or may not be applied (5,6). However, independent of the instrumentation utilized to achieve fusion, the local milieu and biological potential for fusion can be altered utilizing a variety of materials.

The characteristics of these biologic materials for the purposes of encouraging arthrodesis can be described as osteogenic, osteoconductive, or osteoinductive. The osteogenic potential of a graft describes the ability of osteoprogenitor cells to proliferate and subsequently differentiate (7). Osteoconduction refers to the ability of the graft material that allows osteoprogenitor cells to attach and migrate to form stabilized bone. Osteoinductive properties of a graft refers to the ability to recruit immature cells and induce their differentiation (7).

In the context of a variety of biologic materials available for achieving arthrodesis, the purpose of this review is to summarize each graft option and their pertinent characteristics and properties.

Methods

Published studies in the literature regarding orthobiologics and biomaterials in spine surgery were searched and identified. Relevant article types such as case series studies, retrospective cohort studies, prospective studies, randomized controlled trials, systematic reviews, and meta-analyses were identified using Medline, PubMed, and the Cochrane Library. Search terms and keywords used included “biologics” “biomaterials” “autograft” “allograft” “spine surgery” “arthrodesis”, and “fusion”. Although only

articles written in English were included, studies were not restricted by the date of publication or country of origin. Results of the literature search relevant to the present topic were identified by title, keywords, abstract, and the full-text if applicable.

Biomaterials

Autologous bone graft

At this present time, autologous bone is regarded as the gold standard based on its osteogenic, osteoinductive, and osteoconductive properties (8). Autologous bone graft is a broad term which describes bone harvested from and implanted in the same individual. The two most common sites that autologous bone grafts are derived from are the iliac crest and the local spinous processes, lamina, or facet joints (9). These autologous grafts may include either cancellous or cortical bone or both (10). Cancellous bone has a characteristic trabecular structure which promotes neovascularization, cellular recruitment, osteoid deposition, and mineralization (10-12). However, the trabecular morphology may limit the structural integrity which can be a concern if utilized in areas of high load. In contrast, cortical bone grafts generally provide a higher degree of stability (10). However, the microstructure cortical bone has a relatively decreased potential for vascularization and biologic activity as compared to cancellous bone (10,13).

Iliac crest bone graft (ICBG) is a commonly utilized harvest option for autologous bone graft (9). Generally, it can be harvested via an anterior or posterior approach along the iliac crest (14,15). In addition, autologous bone graft from the local spinous processes, laminae, or facet joints may also be applied to avoid the additional morbidity of the donor site. However, the volume available from the local operative field in the spine as a fusion material renders it less useful in multi-level fusion procedures which may require a high volume of material (16).

Despite the advantages of autologous bone graft material, the potential for (I) increased surgical time, (II) limited volume of material, and (III) increased donor site morbidity and pain have contributed to its decrease in overall usage (16,17). For example, Ohtori *et al.* reported donor site pain was frequent and occurred in 8 out of 12 patients (18). Furthermore, Peng *et al.* reported that 2 out of 29 cases required wound debridement and antibiotic treatment postoperatively (19). While autologous bone grafts have been the main source of biologic materials for spinal fusion, the disadvantages are becoming more apparent, which has spawned interest into alternatives methods.

Allogeneic bone graft

Since their introduction, allografts have offered an alternative to autologous bone graft (20). Allogeneic bone may be sourced from human cadavers or live donors (21). Allografts that maintain a mineralized portion of their bone matrix are used as an osteoconductive scaffold for bone formation (8). While allogeneic bone grafts maintain both osteoconductive and osteoinductive characteristics, they lack osteogenic properties as they do not contain viable cells (22). In addition, further processing is required in preparing the allogeneic material for medical use. Processing often refers to freezing, freeze-drying, or gamma irradiation that allow (I) preservation of the allograft and (II) risk reduction in disease transmission (23). Importantly, osteogenic, osteoconductive, and osteoinductive potential may be altered depending on the type and extent of processing (8).

Although allogeneic bone graft materials avoid donor site morbidity and are readily available, their biologic incorporation is often slower and the potential for vascularization is lower than that of autologous materials (21,23). In addition, although the risk of disease transmission remains low, there have been reported cases of allograft pathogen transmission including human immunodeficiency virus (HIV), *Clostridium difficile*, Hepatitis B, and bacterial infections (24,25).

At this time, allografts are often used in conjunction with other materials such as autologous bone, bone marrow aspirate (BMA), demineralized bone matrix (DBM), or biologics [e.g., human recombinant bone morphogenetic proteins (rhBMP-2)] (26,27).

Bone marrow aspirate (BMA)

BMA is a cell-based alternative for ICBG and can be harvested from the iliac crest or the pedicle of the spine (28). BMA is generally believed to lack structural integrity and is likely to diffuse from the application site without a matrix. As such, BMA is often combined with a carrier material such as autograft, allograft, ceramics, or DBM prior to implantation.

While the harvesting and processing of the BMA can be challenging (23), the rate of fusion following the application of BMA in conjunction with local bone graft and rhBMP-2 in lumbar spinal fusion may be as high as 93% (29). BMA

contains pluripotent mesenchymal stem cells (MSCs) that differentiate into osteogenic progenitor cells (30). In addition, following the harvest of BMA, the material may be readily preserved for future application. BMA's osteoinductive capacity has been previously described as a result of cytokines and growth factors released from the cell populations within the graft (9).

Demineralized bone matrix (DBM)

DBM is used as a bone graft extender that is created from allograft. Demineralization refers to the process by which the mineral components of the human cadaveric bone are removed (31). Despite the removal of minerals, processing through acid extraction still preserves the Type I collagen, non-collagenous proteins, and a variety of growth factors according to the manufacturer (9). The organic matrix (composed of the non-collagenous proteins and collagens) provides osteoconductive properties, while the growth factors provide osteoinductive potential (32). As such, DBM provides osteoconductive and osteoinductive potential in the fusion environment. However, despite these advantages, the composition of DBM can differ between manufacturers as well as between products from the same manufacturer (33).

DBM is generally versatile in its application, largely because it is available in a variety of forms including powder, gels, paste, and putty formulations (33). However, some forms of DBM may not be able to provide mechanical strength per se and often necessitate utilization of other bone graft material to bolster its osteoconductive and handling properties (32). The efficacy of DBM as a bone graft extender has been previously studied. In particular, Morone and Boden determined that DBM can supplement a lower volume of autograft and yield similar fusion rates in a rabbit posterolateral spine fusion model (34-36).

Kang *et al.* compared the efficacies of commercial DBM with local autograft *versus* ICBG in patients undergoing a single-level posterior lumbar fusion, the authors reported fusion rates of 86% and 92%, respectively (37). In addition, the DBM cohort demonstrated potentially improved clinical outcomes with lower intraoperative blood loss and higher physical function scores at 24 months postoperatively (37).

Ceramics

Bioceramic scaffolds are synthetic calcium-based bone graft extenders that often function in conjunction with autologous bone or BMA (38). Generally, ceramics have a high degree of utility because they are biodegradable, non-toxic, non-inflammatory, and can be produced in larger quantities. However, the advantages must be tempered with the fact that ceramics possess a lower tensile strength due, in part, to the intrinsic brittleness of the material. Though this represents a disadvantage to ceramics, the porous microstructure increases their osteoconductive potential and may facilitate stem cell migration and adhesion (39).

The currently available ceramics may feature (I) β-tricalcium phosphate (β-TCP), hydroxyapatite (HA), (II) calcium phosphate, or (III) calcium sulfate which can vary in their porosity. In particular, β-TCP demonstrates greater porosity and larger pores than HA, allowing for greater osteoconductive properties, but potentially decreased mechanical strength (12). Conversely, HA is much denser and may not incorporate as readily as β-TCP, but may offer greater mechanical strength under load (9). In one study, the utilization of HA as a bone graft extender with autologous bone have demonstrated fusion rates as high as 86% (40,41). Additionally, Alimi *et al.* demonstrated a fusion rate of 76.3% when ceramics were applied without additional graft material in direct lateral interbody fusion procedures (42).

In summary, ceramics are commonly used as a bone graft extender that may be composed of a variety of materials. This composition within the ceramic implant determines the osteoconductive potential as well as the mechanical strength of the construct.

Growth factors

Bone morphogenetic proteins (BMPs) are soluble cytokines that are a part of the transforming growth factor-β (TGF-β) family. BMPs are described for their capacity to accelerate bone growth and promote the differentiation, maturation, and proliferation of osteogenic progenitor cells (43). In particular, rhBMP-2 is currently approved by the Food and Drug Administration (FDA) in the setting of a single-level anterior lumbar fusion involving levels from L4 to S1 (44). When delivered on absorbable collagen, rhBMP-2 can lead to high rates of fusion (45,46).

Parajón demonstrated, through a meta-analysis, that in patients using rhBMP-2 with autograft and bone graft extender were able to reach fusion rate of 99.1% (47). Furthermore, when compared with patients treated with other materials such as isolated autologous bone, patients in the rhBMP-2 group demonstrated a higher overall fusion rate (91.8% *vs.* 99.1%) (47).

Despite its positive effect on achieving fusion, a number of complications related to BMP-2 have been noted, including hematoma formation, heterotopic ossification, and retrograde ejaculation (48,49). Fu *et al.* further describes, in a systematic review, that when compared to controls, studies in which rhBMP-2 were associated with a higher risk of cancer (49).

In addition, the potential of platelet-rich plasma (PRP) to facilitate arthrodesis has been a topic of interest (50). Elder *et al.* sought to analyze the efficacy of PRP in the context of spinal fusion procedures (51). In doing so, the authors were not able to make any significant conclusions. The authors primarily attributed this observation to lack of standardization in the PRP preparation protocol, resulting in preparations with varying amounts of platelet number and concentration (51). Furthermore, the authors demonstrated that despite extraction of similar platelet number and concentration between samples, the concentration of growth factors available for biologic activity may vary (51).

Most investigation of PRP for the purposes of promoting arthrodesis are in animal models. Kamoda *et al.* reported fusion rates of 100% in a rodent model when PRP was used with HA (52). Additionally, Okamoto *et al.* demonstrated a fusion rate of 86% in a rabbit posterolateral spinal fusion model (53). However, Scholz *et al.* reported no significant osteoinductive effects of PRP with mineralized collagen in a sheep interbody fusion model (54).

Despite the paucity in literature regarding the efficacy of protein-rich platelets, there has been an increase in overall interest in the applicability of PRP as an enhancer of bone regeneration. This interest has been met with an increased number of studies that have reported varied results with varied methodology. As such, there is a need for a stronger, more standardized way of conducting research to understand the true applicability of PRP in the orthopedic field.

Conclusions

With an ever-increasing array of biologic graft materials available for use in spine surgery, maintaining a comprehensive understanding of the characteristics, benefits, and drawbacks of each option is essential for the practicing spine surgeon. Although ICBG is still considered the gold standard in spinal fusion surgeries, their disadvantages have preempted research into alternatives. While investigation into the development and refinement of technologies such as biologics and bone graft materials continues to become more refined and widely implemented, it is increasingly necessary to critically analyze their major characteristics and best usages so that surgeons can select material that can best maintain a high level of osteogenic, osteoconductive, or osteoinductive potential. As such, further research endeavors should investigate the best available options specific to the patient population while considering the overall cost-effectiveness and efficacy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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