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Osteobiologics and Value-Based Care: Challenges and Opportunities

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ABSTRACT

Background: Autologous bone grafts, sourced from the iliac crest, are the gold standard for bone substitution in spine surgery. However, harvesting autografts increases the risk of postoperative complications. Bone allografts are another popular source of graft material, but their use is rapidly surpassing their availability. There has been considerable interest in manufactured bone graft substitutes, commonly referred to as osteobiologics, which mimic the properties of autologous bone and may be osteoconductive, osteoinductive, osteogenic, or a combination.

Objective: Osteobiologics have been developed to mimic the properties of autologous bone, but their high cost and variable effectiveness raise questions about their value. This article explores the challenges and opportunities associated with the use of osteobiologics used to aid in bone healing in spinal fusion surgery within a value-based care framework. Spinal fusion treatments such as bone morphogenetic proteins, platelet-rich plasma, autologous conditioned serum, demineralized bone matrix, biomaterial scaffolds, stem cells, and cellular bone matrices are compared.

Summary: Bone morphogenetic proteins are highly effective but often associated with serious risks; platelet-rich plasma shows promising results but lacks standardization in research protocols. Autologous conditioned serum is inconclusive and cost-effective, while demineralized bone matrix has variable effectiveness and limited data to use in anterior spinal fusions. Biomaterial scaffolds have limited application in the anterior spine but demonstrate high efficacy when it comes to spinal fusion. Stem cells demonstrate improved postsurgical outcomes but have low yield from bone marrow and potential risks associated with genetic engineering and cell therapy. Cellular bone matrices show promising results and have high fusion rates, yet there is currently no US Food and Drug Adminstration requirement for preclinical or clinical data before commercial usage. Although osteobiologics have considerable potential, their high price and uncertain efficiency raise questions concerning their usefulness in spinal fusion surgery. To ensure better patient outcomes, extensive research is needed to explore their utilization within a value-based care framework.

Biologics

Keywords: osteobiologic, DBM, stem cells, CBM

INTRODUCTION

Osteobiologics are substances that promote bone healing and are being utilized more frequently in spine surgery to avoid nonunion.[1] The gold standard for bone replacement in spine surgery continues to be autologous bone grafts, which are harvested from iliac crest bone grafts (ICBGs). However, harvesting autografts increases the risk of postoperative pain, wound complications, longer operating times, and donor site pain.[2]

Bone allografts, sourced from human cadavers,[3] are another popular source of graft material. Earlier studies provided evidence in favor of allografts with comparable fusion rates and clinical outcomes to autografts.[4,5] According to more recent studies, autologous bone grafts have better fusion rates than allogeneic bone grafts,[6] which may be due to the absence of viable cells, rendering the allografts nonosteogenic. Moreover, postexcision processing techniques, such as gamma irradiation, reduce the load-bearing capacity of allografts in comparison to autografts. Despite the variability in literature, allografts have historically been used to substitute autografts until now as their high demand is rapidly surpassing their availability.[7]

Consequently, there has been considerable interest in manufactured bone graft substitutes, commonly referred to as osteobiologics. The use of osteobiologics, such as growth factors, demineralized bone matrices (DBMs), biomaterial scaffolds, as well as bone marrow aspirate (BMA) and its derivatives, have become an integral part of spinal fusion surgery. Osteobiologics can be osteoconductive, osteoinductive, osteogenic, or a combination of the 3, and they mirror the characteristics of an autologous bone. The use of osteobiologics in spine surgery has been shown to enhance clinical results and fusion rates and improve pain management.[8] However,

Table 1. Comparing efficacy, utility, and cost challenges of osteobiological agents.

Agent	Properties	Efficacy	Costs	Challenges	Opportunities
Bone morphogenetic proteins	Proteins involved in the differentiation of osteoblasts and chondroblasts	Comparable and high	High	Variable fusion rates across different procedures, associated with serious complications	New delivery methods to reduce dose-limiting effects; advantages outweigh risks in vulnerable population
Platelet-rich plasma	Contains growth factors	Promising	Unavailable	Lack of standardization in research protocols	High fusion rates
Autologous conditioned serum	Growth factors extracted from the patient's serum	Inconclusive	Unavailable	No evidence regarding improving fusion rates	Cost-effective
Demineralized bone matrix	Graft extender containing growth factors	Effective, but as an adjunct	Lower than nonautologous graft materials but still relatively high	Extreme variability in the number and types of products available for an accurate comparison, limited data for use in anterior spinal fusions	Improved clinical outcomes, lower intraoperative blood loss, and improved physical function.
Biomaterial scaffolds (ceramics and polypeptide-based compounds)	Synthetic grafts made of osteoconductive materials	Variable	High	Limited use in the anterior spine, increased resorption rates, brittle and weak in tension-based posterior spinal fusions	High efficacy in spinal fusion, synthetic, biodegradable, nontoxic, and noninflammatory.
Stem cells (mesenchymal and adipose-derived)	Possessing autocrine and paracrine properties, effective for lineage progression and differentiation	Limited studies in humans	High	Low yield of mesenchymal stem cells from bone marrow, difficulty in increasing their concentration in implanted grafts, potential risks associated with systemic viral or bacterial toxicity, immunity to certain viral strains, and ethical concerns surrounding genetic engineering and cell therapy.	Improved postsurgery outcomes, comparable uptake, reduced healing time, comorbidities and systemic factors do not affect their outcomes adversely.
Cellular bone matrices	Osteoconductive grafts made by combining allogeneic bone with allogeneic stem cells	Promising	High	Lack of FDA requirement for preclinical or clinical data before commercial usage, effective concentration threshold rates still unknown.	High fusion rates

Abbreviation: FDA, US Food and Drug Adminstration.

their high cost and varying efficacy have raised concerns about their value in spinal fusion surgery. This article explores the challenges and opportunities associated with the use of osteobiologics in spinal fusion surgery within a value-based care framework.

EXPLORING THE CURRENT EVIDENCE IN THE USE OF OSTEOBIOLOGICS: EFFECTIVENESS, LIMITATIONS, AND REGULATORY CHALLENGES

Currently available osteobiologics include growth factor derivatives, which include bone morphogenetic proteins (BMPs) and platelet-rich plasma (PRP), DBM, biomaterial scaffolds or synthetics, and BMA derivatives (Table 1). Although each of these have shown a potential to enhance bone fusion rates in spinal surgeries, each material has its limitations and complications.

Bone Morphogenetic Proteins

The effects of BMP on fusion rates are not consistent across various spine procedures and must be approached with caution. Compared with other materials, BMP has shown improved fusion rates in anterior lumbar interbody fusion and posterior lumbar fusion (PLF) but not as much in posterior lumbar interbody fusions (PLIFs) and transforaminal lumbar interbody fusions (TLIFs).[9] Therefore, the use of rhBMP-2 is only FDA-approved for anterior lumbar interbody fusion (ALIF), while its use in PLIF,[10] TLIF,[11] and PLF[12] remains off-label. Despite showing augmented fusion rates and clinical outcomes in the cervical spine,[13–15] the FDA continues to have a black box warning for its use in cervical procedures due to complications such as cervical airway edema and dysphagia.[16] BMP has also been linked to various complications, including seroma/hematoma formation, prevertebral swelling, radiculitis, retrograde ejaculation, vertebral osteolysis, heterotopic ossification, allograft resorption,[17–22] and increased cancer risk,[23] which create barriers to its widespread adoption in spinal arthrodesis. The limited ability of carrier molecules to bind and release the product results in such complications.

Methods to enhance localized delivery of rhBMP-2 to the site of healing using nanostructure biomaterials which enhance growth factor retention resulting

in reduced supratherapeutic doses of rhBMP-2 have shown efficiency in animal studies.[24,25] These delivery techniques help to mitigate dose-limiting side effects by decreasing the therapeutic dose of growth factors.[25] Despite the apprehensions regarding its use, rhBMP-2 is widely used across various spinal fusion surgeries, including cervical and thoracic procedures. Between 2002 and 2011, rhBMP-2 use skyrocketed from slightly more than 1000 to nearly 80,000 cases, and approximately 85% of rhBMP-2 use was deemed off-label.[2,26] Currently, the evidence regarding the benefits of rhBMP-2 is more tangible, especially in vulnerable populations with poor bone quality, those undergoing revision surgery, and smokers, than the evidence concerning the risks.[25]

Platelet-Rich Plasma

The use of PRP for spinal arthrodesis and its role in regenerating bone has been explored in animal models with promising results, with fusion rates of 100% and 86% reported in rodent and rabbit models, respectively, when used in conjunction with other substances. However, a sheep model did not demonstrate significant osteoinductive effects of PRP. Consequently, there is a need for standardized research exploring PRP use in spine surgery.[27,28] A step ahead of PRP is an autologous conditioned serum (ACS), which is created by extracting and modifying a patient's serum containing growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) and reintroducing it to the patient. Although ACS is a cost-effective way to enhance new bone formation, studies have not yet been able to prove the superiority of using ACS in enhancing posterior spinal fusion or TLIF fusion rates.[3]

Demineralized Bone Matrix

The use of DBM in spinal fusion presents both challenges and opportunities. Multiple studies have found no significant disparities in fusion or pseudoarthrosis development rates between DBM and other bone graft materials.[25–27,29,30] DBM has been extensively studied as an autograft extender in posterior spinal fusions, but limited data are available regarding its use in anterior spinal fusions.[31–33] Despite this, using DBM as an adjunct has been found to improve clinical outcomes, lower intraoperative blood loss, and improve physical function.[31] However, it is important to note that these studies explored the use of DBM as an adjunct to local autograft, BMA, or ICBG, and there is currently no evidence to support the use of DBM as an autonomous osteobiologic. Surgeons must be diligent in selecting DBM products due to the extreme variability in the number and types available. DBM products are effective in treating multilevel cervical disc disease and augmenting spinal fusions, and several authors have suggested standardized paradigms for selecting DBM products.[34] For routine spinal fusions, it is advisable to use a pure 100% DBM paste without a carrier as a complement to autologous bone grafts. In posterior spinal surgery, one may consider using a soft and porous DBM bone strip, which provides immediate support and scaffolding. This approach can be particularly beneficial when combined with autologous Bone Marrow Aspirate Concentration (BMAC). In cases where there is a need to inject DBM into a bone defect, such as those resulting from the removal of a pedicle screw, it is preferred to use DBM with a carrier in a viscous formulation.[34] Manufacturing companies and the FDA should provide more information on the origin, processing, storage parameters, and final DBM content of these products to aid in product selection.

Synthetics: Ceramics and Polypeptide-Based Compounds

Ceramics, such as hydroxyapatite and tricalcium phosphate, have shown high efficacy in spinal fusion and have the advantage of being synthetic, biodegradable, nontoxic, and noninflammatory.[35–37] Since they need to be shielded from severe compression load, their use in the anterior spine is limited,[38] and their increased resorption rates[39] may limit their applicability. The major challenge is that ceramics are weak and brittle and susceptible to the same disadvantages as allograft in tension-based posterior fusions.[38] While earlier studies suggest ceramics may serve as viable alternatives to autograft bone, newer studies have evaluated their use without standard control or comparison groups.[40–42] Several studies have reported varying fusion rates, depending on surgical technique, number of levels fused, criteria for radiographic fusion assessment and follow-up period, and patient factors such as smoking. Consequently, it is challenging to draw fair comparisons between these studies.[43] New evidence has surfaced regarding the practical application of synthetics (ie, AttraX Putty) as a standalone bone graft substitute for autograft in instrumented thoracolumbar PLF.[44]

Polypeptide-based compounds like ABM/P-15 offer an opportunity for spinal fusion because they are noninferior to autograft in fusion rates and adverse events,[45,46] and some studies indicate higher success rates.[47] However, more research is needed to assess their effectiveness and safety fully. While ABM/P-15 has shown promising results in Europe, it has not undergone comprehensive

investigation in the United States and lacks FDA clearance as a lumbar fusion device, thereby hindering its application in this clinical setting. P-15 is currently undergoing an active FDA study, focusing on its PLIF indication, and this study is nearing completion.[48] Successful results from this study would result in the attainment of an on-label indication, significantly enhancing the product's value. Recently, insurance carriers have been placing a growing emphasis on FDA-approved indications for medical products. Recognizing this trend, P-15 aims to leverage the potential on-label status to its advantage. As a consequence, spine surgeons may contemplate the use of P-15, particularly when seeking pre-authorization, as it could streamline the process of obtaining insurance approval for a given case.

Stem Cell Derivatives

Stem cell derivatives offer potential for spinal fusion, but their use in humans is still limited. Animal studies have shown success with autologous stem cells and BMAC, but the yield of mesenchymal stem cells from bone marrow is low,[49] and methods to increase their concentration in implanted grafts are ineffective and expensive, and it is challenging to maintain sterility during surgery where cells are required to be added into the bone graft Additionally, there have been no investigations into commercial methods yet. Although studies in animals have shown promising results with cultured and engineered stem cells, the use of stem cell derivatives in spinal fusion is still limited in human trials. The main challenge is the potential risks associated with systemic viral or bacterial toxicity, immunity to certain viral strains, and ethical concerns surrounding genetic engineering and cell therapy. However, recent research has shown that BMAC can be an effective alternative to the "gold standard" ICBG in posterior lumbar fusions, with comparable fusion rates.[50] Stem cell product lines are also more favorable compared with synthetic materials because comorbidities and other systemic factors do not affect their outcomes adversely. Inadequate fusion following spinal surgery can lead to reduced quality of life and patient morbidity. Stem cell therapy has the potential to improve postoperative outcomes, especially in terms of fusion, with uptake comparable to or even better than traditional materials while also reducing healing time.

Cellular Bone Matrices

The use of cellular bone matrices (CBMs) in spinal fusion has shown promise in achieving high rates of fusion. However, the content of CBMs varies greatly regarding total mesenchymal stem cell concentration, donor age, shelf life, and cell viability. Moreover, the concentration thresholds required for satisfactory fusion rates are still unknown.[51] The lack of FDA requirements for preclinical or clinical data prior to commercial use makes an accurate comparison between different commercial CBMs challenging. Additionally, the evidence regarding CBM outcomes has been largely derived from industry-sponsored studies, and the lack of standardized regulation and data raises concerns about their efficacy and safety in spinal fusion surgery.

COST CHALLENGES

In the context of using osteobiological agents in spinal fusion surgery, there are numerous cost-related challenges to consider. One should exercise caution when evaluating studies that compare osteobiologics because several of these studies are industry-sponsored and necessitate a smaller patient population in comparison to studies that are intended to assess the superiority of the product. FDA clearance is frequently granted for a limited indication, but it is frequently extrapolated to other surgical procedures based on the surgeon's understanding of the literature, resulting in off-label usage and potential hazards for patients. A recently published systematic review highlighted the lack of consensus on the cost-effectiveness of using alternative osteobiologics compared with ICBG for spinal fusion procedures.[52] The authors concluded that while alternative osteobiologics usually result in greater costs than ICBG, there is wide variability of parameters in each study, such as levels of fusion and variability in the factors that affected the overall costs, which made accurate comparisons unlikely. Additionally, this variability also exists across different health care systems and countries. However, one principle holds: nonautologous graft materials are the most expensive, followed by synthetic and autologous graft materials.[53] For example, in New York, USA, the cost of Stryker bioactive foam, Stryker bio4, and Medtronic extra small BMP was $215, $255, and $2010, respectively. Santiago, Chile had 1 cc DBM costing $319 and 5 cc Tricalcium phosphate costing $352. Switzerland had 5 cc BMP costing $952 to $1270 and a large Induct Os kit costing $4762. In Egypt, the cost of Tricalcium phosphate ranged from $49 to $82, while the cost of BMP and polyetheretherketone cages ranged from $286 to $408 and $61 to $102, respectively. In Singapore, the cost of Zim Vie, a type of osteobiologic, was $729.[52]

The most widely studied agents are allografts and BMPs. Critics frequently argue that the elevated expenses associated with utilizing osteobiologics can

be balanced out by the reduced long-term incidence of complications when compared with conventional autologous ICBG. However, this argument should be approached with caution, as their associated higher hospital-reported charges may not be worth it especially when patients show similar fusion rates, postoperative complication rates, and time-to-readmission regardless of osteobiologic type.[53] For example, rhBMP-2 in spinal deformity surgery can add as much as $20,000, but it mitigates the probability of surgical intervention for pseudarthrosis, which would otherwise result in expenses ranging from $30,000 to $60,000 per surgery.[54,55] Data from a multicenter, prospective registry of 522 patients with adult spinal deformity were analyzed by the International Spine Study Group. The findings indicated that the incidence of revision surgery for symptomatic pseudoarthrosis was twice as high in patients who did not receive rhBMP-2 compared with those who received rhBMP-2. Additionally, patients who necessitated revision surgery for pseudoarthrosis incurred direct costs that were more than twice as high as patients who did not require surgery for pseudoarthrosis, as determined by the mean 2-year direct costs.[55,56] Therefore, the use of rhBMP-2 seems to be a cost-effective option, given the high patient and economic costs of failed fusion surgery. This principle may not apply to anterior cervical discectomy and fusion (ACDF) surgeries where BMP is associated with dysphagia and/or hoarseness.[57] Therefore, it remains unclear whether its use in ACDF can be deemed cost-effective even when considering the fusion and complication rates. Regardless, utilizing rhBMP-2 in spine surgeries has always been a costly approach, and to date, there are no cheaper variants of rhBMP-2 available. Efforts have been geared toward developing guidelines for appropriate use of rhBMP-2, with indications including adult spinal deformity surgery, revision spine surgery, and surgery involving long constructs.[58]

Contemporary medical advancements, including BMAC and DBM, have been preliminarily investigated for their cost-effectiveness in comparison to other products. These investigations have suggested similar clinical efficacy at reduced costs.[59] According to Patel and Silver, patients who were treated with BMAC had a shorter average hospital stay and fewer days from discharge to the commencement of physical therapy compared with patients who received autograft or BMA for spinal fusion. Additionally, the average cost of treating spine fusion patients with significant comorbidities was found to be lower in patients treated with BMAC in comparison to those treated with BMP.[60] The presented data demonstrate the potential benefits of utilizing BMAC as a biological agent in the treatment of spinal fusion patients, including the reduction of expenses and a positive impact on health outcomes. However, these are preliminary results, and there is an eminent need for further research to determine the efficacy and cost-effectiveness of different osteobiologic materials.

The interest of spine surgeons in stem cell therapies is notable; however, it should be noted that these therapies are not associated with lower costs. Although few studies report costs to patients, or the funding institution, stem cell therapy can incur greater costs than traditional therapy.[61] As with any relatively new modality, we can expect these costs to decrease with greater adoption and optimization. The direct expenses associated with these alternatives do not significantly differ from those of commonly employed methods. However, the hidden costs involved in processing, activating, testing for infections, and other tasks associated with high sterility procedures serve as significant hurdles in effectively comparing their utility in value-based health care.[62]

Estimating based on the previously defined nonfusion rate of 10% to 28%,[63,64] it becomes evident that a substantial number of individuals experience nonfusion following spinal surgery. Importantly, nonfusion patients exhibit a significantly higher early loosening rate of pedicle screws, contributing to 62.5% of subsequent reoperations.[65,66] Therefore, justifying a high cost of an agent becomes possible only if it significantly contributes to fusion. This is particularly important because spinal nonfusion is a common and severe postoperative complication that can profoundly affect patient satisfaction, postoperative function, and mental well-being.[65]

Disclosing costs for osteobiologic products from different companies has proven to be challenging due to the sensitivity and confidentiality surrounding dealings with each hospital. Our attempt was to comprehensively summarize and compare the costs of each biologic based on published data across 3 different states in the United States (Table 2),[52,67] with fusion success serving as the measure of benefit. It is crucial to note that these opinions are based on available literature.

While the high costs of BMP are justified as they provide superior fusion benefit, DBM's low costs and noninferiority to autograft bone favor its independent use to avoid autograft morbidity. PRP has low costs

Table 2. Cost comparisons and noninferiority evidence for various osteobiologics in 3 US states.

Osteobiologics	Costs Across 3 States			Cost Range	Noninferiority	Verdict
	Maryland	New York	California			
Bone morphogenetic proteins	Infuse, large kit, 8 cc: $6,000	Medtronic extra small BMP: $2010	inFUSE large pack: $5100–5408	$$–$$$$	Superior effect in combination with autograft	High costs justified
Platelet-rich plasma			$450–475	$	No evidence to establish noninferiority	Low costs justified for trial exploration, not for routine use
Demineralized bone matrix	Optium, 10 g: $900	Stryker, 1 cc: $191	DBX: $576–$880, Grafton: $575–600	$	Noninferiority to autograft bone	Low costs justified for independent use, avoiding autograft morbidity
Biomaterial scaffolds						
Tricalcium phosphate	Chronos, 10 g: $635	Stryker, 1.2 cc: $211		$	No evidence to establish noninferiority	Not enough evidence to comment
Bioactive glass	Fibergraft, 10 g: $2,900	Stryker vitoss bioactive foam, 1.2 cc: $215		$-$$	No evidence to establish noninferiority	Not enough evidence to comment
Stem cells (mesenchymal and adipose-derived)	Vivigen, 10 g: $3,300	Stryker bio4, 1 cc: $255		$–$$$	No evidence to establish noninferiority in spinal fusion	Not enough evidence to comment

Note: Costs are represented in US dollars ($). The cost range indicates the relative costliness of each biologic and is based on the following scale: <$1000: $, >$1000: $$, <$5000: $$$, >$5000: $$$$.

justified for trial exploration but not routine use due to insufficient evidence for noninferiority. Biomaterial scaffolds like tricalcium phosphate and bioactive glass lack evidence for noninferiority, making it difficult to comment on their cost-effectiveness. Stem cells (mesenchymal and adipose-derived) also lack evidence for noninferiority in spinal fusion, with insufficient data for a cost-effectiveness assessment.

CONCLUSION

In conclusion, the use of osteobiologics in spinal fusion surgery has presented both challenges and opportunities for spine surgeons. While autologous bone grafts remain the gold standard, their use presents a risk of postoperative complications. Allografts, on the other hand, are inferior to autografts due to the absence of viable cells and processing techniques that reduce their load-bearing capacity. As a result, osteobiologics have become an integral part of spinal fusion surgery, mimicking the properties of autologous bone and improving pain reduction, fusion rates, and clinical outcomes. While osteobiologics have shown promising results, their high cost and varying efficacy have raised concerns about their value in spinal fusion surgery. Therefore, further research is needed to explore the use of osteobiologics within a value-based care framework to ensure that the benefits of these materials outweigh their cost and complications, ultimately leading to better patient outcomes.

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