Review Article

Recombinant human bone morphogenetic protein-2 in spine surgery: recommendations for use and alternative bone substitutes—a narrative review

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Background and Objective: Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been extensively studied in preclinical, animal, and human studies and has been used widely in spine fusion surgery. Evidence demonstrates that fusion rates with rhBMP-2 are similar to or higher than those achieved with autologous bone graft. However, there have been concerns regarding the cost, optimal dosage, and potential complications of rhBMP-2 use in spine surgery. The objective of this paper is to provide a current review of the available evidence regarding rhBMP-2 and other bone graft substitutes used for spinal surgery.

Methods: We searched Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, and Database of Abstracts of Review of Effectiveness for 2 studies regarding physiology of bone fusion in spine surgery, formulations and indications of rhBMP-2, cancer risk of rhBMP-2, and alternatives to rhBMP-2 published from 1965 to 2022 in English.

Key Content and Findings: The debate regarding indications and cost effectiveness of rhBMP-2 is presented based on increasing data and use criteria. Here, we focus on the effectiveness and economic costs (both direct and indirect) of rhBMP-2 and alternative bone graft substitutes. Based on the cumulative literature, we provide recommendations for rhBMP-2 use in spine surgery.

Conclusions: Based on our review of the literature, we recommend the following: (I) clear informed consent processes between surgeons and patients regarding current evidence of the benefits and risks of using rhBMP-2 and available alternative bone graft substitutes. (II) Consideration of rhBMP-2 for spinal fusion surgery (excluding anterior cervical procedures), especially adult spinal deformity (ASD) surgery, lumbar surgery for multilevel degenerative disease, revision surgery for pseudoarthrosis, and surgery in patients with a low-quantity or low-quality autograft. (III) Regulatory oversight of the type, volume, and dose of bone graft substitute (both per level and per procedure) to ensure appropriate indications, prevent excessive usage, and thereby enhance cost containment.

Keywords: Complication; cost; fusion rate; indications; recombinant human bone morphogenetic protein-2 (rhBMP-2)

Submitted Mar 14, 2022. Accepted for publication Aug 16, 2022.
doi: 10.21037/jss-22-23
View this article at: https://dx.doi.org/10.21037/jss-22-23

Introduction

Recombinant human bone morphogenetic proteins (rhBMPs) have been used widely in spine fusion surgery as a substitute for harvested iliac crest bone graft (ICBG) and provide fusion rates that are comparable to or higher than those achieved with ICBG (1-9). However, there are concerns about the appropriate use, potential complications, and costs of rhBMP in spine surgery.

BMPs are naturally occurring, soluble members of the transforming growth factor-beta (TGF-β) superfamily of proteins. They were first reported in 1965 by Marshall R. Urist, MD, from the UCLA Department of Orthopaedic Surgery in Los Angeles, CA, USA (10).

Because of the limited yield of naturally extracted and purified BMP, large-scale production of rhBMP began in the mid-1990s using human recombinant genetic technology (11). Over the next decade, extensive basic science and animal research was conducted to determine the optimal carrier, concentration, and dose for clinical use in spinal fusion. To date, 20 BMPs have been identified; rhBMP-2 and rhBMP-7 are osteoinductive, inducing the transformation of pluripotent mesenchymal stem cells (MSCs) into active osteoblasts. These growth factors initiate the complete bone formation process *de novo* (12).

In 2002, the United States Food and Drug Administration (FDA) approved Infuse® (Medtronic, Inc., Dublin, Ireland), a form of rhBMP-2, for use in spine surgery in combination with a metallic spinal cage (LT-CAGE®; Medtronic, Inc.) in skeletally mature patients with degenerative disc disease at 1 level from L4-S1. Since then, Infuse has dominated the spine market, being used alone without an LT-CAGE.

The purpose of this article is to provide a historical perspective of rhBMP-2; describe its principles of action, indications for use, complication profile, and costs; and explain how these issues impact current usage of rhBMP-2. We also discuss several alternative bone graft substitutes and provide recommendations for rhBMP-2 use in spine surgery. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jss.amegroups.com/article/view/10.21037/jss-22-23/rc).

Methods

When reviewing the clinical evidence on rhBMP-2 use, studies were selected according to the following approach and considerations. The study population included patients who underwent treatment of cervical and lumbar degenerative disc disease, spondylolisthesis, and any other relevant spine conditions. Only studies evaluating rhBMP-2 in spinal fusion were included; studies of other recombinant forms of BMP (rhBMP-7) were not included. Inclusion was not restricted by operative approach; anterior lumbar interbody fusion (ALIF), lateral lumbar interbody fusion (LLIF), oblique lumbar interbody fusion (OLIF), posterior lumbar interbody fusion (PLIF), posterolateral fusion (PLF), transforaminal lumbar interbody fusion (TLIF), and anterior cervical discectomy and fusion (ACDF) procedures were all eligible. Likewise, open, minimally invasive, and endoscopic procedures were all considered. Studies involving nonspinal surgery were excluded. For comparative studies, studies comparing rhBMP-2 with ICBG were included. Outcomes included clinical improvement, patient-reported measures, complications, and radiologic fusion rates. Evidence from both randomised controlled trials (RCTs) and retrospective databases was considered.

A comprehensive search of published reports was performed using six electronic databases: Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, and Database of Abstracts of Review of Effectiveness. Searches identified articles published from the January 1996 to January 2022. To maximise the sensitivity of the search strategy, the terms "bone morphogenetic proteins", "BMP", "rhBMP-2", "infuse", "spinal fusion", "lumbar interbody arthrodesis", "lumbar or cervical or posterior or anterior or lateral or oblique or transforaminal or posterolateral", and "fusion cage" were combined as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed to identify additional potentially relevant studies. Studies were assessed according to inclusion and exclusion criteria to determine whether they were eligible for discussion in this

Table 1 Search strategy summary

Items	Specification
Date of search	28th January 2022
Databases and other sources searched	Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, and Database of Abstracts of Review of Effectiveness
Search terms used (including MeSH and free text search terms and filters)	"bone morphogenetic proteins", "BMP", "rhBMP-2", "infuse", "spinal fusion", "lumbar interbody arthrodesis", "lumbar or cervical or posterior or anterior or lateral or oblique or transforaminal or posterolateral", and "fusion cage"
Timeframe	January 1996 to January 2022
Inclusion and exclusion criteria	All study types regarding physiology of bone fusion in spine surgery, formulations and indications of rhBMP-2, evidence about cancer risk with rhBMP-2, quality of the available evidence, alternatives to rhBMP-2, and patient preferences were included. Only studies evaluating rhBMP-2 in spinal fusion were included; studies of other recombinant forms of BMP (e.g., rhBMP-7) were not included. Inclusion was not restricted by operative approach; ALIF, LLIF, OLIF, PLIF, PLF, TLIF, and ACDF procedures were all eligible. Likewise, open, minimally invasive, and endoscopic procedures were all considered. Studies involving non-spinal surgery were excluded. English language only
Selection process	One author conducted the search of six databases. The reference lists of all retrieved articles were reviewed and assessed based on inclusion and exclusion criteria, with consensus obtained from all authors
Additional considerations	Outcomes included clinical improvement, patient-reported measures, complications, and radiologic fusion rates. Evidence from both RCTs and retrospective databases was considered

rhBMP-2, recombinant human bone morphogenic protein-2; ALIF, anterior lumbar interbody fusion; LLIF, lateral lumbar interbody fusion; OLIF, oblique lumbar interbody fusion; PLIF, posterior lumbar interbody fusion; PLF, posterolateral fusion; TLIF, transforaminal lumbar interbody fusion; ACDF, anterior cervical discectomy and fusion; RCTs, randomised controlled trials.

narrative review. The search strategy is summarised in the *Table 1*.

Results

Bone grafting in spine surgery often requires some type of bone graft material (autograft, allograft, synthetics, or combinations) to serve as a matrix for new bone formation or encourage healing in an area stabilized by implants. Paramount for successful bone fusion is the use of good surgical technique when preparing the decorticated vertebral endplates and/or posterolateral gutters, as well as minimizing injury to surrounding soft tissues. Large volumes of potent and expensive bone substitutes will not overcome a poorly prepared or devascularised fusion bed. Bone is composed of organic matrix (90% type 1 collagen), an inorganic mineral phase (calcium and phosphorus), and water. Proteins in the organic matrix, including BMP, stimulate bone healing (13). Maintaining an adequate blood supply to the bone graft is vital.

Three key factors involved in bone healing are important to consider when choosing the most appropriate bone graft material (14):

- Signal: this refers to bioactive molecules (primarily growth factors) that induce MSCs to differentiate into osteoprogenitor cells, then osteoblasts (the process of osteoinduction).
- Cells: these refer to new osteoblasts that lead to new bone formation (the process of osteogenesis).
- Matrix: this refers to the scaffold that allows cell infiltration and fusion of graft bone with the patient's bone (the process of osteoconduction) (12). Although autograft provides some of these factors and can be harvested from local bone at the site of surgery or from the iliac crest, rib, fibula, or elsewhere, it is not osteoinductive *per se*. This is in contrast to demineralized bone matrix (DBM) and exogenous rhBMP-2, which are osteoinductive. Disadvantages of ICBG include the additional 30–40 minutes of operation time, the second incision at the harvest site, donor site morbidity, variable graft quality, limited supply of graft material, and potential prolongation of the hospital length of stay (15). Infection, fracture, haematoma, and nerve

Table 2 Recommendations for rhBMP-2 use according to indication for spine surgery

Spine indication	Recommendation for rhBMP-2
Adult spine deformity	+++
Revision for pseudoarthrosis	+++
Lumbar fusion for degenerative disease	+++
Low-quantity or low-quality ICBG	+++
Posterior cervical fusion	++
Trauma	++
Tumour	++
Infection	++
ACDF	–

+++, excellent option; ++, good option; –, poor option or unsuitable. rhBMP-2, recombinant human bone morphogenic protein-2; ICBG, iliac crest bone graft; ACDF, anterior cervical discectomy and fusion.

injury have been reported in approximately 5–6% of patients undergoing spinal fusion with ICBG, and patient-reported acute or chronic pain at the donor site occurs in approximately 20–32% of patients (15-17).

There is controversy in the literature regarding donor site morbidity related to ICBG harvesting. Several techniques describe a primary posterior lumbar midline incision with separate fascial incision(s) to access the superior iliac crest (unilaterally or bilaterally), as well as bone graft harvesting by lifting a cortical window or subsequent reconstruction of the graft defect with an allograft or synthetic block.

Similarly, other minimally invasive ICBG techniques have been introduced and demonstrated to reduce donor site morbidity (18-20). Small prospective studies of patients receiving ICBG for elective lumbar fusion found no significant differences in reported pain between donor and non-donor sides (21,22), and a retrospective chart review reported no donor site complications (23).

Formulation of rhBMP-2

Infuse consists of rhBMP-2 applied to absorbable collagen sponge (ACS). The ACS functions to contain as much of the biologic as possible. Infuse is prepared at a fixed concentration of 1.5 mg/mL (24). The volume of ACS is cut to match the internal volume of the interbody cage. When developed, the Infuse dose was intended to be volume-dependent, with the Infuse volume equalling the internal volume of the cage; however, surgeons can underfill or overfill the cage, varying the delivered dose of rhBMP-2.

Indications for rhBMP-2

The initial approved indication for Infuse was ALIF surgery, which was studied in a 279-patient multicentre, prospective RCT in which a titanium lumbar-tapered fusion device (LT-CAGE) was filled with either Infuse or ICBG (25). Fusion rates were 94.5% for Infuse and 88.7% for ICBG at 24 months, confirming the efficacy of rhBMP-2 as a bone graft substitute for single-level ALIF.

Subsequently, over 20 RCTs have compared rhBMP-2 with ICBG (26). The off-label use of rhBMP-2 in PLF and TLIF/PLIF surgeries became widespread, with RCTs and case studies showing equivalent or superior efficacy to ICBG (27). In another study, rhBMP-2 demonstrated superior fusion rates to ICBG (93.5% versus 71.9%) in adult spinal deformity (ASD) over a minimum 4-year follow-up (28).

The LT-CAGE requirement for on-label use of Infuse was not supported by surgeons because the large cage windows allowed seepage of rhBMP-2, and superior cage designs and biomaterials became available (29). Additionally, rhBMP-2 does not require containment within a cage given its high potency for forming intertransverse bone. Hence, the FDA expanded its approval of rhBMP-2 to include use in polyether ether ketone (PEEK) cages for single-level ALIF and OLIF in May 2018 and then for PLF in 2019.

In current clinical practice, rhBMP-2 is commonly used for posterior cervical fusion, posterior and anterior lumbar fusion for degenerative disease, surgery for ASD, surgery with long posterior constructs, and revision surgery for pseudoarthrosis (*Table 2*). Additionally, rhBMP-2 is particularly beneficial as a bone graft substitute or graft extender when autograft harvest is of low yield or poor quality. This typically includes patients with frailty, elderly, chronic smoking, reduced bone density, chronic renal or hepatic disease, inflammatory bowel disease, rheumatoid arthritis, Parkinson's disease, low testosterone, diabetes mellitus, and prior radiotherapy with or without chemotherapy (30,31). rhBMP-2 can also be used safely in the presence of a spine infection. In a retrospective database study of 2,762 patients followed for more than 2 years, use of rhBMP-2 during fusion surgery for spine infection was associated with lower overall costs but no difference in

complication or reoperation rates (32).

A systematic review and meta-analysis of lumbar fusion rates with or without the use of rhBMP-2 found significant improvement in 24-month fusion rates with use of rhBMP-2 in ALIF (97.8% versus 88.2%), PLF (93.6% versus 83.1%), and PLIF (95.7% versus 89.5%) (1). Another meta-analysis, comprising 40 studies of patients undergoing minimally invasive TLIF, found that fusion rates were higher with rhBMP-2 than without rhBMP-2 (96.6% and 92.5%, respectively) (6). Prospective cohort studies demonstrated high fusion rates (assessed by CT) at 12 months when rhBMP-2 was used for ALIF (96.9%) (33), TLIF/PLIF (93.7%) (34), and LLIF (95.2%) (35).

Dosage of rhBMP-2

In a study published in 2015, dosages of rhBMP-2 used off-label in various types of spinal fusion were reported over a 10-year follow-up period in 527 patients. The mean Infuse dose per level was 8.4 mg for PLIF, 3.6 mg for ALIF, 4.2 mg for LLIF, and 8.4 mg for PLF (36), with a total mean dose per level of 6.2 mg. This was lower than the mean Infuse dose per level of 11.2 mg used during long fusions to the sacrum for ASD at Saint Louis, MO, USA (28).

Dose specification is important, as high doses of rhBMP-2 have been correlated with increased rates of deep infection (2.4%), arrhythmias (2.4%), and pseudarthrosis because of bone resorption (5%) (37). May *et al.* in 2019 reported that rhBMP-2 at supraphysiologic levels provides no beneficial effects in patients undergoing spine fusion (38). Data describing more contemporary use of rhBMP-2 have shown that smaller doses of rhBMP-2 are now being used in spine fusion surgery to optimise fusion rates and minimize the risk of complications. Mannion *et al.* in 2011 reported a 12-month interbody fusion rate (according to CT) of 97.2% after PLIF/TLIF using low dose rhBMP-2 of only 1.4 mg per level (39). A systematic review and meta-analysis of 2,729 patients between 2011 and 2019 reported an overall fusion rate of 94%, with rhBMP-2 doses ranging from 1.3 to 12 mg per level. Thus, lower doses of rhBMP-2 are now being used in spinal fusion surgery, with fusion rates remaining high and similar to those of previous studies using higher doses (37,39).

Complications of rhBMP-2

Use of rhBMP-2 is associated with well-documented potential complications (33,40-42). Early studies involved excessive doses of rhBMP-2 within the interbody space, as surgeons sought to improve fusion rates (41,43). Subsequently, it was learned that rhBMP-2 induces rapid cell turnover, and in the first 4–6 weeks postoperatively, there is an initial rhBMP-2-induced osteoclastic inflammatory response with a resorption phase (osteolysis) before onset of osteoblastic bone formation and consolidation. This can result in vertebral endplate cysts, cage subsidence, and screw loosening (44). Later osteoblastic reactions may cause ectopic bone formation and neural compression requiring reoperation (45).

Use of rhBMP-2 can cause swelling and oedema when placed in soft tissues, such as lumbar paraspinal muscles and cervical tissues, and seromas have been commonly reported (46). The FDA issued a black box warning against the use of rhBMP-2 in ACDF surgery because of reports of airway obstruction, need for reintubation, and death (47). Radiculitis from rhBMP-2 leakage around lumbar nerve roots in open or minimally invasive TLIF/PLIF (31) is sometimes severe, requiring pregabalin medication or epidural steroid injections. This can be reduced by using a sealant, such as fat or fibrin glue, to prevent rhBMP-2 leakage from interbody cages.

Radiculitis is less problematic with ALIF and LLIF cages, in which rhBMP-2 does not directly contact neural structures (34).

Earlier reports of higher retrograde ejaculation rates in patients undergoing ALIF with rhBMP-2, compared with autograft (7.2% versus 0.6%) (48) have not been supported by the results of large cohort studies (33). The difference in retrograde ejaculation rates was likely due to the surgical exposure technique rather than rhBMP-2-induced inflammation of the superior hypogastric plexus.

Regarding overall complication rates, Savage *et al.* in 2015 found that rhBMP-2 use did not increase the overall risk of postoperative complications after lumbar spinal fusion surgery (49). In this large institutionalized retrospective database study of 460,773 patients who underwent lumbar spinal fusion with or without rhBMP-2, the overall complication rate was 18.2% with rhBMP-2 and 18.7% without rhBMP-2. Similarly, in a retrospective cohort study of 7,115 patients, those who received rhBMP-2 had no increased risk of complications or reoperation at 24-month follow-up, compared with patients who did not receive rhBMP-2 (49).

Cancer risk with rhBMP-2

Carragee *et al.* published two reports indicating that

rhBMP-2 was associated with an increased risk of cancer (50,51). Other researchers reported no increase (43,52), inconclusive results (5), or a non-significant increase in cancer risk with rhBMP-2 (2).

Because of the discordant findings, Medtronic submitted all available Infuse data for an independent review of industry-sponsored data as part of the Yale University Open Data Access (YODA) project. In the YODA review (2,5), independent assessments at Oregon Health and Sciences University and the University of York (UK) in 2011 demonstrated no significant difference in outcomes with rhBMP-2, compared with ICBG, and that the risk of cancer associated with rhBMP-2 use remained low, compared with the risk in the general population. An association between elevated cancer risk and Infuse was further refuted in an Australian study independently analysed by the Cancer Council of Victoria (33) and in an observational study with long-term follow-up of 4,246 patients from WA, USA (53). Both studies found no difference in cancer risk between patients treated with rhBMP-2 and the general population. Likewise, a systematic review published in 2015 of all available basic science literature found no evidence of *de novo* cancer caused by rhBMP-2 (54).

Cost/benefit analysis of rhBMP-2

Concerns about the cost of rhBMP-2 have been longstanding. First available 20 years ago, the product cost has not decreased. To date, lower cost versions of rhBMP-2 have not been produced. Representative surgeon bodies and hospitals have tried to develop guidelines for appropriate usage of rhBMP-2, with indications including ASD surgery, revision spine surgery, and surgery involving long constructs (28). The International Spine Study Group analysed data from a multicentre, prospective registry of 522 patients with ASD, 267 (73%) of whom received rhBMP-2. The mean (± SD) direct cost of BMP-2 for the index surgery was US$14,000±$6,400. The rate of revision surgery for symptomatic pseudoarthrosis was two times higher in patients who did not receive rhBMP-2 than in those who received rhBMP-2 (17% versus 8.6%).

The mean 2-year direct costs were more than two times higher in patients requiring revision surgery for pseudoarthrosis (US$138,000±$17,000) than in those not requiring surgery for pseudoarthrosis (US$61,000± $25,000) (55). Thus, use of rhBMP-2 seems to be a cost-effective option, given the high patient and economic costs of failed fusion surgery.

Quality of evidence for rhBMP-2 use

The most up-to-date level of evidence classification system for osteobiologics is the AOSpine BOnE (Bone Osteobiologics and Evidence) Classification (56). This BOnE classification has three tiers of evidence: level A, human studies; level B, animal studies; and level C, *in vitro* studies. Level A is the highest level of evidence. Each level is organized into four subgroups (1 through 4) based on the quality of data. White papers are not considered.

According to this classification system, the level of evidence is highest for rhBMP-2 (A1 and B1), based on the existence of both animal and human studies. No osteoinductive agent has been more extensively studied in animals and humans than rhBMP-2. Although there are other osteoinductive products (allograft-based DBMs) with A2 evidence (56), the volume and level of evidence is not as robust as for rhBMP-2.

A network meta-analysis of 27 RCTs comparing different bone grafts found that rhBMP-2 provided the highest fusion rate in lumbar arthrodesis, being significantly superior to ICBG, allograft, DBM, or synthetics with local bone (57,58).

Alternative Bone Graft Substitutes to rhBMP-2

Glassman *et al.* has rephrased the previous question of spine surgeons from "How does the fusion rate compare to that of ICBG?" to "How does the fusion rate compare to that of BMP?" (59). Currently, the level of evidence supporting the use of different commercially available bone graft substitutes varies greatly. Many marketed products are supported by only minimal evidence of efficacy (56). A comprehensive review of all aspects of alternative graft materials is beyond the scope of this manuscript; the following presents a brief summary of current alternatives.

Autologous cellular grafts

Bone marrow aspirates (BMAs)

BMAs require introducing a large-bore needle into the iliac crest (usually with minimal morbidity) to obtain osteoprogenitor cells. However, these cells require osteoconductive support from allografts or synthetic bone substitutes. Systematic reviews found that fusion rates of BMAs with synthetic (60) or allograft scaffolds (58) were similar to those of autografts, with fusion rates between 75% and 84% at 12 months after PLF surgery (61).

Autologous growth factors (AGFs)

AGFs from platelet degranulation contribute to both

bone and wound healing. Platelet-derived growth factor (PDGF) increases the replication and synthesis of matrix proteins involved in the remodelling and construction of new bone (12). TGF-β regulates extracellular bone matrix synthesis and stimulates angiogenesis. PDGF and TGF-β are extracted and prepared via ultra-concentration of platelets from platelet-rich plasma (PRP) and may be used in combination with autografts, allografts, or ceramics to enhance spinal fusion. AGFs are relatively inexpensive and free from the risk of disease transmission.

There is conflicting evidence regarding the efficacy of AGFs in lumbar fusion. No benefit of AGF use was demonstrated in TLIF (62) or anterior thoracolumbar fusion after trauma (63). A systematic review concluded that AGFs did not increase spinal fusion rates compared with traditional autografts (64). A prospective RCT of 50 patients found higher fusion rates (assessed by CT) at 24 months after PLF surgery in patients receiving PRP with autograft, compared with autograft alone (94% versus 74%, P=0.002) (65). However, a recent systematic review on overlapping meta-analyses found PRP was associated with lower spinal fusion rates (66).

Allografts

Allograft cadaver bone avoids donor site morbidity, but bone consolidation is slower and vascularization is less than with autograft (67). Allografts are accompanied by the risk of transmitting infectious diseases. Screening protocols can reduce this risk, but specific processing is essential to ensure the safety of allograft products. Common manufacturing processes include radiation, freeze-drying, or chemical treatments for cleaning and sterilisation. Chemical modifications include supercritical carbon dioxide (SCCO2 384) treatment (68). Allograft bone can be chemically treated to remove the organic phase, resulting in anorganic bone, or to remove the inorganic phase with acid, resulting in the creation of demineralised bone consisting of only organic matrix. The organic matrix of bone in composed of type I collagen (approximately 90%) and noncollagenous proteins (approximately 10%), including BMP, fibroblast growth factor, and TGF-β. With appropriate validated processing, BMPs that assist with bone formation are retained, thereby creating an osteoinductive DBM.

Allografts also provide osteoconductive scaffolding for bone formation in a structurally intact form (struts) or as reduced particulates (granules). SCCO2 394 treatment maintains the mechanical osteoconductive properties of the allograft, in contrast to the deleterious effects of gamma irradiation (69). Additionally, gamma397 irradiated allografts elicit an acute inflammatory reaction that increases the amount of graft resorption, compared with SCCO2 398-treated allografts (70). SCCO2 has properties of both a gas and a liquid and removes organic debris, exposing the nano400 structure of bone. The exposed nano-topography of the bone matrix (visualised on scanning electron microscopy) facilitates protein and cellular interactions (68).

Demineralised bone matrices and fibres

Malleable bone grafts, in the form of bone fibres, paste, putty, and strips, provide superior handling properties. The surgeon can compress these grafts into the aperture of an interbody cage to provide the best fit and optimal packing.

DBM powders require an exogenous carrier, such as collagen, gelatin, or glycerol, to facilitate handling and formulation (71). The donor's age, sex, and different manufacturing processes affect the characteristics of DBM (72). There is considerable variability in BMP levels between DBMs because of different processing methods (73), and different volumes of DBM (74) are used, making comparative studies difficult (12). Grafton (Osteotech Inc., Eatontown, NJ, USA) uses a glycerol carrier with a DBM content of 17–31%. RCTs revealed no differences in fusion rates between Grafton mixed with local bone and autografts when used for PLF (75,76). A meta-analysis comparing 337 patients who received DBM and 204 patients treated with autografts found no significant differences in fusion rates between groups for either PLF (72% versus 68%) or PLIF (70% versus 63%) (74). The addition of stem cells to DBMs have not shown any substantial improvement in fusion rates above DBMs alone (77).

Demineralised bone fibres (DBF) can be manufactured by demineralizing cortical struts and producing fibres or by using computer numerical control milling or some other mechanical method, followed by demineralization in acid. Particulate-based allograft bone products, even when mixed with autologous blood or BMA (58), are often partially lost when transferred from the preparation area to the surgical bed.

Allograft bone mixed with DBF improves handling and facilitates tighter packing of graft material into the interbody cage, disc space, and posterolateral gutters. The combination of DBF with SCCO2-treated allograft bone mixed with 2 mL of the patient's blood was recently

reported in two patients who underwent ALIF; solid interbody fusion (assessed by CT) was achieved at 12 months in both patients (78).

Synthetics

Ceramics are synthetic grafts and typically consist of calcium phosphate combined with hydroxyapatite (HA). Ceramics have a long shelf-life, are easily manufactured, and can be used alone, either as a bone graft extender or combined with bone graft substitutes with osteogenic capacity (such as BMA and DBM). However, use of ceramics alone leads to low fusion rates because they are only osteoconductive and lack osteoinductive potential. A prospective single-centre study of 135 patients undergoing LLIF with a beta tricalcium phosphate (β-TCP)/HA bone substitute (Attrax; NuVasive, Inc., San Diego, CA, USA) or Infuse found lower overall interbody fusion rates (assessed by CT) with Attrax (80%) than with rhBMP-2 (96%) at 24 months postoperatively. However, subgroup analysis noted similar fusion rates between Attrax and rhBMP-2 groups in patients who underwent LLIF with supplemental pedicle screw-rod fixation (91% versus 100%, respectively) (79). A multicentre RCT of 87 patients comparing Attrax putty versus autograft in single or multilevel instrumented thoracolumbar PLF procedures found fusion rates (assessed by CT) of 55% versus 52%, respectively, at 12 months after surgery. The authors concluded that Attrax putty alone was noninferior to autograft when used for PLF (80). In a rabbit model of PLF evaluating another β-TCP/HA blended ceramic (Mastergraft; Medtronic, Inc.), the rate of fusion was 73% with Mastergraft plus autograft and 63% with autograft alone (81).

A silicate-substituted calcium phosphate (SiCaP) (ACTIFUSE™; ApaTech and Baxter Ltd, Elstree, Hertfordshire, UK) contains 0.8% silicon by weight, which is similar to the level found in naturally growing bone. The silicate substitute stimulates new bone formation by increasing vascularity and bony in-growth of host bone (82). In a prospective non-randomised multicentre study from the Republic of Ireland of 102 patients undergoing PLF with SiCaP, the fusion rate (assessed by CT) was 86% at 12 months postoperatively (83). A prospective single-centre RCT of 19 patients undergoing PLF surgery with SiCaP or rhBMP-2 found comparable lumbar fusion rates by CT (100% versus 89%, respectively) at 12 months (84). Likewise, a larger multicentre RCT of 103 patients undergoing PLF found similar 12-month fusion rates (assessed by CT) for SiCaP (71%) and rhBMP-2 (74%). In a meta-analysis of 10 studies including 694 patients undergoing spinal fusion, the overall mean fusion rate was 93% (range, 79–100%) with SiCaP. Meta-analysis of the three studies comparing SiCaP with rhBMP-2 revealed no difference in fusion rates between the two types of bone graft substitutes (85).

Bioactive glass (BG) contains biodegradable particles, most commonly 45S5 or S53P4, as granules that promote osteoconduction and stimulate osteoblast recruitment, enhancing fusion in patients undergoing PLF surgery. BG is not osteoinductive and is therefore unable to form ectopic bone. It may also inhibit bacterial adhesion and growth by increasing the local pH (86). Prospective single centre long-term studies from Finland using BG reported a 71% fusion rate (assessed by CT) after PLF for unstable lumbar burst fractures (87) and an 88% fusion rate (according to CT) after PLF surgery for degenerative spondylolisthesis (88). Adding BG particles to a TCP/HA collagen composite was demonstrated to accelerate the fusion process in an animal model of PLF, compared with composite alone (89).

Despite the above results, it is important to note that the literature regarding synthetic bone substitutes is limited. Authors of a systematic review concluded that the overall evidence of the effectiveness of synthetic bone substitutes for spinal fusion, compared with autograft or allograft, was low or insufficient, largely because of a high potential for bias and small sample size in the available studies (90).

Peptide-based grafts

In 2000, a bone graft substitute called i-FACTOR™ (Cerapedic Inc., Westminster, CO, USA) was created, consisting of a combination of P-15 and anorganic bone mineral (ABM) suspended in a hydrogel carrier. P-15 is a synthetic 15-amino acid peptide that enhances new bone formation (91) by mimicking the cell-binding domain of type 1 collagen, which is the major extracellular matrix component of bone. It also induces the proliferation and differentiation of MSCs (92). ABM consists of calcium phosphate granules derived from bovine bone, which have osteoconductive properties. In a prospective single-centre study of 110 patients undergoing ALIF with i-FACTOR, Mobbs *et al.* in 2014 demonstrated a 94% fusion rate by CT at 2-year follow-up (93). Lauweryns *et al.* in 2015, in a single-centre prospective study from Belgium of 40 patients undergoing PLIF, found a 97.8% fusion rate (assessed by CT) with PEEK cages containing i-FACTOR,

and an 82.2% rate with PEEK cages containing interbody autograft bone (94).

Patient preferences for bone graft substitutes versus autografts

There is scant evidence in the literature regarding patient preferences for bone graft substitutes versus autograft. A single-centre retrospective study of 574 patients treated with ACDF surgery over a 9-year period included a small sample size of 22 patients who initially underwent ACDF surgery with an autograft (ICBG) and then subsequently underwent ACDF with a bone graft substitute. Of these 22 patients, 21 (95%) reported preferring the procedure with a graft substitute, and 91% (20/22) reported that the ICBG incision was more painful than the neck incision. Based on these results, the authors of this study questioned the traditional recommendation that autograft is the gold standard for ACDF (95). Alternative "less morbid" bone graft substitutes compared to autograft are now available.

Discussion

No other bone substitute has been more rigorously investigated in both animal and human studies than rhBMP-2. Over 20 RCTs have demonstrated superior efficacy in fusion rates, compared with autologous bone graft. When used in the correct dosage, rhBMP-2 is safe and efficacious for all levels of spinal fusion except anterior cervical procedures. To provide guidance and clarity, various surgical organizations have developed guidance regarding when rhBMP-2 should be considered (55,96), given the clinical and long-term economic implications of its use. In *Table 2*, we have separated each procedure type and rated the suitability of rhBMP-2 use when considering the available evidence and the risk/cost of reoperation for each group (97).

Thus, we recommend the use of rhBMP-2 for four indications: (I) ASD surgery, (II) lumbar fusions at all levels for degenerative disease, (III) revision surgery for posterior cervical and anterior/posterior lumbar pseudoarthrosis, and (IV) surgery in patients with low-yield or poor-quality harvested autograft.

Spine surgeon leadership is vital for providing high-value care for spine patients; otherwise, suboptimal outcomes may result from isolated interventions of regulatory bodies or payer groups (98). Enhancing the safety, quality, and value based care of adults undergoing spine surgery is vital (99). Using lean methodology to stratify evidence around biologics and bone graft substitutes, Sethi *et al.* in 2017 concluded that rhBMP-2 was the best option to optimise the cost/benefit ratio of multilevel thoracolumbar fusion (96). The alternative bone substitutes discussed in this manuscript are currently not on formulary at many major US healthcare organizations because of limited evidence of their effectiveness. Despite the high cost of rhBMP-2, the amount of product used in each operation is relatively low because it is more potent than the available alternative bone graft substitutes. Current doses of rhBMP-2 are lower than those used a decade ago, while fusion rates have remained high (37). The net effect is that private payers may spend more per case using non-rhBMP-2 bone graft substitutes, with no clinical or economic benefits for patients or the private healthcare system. Hence, hospitals and insurance companies will be paying more per case for an inferior product with an increased risk of reoperation. Revision surgeries are complex, with higher risk and cost profiles (55).

Akin to many technologies, rhBMP-2 may represent a Gartner hype cycle (100) in which an initial period of high enthusiasm and inflated expectations is followed by a fall from grace with reports of complications, leading to a "trough of disillusionment". Increased understanding of rhBMP-2 biology will provide a "phase of enlightenment" for rhBMP-2 and alternative bone graft substitutes, allowing entry into a more controlled "plateau of productivity" phase.

Recommendations for rhBMP-2 use

Based on clinical evidence, product costs, and economic considerations of both fusion rates and reoperation risk, we recommend the following:

(I) Clear informed consent processes between surgeons and patients regarding current evidence of the benefits and risks of using rhBMP-2 and available alternative bone graft substitutes.
(II) Consideration of rhBMP-2 for spinal fusion surgery (except anterior cervical procedures), especially for ASD surgery, lumbar fusion irrespective of the number of levels for degenerative disease, revision surgery for pseudoarthrosis (posterior cervical, anterior/posterior lumbar), and surgery in patients with low-quantity or low-quality autograft.
(III) Regulatory oversight of the type, volume, and dose of bone graft substitute (both per level and per procedure) to ensure appropriate indications,

prevent excessive usage, and thereby enhance cost containment.

We acknowledge the limitations of this narrative review basing the conclusion on the studies and literature included in the analysis. Secondly, these studies may have an inherent bias on behalf of the authors, as they are describing their experience or option of a range of studies that could skew the conclusion towards a particular view or opinion. Additionally, reporting bias was a potential concern in earlier studies of rhBMP-2 funded by industry leading to the YODA reviews.

Conclusions

There is no doubt about the efficacy of rhBMP-2 for promoting high fusion rates in spinal fusion surgery. Nevertheless, debate remains about the indications, safety profile, cost effectiveness, and optimal dosages for rhBMP-2. This uncertainty has focused attention on the effectiveness of alternative bone graft substitutes, the use of which may lead to increased risk of failed fusion and costly revision surgery. Biologic adjuncts are becoming increasingly important in surgical procedures and continued understanding of the physiology and biomechanics of spine fusion is required to advance this field.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jss.amegroups.com/article/view/10.21037/jss-22-23/rc

Peer Review File: Available at https://jss.amegroups.com/article/view/10.21037/jss-22-23/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jss.amegroups.com/article/view/10.21037/jss-22-23/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Malham GM, Louie PK, Brazenor GA, Mobbs RJ, Walsh WR, Sethi RK. Recombinant human bone morphogenetic protein-2 in spine surgery: recommendations for use and alternative bone substitutes—a narrative review. J Spine Surg 2022;8(4):477-490. doi: 10.21037/jss-22-23