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MINIREVIEWS

Bone morphogenetic protein in complex cervical spine surgery: A safe biologic adjunct?

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Abstract

The advent of recombinant DNA technology has substantially increased the intra-operative utilization of biologic augmentation in spine surgery over the past several years after the Food and Drug Administration approval of the bone morphogenetic protein (BMP) class of molecules for indications in the lumbar spine. Much less is known about the potential benefits and risks of the "off-label" use of BMP in the cervical spine. The history and relevant literature pertaining to the use of the "off-label" implantation of the BMP class of molecules in the anterior or posterior cervical spine are reviewed and discussed. Early prospective studies of BMP-2 implantation in anterior cervical spine constructs showed encouraging results. Later retrospective studies reported potentially "life threatening complications" resulting in a 2007 public health advisory by the FDA. Limited data regarding BMP-7 in anterior cervical surgery was available with one group reporting a 2.4% early (< 30 d) complication rate (brachialgia and dysphagia). BMP use in the decompressed posterior cervical spine may result in neurologic or wound compromise according to several retrospective reports, however, controlled use has been reported to increase fusion rates in select complex and pediatric patients. There were no cases of *de novo* neoplasia related to BMP implantation in the cervical spine. BMP-2 use in anterior cervical spine surgery has been associated with a high early complication rate. Definitive recommendations for BMP-7 use in anterior cervical spine surgery cannot be made with current clinical data. According to limited reports, select complex patients who are considered "high risk" for pseudoarthrosis undergoing posterior cervical or occipitocervical arthrodesis or children with congenital or traumatic conditions may be candidates for "off-label" use of BMP in the context of appropriate informed decision making. At the present time, there are no high-level clinical studies on the outcomes and complication rates of BMP implantation in the cervical spine.

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DECADE OF BONE MORPHOGENETIC PROTEIN EMERGENCE IN THE UNITED STATES

Biological augmentation of spinal surgery procedures has substantially increased in the United States over the past decade with the advent of genetic engineering techniques and the Food and Drug Administration (FDA) approval and marketing of several synthetic products. A great deal of therapeutic potential has been associated with the "Bone Morphogenetic Protein" (BMP) class of molecules since the Nobel Prize nominated work of Marshall Urist in 1965 demonstrated their ability to transduce intracellular signaling pathways towards the genesis of bone and cartilage tissues[1]. Basic science studies laid the groundwork for later pre-clinical studies that demonstrated definitive evidence of rhBMP-2 induced os-

teoinduction in a small series of 11 humans[2]. The more recent foray of these powerful signal transduction agents into the clinical realm has brought to light both powerful efficacy and the potential for serious and even fatal complications.

In 2002, the FDA granted pre-market approval of rhBMP-2 (rhBMP-2 - Infuse Bone Graft, Medtronic Sofamor Danek, Memphis, TN) for use in adult patients undergoing single-level anterior lumbar interbody fusion (ALIF) from L2 to S1 for degenerative disk disease[3]. Two years later, a second subtype of recombinant BMP molecule was also approved by the FDA, BMP-7 (rhBMP-2 - OP-1 Putty, Stryker Biotech, Hopkinton, MA) as an alternative to autograft in patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion (patients with osteoporosis, smokers, and diabetes)[4].

Any new therapeutic procedure, technique, or medication will bring a finite number of associated complications. In the ensuing time period following the translation of these biological adjuncts into the operating room, a series of reports has sparked great concern about potential adverse sequelae. In July of 2010, a 33% higher concentration formulation of Medtronic's rhBMP-2 product featuring a compression-resistant matrix (AMPLIFY Matrix - 2.0 mg/cc compared to INFUSE 1.5 mg/cc) that was designed to induce *de novo* bone formation without iliac crest bone graft (ICBG) was rejected by the FDA due to possible increased cancer risks in susceptible individuals[5]. In 2011, secondary analysis of Medtronic-funded studies found an increased cancer risk associated with rhBMP-2 (AMPLIFY) in patients undergoing posterolateral lumbar fusion. Reports of increased retrograde ejaculation following ALIF procedures[6,7] and that complication rates associated with BMP are 10 to 50 times higher than the original estimates in industry-sponsored peer-reviewed publications have recently been publicized[6]. The ensuing media attention to these studies has resulted in a decline in the use of biologics in spine surgery applications[8].

Much less is known about the "off-label" use of the BMP class of molecules in the cervical spine. To understand the incidence and spectrum of reported complications associated with BMP use in the cervical spine, the relevant clinical studies reported in the literature are reviewed and discussed.

ANTERIOR CERVICAL SURGERY WITH BMP

The efficacy of rhBMP-2 use in the anterior cervical spine has been evaluated by several groups as "off-label" indications have been found in parallel with those approved by the FDA.

Prospective studies

An early pilot study in 2003, was designed as a prospective randomized trial comparing rhBMP-2 to cancellous autogenous ICBG inside a fibular allograft in 33 patients. All patients underwent plated anterior cervical discectomy and fusion (ACDF) for degenerative cervical disk disease[9]. At 2-years follow-up, both groups demonstrated solid fusion in all patients. Interestingly, the rhBMP-2 group had superior improvement in neck disability and arm pain scores. In this pilot study, anecdotal observation of two cases of heterotopic bone anterior to the graft in the rhBMP-2 group and one in the autograft group were made. Given the limited numbers of patients, conclusive statements on potential adverse events could not be made. In 2004, a second pilot study prospectively followed 20 patients that underwent ACDF with rhBMP-2 contained within a bioabsorbable spacer demonstrated bridging bone across the interspace in 100% of patients[10]. Buttermann confirmed these reports in a prospective nonrandomized consecutive series of 66 patients with either ICBG or BMP-allograft. Two patients in the ICBG group had pseudarthrosis compared to one patient in the BMP-allograft group at 2-3 year follow-up. However, 50% of the patients in the BMP allograft group had "neck swelling" presenting as dysphagia compared to 14% in the ICBG group[11].

Retrospective studies

Several retrospective studies raised concerns about the use of BMP in the anterior cervical spine. In 2005, Boakye *et al*[12] reported an uncontrolled retrospective report of good clinical outcomes and solid fusion with rhBMP-2 implanted inside of a polyetherehterketone (PEEK) spacer for single and multi-level ACDF in 24 patients. By 2006, retrospective reviews of 151 patients who underwent either anterior cervical corpectomy (n = 13) or ACDF (n = 138) augmented with high dose INFUSE (up to 2.1 mg/level) reported a complication rate of 23.2% due to hematoma requiring surgical evacuation or readmission due to swallowing/breathing difficulties or dramatic swelling in the absence of a hematoma[13]. A subsequent retrospective report of 69 patients confirmed the high complication rate associated with BMP-2 use in ACDF constructs with 27.5% having clinically significant swelling[14]. In 2007, retrospective reports of significantly more dysphagia following ACDF with rhBMP-2 and increased anterior soft tissue shadow for the first 6 wk postoperatively on lateral C-spine radiograph were accompanied by similar clinical outcomes at 2-years[15].

Radiographic reports

These early reports of excellent fusion rates were later accompanied by radiographic reports of endplate erosion and subsidence associated with rhBMP-2. In 2007, a prospective study of cervical interbody fusion with allograft and rhBMP-2 demonstrated significant subsidence of cervical interbody grafts of a mean height of 53% that occurred in more than half of the operative levels[16]. Further radiographic studies comparing polyetherehterketone (PEEK) cages and BMP for spinal fusion demonstrated an enhanced fusion rate with a concomitant

prevertebral soft-tissue swelling in patients who underwent ACDF. Radiographic evidence of a resorptive phase of BMP-2 resulting in endplate absorption has been reported by several groups to occur in 100% of patients undergoing ACDF[15,17,18].

FDA public health advisory

In March of 2007, a case report of a 54 year-old male presenting with neck swelling and difficulty swallowing 5 days after ACDF with rhBMP-2 resulting in respiratory distress and reintubation was published[19]. By July of that year, early "off-label" use of BMP in the cervical spine resulted in at least 38 reports of complications over the preceding 4 years[20]. This provided the impetus for the FDA to issue a public health advisory of "life-threatening complications" due to severe swelling and airway compromise. Many practitioners continue to implant BMP in the cervical spine despite this advisory in a select group of patients in the context of thorough patient education and informed decision making.

BMP use after the FDA advisory

Following the FDA advisory in 2007, reports of acute airway obstruction between postoperative days 2 and 7 remained a significant concern. Yaremchuk reported in 2010 a retrospective review of 260 patients who underwent cervical procedures augmented by BMP between 2004 and 2009. Patients treated with BMP had significantly longer hospital stays, higher hospital charges, a higher number of tracheotomies, unplanned intubations after surgery, dysphagia, dyspnea, respiratory failure, readmissions, intensive care unit admissions, and 90-d mortality rates. Despite these warnings, surgeons have advocated rhBMP-2 use in the anterior cervical spine in a controlled manner. A retrospective study by Tumialan *et al*[21] reported 200 patients that underwent one to four level ACDF with PEEK spacer, titanium plate, and rhBMP-2 reported a fusion rate of 100%, an incidence of clinically significant dysphagia of only 7%, and suggested that the incidence of dysphagia may be decreased by a lower dose of rhBMP-2 that is placed only within the PEEK spacer.

Anterior cervical surgery with BMP-7 (OP-1)

Data on the use of OP-1 in the anterior cervical spine is much more sparse than that of rhBMP-2. A PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) query for "BMP-7" or "OP-1", and "anterior cervical" yielded only one study in the literature at the present time. In 2009, surgeons in Australia reported early outcomes and complications (within 30 d) of a prospective consecutive cohort study of 123 patients who underwent ACDF with a controlled dose of OP-1 augmentation. They reported a 2.4% complication rate (transient brachialgia and dysphagia), no reoperations, and concluded that BMP-7 can be used safely in anterior cervical procedures. This report remains to be reproduced by other groups and long-term data on fusion and complication rates have yet to be reported.

POSTERIOR CERVICAL SURGERY WITH BMP

Therapeutic applications of rhBMP-2 in the posterior cervical spine avoid the putative inflammatory effects on critical anterior airway structures suggesting indications may be more plausible. However, there have been few reports on the safety and efficacy of the "off-label" use of BMP products in the posterior cervical spine. At the present time, there are no prospective studies on the use of BMP in posterior cervical spine procedures.

A potential role for OP-1 in posterior cervical spine surgery in patients considered to be high risk for psuedoarthrosis was examined in a 2007 invited submission of the American Association of Neurosurgical Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves. This report by Furlan *et al*[22] was an uncontrolled prospective non-randomized study of 14 patients undergoing posterior cervical or occipitocervical spine surgery that resulted in no "allergic reactions" and no postoperative hematomas. In this patient population that included heavy smokers, patients with genetic disorders (mucopolysaccharidosis), rheumatoid arthritis, lupus, and previous nonunions, a fusion rate of 80% was reported at mean follow-up of 24 mo. All patients underwent MR imaging between 6 months and 1 year postoperatively and one patient who underwent posterior occipitocervical fusion demonstrated an asymptomatic linear opacification in the soft tissues representing heterotopic ossification.

In 2009, a retrospective evaluation of 77 patients undergoing posterior cervical arthrodesis with either rhBMP-2 absorbable sponge or ICBG demonstrated a trend towards more posterior cervical wound complications requiring treatment in the rhBMP-2 group (14.6%) *vs* the ICBG group (2.8%), however, this result did not reach statistical significance[23]. In 2011, Xu *et al*[24] reported a retrospective review of 204 patients that underwent posterior spinal fusion augmented with and without rhBMP-2 over a 4-year period and found at 2-year mean follow-up there was no significant difference between the two cohorts in duration of hospitalization, CSF leakage, infection, hematoma, C5 palsy, wound dehiscence, reoperation rates, or Nurick/ASIA scores. There were no patients in the rhBMP-2 group with instrumentation failure, however, a trend was observed towards increased rates of instrumentation failure in the non-BMP group due to 11 patients (7.1%) with this complication (P = 0.06). Patients receiving rhBMP-2 did have a significantly increased fusion rate (P = 0.01), however, they also had higher rates of recurrent/persistent neck pain (chi-square test P = 0.003, log-rank test P = 0.01)[24].

Case reports have suggested the potential for catastrophic neurological complications with rhBMP-2 use in the posterior cervical spine following laminectomy. Anderson *et al*[25] reported two cases of posterior cervical

decompression and instrumented fusion procedures resulting in a substantial decline in neurological status due to exuberant seroma formation causing cord compression at 5 d and 2 wk postoperatively.

A role for rhBMP-2 augmentation in the pediatric population for congenital and traumatic conditions has been supported by recent case reports. In 2007, a 4-mo-old infant with Down syndrome who suffered a high cervical spine injury due to craniovertebral instability and two previous failed arthrodesis attempts later underwent successful salvage fusion procedure with rhBMP-2 augmentation. The patient subsequently went on to fusion without a reported complication at 4 years follow-up[26]. The surgical challenges of occipitocervical stabilization in infants with complex trauma may also benefit from BMP-2 augmentation. Benzel *et al*[27] reported a case of a 12-mo-old female with traumatic atlanto-occipital dislocation after a motor vehicle accident that was stabilized by autologous rib graft, Mersilene suture, ethibond sutures as "cross-connectors" and rhBMP-2 augmentation with excellent alignment and modest but progressive neurological improvement by 12 wk.

CONCLUSION

Recombinant DNA technology has hastened the arrival of powerful biologically engineered molecules capable of intracellular signal transduction pathways into the operating theatre. Approval by regulatory agencies and the subsequent proliferation of these products to "off-label" indications such as the cervical spine has provided new clinical data and novel complications associated with their use. At the present time, widespread international utilization of BMP products has been self-limited by a prohibitively high cost. In the coming years, as proprietary patents expire and generic formulations become commercially available, an international dialogue in the academic community will aid in the understanding of not only the clinical efficacy of biologics, but also help to mitigate potential harm.

Several studies have reported excellent fusion rates and the avoidance of donor site morbidity with the use of rhBMP-2 in the anterior cervical spine. However, concomitant increased complication rates are reported that may involve catastrophic airway compromise. The soft-tissue complications may be dose dependent, with higher rates reported for higher concentrations by several authors.

Patients who are considered high risk for pseudoarthrosis undergoing posterior cervical or occipitocervical arthrodesis or children with complex congenital or traumatic conditions may be candidates for "off-label" use of BMP according to limited current reports. At the present time, there are no high level clinical studies of the outcomes, complication rates, safety and efficacy of BMP use in the cervical spine.

When painted with broad strokes, the powerful effects of BMP are implicated by several studies to result in increased complication rates in the cervical spine. In a comprehensive database review of the Scoliosis Research Society Morbidity and Mortality database of 55862 spinal fusion procedures, multivariate analysis demonstrated that anterior cervical spinal fusion with BMP remains a significant predictor of complications after adjusting for patient age and revision procedures[28].

In a retrospective cohort study of the Nationwide Inpatient Sample database (a sample of 20% of United States community hospitals) consisting of 328468 spinal fusion procedures, BMP use was associated with greater complications for anterior cervical fusions and greater hospital charges[29]. Nonetheless, in select complex cervical patients, the use of BMP in a controlled fashion may have benefits that outweigh the risks as supported by several authors[21,22,26,27].

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