Point-counter-point debate: the association between recombinant human bone morphogenetic protein utilization and complications in spine surgery

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Abstract Bone morphogenetic proteins (BMPs) have been utilized in spine surgery for over 10 years as a bone graft substitute. Potential BMP-related adverse effects including retrograde ejaculation and heterotopic neuroforaminal bone formation have been described. Additionally, some studies have suggested an association between BMP and cancer. Inconsistencies exist in the published spine literature with regards to the incidence and association of complications with BMP utilization. In a point-counterpoint format, this article discusses the current evidence concerning the relationship between the utilization of BMP in spinal fusion and the risk of cancer, retrograde ejaculation (RE), neuroforaminal bone formation, and its role in anterior cervical spine surgery and adolescents.

Keywords Bone morphogenetic protein · Retrograde ejaculation · Anterior cervical fusion · Neuroforaminal bone growth · Cancer

Point-counterpoint

Retrograde Ejaculation (RE)

RE occurs secondary to impaired function of the internal vesicle sphincter muscle. Anterior lumbar approaches,

particularly at the L5-S1 level, carry a greater potential for damage to the superior hypogastric sympathetic plexus, which innervates the internal vesicle sphincter muscle. Other etiologies of RE including diabetes, benign prostate hypertrophy and its treatment, multiple sclerosis, pelvic trauma, and pelvic or rectal surgery [1–6]. RE following anterior lumbar spine surgery is also purported to be related to the surgical approach [7–9].

Burkus et al first published a prospective, randomized, nonblinded FDA-approved study concerning the use of rhBMP-2 in ALIF [8]. Six males (4.1 %; 6/146) reported RE following surgery, of which 4 underwent a transperitoneal approach (TPA) (13.3 %; 4 of all 30 males that underwent TPA) and 2 underwent a retroperitoneal approach (RPA) (1.8 %; 2 of 116 males that underwent RPA). Since the difference in RE between the TPA and RPA groups was statistically significant the authors concluded that a TPA was associated with a higher risk of RE. No comparison in RE between the investigational and control group was performed. The reported differences between the 2 approaches persisted at the 2-year follow-up period [10]. However, in 2010 Smoljanovic et al reviewed the data by Burkus et al [11] and reported that all 6 patients with RE had received rhBMP-2. Thus, the prevalence of RE in the investigational group (rhBMP-2) would have been 7.7 % (6/78 males), which was significantly greater than the control group (ICBG). The reason for ignoring the relationship between RE and rhBMP-2 was questioned, which sparked an intense debate over the potential association between the utilization of rhBMP-2 and RE.

Correlation between rhBMP-2 utilization and RE

In 2011 Carragee et al conducted a retrospective analysis of consecutive patients who underwent an ALIF of the lowest 1 or 2 lumbar levels with or without rhBMP-2 [12•]. Five of 69

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patients (7.2 %) in the rhBMP-2 group developed RE while only 1 of 174 patients (0.6 %; 1/69) reported RE in the control group. Significant differences in RE were also evident among patients that underwent a single-level L5-S1 ALIF with 6.7 % of the rhBMP-2 group reporting RE compared with 0 % in the control group. This was the first study, after Smoljanovic et al's analysis, which demonstrated an association between rhBMP-2 and RE in the setting of an ALIF.

In a similar study, Comer et al reported a greater rate of RE in patients who received rhBMP-2 during an ALIF procedure [13•]. Fifteen of 239 subjects (6.3 %) in the rhBMP-2 cohort were diagnosed with RE postoperatively, compared with only 2 of 233 (0.9 %) in the control group. A higher incidence of RE was associated with two-level ALIFs regardless of rhBMP-2 utilization; however, this was not statistically significant.

No relationship between rhBMP-2 utilization and RE

In 2012, Lindley et al conducted a retrospective review of males who underwent an ALIF with rhBMP-2 or an artificial disc replacement (ADR) without rhBMP-2 [14•]. Both procedures were performed via the RPA by a highly experienced vascular access surgeon (85.3 %) or spine surgeon (14.7 %). The rate of RE was not significantly different between the 2 procedures, with 7.4 % (4/54) in the ALIF group and 9.8 % (4/41) in the ADR group. In addition, 2 of the 8 patients who experienced RE reported resolution of their symptoms at last follow-up (1 in each group). The authors hypothesized that postoperative RE is likely associated with the surgical approach (RPA) rather than the use of rhBMP-2.

Lubelski et al also demonstrated no significant differences in the rate of postoperative RE between the rhBMP-2 treated patients and the control group [15•]. In their retrospective review of 110 males who underwent an L4-L5 and/or L5-S1 ALIF, the authors reported similar rates of RE between the rhBMP-2 and control groups after an ALIF procedure (8.5 % (5/59) vs 7.8 % (5/51), respectively).

Summary

Several literature reviews, meta-analyses, and letters to editors have been published regarding the results from the above mentioned studies [16–18]. However, Mroz et al emphasized a very important question regarding the association between rhBMP-2 and RE. The authors highlighted the lack of standardized assessment for RE in the published literature [19•]. Thus, the incidence of RE might have been underreported. Mroz et al suggested that a validated method for pre- and postoperative assessment of RE should be developed and implemented for patients scheduled to undergo an ALIF procedure.

As such, we believe that the current evidence is tipped in favor of a positive correlation between the use of rhBMP-2 and RE [19•]. However, further studies with validated and standardized methods to objectively measure RE in the pre- and postoperative periods are warranted to determine a true causal association. A significant concern regarding the methodology of validating retrograde ejaculation needs to be addressed prior to drawing any definitive conclusions regarding BMP and RE.

Cancer

Bone morphogenetic proteins (BMPs) belong to the alpha (OP-1) and beta (rhBMP-2) superfamily of transforming growth factors (TGF). TGF peptides bind to receptors in the cell-membrane and induce a variety of intracellular pathways that promote cell proliferation, differentiation, and migration. These pathways carry an important role in the regulation of tumor cells. Potential relationship between BMP and bone tumors was first reported in the 1980s [20–23]. In 2002, Poynton and Lane reported that BMP might be associated with cancer, but the potential carcinogenic effect could not be ascertained [24].

Correlation between rhBMP-2 utilization and cancer

Numerous publications have reported the incidence of new cancers with rhBMP-2 utilization. In a randomized controlled trial (RCT), Dimar et al demonstrated that rhBMP-2 was associated with a decrease in blood loss and operative time along with a higher fusion rate when compared with ICBG for posterolateral fusions [25]. The authors utilized a high dose of rhBMP-2 (40 mg, AMPLIFY) and, after a 2-year follow-up, 3.3 % of the rhBMP-2 treated patients developed a new cancer when compared with 0.9 % in the control group. Furthermore, a 5-year follow-up of the same cohort was reported in an FDA summary with comparable results (3.8 % in the rhBMP-2 group vs 0.9 % in the control group) [26]. Although these differences were not statistically significant, many surgeons did not overlook the association between rhBMP-2 and cancer.

In 2013 Carragee et al utilized publicly available data from the FDA approved RCTs of patients with degenerative lumbar spine conditions who underwent a single-level posterolateral instrumented fusion with high-dose rhBMP-2 vs autologous bone graft [27•]. At 2 years follow-up, the rhBMP-2 cohorts demonstrated a significantly greater incidence of new cancer events (3.37 (95 % CI, 1.89–5.56) vs 0.50 (95 % CI, 0.06–1.80)). The reported cancer types included pancreatic, ovarian, colon, hematologic, and skin cancer. The authors eloquently discussed the plethora of laboratory research that demonstrates the role of rhBMP-2 in tumor progression in many

different cell lines including lung, breast, and epithelium. As such, the authors suggested that high doses of rhBMP-2 might have stimulated the growth and aggressiveness of preexisting, subclinical, and less malignant tumors. The results from this study demonstrated that high-doses of rhBMP-2 were associated with an increased risk of new cancers, which raised concerns regarding the widespread off-label utilization of rhBMP-2 among spine surgeons.

No relationship between rhBMP-2 utilization and cancer

Despite the concerning findings reported in the studies by Dimar et al and Carragee et al, both studies failed to compare the heterogeneity of cancer types between cohorts. As such, concluding that rhBMP-2 increases the risk of cancer in general is to underestimate the biological complexity of these pathologies. In addition, many studies have failed to demonstrate any significant association between BMPs and cancer.

In 2010, Medicare claims data was utilized to perform a retrospective cohort study of patients who underwent lumbar spinal fusion with and without BMP [28•]. At 1.4 years follow-up, 91 of all 93,654 patients developed pancreatic cancer (8 in the BMP group and 83 in the non-BMP group). Similarly, Cooper and Kou [29•] identified 146,278 patients, of which 15.1 % received rhBMP-2 for spinal fusion. After an average follow-up of 4.7 years, the incidence of new cancer was 15.4 % in rhBMP-2 group and 17.0 % in the non-rhBMP-2 group. In both studies, the authors failed to demonstrate the correlation between rhBMP-2 and cancer.

Unfortunately, the ICD-9-CM code (84.52) used to identify the BMP-treated patients in the Medicare database failed to specify the dose or type of rhBMP-2 (rhBMP-2 or OP-1). However, other authors have studied the safety of BMP as a function of dosage and type. In a RCT, Vaccaro et al assessed the utilization of OP-1 for posterolateral fusion and failed to demonstrate any significant differences in the risks of adverse events (including cancer) between the OP-1 and ICBG groups at the 12, 24, and 48 month follow-ups [30–33]. Furthermore, Mesfin et al analyzed the relation between the dosage of rhBMP-2 and cancer risk [34•]. After reviewing 502 consecutive patients who received high-dose rhBMP-2 for spinal fusion, the authors failed to demonstrate a correlation between the high dosage and cancer.

Summary

The evidence regarding the increased cancer risk associated with rhBMP-2 utilization is clearly divergent. The concerns put forward by authors like Dimar and Carragee have led others to avoid rhBMP-2 in patients with a history of cancer

[35]. However, in our opinion the lack of strong evidence that correlates rhBMP-2 and cancer does not support denying rhBMP-2 to patients with a cancer history who may benefit from it. Clearly a large, prospective RCT to analyze the risk of cancer associated with rhBMP-2 or OP-1 is unlikely to occur from a financial and ethical standpoint. However, as the on- and off-label use of BMPs continues to increase, surgeons should be encouraged to carefully follow-up with their patients in order to characterize the association between BMP and cancer.

Neuroforaminal bone formation

The original FDA approved trials for rhBMP-2 in ALIF did not report any ectopic bone formation within the spinal canal or neuroforamen. However, subsequent reports demonstrated that the off-label utilization of rhBMP-2 in posterolateral spinal fusion (PLF), transforaminal lumbar interbody fusion (TLIF), and posterior lumbar interbody fusion (PLIF) could potentiate heterotopic bone formation that may result in significant morbidity and need for reoperation.

Correlation between rhBMP-2 utilization and neuroforaminal bone formation

The risk of new bone formation outside the interbody space was analyzed by Haid et al in a RCT of 67 patients who underwent a PLIF with 2 paired cylindrical threaded titanium cages [36]. New bone formation, within the neuroforamen or spinal canal, was significantly greater in the rhBMP-2 treated cohort (70.6 %, 24 out of 34 patients) compared with the control (ICBG) group (12.1 %, 4 out of 33 patients). Interestingly, the heterotopic bone formation did not correlate clinically with recurrent leg pain. Moreover, 7 of 22 patients who reported increased leg pain during the follow-up had absolutely no bone formation outside the disc space. The authors concluded that although rhBMP-2 may increase the risk of neuroforaminal bone formation, this might not be clinically relevant.

The risk of neuroforaminal bone growth with rhBMP-2 utilization has also been analyzed in the setting of minimally invasive spine surgery (MIS). Joseph et al reported a 20.8 % rate of heterotopic bone formation with rhBMP-2 compared with 8.3 % in the controls following an MIS-TLIF [37]. Similarly, Chen et al reviewed 147 patients who underwent an MIS-TLIF and reported that 10.8 % (4 out of 37 patients) of patients who received rhBMP-2 developed ectopic bone formation in the spinal canal and neuroforamen that resulted in delayed neural complaints after the initial resolution of clinical symptoms [38].

No relationship between rhBMP-2 utilization and neuroforaminal bone formation

Despite the theoretical risk of ectopic bone formation with the utilization of rhBMP-2, many studies have failed to demonstrate such an association. Mummameni et al reported on the outcomes of 40 patients who underwent a TLIF (21 received rhBMP-2 and 19 autologous ICBG) [39]. None of the patients demonstrated significant neuroforaminal bone formation within the 2-year follow-up. In addition, Villavicencio et al presented similar findings [40]. No bone overgrowth or other rhBMP-2 related complications were noted during the mean 20-month follow-up period. Singh et al evaluated 39 patients that underwent a posterolateral lumbar spinal fusion with ICBG and rhBMP-2 [41]. The authors did not report any cases of ossification within the spinal canal or any laminar bone regrowth after a 2-year follow-up.

Summary

Neuroforaminal bone formation seems to be more prevalent with rhBMP-2. However, the published literature does not provide enough evidence to determine causation. In addition, neuroforaminal bone formation may not be clinically relevant if it is not associated with increased or recurrent postoperative leg pain. Further studies are warranted to characterize the risk of ectopic bone formation with rhBMP-2 utilization and its long-term impact on patient outcomes.

BMP and anterior cervical spine surgery

Nandyala et al reported on the utilization of BMP in anterior cervical fusion (ACF) procedures from 2002–2011. The authors demonstrated an initial steady increase in the percentage of ACF cases with rhBMP-2. The rate peaked in 2007 at 10.6 % of ACF cases and then declined to 6.4 % in 2011 [42]. These trends coincided with the surfacing of multiple complications associated with BMP utilization in the cervical spine and a FDA warning regarding its off-label application. Controversy still exists regarding the administration of BMP in ACF. Some groups maintain that it is safe and efficacious [43, 44] while others report multiple serious complications [45, 46].

Argument against BMP utilization in the anterior cervical spine

On July 1, 2008 the FDA issued a public health notification warning about the utilization of rhBMP-2 in cervical spine fusion procedures. The notification cites “life-threatening complications” and emphasizes that “the safety and

effectiveness of rhBMP-2 in the cervical spine have not been demonstrated and these products are not approved by FDA for this use” [47]. Osteolysis, graft subsidence, neck swelling, hematoma formation, dysphagia, and dyspnea have been associated with the utilization of BMP in this off-label setting.

Perhaps the most concerning complication associated with BMP utilization in ACF is neck swelling, which is thought to be related to a local inflammatory response. Mroz published a systematic review reporting a mean 5.8 % of postoperative soft tissue problems including dysphagia in patients who underwent an ACF with BMP [45]. In a prospective nonrandomized study of 66 consecutive patients, Buttermann reported on the results of ACF with the use of either rhBMP-2 or ICBG. In the rhBMP-2 cohort, 50 % of patients demonstrated postoperative neck swelling that presented as dysphagia compared with only 14 % in the ICBG group. Even more alarming was the 10 % ICU readmission rate and application of intravenous steroids for patients in the BMP group compared with 0 % in the ICBG group [48]. Cahill et al performed a database review of in-hospital complications and reported a higher overall complication rate when BMP was utilized in ACF compared with ACF without BMP. There was a significant increase in dysphagia or hoarseness in the ACF with BMP cohort (OR 1.63 %) [46]. These results have been substantiated by Singh et al who demonstrated that BMP utilization is an independent predictor of dysphagia [49].

In addition to pharyngeal edema, other complications have been reported after ACF with BMP. Shields et al reported a 9.9 % rate of hematoma formation after ACF with high-dose rhBMP-2 and half of those patients required repeat surgery for evacuation [50]. High rates of subsidence, endplate resorption, and graft lucency have also been reported [51, 52].

Arguments in favor of BMP utilization in the anterior cervical spine

Although multiple complications associated with BMP utilization in cervical fusion procedures have been reported, there is evidence that the complication rates are dose related and decrease with lower doses [53]. Importantly, Frankel et al reported no complications when the dosage of rhBMP-2 was less than 1.1 mg/level [44].

BMP may help reduce the rate of pseudarthrosis in multi-level ACF. Shen et al reported on 127 patients who underwent a 3 to 5-level ACF with rhBMP-2 in lieu of a circumferential fusion. The authors noted a 10.2 % pseudarthrosis rate and compared that with studies with multilevel ACF pseudarthrosis rates ranging from 37 % to 53 % [54, 55]. The authors also reported that while most patients complained of neck swelling there were no cases of reintubation due to airway compromise and no patients returned to the operating room for postoperative hematoma or seroma evacuation. Similarly, Stachniak et al reported a 95 % fusion rate at 6-

months and a 100 % fusion rate at 9-months following a 2- or 3-level ACDF with rhBMP-2 in a group with substantial risk factors for pseudarthrosis (33 % smoking, 13 % diabetes, and 43 % obesity) [53]. In another retrospective cohort study comparing multilevel ACF with and without rhBMP-2, the authors demonstrated a 100 % fusion rate in the rhBMP-2 cohort vs an 82.6 % fusion rate in the group without rhBMP-2 [44]. Lastly, Lu et al demonstrated lower rates of pseudarthrosis with the application of BMP in multilevel ACF, especially in patients who underwent a 4-level ACDF and in smokers [56]. As such, some authors contend that the application of rhBMP-2 may help prevent pseudarthrosis, especially in multilevel ACF. Potentially, this benefit can enable surgeons to treat multilevel disease with an anterior surgery only and prevent the necessity for circumferential fusion.

Summary

Multiple complications have been associated with the utilization of BMP in ACF procedures, the most common of which is neck swelling and dysphagia. While there is evidence that suggests that the complication rate is dose related and that BMP may increase multilevel ACF arthrodesis rates, we recommend exercising caution regarding the decision to use BMP in the cervical spine.

BMP utilization in adolescents

Similar to adult patients, there is significant morbidity associated with bone graft harvesting and up to 31 % of adolescent patients complain of persistent harvest site pain 2 years after surgery [57]. The reported success of bone graft substitutes in the adult spine literature has led to the use of rhBMP-2 in pediatric and adolescent patients.

Argument against BMP utilization in adolescent patients

Although pseudarthrosis continues to be a significant concern in adult spine patients, children and adolescent patients rarely experience this complication [58]. Furthermore, there is limited evidence to support the need for spinal fusion augmentation beyond instrumentation and local autograft. Despite the lack of prospective evidence, Jain et al reported an increasing trend of rhBMP-2 utilization from 2.7 % in 2003 to 9.3 % in 2009 among pediatric and adolescent patients [59]. This is concerning particularly due to the reported complications in the adult literature including cancer, ectopic bone formation, and urogenital complications. In addition, the pediatric spine literature has also reported a number of adverse events associated with rhBMP-2 including wound infection, seroma

formation causing neurologic damage, and symptomatic ectopic bone formation [60]. Although the largest retrospective reviews analyzing rhBMP-2 in adolescent patients do not report an increased risk of postoperative complications [59, 61], these studies are limited to in-hospital outcomes, which disregard the more common long-term complications demonstrated in other reports. In addition, rhBMP-2 is associated with a significantly greater total mean costs compared with non-BMP patients (\$47,136 vs \$43,126, $P < 0.001$; from the national inpatient sample database).

Argument in favor of BMP utilization in adolescent patients

Although there are limited published reports, rhBMP-2 appears to be a safe and effective alternative to promote spinal fusion in a selective group of adolescent patients [57]. Fahim et al reported a 100 % fusion rate with rhBMP-2 in cervical, thoracic, and lumbar fusions after a mean 17–25 month follow-up [62]. In this study, only 1 complication of bony overgrowth requiring reoperation and 2 superficial wound infections were reported. The theoretical benefit of bone graft substitutes and individual surgeon experience has expanded in the utilization of rhBMP-2 for spinal fusion in adolescent patients. In the last decade, the rate of rhBMP-2 utilization in this patient population has significantly increased particularly in the treatment of spondylolisthesis [59]. Isthmic spondylolisthesis in adolescent patients poses a challenging fusion environment, which has encouraged surgeons to implement rhBMP-2 in order to increase the likelihood of arthrodesis [63].

Summary

There is insufficient evidence to recommend for or against the utilization of rhBMP-2 in pediatric and adolescent patients. Challenging fusion environments, such as high-grade isthmic spondylolisthesis, may theoretically warrant adjunct osteobiologic utilization. Patients and their families should be made well aware of the potential risks and costs associated with rhBMP-2. As an increasing number of surgeons continue to utilize this bone graft substitute in pediatric and adolescent patients, future long-term follow-up studies may surface to help characterize the effectiveness and safety of rhBMP-2 in this patient population.

Conclusions

The utilization of rhBMP-2 in spine surgery potentiates arthrodesis without the morbidity associated with harvesting ICBG. However, rhBMPs, as with other drugs, are associated with adverse effects. Some complications may take years to

develop. Therefore, the results and conclusions from short-term clinical outcomes should be interpreted with caution. Surgeons who offer rhBMPs to their patients, especially in the off-label setting, should be cautious of potential risks associated with its use. More importantly, the benefits and potential risks associated with rhBMP-2 should be clearly presented and discussed with the patient prior to surgery.

Compliance with Ethics Guidelines

Conflict of Interest Kris Siemionow, Eric Sundberg, Marcin Tyrakowski, and Sreeharsha V. Nandyala declare that they have no conflict of interest. Kern Singh has board membership with Vital 5 LLC, has been a consultant for Zimmer, Stryker, Globus, and receives royalties from Pioneer, Stryker, Zimmer, and Tieme.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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