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Complications due to the use of BMP/INFUSE in spine surgery: The evidence continues to mount

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Abstract

Increasingly, adverse events (AE) attributed to utilizing BMP/INFUSE (Bone Morphogenetic Protein, Medtronic, Memphis, TN, USA) “off-label” in spine surgery are being reported. In 2008, the Food and Drug Administration (FDA) issued a warning that in anterior cervical spine surgery, the “off-label” use of BMP/INFUSE contributed to marked dysphagia, hematoma, seroma, swelling, and/or the need for intubation/tracheostomy. Subsequent studies have cited the following AE; heterotopic ossification (HO), osteolysis, infection, arachnoiditis, increased neurological deficits, retrograde ejaculation, and cancer. Furthermore, in 2011, Carragee *et al.* noted that 13 of the original industry-sponsored BMP/INFUSE spinal surgery studies failed to acknowledge multiple AE. Additionally, in 2012, Comer *et al.* observed that the frequency of retrograde ejaculation reported for BMP/INFUSE used “on-label” to perform Anterior Lumbar Interbody Fusion/Lumbar Tapered Fusion-Cage Device (ALIF/LT-Cage) was also largely “under-reported.” To summarize, there is mounting evidence in the spinal literature that utilizing BMP/INFUSE in spinal fusions contributes to major perioperative and postoperative morbidity.

Keywords: Adverse events, BMP/INFUSE, fusions, morbidity, “off-label”, spinal surgery

INTRODUCTION

Major complications, adverse events (AE) and reoperations have increasingly been attributed to the “off-label” use of BMP/INFUSE (Bone Morphogenetic Protein, Medtronic, Memphis, TN, USA) in spine surgery. These include; heterotopic ossification (HO), osteolysis, seroma/hematoma, infection, arachnoiditis, dysphagia (anterior cervical surgery), increased neurological deficits (myelopathy, radiculopathy), retrograde ejaculation (RE), and cancer [[Table 1](#)]. In the newer studies, evidence continues

to mount regarding the increasing AE attributed to utilizing BMP/INFUSE "off-label" in spinal surgery.[3,5,9,10,13]

FDA APPROVAL OF BMP/INFUSE FOR ANTERIOR LUMBAR INTERBODY FUSION WITH LUMBAR TAPERED FUSION DEVICES (LT-CAGE) IN 2002

BMP/INFUSE (Medtronic, Memphis, TN, and USA) was approved by the Food and Drug Administration (FDA) in 2002 as a bone graft expander/substitute for performing single-level Anterior Lumbar Interbody Fusions (ALIF) within the Lumbar Tapered Fusion Device system (LT-Cage) [Table 1]. The web site for FDA public health notification, stated that rhBMP-2 was FDA approved in the spine for fusion of the lumbar spine in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, and Grade I spondylolisthesis. Additionally, the rhBMP-7 (OP-1 and OP-1 Putty) device was approved as an "alternative to autograft in compromised patients requiring revision posterolateral (PL) (intertransverse) lumbar spinal fusion for whom autogenous bone and bone marrow harvest are not feasible or are not expected to promote fusion" (e.g., osteoporosis, smoking, diabetes) (www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm). The www.drugwatch.com/infuse site estimates since the release of BMP/INFUSE in 2002, over 100,000 spinal fusions are being performed per year utilizing BMP/INFUSE in a largely "off-label" capacity.

BMP AND SPINAL SURGERY FOR DEGENERATIVE DISC DISEASE: AN EVIDENCE-BASED ANALYSIS BY HEALTH QUALITY ONTARIO IN 2004

Health Quality Ontario reviewed the safety and efficacy of BMP/INFUSE in spinal fusion surgery in Canada in 2004 [Table 1].[17] BMP/INFUSE was offered as an alternative to autogenous bone grafting for ALIF, and was combined with the LT cage and a bovine collagen sponge. Studies reviewed included MEDLINE and EMBASE databases (e.g., those submitted to the United States FDA). BMP/INFUSE was deemed safe, as ALIF fusion rates appeared to occur faster and the utilization of BMP/INFUSE avoided donor site pain. Notably, clinical results were comparable to other fusion constructs, and outcomes for the minimally invasive surgical procedures (MIS) were comparable to open surgery.

FDA RECEIVES OVER 38 REPORTS OF MEDTRONIC'S BMP/INFUSE COMPLICATIONS FOR "OFF-LABEL" USE IN ANTERIOR CERVICAL SURGERY IN JULY 2008

By 2008, the FDA had received at least 38 reports of complications (over a 4-year period) of "swelling of the neck and throat tissues which resulted in compression of the airway and/or neurological structures of the neck," and "difficulty swallowing (dysphagia), breathing, or speaking." Patients required "respiratory support with intubation, anti-inflammatory medications, tracheostomy, and most commonly secondary surgeries to drain the surgical sites;" some also reported the need for feeding tubes (www.infuseboneproblemlawsuit.com). The safety and effectiveness of rhBMP in the cervical spine have not been demonstrated, and these products are not approved by the FDA for this use (e.g. cervical procedures) [Table 1](www.fda.gov/MedicalDevices/Safety/Alertsand%20Notices/PublicHealthNotifications/ucm0620000).

PERIOPERATIVE COST OF BMP/INFUSE IN POSTEROLATERAL LUMBAR FUSION IN 2008

In 2008, Glassman *et al.* performed a prospective, randomized study involving 102 patients over the age of 60, to compare the perioperative costs of utilizing rhBMP-2 or BMP/INFUSE (50 patients) vs. iliac crest bone graft (ICBG) (52 patients) as bone graft extenders for performing posterolateral lumbar fusions (PLF) [Table 1].[16] All AE were recorded during the hospitalization and for a 3-month postoperative period. Perioperative complications were less for patients receiving BMP/INFUSE (8 of 50 or 16%; including 1 wound infection) vs. ICBG (12 of 52 or 23%; including 4 wound infections, and 1 neurological deficit). Notably, the combined first admission and 3-month postoperative costs were lower for BMP/INFUSE (\$33,860) vs. ICBG (\$37,227), and there were lower physician costs (\$5,082 vs. \$5,316), and rehabilitation costs (\$4,906 vs. \$6,820) attributed to BMP/INFUSE vs. ICBG. Therefore, despite the increased initial cost of BMP/INFUSE vs. ICBG, the former proved more cost-effective.

HIGH-DOSE BMP PRODUCES HETEROTOPIC RETROPERITONEAL OSSIFICATION IN 2010

In 2010, Deutsch *et al.* reported a 55-year-old male who underwent a combined anterior/posterior thoracic T8 to pelvis fusion for degenerative lumbar disc disease utilizing multiple packages of BMP [Table 1].[7] The patient developed a pseudarthrosis accompanied by “weight loss, pain, tenderness, and (an) increasing solid growth in the left lower quadrant several months after his (initial) surgery.” The computed axial tomography (CT) documented an ectopic retroperitoneal bone growth in the pelvis in an area “contiguous to the anterior lumbar exposure site” consistent with HO; it was subsequently successfully removed, and the patient's symptoms resolved.

COSTS AND FREQUENCY OF “OFF-LABEL” USE OF INFUSE FOR SPINAL FUSIONS IN 2010

In 2010, Epstein and Schwall compared the frequency and costs of “off-label” vs. “on-label” use of BMP/INFUSE to perform cervical, thoracic, and lumbar fusions at a single institution [Table 1].[13] During 177 spinal fusions, 96% (170 of 177) utilized BMP/INFUSE “off-label” (cost \$4,547,822), while only 4% (7 of 177) of fusions utilized BMP/INFUSE “on-label” (e.g., ALIF cost of \$296,419).[13] Of interest, there was a 40% reoperation rate for patients over the age of 65, with a 20% overall reoperation rate in all age groups.

UNREPORTED ADVERSE EVENTS AND UNDER-REPORTED SHORTCOMINGS OF INDUSTRY-SPONSORED BMP/INFUSE TRIALS IN SPINAL SURGERY IN 2011

In 2011, Carragee *et al.* noted that multiple clinical trials utilizing BMP/INFUSE in spinal surgery unreported and under-reported AE [Table 1].[2] They observed that in multiple original “peer review, industry-sponsored publications,” AE were “either not reported at all, or not reported to be associated with rhBMP-2 use.”[2] To better determine the accuracy of reports regarding the safety/efficacy of BMP/INFUSE, the authors compared industry trial results with those submitted to the FDA, to those associated with subsequent publications, and to other databases. Notably, the 13 industry-sponsored, prospective, controlled trials involving 780 patients reported no complications or AE attributed to rhBMP-2. Investigation into study designs also revealed biases that favored study vs. control patients following posterolateral fusions (PLFs) and posterior lateral interbody fusions (PLIF).[2] Additionally, review of FDA documents and subsequently published data revealed “originally unpublished adverse events and internal inconsistencies.” These findings led Carragee *et al.*, to conclude that the actual incidence of AE attributed to BMP/INFUSE is between 10% and 50% (varying with the procedure). A 40% risk of AE was associated with anterior cervical surgery utilizing BMP/INFUSE; these risks also included “life-threatening events.” AE attributed to ALIF, an “on-label” use with the LT-Cage, includes a higher risk than previously reported of “implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation” for those treated with rhBMP-2 vs. control patients. AE associated with posterior lumbar interbody fusion (PLIF) utilizing BMP/INFUSE also resulted in an increased incidence of “radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes.” They also found significantly exaggerated reports of ICBG morbidity when utilized to perform PL fusions, while in fact, AE due to BMP/INFUSE were equal to or greater than those attributed to ICBG. An additional 15% to 20% of patients complained of early back pain and leg pain. Higher doses of BMP/INFUSE were now increasingly correlated with rising cancer rates.

RETROGRADE EJACULATION AFTER ALIF USING RHBMP-2: COHORT CONTROLLED STUDY IN 2011

In 2011, the FDA reported that RE was observed in 8% of ALIFs (12 cases) performed to address lumbar spondylosis or spondylolisthesis at either the L5-S1 or the L4-L5/L5-S1 levels utilizing BMP/INFUSE vs. a 1.4% incidence performed without BMP/INFUSE (control patients) [Table 1]. In the same year, Carragee *et al.* observed an increased risk of RE and other AE (e.g., inflammatory responses, heterotopic bone formation, radiculitis, osteolysis with cage/graft dislodgement/subsidence) for ALIF fusions utilizing BMP/INFUSE “on-label.”[3] Their study included 69 L5-S1 ALIFs (24 two-level L4-L5/L5-S1 with

BMP/INFUSE vs. 174 L5-S1 ALIFs (64 two-level L4-L5/L5-S1) performed without BMP/INFUSE. Five RE events (7.2%) occurred in patients receiving rhBMP-2 (BMP/INFUSE) vs. only 1 (0.6%) among control patients. For L5-S1 ALIFs alone, the rates were 6.7% and 0%, respectively. Unfortunately, one year postoperatively, RE resolved in only three of six patients.

COMPLICATIONS OF BMP/ INFUSE IN SPINE SURGERY IN 2011

In 2011, BMP/INFUSE was widely utilized in an “off-label” capacity for anterior and/or posterior cervical, thoracic, and lumbar surgery [Table 1].[10] Direct contraindications for utilizing BMP/INFUSE included; pregnancy, allergy to titanium, allergy to bovine type I collagen or rhBMP-2, infection, tumor, liver or kidney disease, immunosuppression (e.g., lupus, HIV/AIDS), those undergoing chemotherapy, or patients on steroids.[10] Multiple complications reported included; HO, paralysis (cord, nerve damage), dural tears, bowel-bladder dysfunction, RE, respiratory failure, inflammation of adjacent tissues, fetal developmental complications, scar, excessive bleeding, and even death.

PREVALENCE OF “UNNECESSARY” CERVICAL SURGERY AND LUMBAR PLIF OFFERED BY OUTSIDE SURGEONS IN 2011

In 2011, Epstein reported that 17.2% (47 patients) of 274 patients seen in consultation for cervical or lumbar complaints over a one-year period had been offered “unnecessary” spinal surgery, that in some cases would have utilized BMP/INFUSE [Table 1].[12] The “unnecessary” surgery was defined as operations being offered for pain alone, without focal neurological deficits, or significantly abnormal radiographic findings [dynamic X-rays, magnetic resonance imaging (MRI) scans, and/or CT scans]. “Unnecessary” cervical surgery had been offered to 21 (23.1%) of 91 patients with cervical pain and included 1–4 level anterior discectomy/fusion (18 patients), laminectomies/fusions (2 patients), and a posterior cervical discectomy (1 patient). “Unnecessary” 1–5 level PLIFs for lumbar pain alone were offered to 26 (14.2%) of 183 patients; these included 1-level (13 patients), 2-level (7 patients), 3-level (3 patients), 4-level (2 patients), and 5-level (1 patient) procedures.

EFFECT OF STEROIDS ON SOFT TISSUE INFLAMMATION ASSOCIATED WITH RHBMP-2 (RODENT MODEL) IN 2012

In an *in vivo* rodent model, Tan *et al.* evaluated the impact of systemic corticosteroids on the reduction of soft tissue inflammation after the local application of rhBMP-2 absorbable collagen sponges (control vs. rhBMP-2) applied subcutaneously (SC) or intramuscularly (IM) in the lumbar regions of rats [Table 1].[20] There were four groups; group I – control sponge; group II – BMP-2 sponge; group III – BMP-2 sponge and preoperative intraperitoneal methylprednisolone, and group IV – BMP-2 sponge with methylprednisolone given on day 2. MRI was utilized to assess postoperative inflammatory changes (soft tissue edema volume) at 0, 2, 4, and 7 days, and rats were sacrificed and analyzed (gross and histological analysis) at 7 days. On MRI scans, the maximal average inflammatory changes were noted intramuscularly on day 2 in all groups. However, the group II cohort (BMP-2 with steroids) had a significantly higher peak mean inflammatory volume (405.46 mm) on day 2 vs. all others (in group I (266 mm), III (278 mm), and IV (291 mm) ($P = 0.001$)). The authors concluded that systemic methylprednisolone did reduce MRI-documented soft tissue edema attributed to rhBMP2, but that this did not impact the histologically documented area of inflammation.

INDUSTRY SPONSORED REPORTS DOCUMENTING NO BMP/INFUSE-RELATED COMPLICATIONS BUT MAGNIFYING RISKS OF ILIAC CREST BONE HARVESTING IN 2012

The frequency of BMP/INFUSE utilized by spinal surgeons rose from 0.7% in 2002 to over 50% for ALIF and 43% for PLIF/TLIF fusions by 2007 [Table 1].[14] In 2012, Even *et al.* noted that in initial studies sponsored by the industry, involving 780 patients, there were no AE that were directly attributed to BMP/INFUSE.[14] Furthermore, these studies magnified the AE/morbidity of harvesting ICBG; complication rates of 40–60% were cited, significantly higher than the historical rates of 3-30%.

Meanwhile, the complications of BMP/INFUSE, which included RE, osteolysis, seroma, postoperative radiculitis, ectopic bone formation, and massive soft tissue swelling went under or unreported.

INCREASED CANCER RISK WITH AMPLIFY (HIGHER DOSE BMP/INFUSE: MEDTRONIC, MEMPHIS, TN, USA) IN SPINE SURGERY IN 2012

Even *et al.* additionally noted in 2012, that Amplifyo (higher dose BMP/INFUSE) is contraindicated for patients with cancer requiring spinal fusions, as BMP receptors are found on the cell membranes of certain cancer cells [Table 1].[14] The FDA subsequently reported “that Amplify increased cancer rates 4 fold with 9 (3.8%) new tumors being found out of 239 Amplify patients vs. only 2 (0.89%) of 224 control patients.” At 60 months, cancer rates increased to 5% for the Amplify group vs. 1.8% for the control patients.

INCREASED CANCER RISK WITH AMPLIFY/BMP/INFUSE (RHBMP) IN SPINE SURGERY IN 2012

Devine *et al.* also evaluated whether utilizing AMPLIFY/BMP/INFUSE in spine surgery were associated with increased cancer risks [Table 1].[8] When assessing the data provided to the FDA regarding Amplify™ (rhBMP-2, 40 mg), they found “a higher number of cancers in the investigational group compared with the control” population. As of January 2012, utilizing PubMed, Cochrane, National Guideline Clearinghouse Databases, and key articles, they identified five peer-reviewed and two FDA studies that looked at cancer risks for patients undergoing spinal fusion with rhBMP-2 (INFUSE™) or rhBMP-7. Off-label use of rhBMP-2 for PLF correlated with a slightly higher risk of cancer (3.8%) vs. controls (0.9%). In two randomized/controlled studies, the rhBMP-7 cancer risks were 12.5% and 5.6%, respectively vs. 8.3% and 0% in the control groups.[8]

INCREASED INCIDENCE OF RETROGRADE EJACULATION AND URINARY RETENTION AFTER ALIF WITH BMP/INFUSE VS. WITHOUT BMP/INFUSE (10 YEAR STUDY) IN 2012

Comer *et al.* evaluated whether BMP/INFUSE (BMP-2) utilized in ALIF fusions promoted inflammatory reactions that increased the risk of RE, an injury typically attributed to mechanical or “inflammatory” injury to the superior hypogastric plexus [Table 1].[5] Ten-year outcomes of ALIF for lumbar spondylosis or spondylolisthesis (L4/L5 or L5/S1) with/without BMP/INFUSE were assessed. Patients were divided into four groups: group 1 (174 patients before BMP/INFUSE), groups 2 and 3 (BMP-2 routinely used, respectively, in 88 and 151 patients), and group 4 (no BMP in 59 patients). They observed a higher rate of RE following open ALIF procedures performed with BMP/INFUSE; 15 (6.3%) undergoing 239 ALIFs with BMP-2 developed RE vs. 2 (0.9%) for 233 control patients. Additionally, disproportionately more patients with underlying benign prostatic hypertrophy (BPH) developed postoperative RE. Furthermore, those receiving BMP developed an increased incidence of urinary retention (9.7%) vs. control patients (4.6%).

RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2: ADVERSE EVENTS REPORTED TO THE MANUFACTURER AND USER FACILITY DEVICE EXPERIENCE DATABASE IN 2012

Woo *et al.* reported other major AE utilizing BMP/INFUSE (including documentation of “off-label” Use of rhBMP-2) in spinal surgery based on the FDA database of postmarketing reports [Table 1].[21] Utilizing the Manufacturer and User Facility Device Experience Database, they analyzed reports from July 2002 to August 2011. Out of 834 reports, only 4 (0.5%) used BMP/INFUSE “on-label”; almost half (370 or 44.4%) of these patients required “revision surgery or other invasive procedures to address reported AE.” The major AEs recorded included: “Swelling, fluid collections, osteolysis, pain/radiculopathy, heterotopic bone, pseudarthrosis, surgical site infections and other wound complications, thromboembolic events, respiratory distress, and cancer.” They concluded; “... serious adverse events can occur after the use of rhBMP-2 in spinal surgery and raises many points that surgeons may wish to consider when deciding when and how to use this product in their patients.”

COMPLICATIONS OF TRANSFORAMINAL LUMBAR INTERBODY FUSIONS ASSOCIATED WITH BMP IN 2012

Chrastil and Patel evaluated 360 transforaminal lumbar interbody fusion (TLIF) fusions performed with BMP/INFUSE for spondylolisthesis, degenerative scoliosis, pseudarthrosis, recurrent discs, and chronic low back pain with degenerative disc disease [Table 1].[4] Complications included: “Intraoperative neurologic injury, implant migration or subsidence, dural tears, infection, heterotopic ossification, BMP-related radiculitis, and osteolysis.” They concluded that utilizing BMP to perform MIS spinal procedures is associated with “unique concerns.”

IMPACT OF BMP ON FREQUENCY OF REVISION SURGERY, USE OF AUTOGRAFT, AND TOTAL HOSPITAL CHARGES FOR LUMBAR DEGENERATIVE DISEASE IN 2012

Dagostino *et al.* noted that the purpose of utilizing BMP/INFUSE in spinal surgery was to avert the morbidity/AE associated with harvesting iliac crest bone autograft (ICBG) [Table 1].[6] Utilizing the Nationwide Inpatient Sample (NIS), a retrospective cohort analysis of 46,452 patients (2002-2008) undergoing thoracolumbar/lumbar fusions for degenerative spinal disease revealed continued growth in the number of lumbar fusions performed with BMP. They observed fewer revisions and interestingly, no change in the frequency of ICBG. Nevertheless, BMP significantly increased the average hospital charge per patient by \$13,362.39, and added over \$900 million to total hospital charges (2002 vs. 2008) for degenerative thoracolumbar procedures.

POOR CLINICAL OUTCOMES OF INSTRUMENTED FUSION FOR FAILED BACK SURGERY IN 2012

Arts *et al.* evaluated the outcomes of 100 patients undergoing instrumented spinal fusions for “failed back surgery syndrome” defined as “persistent chronic low-back pain and/or leg pain lasting more than 1 year, despite one or more surgical procedures [Table 1].”[1] Recovery was assessed utilizing; the Likert scale, Visual Analog Scale (VAS), Roland Disability Questionnaire for Sciatica (RDQ), Oswestry Disability Index (ODI), and Hospital Anxiety and Depression Scale (HADS). Questionnaires were returned by 82 patients who were followed over an average postoperative interval of 15 months; of these, 35% reported good outcomes, but 65% claimed unsatisfactory outcomes. Of interest, the HADS score demonstrated possible anxiety disorders in 28% of the patients, with 30% exhibiting possible depression. A lower education level was the only clinical factor demonstrating a significantly negative correlation with outcome. The authors concluded that the majority (65%) of outcomes for instrumented fusions for failed back surgery were poor, and recommended that in the future patients should be more carefully selected “to prevent unnecessary surgery.”

TLIF AND PLIF UTILIZING BMP-2 IN THE TREATMENT OF DEGENERATIVE SPONDYLOLISTHESIS: NOT SIGNIFICANTLY BETTER CLINICAL OUTCOMES IN 2013

Moatz and Tortolani observed that as health care expenditures rise, more emphasis is placed on the cost of spinal surgery per quality adjusted life year (QALY) [Table 1].[19] Although spinal surgery for degenerative spondylolisthesis (DS) is as cost-effective as total joint replacement surgery, the literature demonstrates that the “value added” of interbody fusion utilizing BMP to perform PLIF or TLIF did not lead to “significantly better clinical outcomes and increases costs when compared with more routine posterolateral fusion techniques.” They concluded that there is not enough evidence to support the routine use of BMP/INFUSE with interbody fusion devices for the management of focal stenosis with DS, and that spinal stenosis with DS could be adequately managed with other PLF techniques without BMP/INFUSE.

THE VALUE OF “ANOTHER” OPINION FOR SPINAL SURGERY: A PROSPECTIVE 14-MONTH STUDY OF ONE SURGEON'S EXPERIENCE IN 2013

Gamache examined the value of another opinion for patients seeking neurosurgical consultation for spinal disease in New York City [Table 1].[15] Over 14-months, he prospectively collected data from 240

consecutive patients that included imaging studies and patients' comments on consultation questionnaires. First opinions were performed in 85 (35%) of the 240 patients (those referred from primary care doctors/neurologists); no surgery was recommended for 37 (43%) of these 85 patients. However, for the 155 (65%) of the 240 patients who came for second, third, or fourth surgical opinions (e.g., earlier surgeons recommended an operation); the author recommended no surgery for 69 (44.5%) patients. Gamache emphasized that neurological findings and neurodiagnostic studies should be carefully correlated with patient's complaints, and that patients should be clearly educated as to why and whether they should be considered nonsurgical vs. surgical candidates.[15]

GENETIC ADVANCES IN THE REGENERATION OF THE INTERVERTEBRAL DISC IN 2013

When Maerz *et al.* evaluated tissue engineering strategies to promote the regeneration of intervertebral discs, they also acknowledged that in animal models (*in vivo*) dating back to the mid 2000s, BMP-2 resulted in greater degenerative changes within the discs, promoted increased bone formation, and inflammatory responses [Table 1].[18]

COMMENTARY ON RESEARCH OF BONE MORPHOGENETIC PROTEIN IN 2013

Commenting on the article by Maerz *et al.*, Epstein noted the *in vivo* and *in vitro* complications observed in animal models attributed to BMP (BMP-2, BMP-7) dated back to the mid 2000s [Table 1].[11,18] Complications, particularly at higher dosages, included "inflammation/inflammatory processes, increased vascularity, fibroblastic proliferation, and catabolism."

CONCLUSION

We continue to recognize multiple major AE in patients undergoing particularly "off-label" spinal fusions utilizing BMP/INFUSE [Table 1].[2,3,4,5,6,7,8,9,10,12,13,14,17,19,21] AE predominantly include: HO, osteolysis, seroma/hematoma, infection, arachnoiditis, dysphagia (anterior cervical surgery), increased neurological deficits (myelopathy, radiculopathy), RE, and cancer.[2,3,4,5,6,7,8,9,10,12,13,14,17,19,21] In 2011, Carragee *et al.* pointed out that 13 of the original industry-sponsored BMP/INFUSE spinal surgery studies failed to acknowledge multiple AE.[3] Also, in 2012, Comer *et al.* noted that the frequency of retrograde ejaculation (RE) reported for BMP/INFUSE used "on-label" to perform ALIF/LT-Cage fusions was also largely "under-reported." [3,5] The remote and mounting recent evidence in the spinal literature now acknowledges that utilizing BMP/INFUSE to perform spinal fusions contributes to major perioperative and postoperative morbidity (AE).[9,10,13]

Footnotes

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REFERENCES

1. Arts MP, Kols NI, Onderwater SM, Peul WC. Clinical outcome of instrumented fusion for the treatment of failed back surgery syndrome: A case series of 100 patients. *Acta Neurochir (Wien)* 2012;154:1213–7. [PMCID: PMC3382643][PubMed: 22588339]
2. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: Emerging safety concerns and lessons learned. *Spine J.* 2011;11:471–91. [PubMed: 21729796]
3. Carragee EJ, Mitsunaga KA, Hurwitz EL, Scuderi GJ. Retrograde ejaculation after anterior lumbar interbody fusion using rhBMP-2: A cohort controlled study. *Spine J.* 2011;11:511–6. [PubMed: 21612985]
4. Chrastil J, Patel AA. Complications associated with posterior and transforaminal lumbar interbody fusion. *J Am Acad Orthop Surg.* 2012;20:283–91. [PubMed: 22553100]

5. Comer GC, Smith MW, Hurwitz EL, Mitsunaga KA, Kessler R, Carragee EJ. Retrograde ejaculation after anterior lumbar interbody fusion with and without bone morphogenetic protein-2 augmentation: A 10-year cohort controlled study. *Spine J.* 2012;12:881–90. [PubMed: 23098617]
6. Dagostino PR, Whitmore RG, Smith GA, Maltenfort MG, Ratliff JK. Impact of bone morphogenetic proteins on frequency of revision surgery, use of autograft bone, and total hospital charges in surgery for lumbar degenerative disease: Review of the Nationwide Inpatient Sample from 2002 to 2008. *Spine J.* 2013 [In Press]
7. Deutsch H. High-dose bone morphogenetic protein-induced ectopic abdomen bone growth. *Spine J.* 2010;10:e1–4. [PubMed: 20006558]
8. Devine JG, Dettori JR, France JC, Brodt E, McGuire RA. The use of rhBMP in spine surgery: Is there a cancer risk? *Evid Based Spine Care J.* 2012;3:35–41. [PMCID: PMC3516460] [PubMed: 23230416]
9. Epstein NE. Spine surgery in geriatric patients: Sometimes unnecessary, too much, or too little. *Surg Neurol Int.* 2011;2:188. [PMCID: PMC3263001] [PubMed: 22276241]
10. Epstein NE. Pros, cons, and costs of INFUSE in spinal surgery. *Surg Neurol Int.* 2011;2:10. [PMCID: PMC3031052] [PubMed: 21297932]
11. Epstein NE. Commentary on research of bone morphogenetic protein discussed in review article: Genetic advances in the regeneration of the intervertebral disc. *Surg Neurol Int.* 2013;4(Suppl 2):S106–8. [PMCID: PMC3642755] [PubMed: 23646271]
12. Epstein NE, Schwall GS. Costs and frequency of “off-label” use of INFUSE for spinal fusions at one institution in 2010. *Surg Neurol Int.* 2011;2:115. [PMCID: PMC3162796] [PubMed: 21886888]
13. Epstein NE, Hood DC. “Unnecessary” spinal surgery: A prospective 1-year study of one surgeon's experience. *Surg Neurol Int.* 2011;2:83. [PMCID: PMC3130462] [PubMed: 21776403]
14. Even J, Eskander M, Kang J. Bone morphogenetic protein in spine surgery: Current and future uses. *J Am Acad Orthop Surg.* 2012;20:547–52. [PubMed: 22941797]
15. Gamache FW. The value of “another” opinion for spinal surgery: A prospective 14-month study of one surgeon's experience. *Surg Neurol Int.* 2012;3(Suppl 5):S350–4. [PMCID: PMC3520076] [PubMed: 23248753]
16. Glassman SD, Carreon LY, Campbell MJ, Johnson JR, Puno RM, Djurasovic M, et al. The perioperative cost of INFUSE bone graft in posterolateral lumbar spine fusion. *Spine J.* 2008;8:443–8. [PubMed: 17526436]
17. Health Quality Ontario. Bone morphogenetic proteins and spinal surgery for degenerative disc disease: An evidence-based analysis. *Ont Health Technol Assess Ser.* 2004;4:1–16. [PMCID: PMC3387739]
18. Maerz T, Herkowitz H, Baker K. Genetic Advances in the Regeneration of the Intervertebral Disc. *Surg Neurol Int.* 2013;4(Suppl 2):S94–105. [PMCID: PMC3642750] [PubMed: 23646279]
19. Moatz B, Tortolani PJ. Transforaminal lumbar interbody fusion and posterior lumbar interbody fusion utilizing BMP-2 in treatment of degenerative spondylolisthesis: Neither safe nor cost effective. *Surg Neurol Int.* 2013;4(Suppl 2):S67–73. [PMCID: PMC3642749] [PubMed: 23646277]
20. Tan Y, Montgomery SR, Aghdasi BG, Inoue H, Kaner T, Tian H, et al. The effect of corticosteroid administration on soft tissue inflammation associated with rhBMP-2 use in a rodent model of inflammation. *Spine.* 2012 [In Press]
21. Woo EJ. Recombinant human bone morphogenetic protein-2: Adverse events reported to the Manufacturer and User Facility Device Experience database. *Spine J.* 2012;12:894–9. [PubMed: 23098616]

Figures and Tables

Table 1

Topic	Summary findings
Introduction	Summary: In newer studies, evidence continues to support the safety of utilizing BMP/INFUSE “off-label” in spinal surgery.
FDA Approval of BMP/INFUSE for Anterior Lumbar Interbody Fusion (ALIF) with Lumbar Tapered Fusion Devices (LT-Cage) in 2002	Summary: BMP/INFUSE (Medtronic, Memphis, TN) received FDA approval from the Food and Drug Administration (FDA) in 2002 for ALIF fusions in conjunction with LT-Cage.
BMP and Spinal Surgery for Degenerative Disc Disease: An Evidence-based Analysis by Health Quality Ontario in 2004	Summary: Health Quality Ontario reviewed the safety and effectiveness of BMP/INFUSE in Canada 2004. BMP/INFUSE was deemed safe, as the use of BMP/INFUSE avoided donor site pain. Clinical outcomes and outcomes for these minimally invasive surgical procedures were similar to those of open surgery.
FDA Receives Over 38 Reports of Medtronic BMP/INFUSE Complications for “Off-Label” Use in Anterior Cervical Surgery in July 2008	Summary: In July of 2008, the FDA issued a Public Health Advisory regarding complications (= $>$ 38 cases) of BMP/INFUSE when used for anterior cervical surgery, including the neck/throat, dysphagia, respiratory complications, and other issues.
Perioperative Cost of BMP/INFUSE in Posterolateral Lumbar Fusion in 2008	Summary: In a prospective, randomized study involving 100 patients, the perioperative costs of utilizing rhBMP-2 or BMP/INFUSE (vs. ICBG) in posterolateral lumbar fusion (PLF) patients) as bone graft extenders for performing posterolateral lumbar fusion (PLF) postoperative costs combined were less for BMP/INFUSE vs. ICBG. Physician and rehabilitation costs were also lower for BMP/INFUSE vs. ICBG. The increased cost of BMP/INFUSE vs. ICBG, the BMP/INFUSE cost was offset by the lower physician and rehabilitation costs.
High-dose BMP Produces Heterotopic Retroperitoneal Ossification in 2010	Summary: Deutsch <i>et al.</i> reported a case of a 55-year-old patient who underwent thoracic T8 to pelvis fusion for degenerative lumbar disc disease. The patient had documented ectopic retroperitoneal bone growth in the psoas muscle, which was consistent with heterotopic ossification (HO). Following surgery, the patient developed retroperitoneal ossification.
Costs and Frequency of “Off-Label” Use of INFUSE for Spinal Fusions in 2010	Summary: At one institution in 2010, the costs (with “on-label” vs. “off-label” in 177 spinal fusions was assessed. The total cost was \$4,547,822 to the institution.
Unreported Adverse Events (AE) and Under-Reported Shortcomings of Industry-Sponsored BMP/INFUSE Trials in Spinal Surgery in 2011	Summary: In 2011, Carragee <i>et al.</i> noted that multiple adverse events (AE) were unreported and under-reporting AE. In multiple original articles, AE were “either not reported at all, or not reported to be attributed to BMP/INFUSE. The actual incidence of AE attributed to BMP/INFUSE should be higher than what was reported. The incidence of AE was attributed to anterior cervical surgery utilizing BMP/INFUSE.
Retrograde Ejaculation (RE) after ALIF using rhBMP-2: Cohort Controlled Study in 2011	Summary: In 2011, the FDA reported that retrograde ejaculation (RE) occurred in 1.4% of cases) performed to address lumbar spondylosis or spondylolisthesis at L5-S1 levels utilizing BMP/INFUSE vs. a 1.4% incidence postoperatively. In Carragee <i>et al.</i> , out of 69 L5-S1 ALIFs (24 two-level and 45 one-level) performed without BMP/INFUSE, 5 RE occurred (11.1%). In the control group, 1 RE occurred (0.6%) for control patients. When L5-S1 ALIF fusion was performed with BMP/INFUSE, 1 RE occurred (1.4%).

Summary: Evidence Continues to Mount For Adverse Events Attributed to BMP/INFUSE

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Commentary

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CONFLICT OF INTEREST

The clinical development and use of BMP- 2 is not a pretty story, as it is one filled with conflicts of interest, dishonest record keeping/reporting, a lack of clinical leadership.[11] While the federal Drug Enforcement Agency (DEA) determines whether a drug or a class of drugs should be available through our standard market system, the Food and Drug Administration (FDA) determines if such availability is permissible and sets the conditions under which a manufacturer may advertise and market the drug.[3,12] A bone morphogenetic protein BMP-2, (Medtronic, Memphis TN, USA) was approved in 2002 by the FDA for use as an adjunct in anterior lumbar spinal fusions.[9] Since its approval, however, there are multiple reports of major conflicts of interest involving clinical investigators receiving generous payments as consultants from the drug/device industry, including Medtronic.[15] Reports indicate that while performing research and writing scientific papers, these same authors not only sat on the editorial boards that reviewed these papers, but also occupied leadership positions within neurosurgery and orthopedic surgery.[6]

SIGNIFICANT COMPLICATIONS AND ADVERSE EVENTS (AE)

A decade later, many significant complications and adverse events (AE) (e.g. up to 15%) directly attributable to BMP-2 were accurately reported.[5,15] Finally, in 2008, the FDA issued stern warnings regarding adverse events following the use of BMP in anterior cervical surgery (e.g. respiratory difficulties, dysphagia, tracheotomy); the response from the leadership of neurosurgery was muted at best.[5,7,10,13] Although these revelations received negative reviews from academicians and editors, larger and more definitive studies regarding BMP-2 related AE to establish its safety/efficacy were never performed.[2,7]

QUESTIONS RAISED ABOUT BMP-2: DOSAGE, INDICATIONS, CONTAINMENT, COST

Nevertheless, as questions were raised about the acceptable dose, indications, cost/ effectiveness and cost/benefit parameters for BMP-2 in spinal surgery, some authors began removing their support for the product, while select hospitals announced they would ban BMP-2 from their premises (e.g. for lumbar or cervical surgery).[7,14] Certainly, the present lack documentation of the safety/efficacy of BMP-2 “off-label” in the anterior cervical spine should make it an investigational drug/device.[1,4,13]

JOINT COMMITTEE ON DRUGS AND DEVICES OF THE AANS AND CNS

Since the mid-1970s, The Joint Committee on Drugs and Devices of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons) CNS was established to advise the leadership regarding adverse trends or developments regarding drugs/devices (e.g. BMP-2). A vigilant committee should have known well before the FDA warning in 2008 that BMP-2 was problematic in anterior cervical surgery.[8] Unfortunately, no timely action was taken, and the AANS/CNS societies only began to pay attention to the issue due to excessive costs rather than AE.[7]

MAJOR INITIAL ERROR: FAILURE TO UNDERSTAND LIMITATIONS OF “OFF-LABEL USE” OF BMP-2

The major initial error in this story was the failure of the individual surgeons and leadership of neurosurgery to highlight the significant limitations of the “off-label” use of BMP-2. It was not sufficient to simply inform the readers that their use of BMP-2 was appropriate because the state's control over their license trumped the FDA's oversight of labeling. Rather, there had to be some reason to believe that the agent was both safe and effective for its intended use.[1,4,13]

COMPLEX CONSIDERATIONS FOR CONVERSION OF BMP-2 FOR SAFE AND EFFECTIVE “OFF-LABEL” USE

For BMP-2 to be utilized in different areas of the spine rather than simply for the “on-label” use in ALIF with the LT-Cage, consideration had to be given to the process of “conversion” (e.g. its use in other unique environments/surgical wounds, its impact on other soft tissues, and the potential for neural injury). The dissimilarity between the surgical wounds make it hazardous to use safety data from the lumbar spine to draw conclusions regarding the safety of BMP-2 in the cervical region. In the absence of such adequate safety data, therefore, utilization of BMP-2 in the cervical spine should have been and should be considered “investigational”.

REFERENCES

1. Aledort LM. Off-label use of recombinant activated factor VII—safe or not safe. *N Eng J Med.* 2010;365:1852–4.
2. Baskins DS, Ryan P, Sonntag V, Westmark R, Widmayer MA. A prospective, randomized, controlled cervical fusion study using recombinant bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. *Spine (Phila Pa 1976)* 2003;28:1218–24.
3. Blair KA. In search of the right Rx: use of the Federal False Claims Act in off-label drug promotion litigation. *The Health Lawyer.* 2011;23:44–54.
4. Brisman R. Trigeminal neuralgia and multiple sclerosis. *Arch Neurol.* 1987;44:379–81. [PubMed: 3493757]
5. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spine surgery: emerging safety concerns and lessons learned. *Spine J.* 2012;20:471–91.
6. Carreyrou J, McGinty T. Medtronic surgeons held back, study says. *Wall Street J.* 2011 Jun 29;:B1.
7. Epstein N. Pros, cons, and costs of INFUSE in spinal surgery. *Surg Neurol Int.* 2011;2:10. [PMCID: PMC3031052] [PubMed: 21297932]
8. Long D, Watts C. Off-label use of drugs and devices: role of medical professionals in the establishment of parameters for their use. *Neurosurgery.* 2013;72:1014–20. [PubMed: 23407286]
9. Samarzis D, Khanna N, Shen FH, An HS. Update on bone morphogenetic proteins and their application in spine surgery. *J Am Coll Surg.* 2005;200:236–48. [PubMed: 15664100]
10. Schultz DG. Silver Springs, MD: U.S. Food and Drug Administration; 2008. Public Health Notification: Life Threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusions.

11. Singer N. Heath bills aim a light at doctors' conflicts. NY Times. 2009 Nov 4;:B1.
12. Stafford RS. Regulating off-label drug use—rethinking the role of the FDA. N Eng J Med. 2008;358:1427–9.
13. Treharne RW. Memphis, TN: Medtronic Sofamor; 2004. Safety Alert, INFUSE graft.
14. Vaidya R, Carp J, Sethi A, Barrol S, Graig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein. Eur Spine J. 2007;16:1257–65. [PMCID: PMC2200768] [PubMed: 17387522]
15. Weaver C. Studies fail to back Medtronic spine product. Wall Street J. 2013 Jun 2;19:B2.