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Perspective

Recombinant human bone morphogenetic protein-2: adverse events reported to the Manufacturer and User Facility Device Experience database

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Abstract

BACKGROUND CONTEXT: Adverse effects of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spinal surgery have previously been observed. However, because of its size, scope, and nature, the US Food and Drug Administration's database of postmarketing reports is useful for detecting new and unexpected safety concerns.

PURPOSE: To characterize adverse events reported to the FDA; to characterize off-label use of rhBMP-2.

STUDY DESIGN: Review of adverse events reported to the FDA after the use of rhBMP-2 (INFUSE Bone Graft) in spinal surgery.

METHODS: The Manufacturer and User Facility Device Experience database was searched for the brand name ''infuse bone graft,'' for reports received from July 2, 2002, through August 31, 2011. Adverse events were reviewed, summarized, and classified by an MD. For each report, the most important clinical entity was identified as the principal adverse event. Off-label uses were summarized.

RESULTS: Of 834 reports, four (0.5%) described procedures in which rhBMP-2 was used in accordance with the approved indication. Nearly half of all the reports, 370 (44.4%), stated that the patient required revision surgery or other invasive interventions to address the reported adverse event. Swelling, fluid collections, osteolysis, pain/radiculopathy, heterotopic bone, pseudarthrosis, surgical site infections and other wound complications, thromboembolic events, respiratory distress, cancer, and other events were reported.

CONCLUSIONS: Because of their duration, scope, and expense, prospective studies designed to estimate the risk of rare adverse events may be impractical. Despite its imperfections, postmarketing surveillance helps to narrow the focus by revealing patterns and prioritizing topics for further research. One should not extrapolate from these results to the rhBMP-2 experience as a whole; the findings reported here might not be representative. This analysis indicates that 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. Published by Elsevier Inc.

Keywords: Bone morphogenetic protein; Adverse event; Off-label use; Postmarketing safety

Introduction

The US Food and Drug Administration (FDA) has evaluated recombinant human bone morphogenetic protein-2 (rhBMP-2; INFUSE Bone Graft; Medtronic Sofamor Danek USA, Inc., Memphis, TN, USA) under a premarket approval application and found reasonable assurance of safety and effectiveness for anterior spinal fusion procedures in skeletally mature patients with degenerative disc disease at one level from L2 to S1 [1,2]. The manufacturer's package insert includes warnings regarding the potential adverse effects during pregnancy and lactation, swelling and airway

FDA device/drug status: rhBMP-2 [INFUSE Bone Graft] is approved for some uses discussed in this article and not approved for others.

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compromise after anterior cervical fusion, the higher incidence of retrograde ejaculation after an anterior laparoscopic approach compared with an anterior open approach, posterior bone formation after posterior lumbar interbody fusion with cylindrical threaded cages, and nerve compression associated with ectopic bone formation [2]. The label further states, ''Inappropriate use of the product, such as preparing it differently than prescribed, compressing the rhBMP-2/absorbable collagen sponge (ACS) implant more than necessary, or overfilling the volume intended for new bone formation, may change the concentration of the rhBMP-2, which may inhibit the ability of the rhBMP-2/ACS to convert to bone and/or cause complications. Such use of the rhBMP-2/ACS implant may result in radiographic evidence of resorption, fluid formation, and/or edema. These findings may be asymptomatic or symptomatic'' [2]. The product is contraindicated in patients with a known hypersensitivity to rhBMP-2, bovine Type I collagen, or other components of the formulation; patients with any active malignancy or patients undergoing treatment for a malignancy; skeletally immature patients, pregnant women, and patients with an active infection at the operative site; and it should not be used in the vicinity of a resected or extant tumor [2].

Adverse effects of rhBMP-2 in spinal surgery have previously been reviewed [3–5] and include bone resorption, sometimes accompanied by cage migration or subsidence; local inflammation, dysphagia, and respiratory compromise; ectopic bone; axial pain and radiculitis; infections; and retrograde ejaculation. Frequencies reported in the literature vary substantially, with some estimates as low as 0% (no device-related adverse events) [6,7] and others as high as 27.5% for neck swelling [8] and 69% for bone resorption defects [9]. However, the true incidence of each complication after the various methods in which rhBMP-2 is used in spinal surgery is not known.

Adverse events reported to the FDA

The FDA's Manufacturer and User Facility Device Experience (MAUDE) database contains reports of the adverse events involving medical devices [10]. Health-care professionals and consumers can voluntarily report adverse events to MAUDE through the MedWatch system:

1. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
2. http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf
3. 1-800-332-1088

From July 2, 2002 to August 31, 2011, MAUDE received 1,035 reports of adverse events involving rhBMP-2. The vast majority, 844 (81.5%), concerned spinal surgery, with far smaller numbers for nonspinal orthopedic (59 reports), oral and maxillofacial (86), or unspecified operations (46). After duplicates were consolidated, 834 reports pertaining to spine surgery remained and were analyzed. The procedures included 514 lumbar operations (the vast majority, 427, were posterolateral, posterior, transforaminal, or lateral interbody fusion); 258 nonlumbar operations, including cervical, occipitocervical, cervicothoracic, thoracolumbar, thoracolumbosacral, and sacroiliac; and 62 spinal operations at unspecified levels. Four reports (0.5%) described procedures in which rhBMP-2 was used in accordance with the approved indication.

Table 1 summarizes the adverse events reported after the use of rhBMP-2 in spinal surgery.

What the results tell us

1. Identify new adverse events
2. Provide greater detail about previously observed events
3. Reveal unexpected patterns that might provide novel clues about risks
4. Data are most useful for *hypothesis generation* and not for *hypothesis testing*.

Strengths of postmarketing surveillance include the ability to detect adverse events that have not previously been documented and to provide descriptive information about events that have already been observed. In this analysis, many of the reports described severe complications that required specific intervention. For example:

1. Nearly half of the reports, 370 (44.4%), stated that the patient required revision surgery or other invasive interventions (eg, tracheostomy or aspiration of a cyst) to address the reported adverse event.
2. Osteolysis was more commonly reported after lumbar than nonlumbar procedures. More than one-third of lumbar cases reportedly required device explantation or other revision surgery because of resorption, compared with only one nonlumbar procedure.
3. Occasionally, heterotopic bone reportedly encroached on and adhered to transversalis, iliopsoas, or dura. For example, one report stated that a patient had experienced early satiety and had lost 18 kg over 6 months because of a sheet of intra-abdominal ectopic bone; the ectopic bone was surgically removed and did not recur.
4. There were three reports of genitourinary complications in men. One report described retrograde ejaculation, one mentioned sterility that reportedly resulted from an inflammatory reaction that injured the superior hypogastric plexus (without any comment about retrograde ejaculation), and one described azoospermia but explicitly stated that the patient did not appear to have retrograde ejaculation.
5. One patient was reportedly diagnosed with a spinal tumor. The location with respect to the site of rhBMP-2 application was not specified.

Table 1
Adverse events reported after the use of rhBMP-2 in spinal surgery

Principal adverse event*	Lumbar procedures (n=514)	Nonlumbar procedures (n=258)	Spine level(s) not specified (n=62)
Swelling/fluid collection	156	166	6
Osteolysis/bone resorption	73	11	15
Pain/radiculopathy	71	9	3
Heterotopic/exuberant bone	68	10	12
Pseudarthrosis	42	16	4
Surgical site infections/wound complications	29	11	15
Complications involving cage, implants, and/or instrumentation	7	2	
DVT/PE	7		
Respiratory distress/pulmonary complications	5	10	
Cardiovascular (excluding DVT/PE)	5	2	
Injury (excluding recurrent laryngeal nerve)	4	4	
Infection (excluding wound)	4	2	
Allergic reaction	4	1	
Cerebrospinal fluid leak/dural tear	4	1	
Fever	3		
Gastrointestinal	3		
Neurological	3		
Retrograde ejaculation/male sterility	3		
Cancer	2		3
Hemodynamic instability	2		
Rash	2		
Renal	2		
Injury to recurrent laryngeal nerve		5	
Other	7†	3‡	
Unspecified	8	5	4

rhBMP-2, recombinant human bone morphogenetic protein-2; DVT, deep vein thrombosis; PE, pulmonary embolism.

* For each report, the most important clinical entity was identified as the principal adverse event. If one condition appeared likely to have caused the others, then it was deemed the principal event. For example, if osteolysis led to pain and pseudarthrosis, then the adverse event was classified as "osteolysis." When multiple serious complications were reported in the same patient, the most immediately life-threatening one was selected as the principal adverse event (eg, respiratory distress necessitating intubation).

† Includes one report of each of the following: arachnoiditis, calcification of psoas, desmoplastic band, hepatic complication, osteoporosis (not osteolysis) of adjacent vertebral bodies, stenosis (not further specified), and weight loss.

‡ Includes one report of each of the following: dural fibrosis, pancreatitis, and syndrome of inappropriate antidiuretic hormone secretion.

6. During a thoracic spine procedure, a surgical resident inadvertently pushed an instrument through the ACS and into the pleural space. The reporting physician asserted that "BMP most likely got into the pleural cavity." The patient developed a pleural effusion that required surgical drainage.

Some of these events are not new and, indeed, are not unique to operations involving rhBMP-2. Nevertheless, this analysis demonstrates that some instances of these adverse events are unusually severe and striking in their presentation. Well-designed studies might elucidate the biological mechanisms of and risk factors for such complications, or—on the contrary—provide reliable evidence that they are not related to rhBMP-2.

What the results cannot tell us

1. Whether the product definitively caused any specific adverse event
2. Rates of adverse events
3. Comparison of complications observed in operations with and without the product

It is usually not possible to determine causal relationships between adverse events and devices or pharmaceuticals based on surveillance data; adverse experiences reported to MAUDE may be purely coincidental. Many might simply reflect risks of the operation itself (eg, injuries to the recurrent laryngeal nerve), surgical complications in general (eg, deep vein thrombosis), or patients' comorbidities (eg, cardiac disorders). As described in more detail in the following sections, it would not be appropriate to calculate risk ratios based on a comparison of these percentages to those reported in other publications. Moreover, even within MAUDE, if one compares reports of operations performed with and without rhBMP-2, the use of the product is not the only difference:

1. Procedures with and without rhBMP-2 can differ in many respects. A one-level anterior lumbar interbody fusion (ALIF) with rhBMP-2 is not comparable to a two-level transforaminal lumbar interbody fusion

(TLIF) with laminectomy chips and allograft. The former is also very different from total disc replacement, anterior cervical discectomy and fusion (ACDF), and long fusions for scoliosis.

2. Patients who receive rhBMP-2 may be different from those who do not. Some individuals might demand rhBMP-2 because they fear the pain of autogenous iliac crest bone graft (ICBG) harvest or because they have already failed two fusion procedures. Demographic and socioeconomic differences may also be present (eg, among uninsured patients, ICBG might be used more commonly than rhBMP-2).
3. Hospitals with high volumes of procedures involving rhBMP-2 may have more extensive resources (eg, interventional radiologists, vascular surgeons, and intensivists) than facilities that rarely perform such operations. This difference could affect the frequency, detection, and management of complications.
4. Surgeons who use rhBMP-2 may be different from those who do not. Some surgeons may preferentially use ICBG because they consider it the gold standard, while others may be more enthusiastic about using newer alternatives, such as rhBMP-2. The first group might be more conservative regarding operative techniques, selection of candidates, and the decision to perform surgery at all.
5. Information that is disseminated in peer-reviewed journals and at professional conferences can influence reporting. Articles or presentations that provide reassuring data may convince practitioners that reporting is unnecessary, whereas those that raise concerns may motivate them to report complications. Some events might be considered so commonplace, such as back pain after TLIF, that surgeons discern little benefit in reporting them unless prompted by concerned colleagues. Table 2 presents several of the many factors that can contribute to differential reporting of adverse events.

Thus, there could be numerous explanations for different reporting frequencies for adverse events after surgery with and without rhBMP-2. These differences do not invalidate the use of surveillance data or the reporting method per se. Rather, they emphasize that the numbers must be interpreted carefully and should not be confused with the results of a well-designed clinical trial. As stated previously, these data are most useful for generating hypotheses—not testing them.

Comment

On July 1, 2008, the FDA issued a public health notification [11] regarding swelling, airway compromise, and compression of neurological structures after the use of rhBMP in cervical fusion. The manufacturer's package insert [2] and previous publications [8,12] also describe these complications. Among the results presented here, one of the most striking is the continued reporting of these potentially life-threatening adverse events and the need for emergent intervention. Similarly, bone resorption [9,13–15] and heterotopic bone [14–18] have previously been observed after the use of rhBMP-2 in lumbar interbody fusion, and the package insert carries a warning about these potential complications [2]. Although randomized controlled trials of rhBMP-2 versus ICBG for posterolateral fusion [7,19] and ACDF [20], conducted under investigational device exemptions, did not reveal a statistically significant difference in device-related adverse events after procedures using rhBMP-2, Carragee et al. [3] have suggested that the risks may have been underestimated. Because most clinical trials are designed and powered to evaluate effectiveness (as opposed to complications), the absence of a statistically significant difference should not be interpreted as the proof that the risks are equal.

Lumbar degenerative disc disease is the only condition for which rhBMP-2 is indicated for use in the spine. Many MAUDE reports described either persistent low back pain or pain that resolved and then recurred after an operation involving rhBMP-2. In some cases, a seroma, hematoma, or other fluid collection in the vicinity of the operative site was thought to be responsible for the patient's pain, and conservative or surgical treatment led to resolution or reduction of the symptoms. However, other reports described no swelling or mass effect, and the pain may have been related to the underlying condition that the operation was intended to treat (ie, confounding by indication [21]) or to adjacent segment disease. Vertebral body resorption and loss of end plate integrity have been observed after the

Table 2
Differential reporting of adverse events

Less likely to be reported	More likely to be reported
Mild events (eg, leukocytosis in afebrile patient)	Catastrophic events (eg, airway compromise)
Common events (eg, nausea in early postoperative period)	Unusual events (eg, syndrome of inappropriate antidiuretic hormone secretion; Guillain-Barré syndrome)
Complications associated with general risks of surgery (eg, deep vein thrombosis)	Adverse events that surgeons have not observed in their previous experience (eg, sheet of intra-abdominal ectopic bone)
Events that were observed in clinical trials but were not considered to be device related	Complications that have been the subject of a major publication, professional conference, warning in the manufacturer's package insert [2], or safety notification (eg, life-threatening cervical edema [11])

use of rhBMP-2, particularly in TLIF [9,15]. If one presupposes that the end plates were incapable of maintaining a normal interface with the discs and supporting normal mechanics in the first place, thereby predisposing the patient to disc disruption and degeneration, then the ability to form a clinically satisfactory fusion might also be impaired. Interaction of rhBMP-2 with a pre-existing biological defect could have a deleterious effect in susceptible individuals. Because many patients have persistent or worsening back and leg pain after lumbar surgery, determining whether rhBMP-2 is contributing to those symptoms is difficult, if not impossible.

Rare adverse events (eg, retrograde ejaculation) and those occurring at locations that are remote from the surgical site (eg, malignancies) are particularly challenging to evaluate. Although an ongoing concern about retrograde ejaculation has recently been highlighted [22,23], the current review did not identify any de novo reports of this complication. The sole report was derived from the earlier publication [22]; the article stated that five patients had experienced retrograde ejaculation after ALIF with rhBMP-2, but a single report summarizing the publication was submitted to MAUDE. Similarly, imbalances in malignancies after AMPLIFY (rhBMP-2 Matrix 2.0 mg/mL; Medtronic Sofamor Danek USA, Inc.) compared with ICBG raised statistical concerns:

> … there were higher rates of cancer events with the use of the AMPLIFY product in the pivotal study, which were not contradicted by all of the pooled Medtronic trials using BMP-2. In addition, higher rates of malignancy were observed when considering all high-dose use of BMP-2. Therefore, this issue requires careful consideration and a cautious path forward [24]

as well as clinical ones:

> The difference in cancer serious adverse events is also a significant concern …. The types of cancer deaths noted in the AMPLIFY group are historically highly morbid cancers that occurred in patients who died relatively soon after being implanted with the device. This suggests the possibility of a synergistic effect of the device that could potentially accelerate pre-existing cancer growth [24].

At this time, only the concentration of 1.5 mg/mL rhBMP-2 is approved for use in spinal surgery in the United States [1,2]. Among the INFUSE reports in the MAUDE database, there were four reports of newly diagnosed cancer and one report of progression of pre-existing cancer after resection of a spinal tumor and a fusion procedure using rhBMP-2; the malignancies were not clustered in time or location. There are several possible explanations (Table 2) for such low reporting of retrograde ejaculation and malignancies: the events have not been widely observed; they have been observed, but surgeons do not believe that they are related to rhBMP-2; or surgeons are concerned about a possible causal relationship but are not aware of the reporting mechanisms (or do not use them).

MAUDE reports do not necessarily reflect a conclusion by the party submitting the report or by the FDA that the device caused or contributed to the adverse event [10]. MAUDE data are not intended to be used to evaluate rates of adverse events or to compare adverse event occurrence rates across devices [10]. It is not appropriate to compare the number of MAUDE reports to the number of adverse events in the clinical trials, nor to the frequencies of complications reported in the literature. Similarly, the results should not be used in conjunction with administrative data [25,26] to estimate the incidence rates of adverse events. Neither the number of individuals who have experienced adverse events related to rhBMP-2 is known nor the number of people who are at risk for such events. Although far more reports in this analysis described adverse events after posterior than anterior lumbar surgery, these findings should not be interpreted as evidence that adverse events are more common after posterior than anterior procedures. These limitations notwithstanding, surveillance data are useful, especially for detecting new and unexpected safety concerns. In the case of rhBMP-2, such information has led to an aforementioned safety alert [11] and changes in the manufacturer's package insert [27]. Postmarketing surveillance has proven to be valuable, insofar as it demonstrates the persistent occurrence of serious complications after ACDF with rhBMP-2, and presents opportunities for educational discussions by professional societies [28,29] to prevent these potentially catastrophic adverse events.

Because of their duration, scope, and expense, prospective studies designed to estimate the risk of rare adverse events may be impractical. Despite its imperfections, postmarketing surveillance helps to narrow the focus by revealing patterns and prioritizing topics for further research. However, one should not extrapolate from these results to the rhBMP-2 experience as a whole. In all likelihood, the findings reported here do not represent the range and frequency of adverse events observed by most practitioners after the use of rhBMP-2 in spinal procedures; there could be focused, inflated reporting (ie, making a mountain of a molehill) or, conversely, underreporting (ie, canary in a coal mine). To obtain more reliable estimates of the risks, other research methods must be applied. Adverse events for which the reporting rate is thought to be low can be evaluated with controlled epidemiologic methods [23]. The author encourages readers to interpret this summary in the context of their clinical experience, taking into account the totality of information available to them, including anatomical, mechanical, and technical considerations; pathophysiology and natural history; indication for surgery; patient characteristics; and alternative surgical approaches. This analysis indicates that 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.

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