

Review Article

A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned

Eugene J. Carragee, MD^{a,*}, Eric L. Hurwitz, DC, PhD^b, Bradley K. Weiner, MD^c

^aDepartment of Orthopedic Surgery, Stanford Medicine Outpatient Center, Stanford University School of Medicine, 450 Broadway, Mail Code 6342, Redwood City, CA 94063, USA

^bOffice of Public Health, University of Hawaii, 1960 East-West Rd, Honolulu, HI, USA

^cDepartment of Orthopaedic Surgery, The Methodist Hospital, 6565 Fannin St, Houston, TX, USA

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Abstract

BACKGROUND CONTEXT: Increasingly, reports of frequent and occasionally catastrophic complications associated with use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spinal fusion surgeries are being published. In the original peer review, industry-sponsored publications describing the use of rhBMP-2 in spinal fusion, adverse events of these types and frequency were either not reported at all or not reported to be associated with rhBMP-2 use. Some authors and investigators have suggested that these discrepancies were related to inadequate peer review and editorial oversight.

PURPOSE: To compare the conclusions regarding the safety and related efficacy published in the original rhBMP-2 industry-sponsored trials with subsequently available Food and Drug Administration (FDA) data summaries, follow-up publications, and administrative and organizational databases.

STUDY DESIGN: Systematic review.

METHODS: Results and conclusions from original industry-sponsored rhBMP-2 publications regarding safety and related efficacy were compared with available FDA data summaries, follow-up publications, and administrative and organizational database analyses.

RESULTS: There were 13 original industry-sponsored rhBMP-2 publications regarding safety and efficacy, including reports and analyses of 780 patients receiving rhBMP-2 within prospective controlled study protocols. No rhBMP-2-associated adverse events (0%) were reported in any of these studies (99% confidence interval of adverse event rate <0.5%). The study designs of the industry-sponsored rhBMP-2 trials for use in posterolateral fusions and posterior lateral interbody fusion were found to have potential methodological bias against the control group. The reported morbidity of iliac crest donor site pain was also found to have serious potential design bias. Comparative review of FDA documents and subsequent publications revealed originally unpublished adverse events and internal inconsistencies. From this review, we suggest an estimate of adverse events associated with rhBMP-2 use in spine fusion ranging from 10% to 50% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation were higher after using rhBMP-2 than controls. Posterior lumbar interbody fusion use was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects

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* Corresponding author. Department of Orthopedic Surgery, Stanford Medicine Outpatient Center, Stanford University School of Medicine, 450 Broadway, Mail Code 6342, Redwood City, CA 94063, USA. Tel.: (650) 721-7616; fax: (650) 721-3470.

E-mail address: carragee@stanford.edu (E.J. Carragee)

reported early back pain and leg pain adverse events; higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy.

CONCLUSIONS: Level I and Level II evidence from original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications. © 2011 Elsevier Inc. All rights reserved.

Keywords:

Critical review; rhBMP-2 trials; Spinal fusion; Safety concerns; Conflict of interest

Introduction

Spinal fusion techniques have historically used autogenous bone grafting, either from local or distant sources, to augment the local techniques used to stimulate fusion. For long spinal fusions or spinal fusions in adverse metabolic or local conditions, traditional techniques of bone grafting can prove inadequate. Accordingly, bone graft substitutes and enhancers have been developed over time to address these needs. One such bone graft substitute, recombinant human bone morphogenetic protein-2 (rhBMP-2), was introduced commercially in 2002.

There has been an appreciation in the more recent spine surgery literature that frequent and occasionally catastrophic complications are associated with the use of rhBMP-2 in spinal fusion surgeries. Adverse events of this sort were not reported as being associated with rhBMP-2 application in multiple early industry-sponsored trials published in peer-reviewed journals. This article critically reviews the evolving safety profile of rhBMP-2; beginning with the original industry-sponsored publications and progressing to later independent assessments of the product and by independent reassessment of publicly available trial data.

In addition to giving perspective to the specific morbidities of rhBMP-2, it is hoped that lessons can be learned from this era in spinal research and publication. Such lessons might prove valuable in the future, allowing us to better serve not only our community of researchers and clinicians but especially our patients who rely on the expeditious but safe introduction of new technologies in health care.

Summary of events leading to the current review

Multiple studies in the 1990s suggested that bone morphogenetic protein-2 (BMP-2) could cause bone induction in various animal models. There was uncertainty, however, regarding appropriate dosing, appropriate carriers, and safety, all of which appeared to be highly variable depending on the species of animal and location of BMP application [1].

When the use later began in humans, there seemed little doubt that bone induction would be possible; but proper dosing and possible adverse reactions with various applications remained uncertain. Preliminary human trials for lumbar fusion were published beginning in 2000 [2] and 2002 [3]. It was clear at the time that the nature and diversity of adverse events could not be well predicted given that rhBMP-2

appeared to be involved in a multiplicity of physiological and pathological events including, but not limited to, the inflammatory response, bone induction and resorption pathways, abnormal growth signaling pathways, certain malignancy pathways, and induction of an altered immune response [1,4]. Accordingly, in a 2002 review article, Poynton and Lane [4] wrote:

“Safety issues associated with the use of bone morphogenetic proteins in spine applications include the possibility of bony overgrowth, interaction with exposed dura, cancer risk, systemic toxicity, reproductive toxicity, immunogenicity, local toxicity, osteoclastic activation, and effects on distal organs.”

The results of several small and large industry-sponsored trials were subsequently published [2,3,5–11]. These reported the use of rhBMP-2 in larger numbers of patients undergoing a variety of spinal fusion techniques, including anterior interbody lumbar fusion (ALIF), posterolateral lumbar fusion (PLF), posterior lumbar interbody fusion (PLIF), and anterior cervical discectomy and fusion (ACDF) (Table 1).

Notably, with each new industry-sponsored trial publication, the safety findings were identical: no adverse events associated with rhBMP-2 were reported to be observed. Given that 780 patients received rhBMP-2 in these industry-sponsored publications and that not a single adverse event had been reported, the estimated risk of rhBMP-2 use could be calculated to be less than 0.5% with 99% certainty. That is, the reported risk of an adverse event with rhBMP 2, based on the industry-sponsored data, was less than one-fortieth the risk of a course of commonly used anti-inflammatory or antibiotic medications [12].

Although initially contemplated as an adjunct to spine arthrodesis to be used in particularly adverse clinical situations, a generalized use of rhBMP-2 was observed [13]. In the United States alone, the usage of BMP increased from 0.7% of all fusions in 2002 to 25% of all fusions in 2006, with 85% being used in single- or two-level fusions [14]. By 2007, more than 50% of primary ALIF, 43% of PLIF/transforaminal lumbar interbody fusion (TLIF), and 30% of PLF were reported to use rhBMP-2 [15]. It has been suggested [16] that, at least in part, the documented rapid increase in rhBMP-2 use in spinal surgery was related to the industry-sponsored trials, which reported virtually no

Table 1
Original industry-sponsored rhBMP-2 clinical studies and reported adverse event rates because of rhBMP-2

Authors	rhBMP-2 Placement	rhBMP-2, n	rhBMP-2 Adverse events (%)	Authors comment regarding rhBMP-2-related observed adverse events in study patients
Boden et al. [2]	Anterior interbody (LT-cage, lumbar, rhBMP-2)	11	0	“There were no adverse events related to the rhBMP-2 treatment”
Boden et al. [3]	Posterolateral (lumbar, ± instrumentation)	20	0	“There were no adverse effects directly related to the rhBMP-2...”
Burkus et al. [5]	Anterior interbody (LT-cage, lumbar, INFUSE)	143*	0	“There were no unanticipated device-related adverse events...”
Burkus et al. [6]	Anterior interbody (bone dowel, lumbar, INFUSE)	[24]‡	0	“There were no unanticipated adverse events related to the use of INFUSE Bone Graft.” (2002)
Burkus et al. [39]		79	0	None reported (2005)
Burkus et al. [40]	Anterior interbody (LT-cage, lumbar, INFUSE)	277	0	None reported
Baskin et al. [7]	Anterior interbody (cervical, INFUSE)	18	0	“There were no device-related adverse events”
Haid et al. [8]	Posterior interbody fusion (lumbar, INFUSE)	34	0	“No unanticipated device-related adverse events occurred”
Boakye et al. [41]	Anterior interbody (cervical, INFUSE)	24	0	“Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy.... a 100% fusion rate and nonsignificant morbidity”
Dimar et al. (2009)	Posterolateral (lumbar, INFUSE, pedicle screws)	53	0	None reported
Glassman et al. [42]	Posterolateral (lumbar, AMPLIFY, and pedicle screws)	[148]†	0	None reported
Dimar et al. [10]	Posterolateral (lumbar, AMPLIFY, and pedicle screws)	239	0	“No adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified”
Dawson et al. [11]	Posterolateral (lumbar, INFUSE, and pedicle screws)	25	0	None reported
Total	All types	780	0	99% CI <0.5% adverse event rate

rhBMP-2, recombinant human bone morphogenetic protein-2; CI, confidence interval.

* Report patients as in Burkus 2003, not included in total rhBMP-2 calculation.

† Possible subgroup of Dimar et al., 2009, not included in total rhBMP-2 calculation.

‡ These patient reported again in Burkus 2005.

complications associated with the use of these powerful biologic products.

In 2002, the United States Food and Drug Administration (FDA) approval was obtained for a single narrow method of spinal fusion: single-level ALIF within specific threaded cages (LT-cage, Medtronic Sofamor Danek, Inc., Memphis, TN, USA). However, over the last 10 years, numerous industry-sponsored articles on rhBMP-2 documented the use for a far wider range of spinal applications. Vaidya [13] summarized the impact of these subsequent publications:

“We have used it [rhBMP-2] in ways that were not originally approved by the FDA because we felt, if it works so well for one indication; why not try it for others. Many of us read early articles on off label use which showed the results were excellent in the c-spine and in PLIF or TLIF surgery.”

Simultaneously, industry-sponsored trials also reported high rates of complications associated with iliac crest bone graft (ICBG) harvesting; the common, practical, and gold standard alternative to rhBMP-2 in most settings. Thus, although complications associated with the rhBMP-2

product were rarely reported, these subsequent publications presented a 40% to 60% morbidity rate with ICBG harvesting [5,8,10].

Beginning in 2006, however, there would be a series of studies detailing serious complications associated with rhBMP-2 use in all settings. Adverse event rates ranged from 20% to 70% in some studies. In June 2008, the FDA issued a Public Health Notification [17] of life-threatening complications associated with rhBMP-2 use:

“These complications were associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurological structures in the neck. Some reports describe difficulty swallowing, breathing or speaking. Severe dysphagia following cervical spine fusion using rhBMP products has also been reported in the literature.... Most complications occurred between 2 and 14 days post-operatively with only a few events occurring prior to day 2. When airway complications occurred, medical intervention was frequently necessary. Treatments needed included respiratory support with intubation, anti-inflammatory medication, tracheotomy and most commonly second surgeries to drain the surgical site [17].”

Shortly after the government safety warning (November 2008), the Wall Street Journal wrote that the US Justice Department was investigating the rhBMP-2 manufacturer, Medtronic Inc. (Memphis, TN, USA), regarding off-label use of the product. The same article also reported three whistle-blower lawsuits seeking damages on behalf of the Federal Government by former Medtronic employees alleging illegal marketing by the company, including “inducements paid to doctors to use Infuse” [18,19]. The Justice Department investigation occurred concurrently with a US Senate Committee investigation into similar issues involving the rhBMP-2 product [18]. Further, a study on rhBMP-2 was retracted from publication by the *Journal of Bone and Joint Surgery [Br]* after allegations of research misconduct and possible fraud by a well-known spinal surgeon [20,21]. It was subsequently reported that the author of the retracted article had extensive, and possibly inappropriate, financial ties with the manufacturer of rhBMP-2 [22].

There has followed in the press an incendiary debate regarding the integrity of and safeguards within spinal research. The media has reported allegations of a wide range of improprieties, including concerns about possible fraudulent data and inappropriate editorial oversight of the rhBMP-2 studies’ publication [23–26].

These allegations, particularly the suggestion that this literature has lacked critical editorial oversight from the publishing medical journals, including *The Spine Journal* [24], led the current authors, including the Spine Journal Editor-in-Chief and both Deputy Editors for Evidence and Methods, to perform this systematic review and critical analysis. We reviewed the original peer-reviewed publications of rhBMP-2 trials along with publicly available FDA data and summaries of adverse events possibly associated with rhBMP-2 use for spinal fusion. By comparing these documents, we hoped to independently address whether there were any important omissions, discrepancies, or systematic bias in apparent reporting of possible adverse events between the original industry-sponsored peer-reviewed publications and other available data sources.

Methods

In collaboration with the Reference Desk Services at Stanford University School of Medicine’s Lane Library, we conducted a systematic search and critical review of the literature and associated public documents. The electronic library database MEDLINE was systematically searched for literature published from 1995 through 2010 on rhBMP-2 use in spinal surgery. The reference lists of relevant articles as well as primary evidence from government and administrative databases (eg, FDA, Centers for Disease Control and Prevention, and so on) from 2000 to early 2010 were systematically checked and, from these, additional references were added for review. Studies on primary rhBMP-2 use in nonspinal conditions, spinal fusion for

infections, major trauma, rheumatoid arthritis, and other inflammatory joint diseases or tumors were excluded.

From these peer-reviewed articles and associated government and administrative documents, a critical topic review was undertaken. The original industry-sponsored trials were identified and a compilation of adverse events associated with rhBMP2 as published in the peer-reviewed literature by the original authors were assessed (Table 1). The conclusions of these original industry-sponsored rhBMP-2 publications regarding safety and, to a limited extent, efficacy (as influenced by adverse effects) were then compared with available FDA data summaries, follow-up publications, and administrative and organizational database analyses. Although the FDA summaries [27–29] and Public Meeting Documents [30] appear to report on the same trials as appear in some of the peer-reviewed publications, it is not known to us if the authors of the industry-sponsored publications had available or reviewed those FDA summaries, data, or minutes before publication of the peer-reviewed publications.

Adverse events of interest

To avoid the methodological error of analyzing all possible adverse event associations, we confined the comparison of adverse events to those prospectively determined—given the known biology and pharmacology of the rhBMP-2 compound—as being suspect adverse effects before any large trial was reported. As reported by Poynton and Lane in 2002, these were the primary areas of concern:

1. Overgrowth and uncontrolled bone formation
2. Osteoclast activity (graft subsidence, migration, loss of fixation, and so on)
3. Local safety (inflammation, edema, wound problems, and infection)
4. Potential negative effects of BMPs on exposed dura and nerves (neurologic events, retrograde ejaculation (RE)/persistent bladder retention [with ALIF], early back pain, leg pain, radiculitis, and functional loss)
5. Carcinogenicity.

Examining only the prospectively identified, biologically and pharmacologically predicted events reduces the risk of a design error in which chance events are considered real effects simply by the number of possible events analyzed.

Sponsorship and author conflict of interest data

Industry support, financial relationships, and compensation have been identified as potential sources of bias in study design, performance, and publication [31,32]. *The Spine Journal* has required a uniform disclosure procedure, and this was retrospectively applied to all the original rhBMP-2 studies from previously published data provided by the original study authors in *The Spine Journal* [33,34], the Medtronic Physician Registry [35], and other public documents

[26,36]. Roseman et al. [37] have recommended that industry relationships from original publications be clearly presented in systematic reviews or meta-analysis of those studies. Accordingly, these industry sponsorship and author's financial relationships are listed per study in the Supplementary Appendix to provide consistent potential conflict of interest data across a range of studies from different journals.

Statistical analysis

Recommendations of the CONSORT group regarding methods for the reporting of harms associated with clinical trials have been detailed and were followed as the data permitted in this critical review [38]. Statistical analyses of original or comparative data were performed and in most cases conformed to the statistical method used or recommended by the original study authors in their publications (eg, if a one-tailed Fisher test was used in the original study to analyze categorical outcome events, this test was also used in the critical review). Confidence intervals (CIs) were calculated for adverse events in rhBMP-2 and control groups. If there was a compelling methodological reason to use an alternate analysis, these are explained in the text. A set statistical significance for adverse events was not used for reporting harms—after the recommendations of the CONSORT group [38]. Instead for serious or catastrophic events (eg, sterility, neurologic injury, and malignancy) 90% CIs are reported, whereas less serious events (eg, osteolysis without loss of fixation) are reported at a 95% CI. In calculating the maximum estimated adverse event rate from the original peer-reviewed publications, a 99% CI for less than one event in 780 subjects was used. Additionally, the number needed to harm (NNH) was computed to determine the number of patients treated with rhBMP-2 to produce one patient suffering harm because of a specific rhBMP-2-associated adverse event treated (eg, if the risk of a certain adverse event in the treatment group is 10% vs. 0% in the control group, the NNH is 10).

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Systematic review and comparison

The original industry-sponsored trials reported rhBMP-2 use in five primary methods of spinal fusion technique and location. Although there were a number of ancillary publications found with partial data sets, commentaries, and promotional material, there were 10 trials with more complete reporting of an identifiable cohort and outcomes. These were reported in 13 separate articles although some apparent

overlap in study subjects remained. The five study areas included (Table 1):

1. Anterior lumbar interbody fusion using the INFUSE Bone Graft preparation (Medtronic Sofamor Danek, Memphis, TN, USA), which is rhBMP-2 on an absorbable collagen sponge within anterior threaded LT cages (Medtronic Sofamor Danek) or threaded bone dowels with or without supplemental posterior fixation [2,5,6,39,40].
2. Posterolateral lumbar fusion using a lower dose rhBMP-2 or INFUSE/carrier preparation (Medtronic Sofamor Danek) and pedicle-screw and rod implant (Medtronic Sofamor Danek) [3,9,11].
3. Posterior lumbar interbody fusion with an INFUSE preparation and two-paired INTER FIX devices (Medtronic Sofamor Danek) [8].
4. Anterior cervical discectomy and interbody fusion using an INFUSE preparation and an anterior cervical plate (ATLANTIS; Medtronic Sofamor Danek) [7,41].
5. A higher dose rhBMP-2 preparation (AMPLIFY; Medtronic Sofamor Danek) with posterolateral lumbar fusion using Cotrel-Dubouset Horizon pedicle screws and rods (Medtronic Sofamor Danek) [10,42].

Disclosures and conflicts of interest

Each of the 10 original rhBMP-2 trials discussed in the following sections were funded in whole or in part by the rhBMP-2 manufacturer, Medtronic, Inc. Consistent with recommendations by Roseman et al. [37] and *The Spine Journal* disclosure policies, the Supplementary Appendix contains the industry sponsorship and financial disclosures for all 13 peer-reviewed articles and as a range of total compensation for all authors of each study [33–35].

As of March 2011, of the 13 original studies, there was one study with no information available regarding the authors financial relationship with the rhBMP-2 manufacturer. Of the remaining 12 studies, the median-known financial association between the authors and Medtronic Inc. was found to be approximately \$12,000,000–\$16,000,000 per study (range, \$560,000–\$23,500,000). For all studies reporting on more than 20 patients receiving rhBMP-2, one or more authors were found to have financial associations with the sponsor of more than \$1,000,000; for all studies reporting on more than 100 rhBMP-2 patients, one or more authors were found to have financial associations with the sponsor of more than \$10,000,000. See Supplementary Appendix.

Part 1: use of rhBMP-2 in PLF

Pilot study

Boden et al. [3], 2002, reported the first randomized controlled trial (RCT) of rhBMP-2 for PLF. This was a small

study with an instrumented ICBG arm (n=5), a noninstrumented rhBMP-2 arm (n=9), and an instrumented rhBMP-2 arm (n=11). The authors reported, “there were no complications attributable to the rhBMP-2/BCP.” There were no independent or FDA data sources available with which to compare these findings. However, the early relevant outcomes of the instrumented arms (ICBG vs. rhBMP-2) as reported by Boden et al. were compared. In assessing for local toxicity or neurotoxicity, the early functional outcome, leg pain, and infection rates were compared. The Boden et al. study, in our opinion, gave some indication of possible adverse events associated with rhBMP-2.

During the early period (when the morbidity of the ICBG harvesting should most adversely impact the control group and favor the rhBMP-2 group), it appears there was a strong paradoxical effect toward increased leg pain in the rhBMP-2 group (Fig. 1). Similarly, the early functional outcome (using the Oswestry Disability Index) was inferior in the rhBMP-2 group (64%; 90% CI: 12.5, 60.2; $p=.18$; Fisher exact test: NNH=2.4) despite the morbidity associated with bone graft harvesting. These data suggested, at an approximately 80% to 90% statistical confidence, that some adverse effect was occurring in the rhBMP-2 group and that this effect was of greater magnitude than bone graft harvesting morbidity. Such an effect might have been related to the known proinflammatory properties of rhBMP-2.

Because the numbers in this trial were small, it is difficult to make firm conclusions on the basis of these data; however, the findings were consistent with pretrial suspicions of possible rhBMP-2–related complications. The larger RCTs of rhBMP-2 formulations used in posterolateral fusions, involving more than 500 subjects (below), would demonstrate this as a consistent effect; there is greater back and leg pain adverse events during the early postoperative period in patients treated with rhBMP-2 compared with control patients exceeding the known expected morbidity of ICBG harvesting [27,32].

Regarding wound problems, in the pilot study by Boden et al. [3] also, there was a 10% rate of wound complications

(95% CI, 0–24%; NNH=10) associated with rhBMP-2 use—again suggesting a possible inflammatory effect of the rhBMP-2. This rate of wound complications was significantly higher than the same group’s published experience [43] with instrumented posterolateral fusion without rhBMP-2 ($p=.03$). Later estimates of wound complications in posterior fusion from the Scoliosis Research Society database would indicate an approximately 500% higher rate of both epidural hematoma and wound complications with rhBMP-2 use and a posterior approach [44].

Infuse/mastergraft RCT

Further industry-sponsored RCTs of rhBMP-2 use in posterolateral fusion included many more patients (Table 1), but subsequent authors again did not identify any complications or adverse events related to the rhBMP-2 use [9–11,42,45]. Again, however, both published and unpublished FDA [27] data suggest a consistent paradoxical effect of apparent rhBMP-2 morbidity in the early postoperative period, similar to that seen in the pilot study [3]. Although in each study, the authors hypothesized that there were serious and functionally impairing effects associated with harvesting ICBG, the clinical outcome scores for the rhBMP-2 groups were worse or no better than ICBG group at the 6- to 12-week postoperative time points in all industry-sponsored RCTs on PLF [46].

Dawson et al. [11], in 2009, reported no adverse events associated with rhBMP-2 in an RCT (n=46) of the INFUSE/MASTERGRAFT formulation compared with ICBG in posterolateral fusion. Food and Drug Administration documents published in 2008 [27], regarding the same trial, demonstrated nearly three times as many back and leg pain adverse events in the rhBMP-2 group (vs. controls) during the first 3 months (Fig. 2). At 3 months after surgery, 16% (90% CI: 3.9, 28.0) of the rhBMP-2 group was reported by the FDA documents to have had an adverse event involving back and leg pain compared with 4.8% of the control group (90% CI: –2.9, 12.4).

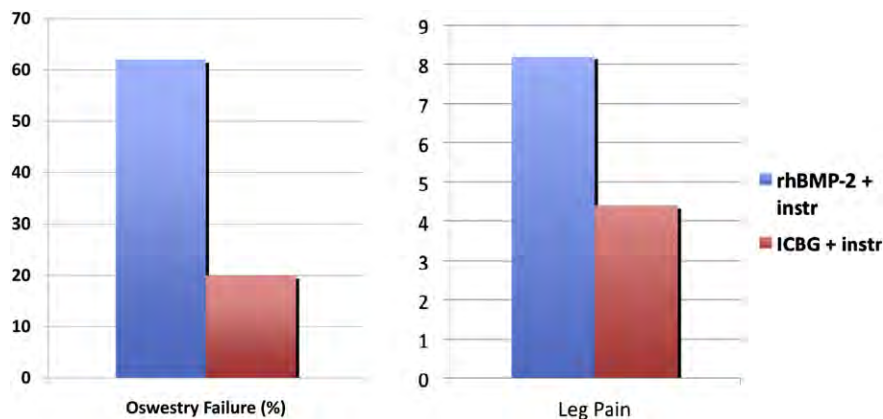


Fig. 1. Six-week postoperative data of early evidence of possible increased functional impairment and radiculitis after posterolateral fusion with recombinant human bone morphogenetic protein-2 (rhBMP-2) compared with control patients [2]. Leg pain is given on a 0 to 20 scale; that is, the leg pain intensity in rhBMP-2 patients was nearly twice that of the control patients.

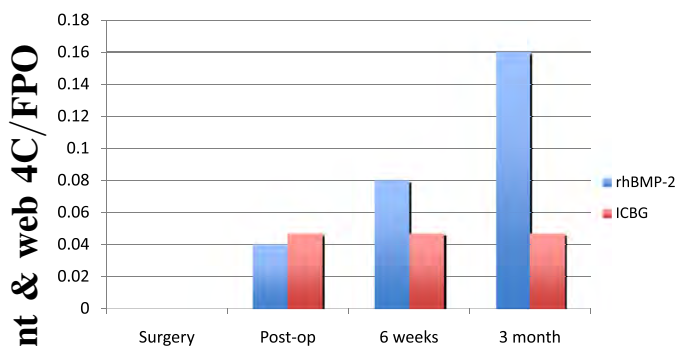


Fig. 2. Early adverse back and leg pain events adverse events (cumulative to the 3 months) after posterolateral fusion using recombinant human bone morphogenetic protein (rhBMP) (INFUSE Bone Graft MASTERCRAFT Granules) compared with iliac crest bone graft (ICBG). Expected outcome of study was less pain in the group without ICBG harvesting, instead paradoxical effect seen of greater back and leg pain morbidity with rhBMP-2 (rhBMP-2 16%, CI: 3.6, 28; ICBG 4.8, CI: -2.9, 12.4; Fisher exact $p=.13$).

These findings, from more than one RCT, suggest that rhBMP-2 causes equivalent or greater pain and functional impairment than ICBG harvesting in the early postoperative period (strong, Level 1 evidence). This observation was not discussed in any of the published studies despite being evident across multiple RCTs including (and to a larger degree) in the findings of the later higher dose rhBMP-2 study on AMPLIFY [27].

Part 2: use of rhBMP-2 in ALIF

There were five industry-sponsored peer-reviewed publications available on the use of rhBMP-2 in ALIF trials. In the pilot study, Boden et al. [2] reported, “there were no adverse effects directly related to the rhBMP-2...” In 2004, summarizing further industry-sponsored trials of rhBMP-2 use with ALIF, Burkus reported:

“I have reported the clinical and radiographic results of three different interbody constructs in a single-level, stand-alone ALIF derived from several prospective multicenter studies....There were no adverse events due to rhBMP-2 [47].”

However, careful review of FDA data and subsequent documentation of the largest of these trials suggests osteolysis, subsidence, and adverse neurologic and urologic events were all more commonly seen with rhBMP-2 use.

Osteolysis, subsidence, and reoperation

Smoljanovic and Pecina [48] had noted that abnormal radiographic findings (end-plate resorption, osteolysis, and subsidence) were apparent in the original radiographs (Fig. 3) from the industry-supported RCT publication by Burkus et al. [6] reporting on rhBMP-2 use with bone dowels. That is, the radiograph presented as a model outcome depicts a loss of stability, collapse of the disc space by 50%, and large osteolytic cystic lesions—some extending 50% of the vertebral height. These findings were not commented on/recognized by the authors in the original publication [6]. In a follow-up publication in 2005, Burkus et al. [39] reported on a larger cohort of patients treated with ALIF and bone dowels and again reported no complications, such as end-plate fracture, collapse, and implant migration associated with rhBMP-2 despite the clear radiographic findings in at least the one presented case.

As reported by Burkus in 2004, industry-sponsored trials of ALIF with rhBMP-2 published from 2002 to 2004 found no adverse events associated with its use. However, FDA documents available as early as 2002 had already suggested that some of these findings were evident with those ALIF cases submitted to the FDA during the regulatory evaluation process. The FDA publication “Summary of Safety and Effectiveness Data” [28] concluded the following from the original data:

“The incidence of adverse events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational [rhBMP-2] groups compared to the control group [28].”

This effect was later corroborated in a 2007 nonindustry supported prospective cohort study of rhBMP-2 use in ALIF that found 70% (14 of 20) of levels showed signs of early lucency and more than 10% graft subsidence with a mean collapse of 27% [49]. Another study, this time

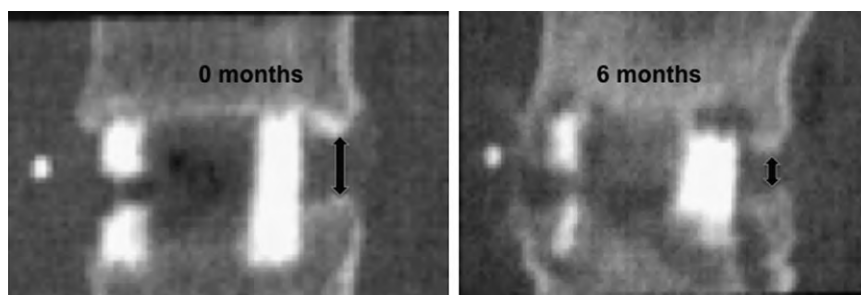


Fig. 3. Computed tomography reconstructions from Burkus et al., showing implant subsidence, disc space collapse (black arrows, 40%), and wide osteolysis (white arrows) with cyst formation extending caudally and around the implanted bone dowel. (From Burkus et al. Spine 2002;27:2396–408, [6], used with permission of publisher; dates and arrows added).

a cohort controlled design, also found greater subsidence and need for reoperation in patients with rhBMP-2 use in an interbody fusion compared with allograft alone [50]. In that study, serial radiographs showed a greater rate of graft subsidence (more than 5 mm) and end-plate failure in the BMP group, all occurring within the first 4 months after surgery. The reoperation rate was higher in the rhBMP-2 group because of revision of graft subsidence complications. These data, again, suggest a clinically important early inflammatory and osteoclastic effect of the rhBMP-2 in soft tissue and bone, respectively.

In a later publication (2009) by the original study group, Burkus et al. [51] appear to contradict the safety conclusions of that group published earlier in 2002 to 2004 [5,6,40,47]. Specifically, a 6-year follow-up study published in 2009 reported again on the original 277-patient cohort discussed above [40]. Here the authors parenthetically reported that there had been seven (2.5%; 90% CI: 0.98, 4.8) early adverse events associated with subsidence in the rhBMP-2 group; but these adverse events were not reported in the original 2-year follow-up study [40]. Subsidence is not at all reported in the 2003 study. Table 2 shows the differences in complication rates reported in the original Burkus et al. study of 2003, the later report by Burkus et al. in 2009, and the original FDA documents available in 2002 [28,40,51].

That is, the authors, in the original 2-year follow-up industry-sponsored publication [40] and summary publication [47], did not report any subsidence or any other specific device-related adverse events; but at 6-year follow-up, more events were reported—and, incongruously, all events were reported to have occurred within the first 2 years [51]. Four of these adverse subsidence events required additional surgery. In fact, 22 additional surgeries for device failure events occurred in the same rhBMP-2 group between 0 and 2 years after surgery according to the FDA summary [28] but were not specifically reported in 2003 or 2004, which were

the same patients over the same time frame. The FDA data [28] reports more complications than either the 2003 or 2009 publications by Burkus et al. [40,51].

Retrograde ejaculation

In the publication of the RCT of ALIF comparing rhBMP-2 against ICBG using the LT-cage, Burkus et al. [5] reported an overall rate of RE of 4.1%. The authors did not report comparative rates of RE in the rhBMP-2 group, nor was this compared with the control arm as was done for other complications. That is, although other complications were reported independently for rhBMP-2 patients and compared with the ICBG patients, the rate of RE was given for the entire cohort without comparison between the two primary study arms.

However, reviewing the same cohort the 2002 FDA Summary of Safety and Effectiveness Data for the use of rhBMP-2 with the LT-cage [28], Smoljanovic et al. [52] noted a higher rate of RE associated with rhBMP-2 use (7.9% rhBMP-2 group, 90% CI: 4.1, 11.6; vs. 1.4% ICBG group, 90% CI: -0.9, 3.8), overall NNH=15, Fisher exact $p=.05$. This association was not reported in the publication of outcomes from this trial by Burkus et al. in 2002 [5], 2003 [40], 2004 [47], and more recently in 2009 [51].

Later, in response to a Letter to the Editor inquiry, Burkus et al. denied any potential association of this complication RE with the use of rhBMP-2 [52]. They felt that the laparoscopic or transperitoneal approach used in some nonrandomized patients in the LT-cage/rhBMP-2 trial accounted for the excess rate of RE observed with rhBMP-2. However, data reported in FDA documents [28] and further publications [52] confirm that the rate of RE was only slightly higher with laparoscopic insertion of rhBMP-2 containing cages (6 of 62, 9.7% compared with 7.9% in the entire rhBMP-2 group).

Table 2

Failure to report possible rhBMP-2 associated adverse events, complications, and reoperations that occurred during the first 2 years after surgery in the same patient cohorts undergoing ALIF with LT-cage as reported by Burkus et al. in 2003, Burkus et al. in 2009, and the FDA Summary of Safety and Effectiveness

Adverse events type	Adverse events reported by Burkus et al. in 2003 and Burkus et al. in 2004	Adverse events reported by Burkus et al. in 2009	Adverse events reported by FDA in 2002
rhBMP-2 Patients (n)	277	277	277
Early infections (<2 mo)	None reported	None reported	26
Delayed infection (2–12 mo)	None reported	None reported	12
Implant malposition, displacement, and loosening (<3 mo)	None reported	9 (3 required reoperation)	10
Subsidence	None reported	7* (4 required reoperation)	7
Reoperation for device-related adverse event	None reported	7	22 [†]
RE	Not reported [‡]	None reported [‡]	12 [‡] (7.9%)
Other urogenital AE (mainly retention)	None reported	None reported	36

RE, retrograde ejaculation; AE, adverse event.

* In 2009, seven subsidence events were reported within 6 months of the index surgery, four required reoperation.

[†] Twenty-two of 30 reoperations considered an adverse event related to device “failure” [28,29].

[‡] Twelve events in eleven patients of 140 males from the Burkus et al. rhBMP-2 group, one of 70 males in the control.

Further, the highest level of evidence from the RCT comparing the open use of rhBMP-2 versus autograft (ie, not laparoscopic), observed higher RE rates in male patients receiving rhBMP-2, 6.4% (5 of 78, 90% CI: 1.9, 11.0) than those receiving ICBG 1.4% (1 of 68, 90% CI: -0.9, 3.9; NNH=20, $p=.14$). In both groups, the approach was retroperitoneal in the large majority of cases; the rate of transperitoneal approach was in fact slightly higher in the control group, which had less RE. That is, the rhBMP-2 group had more RE despite a slightly lower rate of transperitoneal approaches. Unfortunately, this finding was not published until 7 years after the original publications [5,6,40], and 8 years after FDA approval of this rhBMP-2 use in ALIF with the LT-cage [28].

Corroborating the finding of an approximately 6% to 7% rate of RE found with ALIF using rhBMP-2, Jarrett et al. [53] reported a 6.4% RE rate (90% CI: 2.5, 10.2) after anterior lumbar surgery, 98% of which used rhBMP-2. However, in ALIF surgery without rhBMP-2, Kang et al. [54], Sasso et al. 2004 [55], and Sasso et al. 2005 [56] reported an RE rate of less than 1% in nearly 1,000 patients, including those followed by FDA protocols. Similarly, Carragee et al. reported a retrospective cohort-controlled study of RE events after lower lumbar ALIF, using an open retroperitoneal approach by a single surgeon [57]. The findings were nearly identical to the eventually disclosed data of Burkus et al.: a 7.2% (90% CI: 2.1, 12.4) RE rate in the rhBMP-2 ALIF patients ($n=69$) compared with a 0.6% (90% CI: -0.4, 1.5) rate in non-rhBMP-2 patients ($n=174$). These findings of Carragee et al. were highly significant statistically, indicating a strong association of rhBMP-2 with RE events (Fisher exact test, $p=.0025$) with a risk ratio of 12.6 and a calculated NNH of 15 (Fig. 4).

In summary, multiple independent studies have found that the rate of RE in ALIF with rhBMP-2 is approximately 5% to 7% and possibly two to four times higher than the rate observed without rhBMP-2. These findings were consistent across multiple studies and designs, including an RCT [28,52], a cohort controlled trial [57], and large observation cohort with more than 1000 patients [52,54].

Urogenital/bladder retention

Other adverse early urogenital events were also more frequently reported in the rhBMP-2 group after ALIF by FDA Summary of Safety and Effectiveness Data: 7.9% of rhBMP-2 (90% CI: 5.4–10.6) compared with 3.6% of control subjects (90% CI: 1.0, 6.2) and was statistically significant at $p=.04$ by chi-square test. Although these adverse events (mainly urinary retention after surgery) were documented in the FDA records as associated with rhBMP-2 (Fig. 5), this finding was not reported by the original study authors in their multiple publications: 2002 [5], 2003 [40], 2004 [47], and 2009 [51].

Infections

A “high” infection rate (39 infections in 35 of 288 rhBMP-2 patients, 12.2%) was reported in the FDA Summary of Safety and Effectiveness in the rhBMP-2 group of the FDA trial [44]. This finding was not reported in any of the publications by Burkus et al. [5,40,47,51].

Food and Drug Administration documents [28] indicate that early infections (less than 6 weeks postoperatively) were equivalent in rhBMP-2 (9.4%) and ICBG (9.4%) groups. However, delayed infections in the first year after surgery were much more common in patients treated with

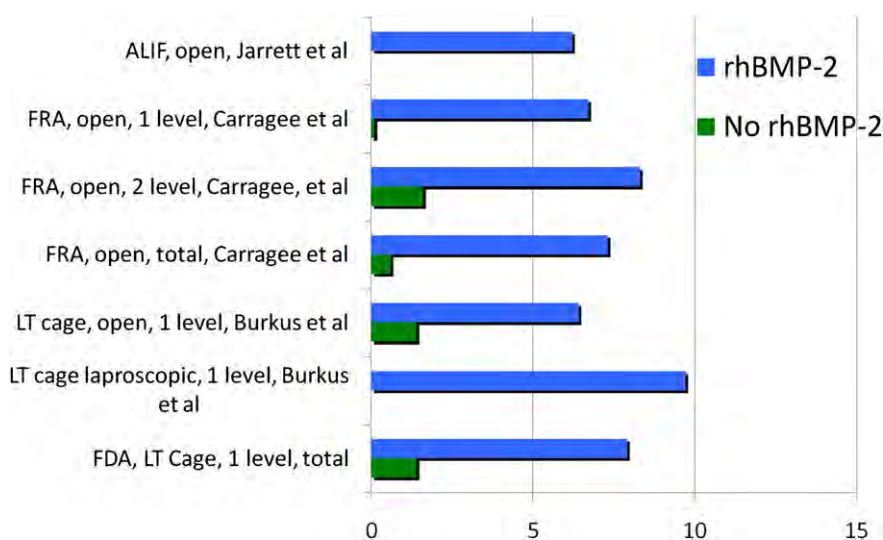


Fig. 4. Comparison of retrograde ejaculation rates (percent) in male patients after anterior interbody lumbar fusion (ALIF) from three studies: ALIF with recombinant human bone morphogenetic protein-2 (rhBMP-2) by Jarrett; femoral ring allograft/rhBMP-2 versus control group (single level and two levels) by Carragee et al., LT-cage/rhBMP-2 versus control (open) group, LT-cage/rhBMP-2 (laparoscopic) group by Burkus et al., and Food and Drug Administration data LT-cage versus control, total cases. See citations in text [28,52,53,57].

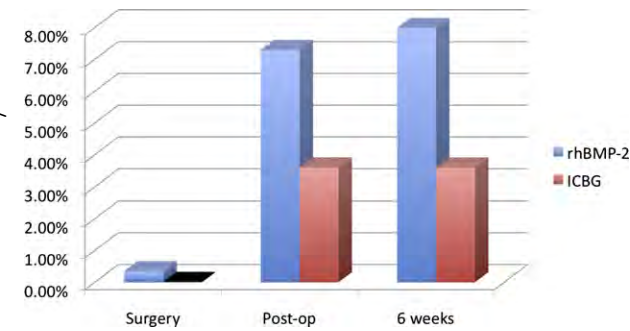


Fig. 5. Cumulative proportion of subjects' urogenital (mainly urinary retention) adverse events after anterior interbody lumbar fusion with LT-cage using rhBMP-2 (INFUSE formulation) versus iliac crest bone graft (ICBG). At 6 weeks rate of this adverse event: recombinant human bone morphogenetic protein-2, 7.9%; 90% CI: 5.4–10.6; ICBG, 3.6%; 90% CI: 1.0–6.2; $p=0.04$ by chi-square test.

rhBMP-2 (12 patients; 4.2%; 90% CI: 2.2, 6.1) compared with the ICBG group (2 patients, 1.4%; 90% CI: -0.02 to 3.1); a threefold difference (chi-square $p=.07$).

Subsequent work from the Scoliosis Research Society has similarly found more frequent deep wound infections in anterior/posterior surgery performed using rhBMP-2 than without. Similar to the FDA data, this was a five times greater rate of infection and highly significant ($p=.001$) [44].

Part 3: use of rhBMP-2 in PLIF

Haid et al. [8] reported an incomplete industry-sponsored RCT comparing PLIF using rhBMP-2 with an ICBG control. These authors reported, “no unanticipated device-related adverse events occurred.” They also reported that no patient required reoperation because of an rhBMP-2 adverse event. They concluded that the study “confirmed the safety” of rhBMP-2 and suggested that the findings might “eliminate the need” for autograft for “successful PLIF.” With this presumption of safety, based on 34 study subjects, PLIF and TLIF rapidly became a popular use of rhBMP-2 in the United States: in 2007, 40% to 50% of PLIF/TLIF procedures used rhBMP [15]. On close review, however, several important observations emerge, which were not part of the authors' conclusions.

Bone overgrowth into the spinal canal in the rhBMP-2 group after PLIF

This trial was peremptorily discontinued because of bony overgrowth at the anulotomy site. Computed tomography scan evaluation found new bone formation into the spinal canal or neuroforamina in 24 of 32 rhBMP-2 patients (70.1%; 95% CI: 55.27, 85.91) as compared with four of 31 control patients (12.9%; 95% CI: 11.1, 24.7; NNH=1.6; $p=.0001$). Although the authors stated that these findings were not associated with adverse outcomes, the curtailed study was not powered to rule out that effect.

Clinical failures in rhBMP-2 group after PLIF

Contrary to expectation, there appeared to be little or no clear clinical advantage in using the rhBMP-2 when compared with ICBG control despite the early morbidity of bone graft harvesting in the control group. At 6 weeks after surgery, there was a 63% greater improvement in the Oswestry score in the ICBG group versus the rhBMP-2 group. Similarly, the global outcomes data at 2 years showed patients were less satisfied with the surgery when BMP was used (Table 3, Fig. 6). The rhBMP-2 group appeared to have more bothersome symptoms, more functional impairment, and less satisfaction (perhaps on an inflammatory basis) than the ICBG group.

The failure to demonstrate clear advantage in the rhBMP-2 group is further complicated by the use of ICBG as the control group. It is now common practice not to use any ICBG in PLIF and TLIF surgeries, but rather to reuse the local bone graft removed to afford access to the disc. Therefore, the Haid et al. data may underestimate the rhBMP-2 relative morbidity compared with local bone graft usage [58–60].

Reoperation in the rhBMP-2 group after PLIF

A surgeon, Dr David G. Malone of Oklahoma, involved in the FDA study reported to the FDA Public Meeting of 2002 that in the experience of his small group with the rhBMP-2/PLIF trial:

“two of the [INFUSE] patients had significant posterior bony over-growth impinging on their nerve roots requiring additional surgery. One patient, who was

Table 3
Global outcomes of patients randomized to undergo PLIF with rhBMP-2 compared with ICBG

	Number	Percent	90% CI
Dissatisfied with surgery			
BMP (n=29)	5	17.24	5.5, 28.8
ICBG (n=30)	1	3.33	$-3.0, 9.5$
Difference		13.91	1.1, 27.6
Surgery did help as much as expected			
BMP (n=29)	5	17.24	5.5, 28.8
ICBG (n=30)	1	3.33	$-3.0, 9.5$
Difference		13.91	1.1, 27.6
Would have surgery again			
BMP (n=29)	20	68.97	54.8, 83.1
ICBG (n=30)	25	83.33	72.1, 94.5
Difference		-14.37	$-32.4, 3.66$

rhBMP-2, recombinant human bone morphogenetic protein-2; PLIF, posterior lumbar interbody fusion; BMP, bone morphogenetic protein; ICBG, iliac crest bone graft.

In all three dimensions measured, the outcomes were perceived as more positive in the ICBG.

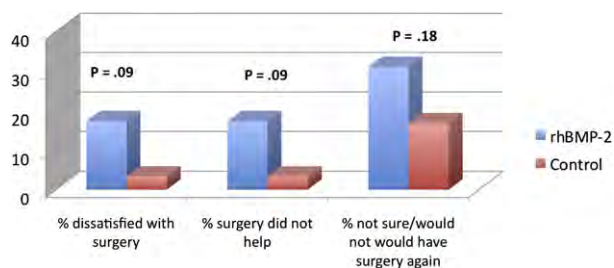


Fig. 6. Patient reported outcomes after posterior lumbar interbody fusion with and without rhBMP-2 from Haid et al. [8]. This industry-supported trial was discontinued with less than 50% enrollment limiting statistical power.

my patient, required two surgeries to clear excessive bone growth from his spinal canal [30].”

This observation was documented in the FDA record years before the Haid et al. study had been published, but these complications were not included in the authors’ comments on unanticipated adverse events related to rhBMP-2 in PLIF surgery [8].

It was Dr Malone’s opinion expressed to the FDA 2 years before the Haid et al. publication that “BMP may lead to excessive bone growth and may cause significant neural impingement if placed in posterior lumbar interbody type of device.” The major adverse events in Dr Malone’s patients resulting in reoperation were not included in the Haid et al. article.

Shortly after that Haid et al. publication, when off-label use of rhBMP-2 in PLIF surgery had begun, Wong et al. [61] reported on five patients with ectopic bone formation in the spinal canal after either PLIF or TLIF using rhBMP-2. These patients reported neurological complaints, and three patients underwent an extensive and “difficult” revision surgery [61]. Since then, more reports of serious adverse events associated with rhBMP-2 use in this setting have followed.

Radiculitis, osteolysis, and loss of alignment after PLIF using rhBMP-2

Adverse events associated with rhBMP-2 in PLIF or TLIF are now commonly recognized and are reported to

occur in most patients, including osteolysis and end-plate resorption, increased rates of radiculitis or root injury, cage displacement, subsidence, wound infection, ectopic bone formation, and others [49,62–64]. The most common complications—postoperative radiculitis and osteolysis—have been reported to occur in between 20% and 70% of cases. Others have reported higher rates of subsidence when rhBMP-2 is used compared with other graft methods [49].

Recent close follow-up of the osteolytic defects associated with rhBMP-2 has shown that these findings are common and may result in massive bone loss and relative kyphosis because of collapse (see figures in Hegleson et al. [65] and Knox et al. [66]). Importantly, these defects have been shown to persist in most patients. Hegleson et al. reported that the incidence at 3 to 6 months was 56%; and 76% of these failed to resolve at long-term follow-up [57]. Subsidence of the anterior cage results in a loss of lordosis and relative flat back [66]; a problem associated with poorer outcomes and accelerated superior segment degeneration. At present, several investigators are exploring strategies to limit these complications of the use of rhBMP-2 in PLIF and TLIF approaches. Alternative technical methods (including atraumatic end-plate preparation, applying a sealant to the anulotomy site, and varying the dosage of rhBMP-2) have been suggested [51,54,57,58]; but none, thus far, has proven to be fully successful.

These frequent adverse events might help explain the finding in the original Haid et al. study that more patients in the rhBMP-2 group felt the surgery had not helped and were dissatisfied with the surgery (see Fig. 6).

Part 4: use of rhBMP-2 in anterior cervical interbody fusion

An initial small industry-sponsored RCT of rhBMP-2 in the cervical spine reported no adverse events and, specifically, none associated with the use of rhBMP-2 [58] (Table 4). Boakye et al. in 2005 similarly reported no swelling or wound complications, no reoperations, and no readmissions [41]. Some authors have stated that it was these reported findings coupled with the “perfect” [16] reports from use in other locations that led to more common use

Table 4
Late recognition and reporting of complications associated with rhBMP-2 use in the cervical spine

	Baskin et al. [7]	Boakye et al. [41]	Smucker et al. [70]	Tumialán and Rodts [71]
Patient number (n)	18	24	69	176
Dose per level	0.6 mg	2.1 mg	1.5 mg/ml	0.7–1.05
Dysphagia, n (%)	0	2 (11)	5 (7.2) “severe”	12 (7)
Required PEG placement, n (%)	0	0	1 (1.5)	4 (2)
Readmission, n (%)	0	0	2 (3)	3 (2)
Wound complication, n (%)	0	0	3 (4)	5 (3)
Early reoperation, n (%)	0	0	5 (7)	4 (2)

rhBMP-2, recombinant human bone morphogenetic protein-2; PEG, percutaneous endoscopic gastrostomy.

Although life-threatening events associated with rhBMP-2 use have been reported by the FDA, a precise estimate of excess mortality is not currently available to the public.

in the cervical spine: 13% of all rhBMP-2 use by 2006 and 18% to 20% of all ACDF surgery in 2007 [14,15].

FDA notification of life-threatening complications

In 2008, the Centers for Disease Control and Prevention and the FDA issued a Public Health Notification: “Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine.” [17] This Notification followed a number of independent reports specifically noting significant complications when using rhBMP-2 in the cervical spine [67,68]. These included reports of high rates of wound problems, soft-tissue swelling, airway compromise, graft subsidence, and end-plate erosion [49,63,67–70].

Precise data regarding numbers or rate of catastrophic complications and mortality are not publicly available. However, Smucker et al. [70] reported a 27.5% rate of “clinically significant” cervical swelling, which was statistically more frequent than control subjects ($p < .0001$). Even after controlling for confounding variables, there remained a 10.1-fold risk of this adverse event with rhBMP-2 use. Two percent of one author’s rhBMP-2 patients required percutaneous endoscopic gastrostomy feeding tube placement because of wound and throat complications impairing nutrition for prolonged periods [71]. Tumialán and Rodts [71] reported a 2% readmission rate and 2% early reoperation when using rhBMP-2, even at a reduced dosage. These figures were similar to Smucker et al., who reported at 1.5% rate of percutaneous endoscopic gastrostomy feeding, 3% reintubation, 4% emergency incision, drainage and decompression of the prevertebral space, and 12% prolonged hospitalization.

Cahill et al. reviewing the National Inpatient Database for acute inpatient complications estimated the adjusted risk of complications to be approximately 40% to 50% higher with the use of rhBMP-2 in anterior cervical fusion than without it. The primary increased events were wound complications, hoarseness, and dysphagia [14].

Osteolysis and loss of alignment

Klimo and Peele [72] reported a 57% moderate or severe osteolysis rate and end-plate resorption with implant migration and loss of sagittal alignment with the use of rhBMP-2 in cervical interbody fusion.

Adverse effects of rhBMP-2 associated with spinal cord injury

Unresolved concerns about the use of rhBMP-2 in the setting of spinal cord injury (and possibly myelopathy) remain—rhBMP-2 appears when penetrating the intradural space appears to adversely impact damaged central nervous system tissue in animal models [73].

Part 5: high-dose rhBMP-2 for posterolateral fusion

The most recently introduced rhBMP-2 preparation proposed for use in the spine is AMPLIFY. This is an rhBMP-2 product with a different carrier and a tripled dose of growth factor (40 mg rhBMP-2 per level) meant for use in posterolateral fusion of the lumbar spine.

The industry-sponsored publication by Dimar et al. [10] compared an RCT of AMPLIFY against an ICBG fusion group similar to that used in previous rhBMP-2 trials of posterolateral fusion (wherein the control included no routine facet fusion, allowed small bone graft volumes, and local bone graft was discarded) [46]. As in previous industry-sponsored trials of this product, the authors reported, “no adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified.”

Early back and leg pain morbidity with AMPLIFY exceeds ICBG harvesting

There was no apparent advantage gained from avoiding ICBG harvesting in the first 3 months after surgery given nearly identical back pain, leg pain, and functional outcome scores. This suggests an equivalent morbidity of rhBMP-2 when compared with the bone graft harvesting procedure it is meant to replace [46].

Furthermore, the FDA Executive Summary of this trial published in 2010 [29] identified several classes of serious adverse events, which appeared to be associated with AMPLIFY use but were not reported as such by the Dimar et al. in publication. The summary noted that major back pain and leg pain adverse events, especially early after surgery, were significantly higher in the group receiving rhBMP-2 (Fig. 7, Table 5). There were more than twice as many back and leg pain complications in the AMPLIFY group at both 4 and 8 weeks after surgery (chi-square test $p = .03$). This would represent a complication rate in approximately 12% to 15% of rhBMP-2 patients; more than twice the rate documented in the control group ($NNH < 15$).

Increased risk of malignancy with AMPLIFY

Of additional concern, the FDA found “notably increased cancer rates in the AMPLIFY group.” [29] Using the higher dose of rhBMP-2 in AMPLIFY, nine new cancers were diagnosed in 239 subjects; a 3.8% rate (90% CI: 1.7, 5.8) incidence of new malignancy compared with two new malignancies in 224 subjects (0.89%; 90% CI: –0.14, 1.92) in controls ($NNH < 33$, $p = .05$ to 0.1 depending on the statistical analysis), meaning that there is an approximately 90% to 95% probability that this is a real association. This finding was not mentioned in the Discussion section by the authors [10], however, of the 68 pages in the FDA Executive Summary, 15 pages were devoted to the analysis and discussion of the increased cancer issue alone [29].

Part 6: possible study design biases against the control groups

The study designs were examined to consider the possibility of design bias suggested by the media and other observers [23,24,46,78]. We considered whether the choice of fusion technique and ICBG morbidity assessment used in the control groups might have impacted the apparent competitiveness of rhBMP-2 fusion.

Control group technique in the PLF group

The biology of fusion promotion by rhBMP-2 and ICBG is inherently different. The rhBMP-2 product is known to work through bone induction in a variety of tissues and can be anticipated to perform well in a muscle bed, as would be the case of lateral intertransverse process fusion. In contrast, ICBG or other autogenous bone graft acts best locally, where the graft can be contained and packed, to bridge short distances between viable bones, such as a facet fusion. The basic techniques of posterolateral fusion [79,80] and posterolateral fusion with transpedicular fixation [81–83] as originally described include meticulous de-cortication of the bone surfaces and preparation of the facets. Curettage of the facets, removal of articular cartilage, and impaction of bone graft into the decorticated facet joint are fundamental parts of posterolateral fusion using autologous bone [83], although it may be less important with a primarily osteoinductive agent such as rhBMP-2.

The randomized trials comparing rhBMP-2 with ICBG in posterolateral fusion did not include facet preparation as part of the required surgical protocol but, instead, focused on the intertransverse process fusion. Specifically, the study authors indicate, “fusion of the facet joint was not specifically required by the protocol” [84]. Similarly, when evaluating the fusion radiologically, “the facet joints were not specifically evaluated for the presence of fusion” [84]. As a result, the study design may have biased the clinical outcomes against the ICBG group.

Similarly, the reported rate of radiographic fusion was based on “the presence of bilateral, continuous trabeculated bone connecting the transverse processes.” [84] A solid facet fusion alone, often a primary intention of posterolateral fusion when autogenous bone is used, would not be reported as a solid fusion by study protocol.

The study protocols also allowed very small quantities of ICBG to be used as the sole grafting source. The studies indicate that ICBG volumes of as little as 7 cc were used in the control group [10]. At the same time, the local bone graft, which is readily harvested in during the surgery, was discarded. Other studies have shown the volume of local graft available ranges between 10 and 30 cc of bone and in some cases would have been greater than the total ICBG used [85,86]. Discarding local bone graft and failure to prepare facets for arthrodesis are not standard surgical procedures for posterolateral arthrodesis and may have

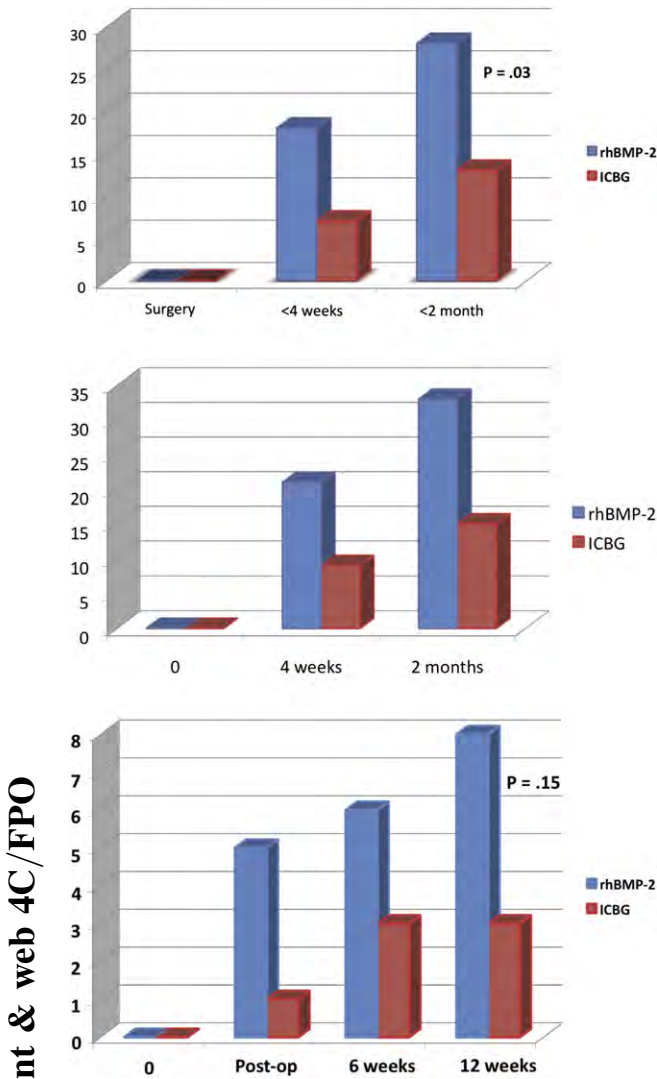


Fig. 7. Cumulative early postoperative complications: (Top) Adverse back and leg pain events in the AMPLIFY trial showing a significantly greater increase in major adverse back and leg pain events in patients receiving and not receiving the rhBMP-2 preparation. (p Values, chi-square test, two tail). (Middle) Combined back/leg pain events and arthritis/bursitis events. (Bottom) Serious back and leg pain events in each group.

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Although the increased incidence of cancer was a serious enough observation to concern both the FDA and other groups [74,75], the company spokespersons stated that there is “no plausible biological mechanism for cancer induction” caused by rhBMP-2 [76]. However, the basic biology of growth factor signaling in carcinogenesis suggests that categorical denial is not supportable. A theoretical concern regarding malignancy risk with rhBMP-2 was clear when human trials began [4]. In March 2011, the *Wall Street Journal* reported that Medtronic received a “nonapprovable letter” from the FDA for the spine device known as Amplify, “amid outside concerns regarding whether an ingredient used in the product might be linked to cancer” [77].

Table 5

Increased back and leg pain adverse events associated with the higher dose rhBMP-2 (AMPLIFY) used in posterolateral fusion compared with control subjects having ICBG harvesting

Adverse event	Post-op	Wk	Wk	Total	Early %	95% CI
Early back and leg pain		<9 wk				
BMP (n=239)	18	11		29	12.13	8.0, 16.3
ICBG (n=224)	7	5		12	5.36	2.4, 8.3
				Difference	6.78	1.7, 11.9
Early back, leg, and bursitis pain		<9 wk				
BMP (n=239)	21	12		33	13.80	9.4, 18.2
ICBG (n=224)	8	6		14	6.25	3.1, 9.4
				Difference	7.56	2.1, 13.0
Early “serious” back and leg pain events		6 wk	12 wk			
BMP (n=239)	5	1	2	8	3.35	1.1, 5.6
ICBG (n=224)	1	2	0	3	1.34	-0.2, 2.6
				Difference	2.01	-0.7, 4.7

BMP, bone morphogenetic protein; ICBG, iliac crest bone graft; rhBMP-2, recombinant human bone morphogenetic protein-2. Paradoxical effect of less back and leg pain events in the control group was seen despite the early morbidity of bone graft harvesting.

biased the fusion outcomes against the ICBG control group. Local bone graft has been shown by some to be equally effective as ICBG in promoting fusion in PLF [86,87].

These methodological choices (Table 6) would be expected to result in an increased risk of poorer quality fusion, nonunion, and potential clinical failure when compared with usual recommended practice. Unfortunately, the control used in this and other rhBMP-2 posterior fusion studies does not afford an accurate estimation of arthrodesis rates and final outcomes for the standard method of lumbar fusion using common surgical techniques [46].

Control group technique in the PLIF trial

The PLIF trial used ICBG as the source of autogenous bone grafting. This introduces the short-term morbidity

of bone graft harvesting from the ilium, which would have been less or absent if local bone graft had been used alone or supplemented the ICBG in the control group. Before the publication of the industry-sponsored trial of rhBMP-2 in PLIF surgery [8], it had been demonstrated that local bone graft was an effective source of bone for PLIF procedures [60]. Further trials have similarly demonstrated that local bone graft harvested during the approach to the posterior annulus is as effective in PLIF surgery as ICBG [58,59,88]. The use of ICBG in the control may have unnecessarily handicapped the control group. Despite this handicap, there was no clear advantage seen to using the rhBMP-2 and possibly poorer global outcomes in the rhBMP-2 group (Fig. 6).

Table 6

Control (ICBG) fusion in the rhBMP-2 posterolateral fusion trials compared with usual practice for short-segment lumbar arthrodesis techniques: potential bias in rhBMP-2 trials against short- and long-term outcomes of attempted fusion in the ICBG cohorts compared with usual recommended practice

Technique	Usual practice	ICBG fusion method in Infuse or AMPLIFY trials	Adverse effect of methodology on ICBG group outcome
Handling of facet	Meticulous removal of facet joint articular cartilage, joint surface decortication, and impaction grafting	No facet preparation required	Preservation of diarthrodial joint in a prospective fusion segment inhibits fusion rate and stability
Local bone graft	Large quantities of local bone graft (10–30 cc) are often available in degenerative segments to be fused	Discarded	Loss of commonly used autogenous graft in study subjects, increases needed for ICBG dissection and bone harvesting, and if inadequate reduces expected fusion rate and success
Handling of low autogenous bone graft volumes	Augment initial graft harvesting with additional ICBG, local bone, marrow aspiration, or multiple other strategies to increased graft volume and efficacy	No bone graft augmentation even with less than 10 cc of harvested bone available	Using inadequate ICBG, which in quality and quantity would be augmented in usual practice, will artificially lower fusion rates, possibly requiring increased reoperation

rhBMP-2, recombinant human bone morphogenetic protein-2; ICBG, iliac crest bone graft.

Estimates of long-term ICBG morbidity

The industry-sponsored trials made various estimates of morbidity in the control groups from the ICBG harvesting procedures for short-segment fusions. The rate of long-term harm was estimated to be 60%, according to the authors' method of assessment [10,84]. This was substantially higher (50–95% higher) than previous estimates [46,89–91]. The industry-sponsored authors' method of assessment ascribed 100% of any ongoing pain in the region of the iliac crest harvesting to be because of the harvesting alone.

Although this was an unusual assumption at the time, given most spine surgeons experience, subsequent studies have indicated that patients, more than 1 year after surgery, do not perceive more pain on the operative side of ICBG harvesting compared with the opposite side, as determined by two independent investigations [92,93]. That is, patients who have undergone posterolateral fusion of the lumbar spinal, commonly have pain around the site of potential ICBG graft harvesting, whether or not this harvesting was actually performed. Moreover, even when harvesting has occurred, patients cannot reliably discriminate which side had the bone graft procedure.

In summary, compared with the industry-sponsored original estimates of long-term ICBG harvesting morbidity, independent and more rigorous estimates appear to be much lower, if any measurable long-term morbidity can be detected at all [46,92,93]. An overestimation of harm in the control groups from the ICBG harvesting might have contributed to a perceived relative benefit of rhBMP-2 in that clinical situation.

Discussion and conclusion

The availability of rhBMP-2, and other bone graft substitutes, in the treatment of some patients with potential or demonstrated compromised fusion capacity can be a great medical advantage, particularly in patients with long or anatomically deficient fusion beds and other special circumstances.

Recent work by Cahill et al. [94] has shown that use of BMP in single-level lumbar fusion may decrease the need for repeat fusion by 1.1% (ie, at least 100 patients need to receive rhBMP-2 to possibly avoid one revision fusion; NNT=100), with an approximately 10% to 14% increase in costs across all patients. Deyo et al. [95] found no decrease at all in lumbar fusion revision rates after BMP use in older patients. Given these marginal benefits in many patients, the risks of using of a highly potent tissue-signaling drug must be carefully weighed against other options.

As described in the Summary of Events Leading to this Review, there had been wide-ranging allegations of possible underreporting of adverse events in this literature, as well as the suggestion that the original published studies lacked critical editorial oversight from the publishing journals. To critically assess those suggestions, we examined the evidence of whether there were any important

omissions, discrepancies, or systematic bias in apparent reporting of possible adverse events between the original industry-sponsored peer-reviewed publication and concurrent or subsequent available data sources.

In this systematic review, we critically assessed the conclusions of authors in 13 published studies regarding the clinical safety and relative efficacy of rhBMP-2 in spinal fusion using CONSORT recommendations for assessing study design and adverse event reporting. Four findings from this review appear clear to us:

1. The estimates of rhBMP-2 safety from the original publications underestimated rhBMP-2–related adverse events of the product. In the small pilot studies [2,3,7], there was inadequate numbers to assess safety, but some suggestion of potential harms was seen in at least one study [3]. In the larger trials, there is evidence in each trial that rhBMP-2 complications may be common and may be serious; but in each publication these were unreported.
2. The presence and magnitude of conflicts of interest and the potential for reporting bias were either not reported or were unclear in each of the original industry-sponsored studies. Some of the conflict of interest statements reported appeared to be vague, unintelligible, or were internally inconsistent.
3. The original estimate of ICBG harvesting morbidity was based on invalid assumptions and methodology. This in turn may have exaggerated the benefit or underestimated the morbidity of rhBMP-2 in the clinical situations tested.
4. The control group methods and technique, as selected for both posterior approach methods (PLIF and PLF), were potentially handicapped by significant design bias against the controls.

As a consequence of these factors, the absolute and relative safety of the rhBMP-2 product was difficult or impossible for readers to ascertain from these original publications. The subsequent reporting of additional studies, the review of administrative, government documents, and subsequent follow-up cohort data have given a fundamentally different picture of morbidity associated with rhBMP-2 use in spinal surgery.

In retrospect, several prominent spine researchers were openly skeptical about the validity of the original publications. Inconsistencies in the data and study conclusions were raised by Smoljanovic et al. soon after the industry-sponsored studies were published. Others questioned the perspective and objectivity of the published presentations. Kahanovitz, commenting on the Haid et al. study, wrote, “Unfortunately, the authors of this study appear to have been overwhelmed by their enthusiasm of using recombinant human bone morphogenetic protein type 2 (rhBMP-2)...” Spengler, former Editor-in-Chief of the *Journal of Spinal Disorders*, commented that he doubted “the (Haid et al.)

article would have been written in such positive terms by authors without financial ties to Medtronic.” Others suspected a fundamental bias calling one article “more of a marketing paper than an objective scientific study.” [24] At the far end of the spectrum, the complaint from qui tam or so-called “whistle-blower” lawsuits, allege a globally corrupt system of publication and promotion [19,26,96].

However, the nature of this systematic review and the methods and material available preclude any conclusion regarding motive or intent on the part of the original study authors. Rather, as an “after action” learning exercise, a number of points are important to highlight:

- At the inception of human trials of rhBMP-2, it was clear that the nature, range, and frequency of adverse events associated with rhBMP-2 were not fully known. This is usually the case with new drug or device applications. However, as early as 2002, in a review article, Poynton and Lane wrote that safety issues associated with the use of rhBMP-2 might include “the possibility of bony overgrowth, interaction with exposed dura, cancer risk, systemic toxicity, reproductive toxicity, immunogenicity, local toxicity, osteoclastic activation, and effects on distal organs.”
- Published trials that should have systematically reported adverse events in the a priori suspect areas did not do so. The evidence for increased early inflammation, back and leg pain events, radiculitis, RE/male sterility, urinary retention, root compression by ectopic bone, osteolysis, and increased cancer rates might have been more clearly recognized and reported via this approach.
- As studies were published from 2000 to 2004, there were no concurrent nonindustry-supported trials available to allow comparison with the reported outcomes of the industry-sponsored trials. Nor were complete data sets made available for analysis by independent reviewers as part of the peer review process. These factors limited the expected external review and analysis expected in high-quality peer-reviewed publications.
- Each of the larger studies, for which independent data could be obtained and reviewed by us, contained findings that could have been considered highly suspicious as direct adverse clinical effects of rhBMP-2 use given the basic biology known a priori; however, these findings were not reported as such in the original publications (See Fig. 8).
- There appears to have been a fundamental error in the statistical analysis of uncommon and serious adverse events within each of the original studies. Three important issues seem deserve consideration:
 - The risk of adverse events should be considered in the context of demonstrated benefits. In trials demonstrating only “noninferiority,” in which a specific benefit may be absent (eg, the near identical mean

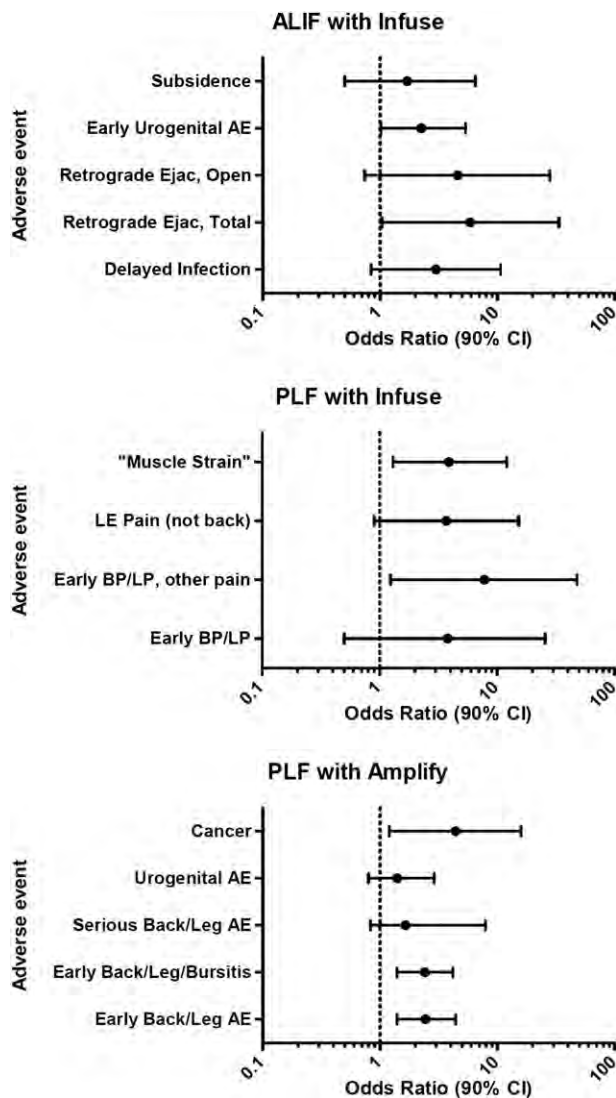


Fig. 8. Odds ratios of adverse events with (Top) rhBMP-2 use in anterior lumbar interbody fusion, (Middle) posterolateral fusion using INFUSE, and (Bottom) posterolateral fusion using AMPLIFY.

clinical outcomes of test and control groups in virtually all these studies), the data analysis must be particularly sensitive to adverse events. These precautions were not observed in these rhBMP-2 publications.

- The use of an arbitrarily determined and set statistical significance level ($p < .05$) as a criterion to identify possible associations with infrequent (but serious) adverse events is not considered appropriate by CONSORT guidelines [38]. Although noninferiority studies are usually interpreted to protect against Type I (alpha) error (rejecting the null when the null is true), with safety issues, protection against Type II (beta) error (accepting the null when the null is false) should be paramount. With rare events, very large numbers are needed to statistically detect associations at the 0.05 or 0.01 level. To guard against

- this, the alpha level should be set higher (eg, 0.1 or 0.2, depending on the seriousness of the event), and CIs computed and shown to reflect that the data are consistent with the possible risk of adverse events. This was not done.
- There was a failure to analyze or report in publication the adverse events occurring during the main pharmacologically active period of the rhBMP-2 drug (weeks). This methodological problem is specifically commented on in the CONSORT recommendation: “Improperly handling or disregarding the relative timing of the events, when timing is an important determinant of the adverse event in question” [38]. Instead investigators followed a cumulative event analysis over years of observation, which is more appropriate to monitor long-term device failure. As a result, increased early adverse events such as urinary retention, radiculitis, and severe back pain episodes occurring during the pharmacologically active period were not reported. The statistical “noise” of random events over years may mask these important and significant complications if considered over an extended follow-up period.
 - In those studies for which other data sources have been made available on the same patient sets (either FDA documents or subsequent reporting of follow-up data), serious contradictory findings have emerged. Major complications, additional surgeries, neurologic/urologic injury, and major back/leg pain events were apparently observed but not reported in the original articles. The authors have defended some of this failure to report by citing that their calculated p values did not reflect a 95% or 99% certainty of the effect. However, as described above, in safety assessments, an 80% to 90% confidence of increased risk of cancer or sterility or infections are all clinically significant findings that should have been fully reported in scientific publication.
 - By reporting “perfect” or “near perfect” safety, the original studies might have led others to widespread off-label use of the product with some potentially catastrophic outcomes. With a wider range of reports and data available from both independent and industry-sponsored investigations, a revised estimate of adverse events associated with rhBMP-2 use in the spine can be made (Table 7):
 - Posterior lumbar interbody fusion techniques—25% to 50% risk of rhBMP-2–associated adverse events for PLIF techniques including osteolysis, subsidence, graft migration, cyst formation, neuritis, and other events.
 - Anterior lumbar interbody fusion—10% to 15% risk of rhBMP-2–associated adverse events including osteolysis, subsidence, graft migration, cyst formation, neuritis, urinary retention, and RE. This estimate is much higher if a greater requirement for supplemental fixation is included (10% to 15% more).
 - Anterior cervical fusion—40% greater risk of adverse events in the acute postoperative period after rhBMP-2 use including potentially life-threatening complications. Food and Drug Administration warnings regarding increased risks of catastrophic complications already exist. Adverse effects on spinal cord injury recovery is highly suspected but not well quantitated.
 - Posterolateral fusions with the INFUSE product—an equivalent or greater early postoperative risk of morbidity compared with ICBG harvesting for this dosage; 16% to 20% of rhBMP-2 subjects had adverse back and leg pain events, a probable two to threefold increase in the first 3 months after surgery over control subjects; as well as an undetermined increased risk of wound problems and inflammatory cyst formation.
 - Posterolateral fusions with the AMPLIFY product—The high-dose rhBMP-2 preparation in the AMPLIFY product was associated with adverse early back/leg pain and other nonspecific pain events in 14% of subjects, approximately twice as many as control subjects. Similarly, there were twice as many early serious back and leg pain events in the rhBMP-2 group in this period. There remains an unquantified increase risk of neuritis, wound problems, and inflammatory cyst formation. Most importantly, there was a greater rate of new malignancy occurrence in the AMPLIFY-exposed subjects, approximately 90% to 95% probability of this being a true effect.
- In conclusion, it is important to consider that identification of problems during the early industry-sponsored lumbar trials may have averted (or at least raised concerns about) complications before significant morbidity and mortality were eventually seen with widespread use. As it was, the presentation of rhBMP-2 morbidity in the original industry-sponsored publications did not fully reflect the data available from those trials as reviewed in FDA documents and subsequent clinical reports.
- Instead, we have found that trial design, particularly in the posterolateral fusion and PLIF trials, may have handicapped the control groups with unnecessary early morbidity and long-term clinical failure. Conversely, the reported extremely high-ICBG morbidity estimates in these studies were not determined with validated methods. Finally, retrospective review of complications and adverse events as reported in FDA and other documents suggests the true risk to patients receiving rhBMP-2 is conservatively 10 to 50 times the original estimates calculated from industry-sponsored publications.

Table 7

Summary of complications, morbidity, and mortality associated with rhBMP-2: listed by application (Column 1), as reported by initial industry-sponsored trials (Column 2), and compared with independent assessment of original FDA data, independent assessment of original industry-sponsored publications and subsequent publications of rhBMP-2 (Column 3)

Application	Industry-sponsored original assessment of rhBMP-2-associated adverse events	FDA data and subsequent publication assessment of rhBMP-2-associated adverse events
Posterolateral fusion with rhBMP-2	<p>Boden et al. 2002: “there were no adverse effects directly related to the rhBMP-2...”</p> <p>Dimar et al. 2006: none reported.</p> <p>Glassman et al. 2007: none reported.</p> <p>Dimar et al. 2009: “No adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified.”</p> <p>Dawson et al. 2009: none reported.</p>	<p>Increased risk of malignancy with high doses (eg, AMPLIFY) suspected, (Level 1 Evidence, single RTC); unclear if risk is also elevated in multi-level usage of INFUSE preparation.</p> <p>Morbidity (pain and functional impairment) equal to or exceeding morbidity of harvesting ICBG. (Strong Level 1 evidence, multiple RCT)</p> <p>Increased early back and leg pain adverse events: 16% to 18% with INFUSE, 25% to 30% of patients with AMPLIFY. Two to three times the rate seen in control patients. (Strong Level 1 evidence, multiple RCT)</p> <p>Wound problems: estimates 2 to 5 times rate of problems without rhBMP-2 use. (Level 3 evidence)</p> <p>Sterile cyst formation: rate not clearly defined. (Level 4 evidence)</p> <p>Adverse events associated with dural leak/tear: major/catastrophic events are likely less than 5%. (Level 4 evidence)</p>
ALIF with rhBMP-2	<p>Boden et al. 2000: “There were no adverse events related to the rhBMP-2 treatment.”</p> <p>Burkus et al. 2002: “There were no unanticipated device-related adverse events...”</p> <p>Burkus et al. 2002: “There were no unanticipated adverse events related to the use of INFUSE Bone Graft.”</p> <p>Burkus et al 2003: none reported.</p> <p>Burkus 2004: “I have reported the clinical and radiographic results of three different interbody constructs in a single-level, stand-alone ALIF derived from several prospective multicenter studies.... There were no adverse events due to rhBMP-2.”</p>	<p>Osteolysis, subsidence and implant-loosening/migration: significantly greater than controls. (Level 1 evidence, multiple RCTs, one cohort control study, and at least one observational study)</p> <p>Retrograde ejaculation: 6–9% of male patients. Rate of RE is 2–4 times greater than control patients without rhBMP-2. (p<.05–.01) (Level 1 evidence, 1 RCT, 1 cohort controlled trial, and observational studies all demonstrating similar effect and magnitude of effect)</p> <p>Urogenital adverse events (mainly urinary retention): rate is 100% more frequent than controls. (Level of evidence 2: one RCT, events poorly described)</p> <p>Infections: increased delayed infections with anterior (p=.02) and anterior/posterior (p=.001) procedures using rhBMP-2. Possibly 5 times greater infection rate compared with controls for delayed wound infections. (Level of evidence 2; one RCT, and retrospective review of Scoliosis Research Society database)</p>
PLIF with rhBMP-2	<p>Haid et al. 2004: “No unanticipated device-related adverse events occurred.”</p> <p>However, authors admit this trial was discontinued due to bony overgrowth into the spinal canal</p>	<p>Morbidity (pain and functional impairment) equal to or exceeding morbidity of harvesting ICBG. (Level 2 evidence, lower quality RCT)</p> <p>Ectopic bone formation into spinal canal/foramen: approximately 6 times more frequent than control patients without rhBMP-2 (p=.0001) (Level 1 evidence)</p> <p>Osteolysis, subsidence, implant migration, and/or loss of lordosis: found in 50–70% of patients with PLIF and rhBMP-2. Usually does not resolve. Sometimes associated with radiculitis. (Level of evidences 1–2; multiple concordant prospective observational trials, phenomenon highly uncommon without rhBMP-2)</p> <p>Radiculitis because of rhBMP-2 exposure: rate unclear, 2 to 4 times that of control subjects in other studies. Perhaps decreased with sealant at anulotomy. (Levels of evidences 2–3, multiple prospective observational trials, cohort-controlled trials)</p> <p>Global poor outcomes scores: rhBMP-2 patients more dissatisfied with surgery; generalizability uncertain as in one RCT, enrollment stopped before enrollment allowed sufficient power for analysis. (Level of evidence 2, one lower quality RCT)</p> <p>Increased reoperation rate: quantification unclear, FDA data and industry-sponsored reporting are conflicting. See text</p>
ACDF with rhBMP-2	<p>Baskin et al, 2003: “There were no device-related adverse events.”</p> <p>Boakye et al, 2005: “Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy....a 100% fusion rate and no significant morbidity.”</p>	<p>Increased perioperative mortality. Magnitude is unclear. (Level of evidence 2; confirmed reporting of an exceedingly rare event in the absence of the rhBMP-2 product)</p> <p>Increased perioperative life-threatening events: magnitude is unclear. (Level of evidence 2; confirmed reporting of an exceedingly rare event in the absence of the rhBMP-2 product)</p> <p>Increased perioperative wound problems, difficulty swallowing, impaired vocalization: 40% higher than in patients without rhBMP-2 in acute</p>

(continued)

Table 7 (continued)

Application	Industry-sponsored original assessment of rhBMP-2–associated adverse events	FDA data and subsequent publication assessment of rhBMP-2–associated adverse events
		hospitalization alone. (Level of evidence 2: analysis of large administrative database; multiple small prospective observational studies)
		Prolonged dysphagia requiring tube feeding: 2% of patients even at low-dose formulation: (Level of evidences 3–4, multiple observational studies, one comparative cohort study, large administrative database)
		End-plate resorption, subsidence and loss of alignment: >50% of patients treated with rhBMP-2 (Level of evidence 3)
		Spinal cord toxicity in the presence of cord injury: high-level animal data only at this point (preclinical data)

rhBMP-2, recombinant human bone morphogenetic protein-2; RCT, randomized controlled trial; ICBG, iliac crest bone graft; FDA, Food and Drug Administration; PLIF, posterior lumbar interbody fusion; ACDF, Anterior cervical discectomy and fusion; ALIF, anterior lumbar interbody fusion.

Supplementary material

Supplementary material can be found in the online version at www.TheSpineJournalOnline.com, and at [10.1016/j.spinee.2011.04.023](https://doi.org/10.1016/j.spinee.2011.04.023).

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