

Editorial

A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors

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- “There were no unanticipated adverse events related to the use of INFUSE Bone Graft.” (n=24) Burkus et al. [1] (industry-sponsored study, 2002).
- “[T]here were no complications attributable to the rhBMP-2/biphasic calcium phosphate [in posterolateral fusion].” (n=20) Boden et al. [2] (industry-sponsored study, 2002).
- “There were no unanticipated device-related adverse events [using rhBMP-2 with an anterior cervical fusion].” (n=18) Baskin et al. [3] (industry-sponsored study, 2003).
- “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.” (n=326) Burkus [4] (industry-sponsored studies, 2004).
- “No unanticipated device-related adverse events occurred [with PLIF using rhBMP-2]... This study seems to confirm the safety results ...[of] using rhBMP-2.” (n=34) Haid et al. [5] (industry-sponsored study 2004).
- “Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy [rhBMP-2]... a 100% fusion rate and no significant morbidity.” (n=24) Boakye et al. [6] (industry-sponsored study).
- “No adverse event that was specifically attributed to the use of rhBMP-2 matrix [Amplify] in the study group was identified.” (n=239) Dimar et al. (industry-sponsored study, 2009) [7].
- “Yes, isn't it pretty to think so.” Ernest Hemingway, *The Sun Also Rises*.

After the original industry-sponsored trials for recombinant human bone morphogenetic protein-2 (rhBMP-2), which were remarkable for the complete absence of reported rhBMP-2–related clinical adverse events, there came many reports of complications by authors unsponsored by the promoting company [8–13]. With these reports, the

safety profile of rhBMP-2 use has devolved, with troubling rapidity and little introspection about the processes, including idiosyncratic trial design, reporting bias, and peer-review/publication shortfalls, that may have promoted widespread poorly considered on- and off-label use, eventual life-threatening complications and deaths [14].

In this issue of *The Spine Journal*, Carragee et al. [15] present a systematic critical review of the original industry-sponsored trials that assesses how the changing safety profile of rhBMP-2 evolved methodologically and in the publication process. As the review points out, none of the original estimates of safety for any of the rhBMP-2 applications cited above proved accurate. More disturbingly, the published

FDA device/drug status: rhBMP-2 use discussed in this editorial concerns both on and off-label use.

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reports underestimated the risks of rhBMP-2 use despite indications from the earliest trials that inflammatory reactions, adverse back and leg pain events, radiculitis, retrograde ejaculation, urinary retention, bone resorption, and implant displacement may have been problems associated with rhBMP-2 use [2,5–7,16,17]. Serious potential problems, such as the association of rhBMP-2 with sterility or cancer risks, which were prominently discussed in Food and Drug Administration documents and hearings [18,19], did not receive one line of discussion in the industry-sponsored publication of those trials [7,20,21]. The current systematic review found that rhBMP-2–related complications and adverse events, as documented in original Food and Drug Administration reports and subsequent publications, are perhaps 10 to 50 times the original estimates calculated from industry-sponsored studies [15]. Those same studies were published by some authors with tens of millions of dollars of financial associations with the manufacturer and may have been an intrinsic confounding factor [15].

This issue of *The Spine Journal* also presents a number of original studies that look at adverse effects of rhBMP-2 in spinal fusion and associated issues (Table). The reader may reflect, in reviewing these studies, on how far we have come from the heady confidence of the original reports claiming not a single adverse event associated with rhBMP-2 use in 780 protocol patients.

Conflict of interest and limitations of industry-sponsored trials

The context for this special issue is the remarkable absence of rhBMP-2–associated complications in any of the 13 original trial industry-sponsored publications on this product [15]. It is important for readers to consider in this special issue the evolving understanding of both the biology of bone growth factors and the limitations of our current methods of assessing new technology through industry-controlled clinical trials. Consumer groups and press reports suggest a rising, if not malignant, doubt about the spine field's ability to honestly assess and report on clinical practice and new technologies [22–33]. With regard to the rhBMP-2 issue, the main objection is clear: Authors of nearly all those trials had financial ties with the manufacturer of rhBMP-2, with various compensations ranging to more than 26 million dollars/per study [15].

The range of critics is formidable; from Consumer Reports to *The Wall Street Journal*, from the *Milwaukee Journal Sentinel* to the US Senate, from the *New York Times* to the Department of Justice, and so on [22–33]. These critics suggest that, on balance, some clinical researchers in the current “market environment” cannot be trusted to resist enormous financial forces that encourage biased reporting. The headlines record a near-constant drumbeat of controversy surrounding the promotion of bone growth factors: These range from alleged improprieties of financial disclosure in BMP research [23,27,34]; failing to report likely

complications with rhBMP-2 [22,23,29,35]; publication and research misconduct of BMP trials [24,36–38]; improper representations at US Senate testimony on BMP [39]; allegations of editorial board improprieties regarding BMP manuscripts [27,35,36], and so on. The list continues and is disheartening.

The choirboy defense versus a threat to scientific integrity

Within the spine community, some contend that there is no systematic problem, that is, the “choirboy defense.” We are an honest profession; our integrity is unimpeachable; our ethical standards are not in doubt; potential conflicts of interest are only “potential”; the fact that the speaker or author may have millions of dollars riding on device royalties or consulting agreements with the sponsoring company is immaterial; that another author gets millions in royalties from the only on-label approved device for rhBMP-2, could never impair his objectivity in assessing its safety or effectiveness. Outside the echo chamber, however, much of this rhetoric fails to pass the test of minimum credibility.

Instead, the press and public assume that multimillion dollar compensation packages can and do alter the balance of objectivity regarding the fortunes of your sponsor [22–26,28,30,40,41]. And within the medical community, serious doubts have been raised from the Institutes of Medicine to American Orthopaedic Association [42]. Roseman et al. [43] in the *Journal of the American Medical Association* suggest that skepticism is warranted. They question any topic review or meta-analysis in which the sponsorship and financial association of the authors are not or cannot be assessed as part of the analysis itself. They insist that these relationships are simply a known and powerful source of research bias. Assessment of the literature must include a clear presentation of financial relationships. These are integral to understanding potential biases in study design and analysis. Failure to take these issues into account may lead readers “to trust the conclusions... when they potentially should not” [43]. That is, even within the halls of medicine, many fail to recognize our self-anointed choirboy exemption.

To complicate any attempt at a valid assessment, disclosures in our journals are more often than not self-contradictory blurbs of improbable nonsequiturs bracketed by misdirection. For example, a recent article on rhBMP-2 use with posterior spinal instrumentation disclosed: “The manuscript submitted does not contain information about medical device(s)/drug(s). Institutional funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript” [44]. Even the most cursory review shows that this was all about devices and drugs used in an off-label manner and reported by authors who, by conservative

Table

Special issue original articles evolving safety profile of rhBMP-2 use in the spine

Validity of adverse event reporting and bias in the original industry-sponsored rhBMP-2 trials	In a critical review by <i>The Spine Journal</i> editors, they found that trial designs may have handicapped the control groups with unnecessary morbidity and long-term clinical failure. Conversely, the reported high ICBG morbidity estimates in these studies were not determined with validated methods. Finally, a review of adverse events as reported in FDA and other documents suggesting the true risk to patients receiving rhBMP-2 is conservatively 10 to 50 times the original estimates calculated from industry-sponsored studies [13]. A complementary study found that large amounts of effective bone graft were potentially discarded in the Medtronic trials of rhBMP-2 in posterolateral fusion, again with potential bias in favor of the rhBMP-2 outcomes [37]
BMP-2 delivery systems and osteolysis	Majid et al. reported on alternative strategies for rhBMP-2 delivery, in part to improve safety. An interesting finding was an increased osteoclast activity in the commonly used adsorption-to-carrier method. This early osteoclast activity is thought to be associated with the osteolysis, bone cyst formation, and subsidence complications now commonly associated with rhBMP-2 use [38]
Osteolysis and complications with PLIF and TLIF surgery	Helgeson et al. reported on extraordinarily high rates of osteolysis after posterior interbody fusion (>50%) and the failure of most of these to resolve over time [39]. Similarly, Mannion et al. examined the rate of radiological and clinical adverse events related to rhBMP-2 in TLIF or PLIF. In a small cohort using a lower rhBMP-2 dosage, adverse events associated with rhBMP-2, namely osteolysis, heterotopic ossification, and cyst formation, were observed in 5 of 30 patients (17%). Complications of rhBMP-2 included cage migration, osteolysis, end plate collapse, and eventual nonunion in one patient and a large inflammatory cyst requiring additional surgery in another. Despite the lower dose and surgical precautions, these events remain a concern [40]
Retrograde ejaculation associated with ALIF surgery and rhBMP-2	A study by Carragee et al. of retrograde ejaculation after ALIF using rhBMP-2 compared with control subjects corroborated the findings of the original FDA data and Smoljanovic et al. that rhBMP-2 may be associated with a higher rate of retrograde ejaculation after ALIF compared with controls ($p < .003$). These additional data suggest that inflammatory reactions to the rhBMP-2, which have been documented in other locations, may be responsible for an injury to the superior hypogastric plexus when placed anteriorly in the lower lumbar spine [50]
Persistent gluteal pain likely unrelated to iliac crest harvesting	After two recent reports suggesting that the morbidity of ICBG harvesting has been exaggerated in recent industry-sponsored rhBMP-2 literature, Howard et al. reports that patients identified no more pain from the ICBG harvest site compared with the contralateral side at follow-up of more than 1 year [41]. These reports, along with a large body of previous literature, confirm that the 40% to 60% long-term ICBG morbidity rate claimed by industry-sponsored studies is exaggerated [5,42] and consequently exaggerated the potential benefits of rhBMP-2
Neurological injury risks with rhBMP-2	Dimetrev et al. reviewed the rhBMP-2 interactions with the nervous system. They concluded that “contrary to the original beliefs in the clinical community, rhBMP-2 does elicit a profound signaling response within the spinal cord and the peripheral ganglia.” Other reports have demonstrated that intrathecal penetration of rhBMP-2 “activates a signaling cascade in all major central nervous system cell types, which may increase glial scarring and impact neurologic recovery” [43]
Dural laceration and rhBMP-2	Glassman et al. [44], in a retrospective industry-sponsored analysis, reports that no clear rhBMP-2-specific neurotoxic effects were apparent when used in the presence of a dural tear. However, the study design limits estimating intradural toxicity events with much precision. The study may indicate that the rate of catastrophic events, when rhBMP-2 is used in the presence of a dural tear, could be less than 5%

rhBMP-2, recombinant human bone morphogenetic protein-2; ICBG, iliac crest bone graft; FDA, Food and Drug Administration; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; ALIF, anterior lumbar interbody fusion.

estimates, have tens of millions of dollars of financial association with the sponsor [15]. If the disclosure lacks even “minimum credibility,” what does this say about the study’s content?

The casual reader of the literature is left to wonder how much skepticism is reasonable when reading such an article promoting a commercial product or treatment strategy? Can the reader make any sense of the fine print “disclosures?” Can the reader tell if the authors have a trivial relationship with the industry (eg, the complementary use of the implant during testing) or do the authors receive millions of dollars each quarter from the sponsor? Do the journal editors have

personal multimillion dollar relationships with an articles’ sponsor? Was the peer-reviewed process of contrary studies hijacked at the editor level? Although you may wonder, you would not likely be enlightened.

Publication and the editorial review

Clearly, the entire concept of peer-reviewed literature, systematic topic reviews, and evidence-based clinical decision-making rests on the assumption that the published literature being reviewed has sufficient integrity to make

the exercise worthwhile. It is this concept of “sufficient integrity” that has been questioned [45]. In the case of rhBMP-2, 13-peer-reviewed articles by industry-sponsored authors did not report a single adverse event associated with rhBMP-2 [15]. Although theoretically controlled trials should be our highest standard of evidence, it is not necessarily the case: Many of the rhBMP-2 publications either overlooked frequent adverse events or overestimated their statistical power to comment on safety. Instead, Dr Sohail Mirza has characterized the industry-sponsored rhBMP-2 trial designs and publications as a “folly” in multiple dimensions [46].

The rhBMP-2 literature is hardly unique. Gelberman et al. [42] have reported on “the threat to scientific integrity and public trust” associated with the complex financial relationships existing between orthopedic surgeons and the medical device industry. They noted that industry funding in orthopedics is strongly associated with “favorable outcomes.” Regarding spinal implant research, they reported a strong pattern of results favorable to the sponsors in approximately three-quarters of the studies. Shah et al. [47] reported an odds ratio of 3.3 favoring industry-supported trials published in the journal *Spine*. The editor of *The Lancet*, Richard Horton, has expressed concerns that in publishing industry-sponsored studies with such a systematic bias to favorable results “[j]ournals have devolved into information laundering operations for ... industry” [48]. There have been allegations that editorial conflict of interest in major spine journals has been a fundamental problem as well, with the implication that editorial boards may collude with industry to bring questionable research to publication [27,48].

“As old as scripture and as clear as the American Constitution”

Nonetheless, the rhBMP-2 affair has thrust this issue front and center in spine care. We find ourselves at a precarious intersection of professionalism, morality, and public safety. We work under a burden of suspicion that new technology research and publication is simply a “broken system” as currently practiced [45]. Our professionalism, according to Gelberman et al. [42], is fundamentally challenged by the threat of “tainted science.” But as Dr Spengler points out in his important commentary in this issue [49], to maintain our professionalism, we must do more than dress the part or protect compensation: rather the professional obligation of physicians is to “our patients who place their trust in... their surgeons.” Dr Spengler suggests that “We must commit to the cardinal rule of *primum non nocere* (first, do no harm). Our patients remain our number one priority. We need to fulfill their trust.”

To change the current climate of suspicion and cynicism, we must look beyond minimal standards of professional conduct or legal compulsion: Beyond the media blitz of the criminal investigations, accusations, and talking-point

denials; beyond another set of improbable safety assessments coupled with astounding compensation disclosures; beyond the fortunes found and reputations ruined; beyond any individual or institutional inadequacy that may have permitted these distortions of clinical research. The core of our professional faith, as Spengler points out, is to first do no harm. It harms patients to have biased and corrupted research published. It harms patients to have unaccountable special interests permeate medical research. It harms patients when poor publication practices become business as usual.

Yet harm has been done. And that fact creates a basic moral obligation. As John F. Kennedy stated, “This moral issue is as old as the scriptures and is as clear as the American Constitution.” *It is the human right in our society to basic protections.*

In the spirit of that obligation, upcoming issues of *The Spine Journal* will describe a number of editorial-, procedural-, and disclosure-related changes, which we hope will achieve a better balance in critical manuscript review, conflict of interest disclosure, and publication presentation. We all must do a better job going forward.

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The disclosure key can be found on the Table of Contents and at www.TheSpineJournalOnline.com.

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