



Letter to the Editor

Science please

I am writing in regard to your recent publication by Carragee et al. [1] concerning retrograde ejaculation (RE) and the use of bone morphogenetic protein-2 (BMP-2). I am concerned not only with the validity of the conclusions drawn but also with the tone of the commentary chosen to accompany the article.

First, retrospective historical control articles are notorious for being misleading. Unless the use of InFuse (BMP-2; Medtronic, Minneapolis, MN, USA) was the only variable changed, this alters the applicability of the data. Certainly, in this case, there is a more obvious confounding variable. Carragee took an 18-month hiatus from performing elective civilian spinal surgery and began using BMP-2 on his return. Although we all like to think of ourselves as infallible, an 18-month hiatus can certainly alter surgical technique, style, equipment, and so on; all of which can alter the incidence of RE.

Second, Carragee used BMP-2 in an off-label manner, within a device never tested for dose or compatibility with BMP-2. He admits that he uses the same dose regardless of patient or implant size. We know BMP-2 to be very dose dependent. This certainly makes the utility of his results suspect. In addition, the implant he used is cortical allograft bone. There are reports of increased inflammatory reaction and bone lucencies when allograft is combined with BMP-2. In fact, the UCLA group found this same combination to have an extraordinarily high rate of complication and ended their study early [2].

Third, unless the questionnaire used is specific to RE and was unchanged over the years of the study, the data are suspect. How patients are approached about RE has changed through the years, and its incidence may have been underreported in the past.

Finally, to suggest that the FDA trial data were somehow obscured by conflict of interest is misleading and inappropriate. No attempt was made to hide data. The results within the FDA trial concerning RE and BMP-2 were not statistically significant, and therefore not in the initial report. Over 40 adverse events were tracked for the FDA, but did not lead to any significance, and were therefore not reported (eg, nausea/vomiting, ileus, urinary retention). The beauty of a prospective, randomized, multicenter trial is that you get pooled concurrent data. I would rather trust this than a poorly performed historically controlled single report in making decisions regarding my patients.

In conclusion, although interesting, a single publication in the medical literature does not constitute a “truth.” The finding by Carragee of a 7.0% incidence of RE is in line with other studies performed before BMP-2. The incidence of RE has been reported to range from 6% to 45% in various pre-InFuse trials [3,4]. Certainly, RE is very technique and surgeon related. I honestly do not know if there is an increase in RE using InFuse. Personally, I have performed hundreds of anterior lumbar interbody fusion procedures, with and without InFuse, and have not noted any difference (less than 1% incidence with either). Maybe the specific techniques that Carragee uses should be compared with those of us that have not seen any difference. That would certainly educate patients and surgeons. But for the editor (also the author) to alert the media prepublication and invite two commentaries alleging some type of cover-up, based on a flawed retrospective trial, is naive and short sided at best and at worst inappropriate and irresponsible.

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FDA device/drug status: Approved (InFuse).

Author disclosures: **TAZ:** Royalties: Medtronic (H); Consulting: MiMedx (B), Annulex (B); Board of Directors: LSRS (none); Other Office: Editor, *Journal of Spinal Disorders and Techniques* (D).

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

I have absolutely no financial interest in InFuse (BMP-2). At no time have I had a financial incentive related to the approval or use of InFuse. I do receive royalties for the LT Cage, which can be used with or without InFuse, was popular, and in use before InFuse.

doi:10.1016/j.spinee.2011.06.005

Accepted Manuscript

Title: Reply to Letter to the editor

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PII: S1529-9430(11)00470-0

DOI: [10.1016/j.spinee.2011.06.018](https://doi.org/10.1016/j.spinee.2011.06.018)

Reference: SPINEE 54633



To appear in: *The Spine Journal*

Received Date: 24 June 2011

Accepted Date: 27 June 2011

Please cite this article as: Carragee EJ, Hurwitz EL, Weiner BK, Scuderi GJ, Bono CM. Reply to Letter to the editor. *The Spine Journal* (2011), doi: [10.1016/j.spinee.2011.06.018](https://doi.org/10.1016/j.spinee.2011.06.018)

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1 It is with some reservation that we respond to Dr. Zdeblick's unwarranted personal and
2 professional attacks in his letter entitled "Science, please." Dr. Zdeblick has been a surgeon
3 of considerable skill and energy. We are sorry to have received and to be obliged to respond
4 to such ill-conceived, abusive and patently unfounded criticism. We made absolutely no
5 personal attacks in our article and we stand by our conclusion that there is substantial
6 evidence indicating anterior lumbar interbody fusion with rhBMP-2 carries an increased
7 risk of a devastating complication that should have been disclosed to physicians and
8 patients.

9 Dr. Zdeblick characterizes the presentation of our article, a 2002-2004 case-controlled
10 study of retrograde ejaculation (RE) in protocol subjects having ALIF with and without
11 rhBMP-2, as "inappropriate and irresponsible." (1) He has told the press that our study "has
12 numerous flaws" (2) and in his letter he details those perceived invalidating flaws. All three
13 objections are possible reasons to doubt a study's validity, if there were an actual basis for
14 those claims. There is not. For each flaw Dr. Zdeblick claims to have observed, the article
15 details that appropriate methodology was used.

16 1. Regarding his contention that the military service of the senior author created an "18
17 month hiatus" in treating the two study cohorts: this is false. No "18 month hiatus" existed
18 between the rhBMP-2 and non-BMP-2 surgeries, period. No "18 month hiatus" or anything
19 like an "18 month hiatus" is ever mentioned in the article. Instead, the subject enrollment is
20 stated in the Methods as follows:

21 "To investigate the possible effects of rhBMP-2 on the rate of RE after ALIF, we have
22 retrospectively analyzed the data from three years, 2002 to 2004...The senior
23 surgeon began using rhBMP-2 in 2003...From this database during the years 2002
24 to 2004, patients having one- or two-level ALIF ... were identified. In 2005, the

1 senior author (EJC) temporarily left his usual university practice for active duty with
2 the US military.”

3
4 To be absolutely clear: all rhBMP-2 and control subjects had their surgery during 2002,
5 2003 and 2004; BMP use began in 2003; the study timeframe ended in 2004; Dr. Carragee’s
6 return to active military duty began in 2005. We are astonished that Dr. Zdeblick would
7 falsely manipulate an Army officer’s wartime service record in this manner. Although this
8 may have been a great sound bite for Dr. Zdeblick, it has no basis in reality.

9 2. Regarding the second of our “numerous flaws,” Dr. Zdeblick claims we used too high a
10 dose of rhBMP-2 in smaller patients or implants. Apparently Dr. Zdeblick again did not read
11 the article closely, as the issue is clear: only the smallest dose was ever used. In the Burkus
12 et al trial of ALIF with cortical dowels, “8.4 to 12 mg” were used.(4) In the original trial by
13 Dr. Zdeblick of ALIF and rhBMP-2, “The total dose of rhBMP-2 ranged from 4.2 to 8.4 mg
14 depending on the size of the cage required in each patient.”(3) As described in our Methods
15 section, we never used more than the absolute minimum dose in either trial -- not once, not
16 in any patient:

17 “If rhBMP-2 was used, two sponges (Small Kit, 4.2 mg rhBMP-2; Medtronic Sofamor
18 Danek, Memphis TN) were placed inside the FRA central canal.” (1)

19
20 Dr. Zdeblick also postulated that there may be a greater inflammatory effect when using a
21 femoral allograft compared to Dr. Zdeblick’s own L-Cage device which he emphasizes had
22 dose “testing” and FDA approval (ie, on-label). He, however, neglects to point out that FDA
23 documents show the same InFuse associated complication (inflammatory osteolysis) was
24 seen with the LT-cage:

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“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.”
FDA Summary of Safety and Effectiveness Data: InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.(5)

He also states we used a stand alone FRA / BMP-2 which was associated with high complication rates in the UCLA study. This too is a fabrication of Dr. Zdeblick: our methods state clearly that **none of our cases were stand alone FRA, all had supplemental rigid fixation.**

Once again, although these made additional neat talking point for Dr. Zdeblick to justify to the press our “numerous flaws” and “irresponsible” behavior, all were simply made up. It may be important for Dr. Zdeblick to consider that this type of PR gambit only works if you can be sure no one will actually read the article or supporting documents.

3. In the third of our “numerous flaws,” Dr. Zdeblick insists that specific data collection was not obtained for retrograde ejaculation in our questionnaire. Once again, the Methods section states:

“Specific data collection on RE was included for follow-up of all subjects undergoing anterior lumbar surgery.” (1)

1 All the protocol ALIF subjects from the entire study period followed the same routine
2 follow-up and received the same questionnaire. A careful reading of the paper would have
3 clarified that concern.

4 This brings us to the most serious misrepresentations of Dr. Zdeblick's letter: First, he
5 states the lower limit of RE rates in trials before BMP-2 use was 6% -- this is categorically
6 false; in fact the rate in Medtronic's previous FDA RCT of ALIF without rhBMP was 1.5%
7 with threaded cages and FRA cages. [Sasso, et al, Spine 2004]. Second, Dr. Zdeblick reports
8 "The results within the FDA trial concerning RE and BMP-2 were not statistically significant,
9 and therefore not in the [Dr. Zdeblick's] initial report." This is, once more, patently
10 incorrect:

- 11 • The "FDA trial" found 12 RE events in the rhBMP-2 group (7.9%) versus 1 (1.5%) in
12 the control group.(5) (Fisher Exact $p = 0.05$) Dr. Zdeblick declined to publish these
13 rates for more than 8 years.
- 14 • In the RCT portion of the FDA trial, the rate of RE in the BMP-2 group was more than
15 4 times higher than the control group (6.4% of 78 patients compared to 1.5% of 68
16 controls); he also declined to report these rates for more than 8 years.
- 17 • The probability that these effects were real and serious BMP-2 related complication
18 was between 85% - 95% despite small subject numbers. For serious complications
19 such as sterility, neurologic injury or cancer, these are clinically significant effects
20 and require reporting in publications (see CONSORT [Consolidated Standards of
21 Reporting Trials] recommendations below(6; 7)).

22 Dr. Zdeblick's discussion regarding whether an RCT or a retrospective cohort-control trial
23 provides more reliable evidence is also misleading. According to multiple sources on
24 evidence-based medicine(8; 9)(10)(11)(12), retrospective cohort-controlled trials are most

1 compelling as evidence **when they reproduce the same effect, in direction and**
2 **magnitude, as an RCT.** These studies can provide strong evidence of the generalizability of
3 an observation outside the artificial RCT environment.

4 That is exactly the situation with our study: Dr. Zdeblick found-- but did not report -- a
5 more than 4 times greater rate of RE with BMP-2 in the industry-controlled RCT; we, as
6 independent investigators, also found a more than 4 times greater rate of RE with BMP-2:
7 **same effect, same magnitude, same direction.** The obvious difference is that when we
8 found such a large increase in a potentially serious complication of BMP-2, we reported it.
9 Dr. Zdeblick is left in the somewhat unenviable position of straining to discredit a study that
10 closely replicates his own findings: findings that, among others, he declined to report in
11 multiple publications over many years. (5)

12 Finally, FDA documents regarding Dr. Zdeblick's FDA trial report:

13 "Differences in the rate of retrograde ejaculation between patients receiving
14 rhBMP-2 and those receiving autograft exist...The rate is higher in the patients
15 receiving rhBMP-2 and this was reported in the labeling for INFUSE...This difference
16 is clearly stated in the PMA SSED [and product labeling".

17 Despite a more than 4 times greater rate in BMP-2 patients in Dr. Zdeblick's RCT, Dr.
18 Zdeblick refused and continues to refuse to follow standard CONSORT recommendation for
19 reporting complications in clinical trials. Regardless of all the evidence collected, regardless
20 of FDA labeling, regardless of the catastrophic nature of this complication to many men and
21 their families, Dr. Zdeblick repeatedly and categorically claims:

22 Quote: "...there is no relationship between the use of rhBMP-2 in stand-alone
23 interbody fusion cages and the postoperative development of retrograde

1 ejaculation.”(13)

2

3 This approach to reporting complications associated with a product, whose manufacturer
4 has compensated Dr. Zdeblick approximately 23 million dollars since the completion of that
5 study, is in our opinion, astounding. Conventional reporting methods (below) suggest Dr.
6 Zdeblick’s practice of adverse event disclosure in this BMP-2 trial is inappropriate (6; 7). His
7 rationale for not systematically reporting patient harms is specifically labeled as *Poor*
8 *Reporting Practices for Harms-Related Data* by CONSORT recommendations for reporting of
9 randomized clinical trials. (6)

10 It is important to consider the CONSORT recommendations specifically in question here:

- 11 • **It is inappropriate not to report “all important adverse events or side effects in**
12 **each intervention group.”(7)** Important adverse events, even catastrophic events like
13 sterility were not reported “in each intervention group” by Dr. Zdeblick and co-authors.
14 These were not reported over many publications and over many years (4; 14-17),
15 despite repeated inquiries. (5)
- 16 • **It is inappropriate reporting of complications when authors provide “statements**
17 **about whether data were statistically significant without giving the exact counts**
18 **of events.”** (6) This is precisely the reporting technique used by Dr. Zdeblick. (4; 14; 15)
19 Complications associated with rhBMP-2 with a more than 85% confidence level were
20 simply dismissed as “statistically insignificant.”
- 21 • **It is inappropriate reporting of complications when authors report “only the**
22 **adverse events that reach a P value threshold in the comparison of the**
23 **randomized arms (for example, P < 0.05).”** (6) This, again, is the reporting technique
24 used by Dr. Zdeblick, with 85%-95% confidence that rhBMP-2 is causing male sterility,

1 Dr. Zdeblick failed to inform the readers in any of his publications from 2002 to 2009.
2 (4; 14; 15)

3 • **It is also inappropriate reporting to “[Fail] to provide separate data for each study**
4 **arm.”** (6) This is the most fundamental procedure for reporting adverse events in
5 controlled trials. Yet, this basic precaution was not followed by Dr. Zdeblick. The 4 times
6 higher rates of RE events with rhBMP-2 was simply not reported “for each study arm” in
7 multiple publications by Dr. Zdeblick from 2002 to 2009.(4; 14; 15)

8 Despite these four major breaches of the CONSORT recommendations in reporting
9 complication,(6; 7) Dr. Zdeblick is highly critical of anyone who attempts to analyze the
10 original FDA InFuse data, or reproduce those results, or even apply CONSORT
11 recommendations to evaluate these serious risks to patients. (2)(13; 18; 19) Why does Dr.
12 Zdeblick seem to refuse to follow the most basic rules of scientific evidence? Why denigrate
13 or obstruct others attempting to report these findings?

14 A clue may be Dr. Zdeblick’s assertion that “I have absolutely no financial interest in InFuse
15 (BMP-2),” a fascinating denial of what, in our opinion, is an obvious and enormous conflict
16 of interest. The old saying is “follow the money” and in this case, there is plenty to follow.
17 The first author of the Medtronic trials of BMP-2 and ALIF, Dr. Burkus, is reported to have
18 received 1.5 million dollars from Medtronic **during the publication period from 2001-**
19 **2006 alone.**(20) And Dr. Zdeblick’s 23 million dollar financial relationships with Medtronic
20 have been the subject of a publicly documented investigation by Senator Charles
21 Grassley.(21)

22 Specifically related to InFuse, Dr. Zdeblick receives millions of royalty dollars from the
23 Novus LT cage. He points out in his letter that his LT cage is the only device **tested and**

1 **approved** by the FDA for spinal fusion with the InFuse product; the only **tested and**
2 **approved** product that can be used on-label.(21) The FDA website confirms:

3 “The LT-CAGE™ Lumbar Tapered Fusion Device component is sold separately from
4 the InFUSE™ Bone Graft component, however, **these two components must be**
5 **used together.**” The FDA SUMMARY OF SAFETY AND EFFECTIVENESS, 2002. (5)

6 To be clear, for a primary spinal fusion patient in the United States to receive the InFuse
7 product in the **tested and FDA approved** manner promoted by Dr. Zdeblick in his letter,
8 they **must** use Dr. Zdeblick’s device. If surgeons wish to use InFuse in this **tested and FDA**
9 **approved** manner, Dr. Zdeblick directly profits. They cannot use an FRA graft, or a PEEK
10 cage, or a mesh cage. They cannot use a BAK cage or any such threaded cage by any other
11 manufacturer.

12 Is this not fundamentally incompatible with Dr. Zdeblick’s repeated claim, “I have absolutely
13 no financial interest in InFuse (BMP-2)”? Public documents indicate that 100% of his latest
14 2 million dollars of royalty payments were all associated with Medtronic products (22).
15 Reports suggest Dr. Zdeblick received more than 23 million dollars in various
16 compensations from Medtronic Inc. (21-23) Can we not even consider that Dr. Zdeblick may
17 in fact have enormous financial ties to InFuse and Medtronic.? Is it not possible these
18 relationships color his perception regarding the safety and efficacy of the LT-cage and
19 InFuse products?

20 There is nothing wrong with making money or even lots and lots of money. But surely it is a
21 very reasonable concern that Dr. Zdeblick’s arrangement gives him a simple, obvious and
22 compelling financial interest in the fortunes of Medtronic and their InFuse product. Dr.
23 Zdeblick’s claim, “At no time have I had a financial incentive related to the approval or use
24 of InFuse,” is in the opinion of many observers, hardly credible.

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THE SPINE JOURNAL

A Multidisciplinary Journal of Spinal Disorders
Official Journal of the North American Spine Society

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If a device or drug requiring FDA approval is identified as an important component of your article, you must indicate the FDA status for use as it will be discussed. Please list the name of the device(s) and drug(s) requiring FDA approval and check the appropriate status for use as it is discussed in the article.

My manuscript does not discuss any drugs or devices requiring FDA approval.

1. Device/Drug _____ rhBMP-2 and LT cage for ALIF _____
 Not applicable Not approved for this indication Approved Investigational
2. Device/Drug _____ rhBMP-2 and other cages for ALIF _____
 Not applicable Not approved for this indication Approved Investigational
3. Device/Drug _____
 Not applicable Not approved for this indication Approved Investigational
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Eric L. Hurwitz, DC, PhD: Consulting: Society for Chiropractic Orthospinology, Inc. (B), Western University of Health Sciences (B), National Institutes of Health (A); Trips/Travel: World Spine Care (B), Palmer Center for Chiropractic Research (B).

Bradley K. Weiner, MD: Board of Directors: Intrinsic Therapeutics (None, Chair of the Data and Safety Monitoring Board).

Gaetano J. Scuderi, MD: Stock Ownership: Cytonics (4000000 Shares, 55%, startup, no revenue, unknown value); Private Investments: K2 Medical (50000 Shares, less than 1%); Board of Directors: Cytonics (None); Scientific Advisory Board: Cytonics (none); Other Office: Biotech (Chairman); Grants: SBIR (F)

Christopher M. Bono, MD: Royalties: Wolters Kluwer (B), Informa Healthcare (B); Other Office: Intrinsic Therapeutics (B) (Data Safety Monitoring Board); Other: JAAOS (B, Deputy Editor), The Spine Journal (None, Deputy Editor).

DEGREES OF SUPPORT:

Level A (\$100-\$1000), Level B (\$1,001-\$10,000), Level C (\$10,001-\$25,000), Level D (\$25,001-\$50,000), Level E (\$50,001-\$100,000), Level F (\$100,001-\$500,000), Level G (\$500,001-\$1M), Level H (\$1,000,001-\$2.5M), Level I (greater than \$2.5M).