Bone morphogenetic protein (BMP) has been increasingly used in the US for a wide range of spinal fusion procedures because of the potential surgical and postsurgical benefits it provides and the perceived reduction in complications related to iliac crest bone graft harvesting. Recombinant human BMP-2 (rhBMP-2, contained in INFUSE Bone Graft, Medtronic Spine and Biologics) has received premarket approval by the FDA for fusion of the lumbar spine in skeletally mature patients with degenerative disc disease at 1 level from L-2 to S-1 and for healing of acute, open tibial shaft fractures stabilized with an intramedullary nail and treated within 14 days of the initial injury. Due to recognized problems associated with allograft bone and other bone substances and the desire to reduce complications associated with autogenous bone graft harvest, the use of rhBMP-2 rapidly expanded beyond the approved indications. For instance, it was found when analyzing Nationwide Inpatient Sample data on the 139,835 various spinal fusion procedures performed in 2002, only 2116 involved rhBMP-2 administration. This number grew to 50,040 BMP-based procedures out of 158,654 total procedures just 4 years later and included cervical, posterior interbody, and posterolateral lumbar applications.

Early clinical studies of the safety and efficacy of rhBMP-2 demonstrated fusion rates equal to or better than iliac crest bone graft with a very low incidence of device-related complications for both approved and unapproved indications. As with most surgical procedures that generate substantial initial enthusiasm, unrecognized complications gradually come to light. Starting with single and limited case series, a progression of complications has gradually emerged at national meeting presentations and in the medical literature. Complications or potential complications, such as dysphagia, osteolysis, ectopic bone formation, radiculitis, sterile cyst formation, seroma, retrograde ejaculation (RE), and increased risk of malignancy, have all been reported or discussed. The initial BMP premarket approval studies were reported by some of the most influential names in spinal surgery, including some who had a potential conflict of interest. It has been suggested that a variety of factors, including the thoroughness of the initial data collection and analysis, a potential bias in interpreting the data and even the peer review and editorial process of bringing these articles to press, were flawed.

Anterior lumbar interbody fusion has clearly been linked to RE and the use of rhBMP-2 has been proposed. In a letter to the editor regarding the recent publication by Burkus et al., Smoljanovic and associates noted that, according to the FDA’s website, RE developed postoperatively in 11 patients (7.9% of 140 men) from the autologous iliac crest bone graft group. In a retrospective cohort-controlled study of RE events after lower lumbar anterior interbody fusion (ALIF), using an open retroperitoneal approach by a single surgeon, Carragee et al. reported that RE events occurred in 7.2% of the rhBMP-2 group and in 0.6% in the control group.

The current study reanalyzed 5 prospective, randomized, multicenter FDA-approved investigational device exemption studies in order to assess the rate of RE. Combining the data from the 5 trials, RE was reported in 7 (3.4%) of the 207 patients who received the rhBMP-2 treatment compared with 5 (1.7%) of the 301 patients who received autograft or lumbar disc treatment. It was also found that RE was reported in 7 (1.6%) of 445 patients who underwent a retroperitoneal spinal exposure and in 5 (8.6%) of the 58 patients who underwent a transperitoneal approach. It was concluded by the authors that “…the use of rhBMP-2 was associated with a higher incidence of RE (3.4% vs 1.7%) but did not reach statistical significance.”

On analysis of the present study, it is clearly underpowered in order to determine if there was a significantly
increased incidence of RE with rhBMP-2. In addition, as noted by the authors, it is likely that the true incidence of RE was underreported in both the control and rhBMP-2 groups. Although the patients were queried regarding adverse outcomes, the patients were not specifically asked about symptoms of RE.

This article does provide further evidence that RE occurs more frequently in a transperitoneal approach to the lumbar spine. It also continues to show a worrisome trend in an increased incidence of RE associated with the use of rhBMP-2. The authors responsibly conclude that “...the use of dual paired interbody cages is associated with an increased risk of postoperative RE.” Every surgical case balances risks and benefits between alternative treatments. Recombinant human BMP–2 clearly compares favorably with autograft in anterior interbody applications. Although the conclusions do not reach statistical significance, enough evidence is present to routinely warn male patients undergoing anterior lumbar interbody fusion with rhBMP-2 that there appears to be an increased risk of RE compared with the use of autograft. The surgeon and patient need to collaboratively decide whether this small risk is acceptable when balanced against potential benefits.

A more detailed prospective analysis of complications of rhBMP-2, such as RE, and other rare events, such as a higher rate of malignancy, is needed to provide more accurate information. Ideally, a Web-accessible registry should be established to easily permit reporting of adverse events associated with new technologies by physicians or patients that provide readily accessible, real-time access to adverse events in order to reduce future delays in recognition of complications.

Disclosures

Dr. Shaffrey is a consultant for Biomet, DePuy, Globus, Medtronic, and NuVasive. He also receives royalties from Biomet and Medtronic. Dr. Smith is a consultant for Biomet, Medtronic, and DePuy and received an honorarium from Globus for teaching a spine course. He also reports receiving study group support form DePuy.

References


Response

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On behalf of my coauthors, I thank the *Journal of Neurosurgery: Spine* for the opportunity to respond to this editorial. We agree that continued clinical assessment of patients undergoing anterior lumbar interbody fusion procedures in the lumbosacral spine should be carried out, and the results of this assessment should be responsibly reported in the literature to identify adverse events associated with new technologies. Since the time our manuscript was submitted to the *Journal of Neurosurgery: Spine*, 3 additional independent studies have been reported. Tepper et al. prospectively studied 41 men who underwent ALIF surgery with and without rhBMP-2. All had preoperative semen analysis. No difference was found in retrograde ejaculation (RE) rates between the 2 groups of patients. In a retrospective study of 141 males undergoing anterior lumbosacral fusion using rhBMP-2, Ghanayem1 reported an RE rate of less than 1% (0.7%). In a retrospective study published in 2012, Lindley et al.2
compared RE rates between cohorts of patients undergoing either ALIF with rhBMP-2 or total disc replacement. Relatively high rates of RE (7.4% ALIF vs 9.8% TDR) were identified; however, there was no a significant difference between the 2 groups. These 3 independent contemporary studies argue against the theory that BMP is responsible for RE.

In our article, we reported analysis of data from multiple centers enrolling patients in sequential randomized controlled trials (RCTs) comparing outcomes, including RE, between ALIF patients treated with and without rhBMP-2. For the combined analysis, data from 5 individual trials were pooled, and standard statistical techniques were applied. The approach of pooling the data was used because it was considered a more sensitive approach and enabled smaller differences in RE to elicit statistical significance. A multivariate analysis of RE was also performed with logistic regression to include the factors of treatment. The multiple analyses of the RCTs presented here did not show a statically significant relationship between the postoperative development of RE and the use of rhBMP-2. This conclusion is in agreement with other contemporary studies.

References


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