

Trends in Bone Morphogenetic Protein Usage since the U.S. Food and Drug Administration Advisory in 2008: What Happens to Physician Practices When the Food and Drug Administration Issues an Advisory?

Janay Mckie¹ Sheeraz Qureshi² James Iatridis^{2,3} Natalia Egorova⁴ Samuel Cho² Andrew Hecht²

¹ Pediatric Orthopaedic Fellow, Texas Scottish Rite Hospital for Children, Dallas, Texas

² Department of Orthopaedics, The Icahn School of Medicine at Mount Sinai, New York, United States

³ Department of Spine Research, The Icahn School of Medicine at Mount Sinai, New York, United States

⁴ Department of Health Evidence and Policy, Icahn Medical Institute, New York, United States

Address for correspondence Andrew Hecht, MD, Co-Director of Spine Surgery, Department of Orthopaedics, The Icahn School of Medicine at Mount Sinai, Faculty Practice Associates Floor 9, 5 East 98th Street, New York, NY 10029, United States (e-mail: andrew.hecht@mountsinai.org).

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Abstract

Study Design Retrospective cross-sectional study of spinal procedures from 2002 to 2010 using the Nationwide Inpatient Sample database.

Objective To determine the patterns of bone morphogenetic protein (BMP) usage in fusion surgery before and after the U.S. Food and Drug Administration (FDA) 2008 advisory for the anterior cervical spine to understand how advisories affect U.S. physician practices.

Methods Procedures were identified through *International Classification of Diseases, Ninth Revision* procedure codes and were plotted over time based on fusion procedure type, site, and area of fusion. U.S. national trends were approximated by polynomial regression analysis.

Results The majority of the data trends of BMP usage reflect a second-order polynomial model. BMP usage in anterior cervical spine fusion procedures plateaued during the fourth quarter of 2007. The most apparent change in trend was noted in BMP usage pre- and postadvisory in the analysis of anterior cervical spine fusions. BMP percentage of use decreased in this area by 5% from the time of the FDA advisory to the fourth quarter of 2010.

Conclusions The decrease in BMP usage in anterior cervical spinal fusion procedures coincided with the timing of the FDA advisory. The fact that BMP continued to be used in cervical spine fusion procedures, even at lower rates, despite the advisory, may reflect the availability of new clinical information that could lessen complications (i.e., lower BMP dose, perioperative steroids, BMP containment). Furthermore, factors like the natural ceiling effect of use or demand for new technology, complications, prohibitive institutional costs, access to information, and insurance compensation may have all contributed to the BMP usage trends observed.

Keywords

- bone morphogenetic protein
- anterior cervical spine
- FDA advisory

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Introduction

Bone morphogenetic protein (BMP) is an attractive product due to its robust bone-forming properties.^{1,2} It may reduce the undesired outcome of pseudarthrosis or nonunion. Since the approval of BMP-2 and BMP-7 by the U.S. Food and Drug Administration (FDA), BMP use has increased in the setting of spinal fusion surgery via on- and off-label usage.^{3,4} Cahill et al noted that since the 2002 approval, nationwide usage of BMP increased from 0.69% in 2002 to 24.89% in 2006 for all fusions.⁵ Beginning in 2006, a series of studies detailed the serious complications associated with BMP use in all settings.^{6–16} In June 2008, the FDA issued a public health notification regarding life-threatening complications associated with recombinant human BMP in anterior cervical spine fusion.¹⁷ This was as a result of reports of complications with the use of BMP in anterior cervical spine fusions. Complications included swelling of the neck and throat tissue, which resulted in compression of the airway and/or neurologic structures in the neck. Also reported was difficulty swallowing, breathing, speaking, and severe dysphagia. In light of all of this, the FDA has maintained that the safety and effectiveness of BMP in the anterior cervical spine have not been demonstrated. Furthermore, it is not approved for use in this area of the spine.¹⁷

Despite all this, off-label use of BMP continues. Studies in the literature show safe use of BMP in the cervical spine with the addition of certain precautions during the intraoperative and perioperative periods.^{7,8,13,18,19} In a commentary, Riew and Carragee state that small doses of BMP (0.2 to 0.4 mg) per level and a small dose (20 to 40 mg) of high-potency particulate steroid in the wound before closure can mitigate the dangerous effects noted in the FDA advisory.¹³ In contrast with this information is the insight into BMP via the Yale University Open Data Access (YODA) Project, where BMP was more critically examined in its role in spinal fusion. The clinical findings of the meta-analyses sponsored by the YODA project about the efficacy and harms associated with BMP suggested that there is no evidence of a clinically important difference between BMP and autologous iliac crest bone graft (ICBG) for inducing spinal fusion and that BMP is associated with higher complications rates than autograft in anterior cervical surgery.^{18,19} This study aims to capture the trends of usage of BMP since the FDA advisory. The goal of this study is to examine the effect of a clinical FDA advisory on the practices of U.S. spine surgeons. Does an advisory change physician practice?

Methods

The Nationwide Inpatient Sample (NIS) database, a nationwide sample of U.S. hospital discharge records, contains data from ~8 million discharges each year. It is the largest publicly available inpatient care database in the United States and includes 20% of U.S. community hospitals. To produce national estimates, the NIS database includes weights. The NIS discharges include all payers and are from ~1,000 U.S. hospitals.²⁰ The NIS has been extensively used for analysis

of trends in spinal surgery. For spinal fusions, the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* procedure codes can be used to study technical changes and advances in spine surgery. We reviewed the NIS database from 2002 to 2010 to determine the trends of usage of BMP before and after the 2008 FDA advisory.

The total number of primary fusions and revision fusions were estimated nationally each year by quarter since 2002 with particular emphasis on trends before and after June 2008 (second quarter). Surgical fusion procedures were identified by *ICD-9-CM* procedure codes for primary (81.00 to 81.09) and revision (81.30 to 81.39) fusions. The fusions using BMP were identified by the secondary procedure code for insertion of recombinant BMP (84.52). Trends of use were determined through further classification of cases into cervical (81.01 to 81.03, 81.31 to 81.33), thoracolumbar (81.04 to 81.05, 81.34 to 81.35), and lumbosacral (81.06 to 81.08, 81.36 to 81.38). Additionally, the trends in use in anterior versus posterior cervical (81.02 and 81.32 versus 81.03 and 81.33) and lumbosacral (81.06, 81.08, 81.36, and 81.38 versus 81.07 and 81.37) were also quantified. Polynomial regression analysis was used in this study to determine the time in which the change in trend occurred relative to the FDA advisory.

Statistics

The statistical analysis took into account the design of NIS database. The estimate of the prevalence of BMP usage was determined by SAS survey procedure (Statistical Analysis System (SAS) Institute, Cary, NC, United States). NIS design variables weight, strata, and cluster were included in the analysis to correctly estimate variance and produce the national estimates. The trends of BMP usage were approximated by polynomial quadratic regression analysis.

Results

The majority of the data trends of BMP usage from 2002 to 2010 reflect a nonlinear model (second-order polynomial model) with rapidly increasing BMP usage rates initially followed by decreased rates of usage and eventual plateau in usage rates (►Figs. 1 to 5). The only exception was found in the thoracolumbar analysis, which showed a linear relationship of BMP usage over time (►Fig. 3). ►Table 1 shows the time in which the change in trend occurred based on year and quarter relative to the FDA advisory (second quarter of 2008) utilizing a second-order polynomial regression analysis.

In the analysis of percent usage of BMP in all fusion procedures (primary and revision fusions), a plateau was reached during the fourth quarter of 2008 of 28.3% (►Fig. 1). In the analysis of primary fusion procedures, a plateau was also reached during the fourth quarter of 2008 of 27.8% (►Fig. 2). In revision fusion procedures, the percent usage of BMP reached a plateau of 38.8% during the first quarter of 2007 (►Fig. 2).

In cervical and lumbosacral spinal fusion procedures, BMP usage achieved a plateau of 10.6 and 41.9% during the second

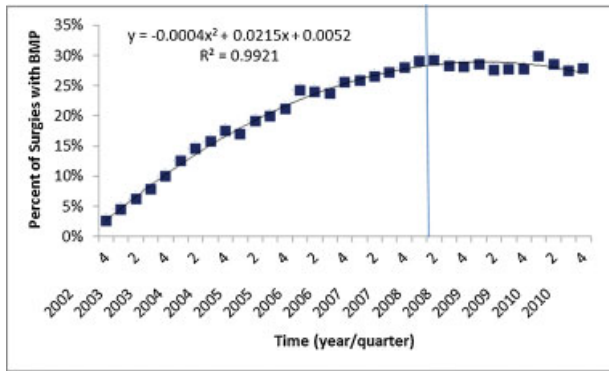


Fig. 1 Trend of bone morphogenetic protein (BMP) use in all spinal fusion surgeries. Vertical line denotes the time of the U.S. Food and Drug Administration advisory (second quarter of 2008).

quarter of 2008, respectively (►Fig. 3). The percentage of BMP usage in thoracolumbar spine fusion surgery exhibited a linear trend and continued to increase since the advisory. By the fourth quarter of 2010, the percentage of BMP usage in thoracolumbar spine surgery was 36.5% (►Fig. 3).

BMP usage in anterior cervical spine fusion procedures plateaued during the fourth quarter of 2007 at 9.1%. In posterior cervical spine fusion procedures, BMP usage plateaued during the third quarter of 2008 at 19.7% (►Fig. 4). In anterior lumbar spine surgery, the percentage of use of BMP plateaued at 43.6% in the first quarter of 2008. In posterior lumbar surgery, the percentage use of BMP plateaued at 47% in the third quarter of 2007 (►Fig. 5).

The most apparent change in trend was noted in BMP usage pre- and postadvisory in the analysis of all cervical spine fusions and anterior cervical spine fusions. BMP percentage of use decreased in these areas by 4 and 5%, respectively, from the time of the FDA advisory (second quarter of 2008) to the fourth quarter of 2010 (►Figs. 3 and 4). This decrease is in marked contrast from the other areas analyzed, where after the time of plateau there was no further increase or decrease of BMP utilization. Using polynomial regression

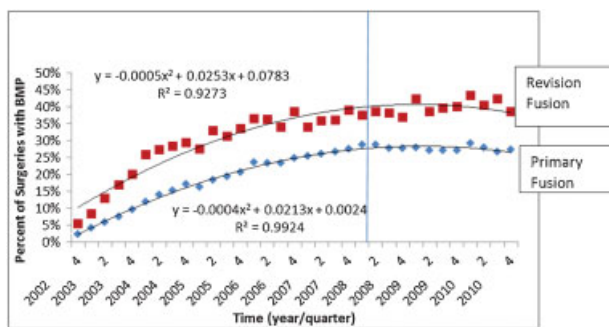


Fig. 2 Trend of bone morphogenetic protein (BMP) use in primary and revision fusion spinal surgery. Vertical line denotes the time of the U.S. Food and Drug Administration advisory (second quarter of 2008).

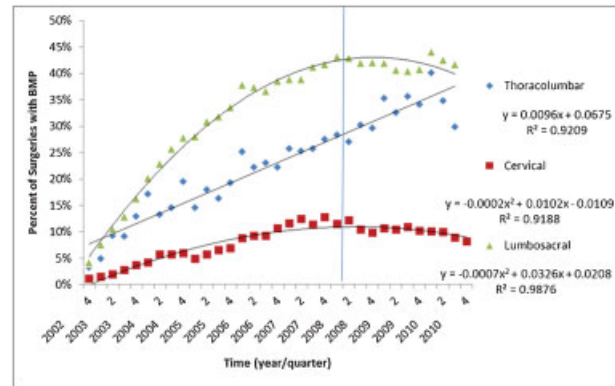


Fig. 3 Trends of bone morphogenetic protein (BMP) use in spinal fusion surgery based on region of spine. Vertical line denotes the time of the U.S. Food and Drug Administration advisory (second quarter of 2008).

analysis on the data, the best-fit curve shows a slight decreasing trend in the cervical and anterior cervical spine as it relates to BMP usage. Additionally, the curves derived from the cervical and anterior cervical spine data are considerably flatter compared with the noncervical areas plotted.

Discussion

BMP is a very potent differentiation factor leading to significant bone formation. Since its approval by the FDA in 2002, there has been significant usage of BMP for on- and off-label indications in the United States. The findings of this study are consistent with those of Cahill et al and Ong et al, who showed increased BMP usage from 2002 to 2007 in spinal surgery.^{5,21} Beginning in 2006, there was a series of studies detailing the serious complications associated with BMP use in all settings.^{6–16} In 2008, the FDA specifically issued an advisory on BMP use in the anterior cervical spine in response to the adverse effects of the product when utilized in this site. Adverse effects were, namely, neck and throat soft tissue swelling, airway compression, severe dysphagia, and difficulty breathing. The goal of this study was to determine if the FDA advisory altered U.S. physician practice as it relates to usage of BMP in spinal fusion surgery.

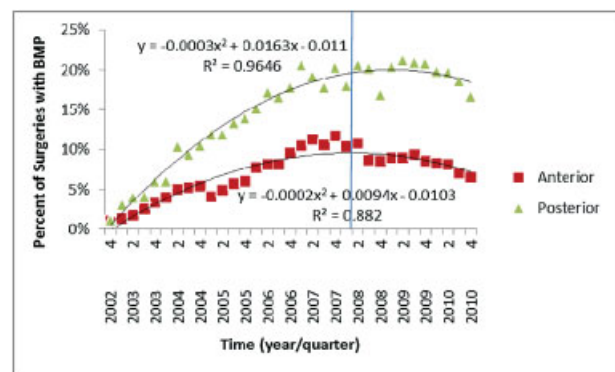


Fig. 4 Trends of bone morphogenetic protein (BMP) use in cervical spinal fusion surgery. Vertical line denotes the time of the U.S. Food and Drug Administration advisory (second quarter of 2008).

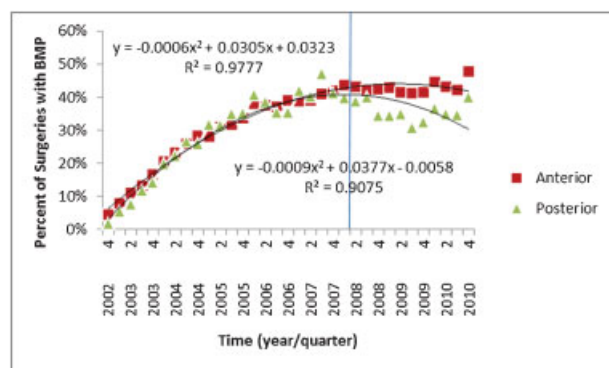


Fig. 5 Trends of bone morphogenetic protein (BMP) use in lumbosacral spinal fusion surgery. Vertical line denotes the time of the U.S. Food and Drug Administration advisory (second quarter of 2008).

The majority of the data trends of BMP usage from the NIS database had areas of increased rates of BMP usage initially, followed by a slowing down of rate of increase, concluding with a potential plateau. The only exception was found in the thoracolumbar analysis. Preadvisory, there was an increase in BMP usage in all fusion surgeries (primary and revision surgery), primary fusion, and revision surgery. Postadvisory, the usage of BMP in fusion surgery showed no further increase in usage in all fusion surgeries (fusion and revision surgery), primary fusion, and revision surgery. There were no drastic changes in the trajectory of the curves after the advisory.

When evaluating the trajectory of each curve analyzed pre- and postadvisory, the most apparent change in usage occurred in cervical spine procedures. A small decrease in trend was found in BMP use in all cervical spine surgery and in the anterior cervical spine surgery that coincides with the timing of the FDA advisory. This may suggest some small association between the FDA advisory and physician practice. The relatively flat trend curve with a small decreased trend noted in the anterior cervical spine data suggests that the contribution of the FDA advisory on physician clinical practice was small. Given the nature of the advisory, it would be expected that a more drastic decrease would be apparent.

Table 1 Summary of plateau time based on polynomial regression analysis

Surgery	Plateau time, year(quarter)	Plateau percentage
All fusions	2008 (4)	28.3
Primary fusions	2008 (4)	27.8
Revision fusions	2007 (1)	38.8
Cervical fusions	2008 (2)	10.6
Lumbosacral fusions	2008 (2)	41.9
Anterior cervical fusions	2007 (4)	9.1
Posterior cervical fusions	2008 (3)	19.7

Several factors may explain the lack of a more profound decrease in BMP usage in the anterior cervical spine. First, several studies have emphasized the ability to mitigate potential complications by lowering the dosage used per level for anterior cervical procedures. Riew and Carragee¹³ as well as Dickerman et al⁸ suggest that lower dosage of BMP per level can decrease the amount of retropharyngeal edema and fluid. A small package of BMP2 is ~4.2 mg.²² The literature suggests that approximately less than one quarter of this amount per level should be sufficient to get the desired effects of BMP. Second, investigators recommended use of perioperative steroids to dramatically reduce the profound inflammatory response encountered in some patients when using BMP in the anterior cervical spine. Steroids can be used in the wound or can be given in the perioperative setting.¹³ Third, there is additional evidence about the importance of containing the BMP within a closed cage or in the center of an allograft to reduce the likelihood of any leakage into the surrounding tissue producing inflammatory effects. Tumialán et al²³ and Patel et al²⁴ suggest that BMP is prevented from leaking into surrounding tissue with use of a polyetheretherketone spacer and fibrin glue, respectively. It should be noted that these measures are just possible explanations and are not meant to fully account for the trends noted above. Other factors could contribute to it.

This study shows very little reduction in BMP usage in anterior cervical spine procedures, suggesting that the FDA advisory may have had a small, if any, effect on physician practice. There was a peak in BMP utilization in this area during the fourth quarter of 2007. Beginning in 2006, there were multiple published reports of the complications with BMP utilization in the anterior cervical spine. The FDA advisory was issued in the second quarter of 2008, and the NIS database does not reflect a drastically significant decrease in utilization in the cervical spine compared with other spine areas of BMP utilization. Again, it is important to note that other factors could contribute to the observed trend in addition to changes in physician practice in the operating room. Factors like the natural ceiling effect of use or demand for new technology, prohibitive costs, complications, and insurance compensation may be some factors that contributed to the trends noted above.^{5-8,22,25-27}

There are strengths and weaknesses in this analysis that are worth noting. The strength of this study revolves around the fact that BMP data trends reported are consistent with earlier literature on BMP trends of usage.^{5,21} Additionally, this article contributes to the discussion regarding safety of BMP in spinal fusion procedures by shedding light on a possible connection between regulatory agencies and their effect on clinical practice. The weaknesses of the study are threefold. First, the NIS database does not have the clinical details of the surgeries and the dosage of BMP utilized during the procedures cannot be determined. Further, the NIS is only a report of discharge information from solely inpatient hospital admissions and it is only a cross-sectional view, not allowing for longitudinal patient follow-up. Second, more data points postadvisory are necessary to definitely make conclusions on the real trend of usage in the cervical spine specifically. A

more informative analysis regarding the true trend would be possible if the same amount of data points before and after the advisory were available. A conclusion could possibly be made with comparison over a similar period of time before and after the advisory. It should be noted, however, that even with more data points, it still difficult to definitively determine whether or not the plateau in trend noted above is due to the advisory versus the natural saturation effect of new technology. Third, NIS database does not allow us to determine differences between physicians who knew about the advisory versus those who did not to compare their practices. Even though there was an FDA advisory in 2008, the effects were not as dramatic as expected, and this may be based on new clinical information on reducing these complications with the use of steroids, containment of BMP, and reduction of BMP dose per level. Otherwise, it could be based on other confounders.

In response to the controversy surrounding BMP utilization in cervical spine procedures, *The Spine Journal* published a systematic review comparing the conclusions regarding the safety and related efficacy published in industry-sponsored trials, FDA data summaries, and other follow-up publications in 2011.^{6,7} This review revealed an underestimation of adverse effects of BMP usage (ranging from 10 to 40% based on approach). Specifically in anterior cervical fusion, there was an estimated 40% greater risk of adverse events with BMP in the early postoperative period. Furthermore, the YODA Project shed further light on BMP use by evaluating all of Medtronic data from their original clinical trials. Meta-analyses generated by the YODA project showed that there is no evidence of a clinically important difference between BMP and autologous ICBG for inducing spinal fusion and that BMP is associated with higher complications rates than autograft in anterior cervical surgery.^{18,19}

Despite the controversy surrounding BMP usage, especially in the cervical spine, some physicians still believe that BMP is still a clinically effective product when used appropriately. This study does show that BMP is still being used in cervical spine procedures. When considering use of BMP in anterior cervical spine procedures, one must evaluate on a case-by-case basis: consider necessity, efficacy, safety, and cost. The trend of usage of BMP pre- and postadvisory is a balance of the risks and benefits of this technology. Suggested ways to avoid BMP anterior cervical spine complications include low dose and containment of BMP when utilized, intraoperative and/or postoperative steroids, and proper irrigation practices intraoperatively.^{8,13,23,24}

In regards to what happens to physician practices after an FDA-issued advisory, the data show that there was a very small, if any, change in trend of BMP use in the anterior cervical spine in the United States. However, the true cause of the data trend is unclear. It is promising that the slowing trend of BMP usage in several spine surgery procedures predates the FDA advisory and suggests that the concerns over complications, which motivated the FDA advisory, may have been partially disseminated and integrated into practice before the advisory. Furthermore, continued use of BMP in the anterior cervical spine most likely reflects data that

mitigate the negative effect of its use. Consequently, surgical literature and practice are more dynamic than the FDA regulations.

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Disclosures

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