Epidemiologic trends in the utilization, demographics, and cost of bone morphogenetic protein in spinal fusions

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Abstract Bone morphogenetic protein (BMP) utilization as an adjunct for spinal arthrodesis has gained considerable momentum among spine surgeons. Despite carrying Food and Drug Administration approval for only single level anterior lumbar interbody fusion from L4-S1, the majority of BMP administration is in “off label” settings. Over the last decade, BMP utilization has increased in all facets of spine surgery with the only exception being the anterior cervical spine, in which a downward trend resulted following the 2008 Food and Drug Administration warnings. The future application of BMP in spinal fusion, especially in anterior cervical fusions, will need to be further clarified in terms of efficacy, complications, and cost-effectiveness.

Keywords Bone morphogenetic protein · Food and Drug Administration · Epidemiology · Spinal fusion · Anterior cervical fusion · Anterior lumbar interbody fusion · Posterior lumbar fusion

Introduction

The prevalence of bone graft substitutes in spinal fusions, specifically bone morphogenetic proteins (BMP), has steadily increased since the initial US Food and Drug Administration (FDA) limited use approval in 2002 [1–5]. As a substitute for autogenous iliac crest bone graft (ICBG), the recombinant versions of BMP (rhBMP-2, rhBMP-7) have been utilized for their osteoinductive properties as an adjunct to promote

arthrodesis in the spine, without the significant donor site morbidity often associated with bone graft harvesting [6–9].

Although the FDA limited the indications of BMP in the spine to anterior interbody lumbar fusions (ALIF) in combination with tapered, threaded intervertebral cages [10], widespread incorporation of BMP is performed in an “off-label” manner for a variety of spinal fusions [4, 11–18]. Various complications have been reported throughout literature associated with BMP use in spinal fusions including: retrograde ejaculation, dysphagia, subsidence, and even cancer [14, 15, 19–22, 23, 24]. As result, the FDA issued a Public Health Notification warning in 2008 with regards to the use of rhBMP-2 in the cervical spine [25].

Given the ongoing uncertainty with the risks and benefits of using BMP in certain off-label applications, various groups have studied the utilization and cost impacts of BMP on a national scale before and after the FDA warnings [2, 4, 16, 20, 26, 27]. Although the recommended guidelines for limited BMP utilization in spinal fusions have not changed, the rate and type of procedures with BMP continue to increase. The objectives of this review are to present contributions to the literature and to discuss national epidemiologic trends in the utilization, demographics, and costs associated with BMP in spinal fusions from 2002–2011 and the resulting impact of the 2008 FDA Public Health Notification.

Utilization

The utilization of BMP for “off-label” purposes in spinal fusions has continued to gain momentum as an alternative to iliac bone graft harvest. Applying the osteoinductive properties of BMP, without the complications associated with bone graft harvesting, studies continue to demonstrate growth in the proportion of spinal fusions utilizing BMP from 2002–2011. As more studies evaluate outcomes associated with BMP use

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in spinal surgery, the primary concern with “off-label” application of BMP continues to be the potential for complications related to such use, thus, the 2008 FDA warning specific to anterior cervical fusions. Although there is a growing amount of literature discussing various complications, a Yale Open Data Access (YODA) meta-analysis was recently published concluding that the BMP literature continues to under-report complications with several studies demonstrating industry conflicted relationships [23•].

Cahill et al. [2] analyzed the prevalence, complications, and resource utilization of BMP and found the usage of BMP in all spinal fusions, on a nationwide basis, increased from 0.69 % in 2002 to 24.89 % in 2006 with more frequent complications observed in anterior cervical fusions. Similar growth was observed by Ong et al. [4] as the annual number of procedures involving BMP progressively increased 4.2-fold from 22,423 procedures in 2003 to 95,912 in 2007. Likewise, the overall rate of BMP use for spine fusion also increased from 7.5 % in 2003 to 27.2 % in 2007. When stratified by spine fusion subtype, steady increases were observed in posterolateral spine fusions (PSF), posterior/transforaminal lumbar interbody fusions (PLIF/TLIF), anterior lumbar interbody fusions (ALIF), thoracolumbar fusions, as well as anterior and posterior cervical fusions (ACF, PCF). As such, it is evident that the use of BMP for all spinal fusion subtypes was gaining momentum up until the 2008 FDA warnings regarding BMP use in the cervical spine.

Nandyala et al. [28•] examined national epidemiologic trends in BMP utilization for spinal arthrodesis from 2002–2011, specifically addressing changes observed following the FDA warning. Similar to previous findings, a steady increase in BMP usage was observed across multiple subtypes of spinal fusions each year. A notable exception was present in the application of BMP in ACFs (Table 1). Following a peak of 10,782 procedures

(10.6 % of ACFs) in 2007, a steady decline associated with several warnings of anterior cervical swelling in 2008 led to only 8315 surgeries (6.4 % of ACFs) with BMP use by 2011. Specifically, there was a decrease of BMP use in ACFs each year from 2008–2011, suggesting that many spine surgeons were influenced by the public health notifications issued by the FDA. There appear to be multiple driving forces associated with this observed decline as multiple large studies continue to reveal various complications in the cervical region following ACF with BMP [1, 4, 11, 19, 21, 23•, 29]. As additional studies focus on identifying complications and improving outcomes, it is unclear if the utilization of BMP, particular in ACFs, will change substantially and mirror trends similar to the other spinal fusion subtypes.

Despite the lack of FDA approval, the majority of BMP application in spinal surgery has continued to be in posterior lumbar fusions [4, 28•]. This growing use of BMP use has also been observed in revision spinal fusion procedures, similar to the overall growth seen with primary fusions [4, 26]. Of additional interest is the uninterrupted rise of BMP application in thoracic arthrodesis. Given that thoracolumbar fusions are generally performed to correct spinal deformity, the increased use of BMP for this procedure suggests that this adjunct may be gaining momentum in the correction of spinal deformities [30]. Although controversy continues regarding the “appropriate” indications for BMP, its application in spinal arthrodesis continues to rise for various forms of spinal arthrodesis procedures.

Demographics

The widespread growth in BMP use seen across multiple subtypes of spinal arthrodesis has led to several changes in

Table 1 Spinal fusion procedures with BMP utilization by year

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	r	P value
Total count	1116	12,355	25,902	38,909	55,146	61,756	73,722	73,855	77,739	79,294	0.97	<0.001
Frequency BMP use (%)	0.6	6.0	13.1	18.9	24.1	26.4	27.3	26.5	26.7	26.9	0.89	<0.001
Anterior cervical fusion	262	2142	3628	4151	8454	10,782	9743	9902	7895	8315	0.82	0.009
Frequency	0.3	2.1	3.9	4.5	8.5	10.6	8.7	8.4	6.9	6.4	0.71	0.02
Posterior cervical fusion	14	229	551	832	1260	1497	1925	1908	2144	2729	0.99	<0.001
Frequency	0.3	3.6	7.8	12.4	16.4	18.9	17.4	20.2	17.4	16.9	0.87	0.001
Thoracic fusion	15	209	481	709	961	994	1301	1593	2330	2539	0.98	<0.001
Frequency	0.8	10.0	21.8	27.9	31.2	201	38.7	40.9	43.1	45.3	0.95	<0.001
Anterior lumbar fusion	438	3333	5112	5283	6761	7000	7248	6791	7321	8637	0.89	<0.001
Frequency	4.7	30.2	51.5	47.9	56.9	54.3	56.1	49.4	54.4	56.7	0.87	0.001
Posterior lumbar fusion	388	6443	16,129	27,934	37,710	41,483	53,504	53,660	58,049	58,561	0.97	<0.001
Frequency	0.5	7.6	18.6	30.0	35.8	38.7	40.8	39.3	40.1	40.7	0.89	<0.001

r = Pearson Correlation Coefficient

Data from the National Inpatient Sample

Table 2 Patient and hospital demographics of BMP utilization by year

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	r	p-value
Total count	1116	12,355	25,902	38,909	55,146	61,756	73,722	73,855	77,739	79,294	0.97	<0.001
Age (Avg)	47.3	50.4	52.1	53.5	53.4	54.2	55.1	55.6	55.3	57.4	0.92	<0.001
% Male	41.2	44.4	44.3	44.6	44.3	45.3	45.2	46.1	45.5	44.1	0.67	0.04
% Female	58.8	55.6	55.7	55.4	55.7	54.7	54.8	53.9	54.5	55.9	−0.67	0.04
Race (% Caucasian)	82.5	85.5	85.7	85.7	86.5	87.2	87.4	85.1	86.5	75.6	0.31	0.4
Hospital location												
Rural	3.4	6.2	1.1	5.4	4.4	6.5	3.8	2.1	5.8	6.0	0.31	0.38
Urban	96.6	93.8	98.9	94.6	95.6	93.5	96.2	97.9	94.2	92.9	−0.38	0.29
Teaching hospital (%)	70.2	48.3	53.8	51.8	51.4	54.0	52.6	50.1	54.1	48.4	−0.53	0.14
Insurance												
Medicare	15.1	21.5	24.3	29.0	28.2	28.7	30.7	33.3	32.6	38.4	0.95	<0.001
Medicaid	2.5	4.9	3.7	4.9	3.9	3.7	4.0	4.0	5.5	4.4	0.4	0.2
Private	62.2	59.1	57.4	52.8	55.1	54.9	52.3	50.8	49.7	45.2	−0.94	<0.001
Other	20.2	14.6	14.7	13.3	12.8	12.8	12.9	11.9	12.1	10.9	0.85	0.001

r = Pearson Correlation Coefficient

Data from the National Inpatient Sample

the demographics of those undergoing these procedures. Ong et al. studied the differential use of BMP demographics from 2002–2007 revealing increased utilization of BMP across all patient groups, hospital types, and census regions with a slight trend toward older patients. However, there appeared to be ongoing disparities in differential rates of BMP application. The use of BMP was more prevalent in white populations compared with racial minority groups (29 % vs 21 %) and significantly less in those of lower socioeconomic levels with Medicaid (21 % vs 28 %). The differences observed may likely be due to the global disparity of access to care, often experienced by minorities and those of lower socioeconomic status. Additional differences were seen in regional utilization with the Midwest and West performing more arthrodeses with BMP. Similarly, Cahill et al. [2] identified several differences in BMP usage rates associated with patient demographics in 2006. Patients were more likely to undergo BMP application if they were women, white, and were Medicare insured. In a similar time period, Deyo et al. [16] selected Medicare beneficiaries who were 68 years and older with primary lumbar stenosis and underwent spinal arthrodesis from 2002–2008. This study found no significant differences in gender, race, or age associated with BMP use. The similar findings observed among different groups in this report may simply be a result of limiting the age and diagnosis of the cohort. However, the group receiving BMP was more likely to have had a previous spine surgery and a complex fusion procedure at the index procedure. Given that the complication rates were similar between those who received BMP and those who did not, the short-term benefit of BMP use for lumbar fusion remains uncertain. Future studies may examine additional beneficial effects of BMP in reducing reoperation rates of more complex patients that were unmeasured by this study.

A trend toward an older patient population with more comorbidities was observed by Nandyala et al. [28•]. This study also observed a 2-fold increase in Medicare recipients receiving BMP from 2002–2011 (15 %–34 %), while those with private insurance declined (62 %–45 %). This trend may reflect the aging population of the United States as 20 % of the US population is expected to be 65 years of age or older by 2030, as compared with 12.4 % in 2000 [31]. Additional research specifically targeting the application of BMP for spinal surgery in this patient population is paramount as BMP clinical trials have not explored patients with specific comorbidities including: inflammatory disease, metabolic illness, or cancer. This need is further emphasized by a recent YODA meta-analysis that discusses the lack of investigation

Fig. 1 Costs obtained from the National Inpatient Sample. Adjusted to 2011 dollar amounts

of older and sicker patients may be a fundamental pitfall of current BMP literature [32]. Although studies have shown that this aging population may not be the majority of patients receiving BMP, the lack of data exploring the safety profile and benefits in this rapidly growing group is a cause for concern. Additional trends have also been identified with an increased prevalence in rural hospitals, and decreased percentage of BMP use in teaching hospitals [28•] (Table 2). These trends speak to the widespread growth across different practice settings and geographic locations as more literature provides information guiding BMP application.

Cost

Debate exists surrounding the cost-effectiveness of BMP use in spine surgery. Several reports on the financial impact of BMP utilization have been published in literature. Although earlier reports have suggested that the use of BMP in spinal fusions will ultimately be cost-neutral because of decreased hospital stay, fewer needs for inpatient rehabilitation, decreased revision surgeries, and avoidable complications associated with ICBG [3, 33], recent publications have found significant increase in hospital charges related to BMP.

In spinal fusion patients receiving BMP from 2002–2008, Dagostino et al. [26], published findings that BMP was responsible for \$13,362 of increased overall hospital charges. When corrected for inflation, hospital charges still increased \$3670 per patient receiving BMP. To note, hospital charges only indirectly correlate with the expenditure health-care related resources and hospital collections. During a comparable time period, Fineberg et al. [20] found BMP use was associated with increased costs for all cervical fusions. On average, there was a \$5092 and \$6272 increase in hospital costs for ACFs and PCFs, respectively. A large percentage of the increase was thought to be from the cost of BMP itself, ranging from \$4,000–\$6,000 per treatment [34]. Cahill et al. [2] reported similar trends for patients who received BMP with spine surgery in 2006. BMP use was associated with significantly greater inpatient hospital charges across all fusion subtypes. Increases ranged from 11 %–41 % of hospital charges, with the greatest percentage increase in BMP application with anterior cervical fusions. This was likely partially related to greater implant charges, although additional sources of cost could not be evaluated. Specifically identifying Medicare patients, Deyo et al. [16] found operations involving BMP incurred a \$15,580 increase per patient compared with those without BMP treatment. However, actual Medicare reimbursements under the DRG prospective payment system are much lower, and the difference smaller. Data as recent as 2011, reveal hospital costs across all spinal fusion

subtypes with BMP application have continued to rise [28•] (Fig. 1).

Given that the use of BMP may increase bony-fusion rates, cost-effectiveness analyses should include longitudinal outcomes to evaluate for long-term hospital costs, rehabilitation, and need for revision. Additionally, the older patients with more comorbidities may partially explain the rising hospital costs associated with BMP application in spinal fusions. Further studies need to evaluate the perceived increased hospital charges correlated with the use of BMP and the clinical impact of this application as an adjunct for spinal fusion procedures.

Conclusions

BMP use as an adjunct in spinal fusion has continued to gain momentum despite the FDA's influence. Because of developing technological advances, it is not uncommon for specific uses of medical products to be considered as “the standard of care” before the FDA has granted full clearance or approval of additional “on-label” indications. Although restrictions have been published for “on-label” use and warning notifications announced for various complications, the spinal literature reveals widespread utilization of BMP use in spinal fusions on a national level. BMP has experienced increased application in PCFs, PLIFs, TLIFs, ALIFs, and thoracolumbar fusions, with PLIFs as the most prevalent subtype of arthrodesis utilizing BMP. The only exception to this rule is BMP utilization in the anterior cervical spine, which resulted in a downward usage trend following the 2008 FDA warning.

Given the fallout of the FDA warnings and growing uncertainty regarding risks associated with BMP in the anterior cervical region, further research may be necessary to determine the safety profile of this biological adjunct. The future application of BMP in spinal fusions, especially in ACFs, will need to be further clarified in terms of efficacy, complications, and cost-effectiveness. Additional large, nonconflicted studies will be necessary to further investigate the economic implications of BMP utilization with long-term follow-up in order to assess clinical function and complications.

Compliance with Ethics Guidelines

Conflict of Interest Philip K Louie and Hamid Hassanzadeh declare that they have no conflict of interest. Kern Singh has board membership with Vital 5 LLC, has been a consultant for Zimmer, Stryker, Globus, and receives royalties from Pioneer, Styker, Zimmer, and Thieme.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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