Prevalence, Complications, and Hospital Charges Associated With Use of Bone-Morphogenetic Proteins in Spinal Fusion Procedures

Kevin S. Cahill, MD, PhD, MPH
John H. Chi, MD, MPH
Arthur Day, MD
Elizabeth B. Claus, MD, PhD

Back pain continues to be a leading cause of disability in the United States and is one of the most common reasons for seeking evaluation by a physician, second only to the common cold.1-3 Non-surgical interventions remain the first-line of therapy; however, many patients eventually progress to surgical treatments with 1 option including fusion. Spinal arthrodesis (fusion) as a treatment for back pain has rapidly evolved with the development of advanced spinal instrumentation and biologics to promote bone fusion.4

Bone-morphogenetic proteins (BMPs) represent a family of differentiation factors that promote bone creation and remodeling.5 Clinical use of recombinant BMP protein was approved by the US Food and Drug Administration (FDA) in 2002 for surgery of the anterior lumbar spine to promote bone fusion.6 Two BMP products are commercially available for clinical use, BMP-2 (INFUSE, Medtronic, Memphis, Tennessee) and BMP-7 (OP-1 Putty, Stryker, Kalamazoo, Michigan). BMP-2 is approved for anterior lumbar interbody fusion in skeletally mature patients and BMP-7 received a humanitarian use device approval in 2003 for revision intertransverse lumbar fusion in compromised patients.6,7 Due to robust bone forming properties, BMP use may increase the likelihood of bony fusion thereby decreasing the undesired outcome of pseudarthrosis or nonunion.8

Context No national data exist to examine use of bone-morphogenetic proteins (BMPs) in spinal fusion surgery.

Objective To determine the patterns of use and rates of complications and financial charges associated with BMP use in spinal fusion nationally.

Design, Setting, and Patients Retrospective cohort study of 328,468 patients undergoing spinal fusion procedures from 2002-2006 identified from the Nationwide Inpatient Sample database, a 20% sample of US community hospitals.

Main Outcome Measures The rates of use of BMP among patients undergoing spinal fusion procedures are examined along with complications, length of stay, and hospital charges associated with use of this fusion adjunct.

Results The nationwide usage of BMP has increased from 0.69% of all fusions in 2002 to 24.89% of all fusions in 2006. Use of BMP varied by patient sex, race, and primary payer with increased use seen in women (56.26% with BMP vs 53.35% without BMP; odds ratio [OR], 1.12; 95% confidence interval, [CI], 1.09-1.16) and Medicare patients (29.62% with BMP vs 27.16% without BMP; OR, 1.43; 95% CI, 1.31-1.56) and decreased use in nonwhite patients (8.69% with BMP vs 10.23% without BMP; OR, 0.80; 95% CI, 0.75-0.85). When comparing immediate postoperative, in-hospital rates of complications for the year 2006 among patients undergoing spinal fusion by BMP use status, no differences were seen for lumbar, thoracic, or posterior cervical procedures. On univariate analysis and after multivariable adjustment, the use of BMP in anterior cervical fusion procedures was associated with a higher rate of complication occurrence (7.09% with BMP vs 4.68% without BMP; adjusted OR, 1.43; 95% CI, 1.12-1.70) with the primary increases seen in wound-related complications (1.22% with BMP vs 0.65% without BMP; adjusted OR, 1.67; 95% CI, 1.10-2.53) and dysphagia or hoarseness (4.35% with BMP vs 2.45% without BMP; adjusted OR, 1.63; 95% CI, 1.30-2.05). Bone-morphogenetic protein use was associated with greater inpatient hospital charges across all categories of fusion. Increases between 11% and 41% of total hospital charges were reported, with the greatest percentage increase seen for anterior cervical fusion.

Conclusion Bone-morphogenetic protein was used in approximately 25% of all spinal fusions nationally in 2006, with use associated with more frequent complications for anterior cervical fusions and with greater hospital charges for all categories of fusions.


©2009 American Medical Association. All rights reserved.
An additional clinical benefit relates to the decreased morbidity from bone-graft harvest because solid fusion may be achieved without the need for autologous graft.9,10 Although BMP is FDA approved for use only in the lumbar spine, recent work has focused on applications at other spine levels, including use in cervical interbody fusion.11,12 Complications following use of BMP in humans have been reported for both lumbar as well as cervical fusion procedures.13-16 The finding of postoperative neck edema following use in the anterior cervical spine has been reported to occur in 7% of patients in a retrospective review of 200 cases, while a smaller study of 30 cases reported a rate as high as 50%.15,16,10 The FDA recently released a public health notification regarding 38 reported complications related to neck edema with resulting airway or neurological compression in the past 4 years following use in cervical spine fusion.20

The current rates and patterns of BMP use since the clinical introduction more than 5 years ago are not known at the national level and no population-based data are available. Likewise, the complication rates and financial impact associated with national BMP usage have not been evaluated. The objective of this study was to examine the national trends in the adaptation of BMP into clinical practice since 2002 and the association between BMP use and postoperative complications, length of stay, and hospital charges.

**METHODS**

The Nationwide Inpatient Sample (NIS) database, a nationwide sample of hospital discharge records, is part of the Healthcare Cost and Utilization Project and contains data from 5 to 8 million discharges each year.21 The NIS discharges include all payers and are from a sample of hospitals that approximates a 20% sample of US community hospitals. The NIS and other administrative databases have been extensively used for analysis of trends in spinal surgery.22-28 For spinal fusions, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes have been continually updated to reflect technical changes and advances in spine surgery. In 2001, the codes were updated to include specific revision fusions and in 2002 to include BMP insertion and the levels of fusion. Data from the year 2002, the year BMP-2 was approved, until year 2006, the latest database publicly available, was used for the retrospective cohort study presented herein. The study was approved by the Partners Human Research Committee.

The total number of primary fusions and revision fusions were examined nationally each year since 2002. Unique ICD-9-CM codes for revision fusion were introduced in 2001 and the secondary procedure code for BMP in 2002. Surgical fusion procedures were identified by ICD-9-CM codes for primary (81.00-81.09) and revision surgery. The fusions using BMP were identified by the secondary procedure code for insertion of recombinant BMP (84.52). Trends in off-label use were determined through further classification of cases into cervical (81.01-81.03, 81.31-81.33), thoracolumbar (81.04-81.05, 81.34-81.35), and lumbosacral (81.06-81.08, 81.36-81.38). The number of vertebral levels fused was categorized as 2 to 3 levels (code 81.62), or 4 or more levels (81.63, 81.64).

Surgical cases were categorized by the spine-related clinical diagnosis that was the likely medical reason for the fusion. Cases were then dichotomized into fusions performed for degenerative disease and disk herniation (ICD-9-CM codes: 722.0-722.7, 722.9, 724.0, 723.7, 721, 738.4) or other diagnoses. Medical comorbidity stratification was performed using the Charlson et al27 co-morbidity index adapted by Deyo et al.28 for use on ICD-9-CM codes.29 Due to the small number of patients with Charlson co-morbidity score greater than 11, patients with a score of 11 or greater were analyzed together. Zip code income quartile was included to evaluate the interaction between BMP use and patient socioeconomic status. Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were determined for the association of patient and operative characteristics with likelihood of BMP use during fusion.

Complications included only those reported during the postoperative inpatient hospitalization following the fusion procedure. Complications were identified using a modified classification scheme as described by Wang et al30 and are listed in TABLE 1. The following ICD-9-CM codes were used for complication classification: dysphagia or hoarseness (478.30, 478.31, 478.32, 478.33, 478.34, 784.4, 787.2); wound-related complications including infection, dehiscence, seroma, and hematoma (998.1, 998.11, 998.12, 998.13, 998.3, 998.31, 998.32, 998.83, 998.5, 999.3, 998.51, 998.59); medical complication including myocardial infarction, shock, deep vein thrombosis, pneumonia, and pulmonary embolus (997.1, 410.0-410.9, 998.0, 997.3, 415.1, 997.2); central nervous system (CNS) complication including stroke, hemorrhage, and other central nervous system complication (997.09, 997.01, 997.00, 997.0); and other unspecified complications not otherwise classified (998.8, 998.89, 998.999.9). The primary outcome was defined as the occurrence of at least 1 complication. To allow practice patterns to stabilize, the analysis of complications was limited to lumbar, thoracic, and cervical fusions performed in the most recent year of the NIS database, 2006, involving patients older than 18 years.

Unadjusted ORs and 95% CIs were determined for the association of any complication with BMP usage. Multivariable logistic regression was used to calculate the ORs for complications after adjusting for age, sex, race, clinical diagnosis other than disk herniation or degenerative disease, category of Charlson co-morbidity score, household income quartile based on patient address zip code, nonelective admission, levels of fusion performed, revision or primary fusion, geographic region, and surgery at a teaching hospital. The NIS database contains the following race.
BONE-MORPHOGENETIC PROTEIN IN SPINAL FUSION

Age, mean (SD), y 53.79 (14.07) 53.26 (13.91) 1.00 (1.00-1.00)
Hospital type
Teaching 9282 (52.67) 31 124 (58.70) 0.78 (0.75-0.80)
Nonteaching or unknown 8341 (47.33) 21 902 (41.30) 1 [Reference]
Hospital location
Northeast 2046 (11.61) 8134 (15.34) 1 [Reference]
Midwest 4293 (24.36) 13 409 (25.29) 1.27 (1.19-1.35)
South 7884 (44.74) 22 421 (42.28) 1.39 (1.32-1.47)
West 3400 (19.29) 9062 (17.09) 1.49 (1.40-1.58)
Primary payer
Medicare 5220 (29.62) 14 400 (27.16) 1.43 (1.31-1.56)
Medicaid 719 (4.08) 2838 (5.35) 1 [Reference]
Private 9324 (52.91) 28 739 (54.20) 1.28 (1.17-1.39)
Other or unknown 5326 (30.22) 16 980 (32.02) 0.89 (0.86-0.93)
Days in hospital, mean (SD)
<25 000 3951 (22.42) 11 971 (22.58) 1 [Reference]
25 000-34 999 4591 (26.05) 13 950 (26.31) 1.06 (1.01-1.12)
35 000-44 999 5067 (28.75) 14 355 (27.07) 1.00 (0.94-1.04)
≥45 000 4013 (22.77) 12 749 (24.04) 0.95 (0.90-1.00)
Diagnosis
Disk herniation or degenerative disease 12 463 (70.72) 40 116 (75.65) 1 [Reference]
Other conditions 5160 (29.28) 12 910 (24.35) 1.28 (1.23-1.33)
Vertebral levels
1-2 14 633 (83.03) 44 846 (84.57) 1 [Reference]
3-4 2990 (16.97) 8180 (15.43) 1.12 (1.07-1.17)
Hospital type
Teaching 9282 (52.67) 31 124 (58.70) 1.27 (1.19-1.35)
Nonteaching or unknown 8341 (47.33) 21 902 (41.30) 1 [Reference]
Hospital location
Northeast 2046 (11.61) 8134 (15.34) 1 [Reference]
Midwest 4293 (24.36) 13 409 (25.29) 1.27 (1.19-1.35)
South 7884 (44.74) 22 421 (42.28) 1.39 (1.32-1.47)
West 3400 (19.29) 9062 (17.09) 1.49 (1.40-1.58)

Postoperative length of stay and the total charge for the hospitalization were directly obtained from the NIS data. The NIS database provides information only on the total charge for the inpatient hospitalization. This charge represents the sum of all charges during the hospitalization except for professional fees. Logarithmic transformation was used for length of stay and total charges when performing the analyses because of the significant positive skew of the data. Multiple linear regression analysis was performed to examine the association between BMP use and hospital charges or length of stay. Statistical significance was defined as a type I error (α) less than 0.05. The large sample size permitted a statistical power of at least 80% to detect the following absolute differences in complication rates between groups: 1% difference for anterior cervical cases, 2% difference for posterior cervical fusions and thoracic fusions, and 0.5% difference for lumbar fusions. Statistical analyses were performed with unweighted data with SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Across spinal fusions performed in 2006, there were 70 649 procedures identified, of which 45 871 cases used the procedure code for insertion of recombinant BMP. The use of BMP in primary and revision fusions has increased yearly since clinical introduction in 2002. In 2002, the year of FDA approval, the estimated total number of spine fusion cases that used BMP was 429, representing 0.69% of all fusions. The number of fusions using BMP increased to 17 623 cases in 2006, representing usage for 24.3% of all primary spinal fusions and 36.6% of revision fusions (P < .001). As seen in the Figure, the percentage of cervical, thoracic, and lumbar fusions that used BMP has increased each year (P < .001).

There were 70 649 fusion procedures identified for the year 2006, 24.89% of which used BMP. The patient and operative demographics according to BMP use status for fusions performed in 2006 are listed in Table 1. The mean age of patients undergoing spinal fusion with BMP was 53.79 years compared with 53.26 years for fusions without BMP (P < .001). There were differences in BMP utilization according to patient and a number of operative characteristics (Table 1).
There were significant differences in BMP use according to patient sex and race. Women and white patients were more likely to receive BMP than were men and nonwhites, respectively (OR, 1.12; 95% CI, 1.09-1.16 for women vs men; OR, 0.80; 95% CI, 0.75-0.85 for nonwhite vs white). The use of BMP decreased with increasing medical comorbidities as determined by the Charlson score (incremental OR, 0.95; 95% CI, 0.93-0.96 per unit increase). The use of BMP did not differ significantly according to income quartile; however, differences were seen in the use of BMP cases according to primary payer with Medicaid patients less likely to undergo a fusion with BMP than all other primary payers.

Fusions performed for clinical conditions other than degenerative disease or disk herniation were associated with increased BMP use (OR, 1.28; 95% CI, 1.23-1.33) and BMP use was more frequent in surgeries with increased levels of fusion as well as in revision procedures (OR, 1.81; 95% CI, 1.69-1.93 for revision fusions). The distribution of BMP use by anatomic segment of fusion indicated that cervical and thoracolumbar fusions were less likely to use BMP. Additionally, the teaching status and geographic location of the hospital were also significantly related to BMP use with less BMP use at teaching hospitals (OR, 0.78; 95% CI, 0.75-0.80) and the highest use in the West region compared with the Northeast region (OR, 1.49; 95% CI, 1.40-1.58).

The rates of complication occurrence following BMP use were analyzed individually for lumbar, thoracic, posterior cervical, and anterior cervical fusions performed in 2006. Table 2 lists the rates of occurrence of complications and the ORs for complication occurrence associated with BMP use by site of fusion. There were no differences in the rates of overall complications based on BMP use for fusions of the lumbar, thoracic, or posterior cervical spine. For anterior cervical fusions, the rate of any complication in cases that used BMP was 7.09%. This was 51.4% higher than the rate of 4.68% in similar cases that did not use BMP (P < .001) and corresponded to an OR of 1.55 (95% CI, 1.31-1.84) for complication occurrence. Analysis of individual complications indicated that this corresponded to increased rates of voice and swallowing related complications for those with vs without BMP (4.35% vs 2.45%; OR, 1.80; 95% CI, 1.45-2.24) as well as wound-related complications such as seroma or hematoma (1.22% vs 0.65%; OR, 1.89; 95% CI, 1.26-2.83).

Complication rates are presented by patient and operative characteristics in Table 3 for all segments of fusion. For anterior cervical fusion procedures in 2006, there was a significant increase in the odds of complications occurrence for cases that used BMP (7.09% vs 4.68%; OR, 1.55; 95% CI, 1.31-1.84). Additional significant univariate predictors of complications for anterior cervical fusions were increasing age (OR per year increase, 1.03; 95% CI, 1.02-1.03), nonwhite compared with white race (5.99% vs 4.89%; OR, 1.24; 95% CI, 1.04-1.47), diagnosis other than disk herniation or degener-
operative disease (12.24% vs 3.90%; OR, 3.43; 95% CI, 3.03-3.83), and increasing number of Charlson comorbidities (OR per unit increase, 1.38; 95% CI, 1.33-1.44). The operative characteristics of performance of revision fusion, increased levels of vertebrae fused, and nonelective fusion also were associated with greater odds of complications. Complications were less frequent in female patients than in male patients (4.34% vs 5.46%; OR, 0.78; 95% CI, 0.70-0.87) and patients with private insurance (4.03% vs 5.70%; OR, 0.69; 95% CI, 0.54-0.88 vs Medicaid).

For fusions performed in the posterior cervical spine, BMP was not associated with increased complication rates (10.04% vs 9.95%; OR, 1.01; 95% CI, 0.72-1.40). The only significant predictors of increased complications were clinical diagnosis other than disk herniation or degenerative disease (13.16% vs 7.18%; OR, 1.96; 95% CI, 1.52-2.51), increasing Charlson comorbidity score (incremental OR, 1.14; 95% CI, 1.06-1.23), and nonelective sur-

### Table 3. Complication Event Rates According to Patient and Operative Characteristics by Anatomic Segment of Fusion

<table>
<thead>
<tr>
<th>Bone-morphogenetic protein</th>
<th>Anterior Cervical (n = 27 067)</th>
<th>Posterior Cervical (n = 2869)</th>
<th>Thoracic (n = 3257)</th>
<th>Lumbar (n = 36 807)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (OR per year increase)</td>
<td>1.03 (1.02-1.05)</td>
<td>0.99 (0.99-1.01)</td>
<td>1.00 (0.99-1.01)</td>
<td>1.01 (1.01-1.02)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>766 (4.89)</td>
<td>168 (10.00)</td>
<td>312 (16.91)</td>
<td>1508 (6.92)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>161 (5.99)</td>
<td>47 (10.44)</td>
<td>89 (23.48)</td>
<td>309 (9.15)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degenerative or disk disease</td>
<td>932 (3.90)</td>
<td>110 (7.18)</td>
<td>71 (11.58)</td>
<td>1670 (6.34)</td>
</tr>
<tr>
<td>Other conditions</td>
<td>389 (12.24)</td>
<td>176 (13.16)</td>
<td>190 (15.23)</td>
<td>943 (9.02)</td>
</tr>
<tr>
<td>Income level, $≤24 999</td>
<td>311 (5.03)</td>
<td>71 (9.86)</td>
<td>128 (17.88)</td>
<td>531 (6.51)</td>
</tr>
<tr>
<td>&gt;25 000-34 999</td>
<td>345 (4.92)</td>
<td>76 (10.30)</td>
<td>130 (16.11)</td>
<td>690 (7.04)</td>
</tr>
<tr>
<td>&gt;35 000-44 999</td>
<td>361 (4.91)</td>
<td>79 (10.45)</td>
<td>147 (16.68)</td>
<td>723 (7.03)</td>
</tr>
<tr>
<td>Healthcare coverage Medicaid</td>
<td>79 (5.70)</td>
<td>32 (14.88)</td>
<td>76 (24.52)</td>
<td>99 (6.21)</td>
</tr>
<tr>
<td>Medicare</td>
<td>410 (7.50)</td>
<td>107 (17.04)</td>
<td>158 (17.32)</td>
<td>1078 (9.04)</td>
</tr>
<tr>
<td>Private</td>
<td>674 (4.03)</td>
<td>121 (5.99)</td>
<td>253 (15.93)</td>
<td>1107 (6.09)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>158 (4.55)</td>
<td>28 (8.10)</td>
<td>74 (16.63)</td>
<td>328 (6.44)</td>
</tr>
<tr>
<td>Surgery type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>955 (4.08)</td>
<td>160 (7.74)</td>
<td>228 (13.15)</td>
<td>2257 (6.77)</td>
</tr>
<tr>
<td>Nonelective</td>
<td>360 (9.20)</td>
<td>258 (2.28-2.93)</td>
<td>322 (21.83)</td>
<td>356 (10.29)</td>
</tr>
<tr>
<td>Fusion type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>1245 (4.73)</td>
<td>262 (10.19)</td>
<td>501 (17.05)</td>
<td>2350 (6.89)</td>
</tr>
<tr>
<td>Revision</td>
<td>76 (7.55)</td>
<td>24 (8.08)</td>
<td>18 (8.07)</td>
<td>32 (6.44)</td>
</tr>
<tr>
<td>Vertebral levels fused</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>1014 (4.33)</td>
<td>158 (9.29)</td>
<td>248 (16.63)</td>
<td>2088 (6.48)</td>
</tr>
<tr>
<td>≥4</td>
<td>307 (8.45)</td>
<td>120 (9.06)</td>
<td>124 (15.23)</td>
<td>525 (11.51)</td>
</tr>
<tr>
<td>Institution type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonteaching hospital</td>
<td>488 (4.14)</td>
<td>68 (8.72)</td>
<td>122 (15.23)</td>
<td>1123 (6.72)</td>
</tr>
<tr>
<td>Teaching hospital</td>
<td>833 (4.55)</td>
<td>218 (10.44)</td>
<td>439 (17.87)</td>
<td>1490 (7.42)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>184 (5.04)</td>
<td>71 (11.32)</td>
<td>123 (20.85)</td>
<td>385 (7.48)</td>
</tr>
<tr>
<td>Midwest</td>
<td>309 (4.70)</td>
<td>64 (11.55)</td>
<td>111 (16.20)</td>
<td>777 (9.75)</td>
</tr>
<tr>
<td>South</td>
<td>539 (4.42)</td>
<td>97 (8.28)</td>
<td>196 (15.60)</td>
<td>967 (6.25)</td>
</tr>
<tr>
<td>West</td>
<td>289 (6.23)</td>
<td>54 (10.44)</td>
<td>132 (18.03)</td>
<td>484 (7.53)</td>
</tr>
</tbody>
</table>
BONE-MORPHOGENETIC PROTEIN IN SPINAL FUSION

The association between BMP use and postoperative complications was examined. BMP use was associated with an increased frequency of complications (16.47% vs 17.41%; OR, 0.93; 95% CI, 0.75-1.16). Significant predictors of complications in thoracic fusions included nonwhite compared with white race (24.38% vs 16.91%; OR, 1.58; 95% CI, 1.21-2.07), diagnosis other than disk herniation or degenerative disease (18.53% vs 11.58%; OR, 1.73; 95% CI, 1.33-2.26), and increasing Charlson morbidity score (incremental OR, 1.04; 95% CI, 1.01-1.08). Female sex and private insurance were associated with reduced odds of complications.

For lumbar fusion, BMP use was not associated with increased frequency of complications (6.97% vs 7.18%; OR, 0.96; 95% CI, 0.89-1.05). Complications were significantly more frequent in lumbar fusions with increasing age (incremental OR, 1.01; 95% CI, 1.01-1.02), nonwhite compared with white race (9.15% vs 6.92%; OR, 1.35; 95% CI, 1.19-1.54), increasing Charlson morbidity score (incremental OR, 1.28; 95% CI, 1.24-1.32), and a diagnosis other than degenerative disease or disk herniation (9.02% vs 6.34%; OR, 1.46; 95% CI, 1.34-1.59). Likewise, complications were more frequent for non elective than for elective surgeries (10.29% vs 6.77%; OR, 1.57; 95% CI, 1.40-1.77), revision fusions compared with primary fusions (9.78% vs 6.89%; OR, 1.46; 95% CI, 1.28-1.67), and fusions with 4 or more vertebrae fused compared with 2 to 3 vertebrae (11.51% vs 6.48%; OR, 1.87; 95% CI, 1.69-2.07).

Multivariable logistic regression was then used to simultaneously adjust for the patient characteristics of age, sex, race, income, diagnosis, medical comorbidities, non elective admission status, primary payer, as well as the operative variables of the number of levels reported fused during the procedure, revision surgery, hospital location, and teaching hospital status. For lumbar, thoracic, and posterior cervical fusion, BMP use was not associated with increased odds of complication after multivariable adjustment (OR for posterior cervical fusion, 1.03; 95% CI, 0.73-1.44; thoracic fusion, 1.05; 95% CI, 0.83-1.32; and lumbar fusion, 1.03; 95% CI, 0.95-1.12). Complications were more frequent in anterior cervical fusions performed with BMP after multivariable adjustment (OR, 1.43; 95% CI, 1.20-1.70). The adjusted ORs for individual complications in anterior cervical fusion are listed in Table 4. Higher adjusted odds for occurrence of wound complications such as hematoma or seroma as well as dysphagia and hoarseness were seen in cases that used BMP (OR, 1.67; 95% CI, 1.10-2.53 for wound complications; OR, 1.63; 95% CI, 1.30-2.05 for dysphagia or hoarseness).

The association between BMP use and postoperative length of stay and total hospital charges for the fusion procedure was determined. The median length of stay and median total charges, as well as the unadjusted and adjusted percentage change with BMP use are listed in Table 5. In unadjusted analyses, the use of BMP was associated with a 3.89% (95% CI, 1.46%-6.38%) longer length of stay in anterior cervical fusion. For thoracic fusions, the use of BMP was associated with a 7.95% (95% CI, –12.96% to –2.66%) shorter length of stay. After multivariable adjustment for patient and operative characteristics, BMP use was a significant predictor of a longer length of stay for anterior cervical fusions (2.30% increase; 95% CI, 0.35%-4.29%); posterior cervical fusions (12.06% increase; 95% CI, 5.84%-18.64%), and lumbar fusions (3.17% increase; 95% CI, 2.24%-4.11%).

BMP use in all categories of fusions was associated with greater total hospital charges. The greatest percentage increase was found for BMP use in anterior cervical fusion, for which the median hospital charge without BMP was $31,179 and with BMP $46,112. This corresponded to 41.58% (95% CI, 38.04%-45.21%) higher charges on univariate analysis and 36.37% (95% CI, 33.36%-39.45%) higher charges after multivariable adjustment. Likewise, for posterior cervical, thoracic, and lumbar fusions with BMP use, total adjusted hospital charges were greater by 13.98% to 37.24%, respectively.

COMMENT

Although no formal utilization guidelines exist, BMP use has been rapidly incorporated into the practice of spinal fusion since the clinical introduction in 2002 and is now used in approximately 25% of all fusions nationally. To our knowledge, this is the first report to examine the national patterns of use of this novel biological agent for spine fusion and provides insight to the widespread application of the product for both FDA approved applications as well as for off-label applications such as cervical and thoracic fusions.

In these data, differences in BMP usage rates were associated with patient demographics, including sex, race, and primary payer, as well as operative and hospital characteristics. Patients more likely to receive BMP were women, white, and Medicare insured, although our findings relative to race

---

Table 4. Association of Postoperative Complications With Bone-Morphogenetic Protein Use by Anatomic Segment of Fusion

<table>
<thead>
<tr>
<th>Complications</th>
<th>Anterior Cervical</th>
<th>Posterior Cervical</th>
<th>Thoracic</th>
<th>Lumbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>1.43 (1.20-1.70)</td>
<td>1.03 (0.73-1.44)</td>
<td>1.05 (0.83-1.32)</td>
<td>1.03 (0.95-1.12)</td>
</tr>
<tr>
<td>Wound</td>
<td>1.67 (1.10-2.53)</td>
<td>1.11 (0.60-2.05)</td>
<td>0.78 (0.53-1.17)</td>
<td>0.93 (0.80-1.08)</td>
</tr>
<tr>
<td>Dysphagia or hoarseness</td>
<td>1.63 (1.30-2.05)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, nonapplicable.

a Adjusted for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, medical comorbidities, levels fused, primary payer, and geographic location of hospital.

b Including central nervous system, medical, or unspecified complications.
must be interpreted cautiously in light of the large percentage of patients in the NIS database with unknown race information (approximately 30%). Although previous work has indicated that spinal fusion utilization rates vary according to race and sex, there has been no data on the disparities in utilization of novel fusion technologies such as biologics or instrumentation.\(^{38}\) Additionally, although not addressed in this analysis, there have been differences in the rates of utilization of high volume hospitals for surgical procedures described for minority and Medicaid patients that may be related to our findings.\(^{39}\) Likewise, geographic variation in utilization of spinal fusion and spinal fusion technology has been documented and our findings indicate differential rates of BMP use according to geographic region.\(^{40}\)

Postoperative complications following BMP use have been the subject of recent national debate with estimates of complications after anterior cervical use ranging from 7% to 50% in case series.\(^{11,14-16,20,22,13}\) These studies are limited by low sample sizes and are obtained primarily from clinical series. The current report allows for an evaluation of complications in national use in more than 17,000 fusions performed with BMP in 2006 and provides enhanced statistical power as well as a known population reference group. We found an approximately 50% higher complication rate after BMP use in anterior cervical fusion, for an overall complication rate of 7.09% (\(P = .01\)). After multivariate adjustment, the odds for wound-related complications and dysphagia or voice-related complications were significantly greater for cases that used BMP. This analysis also indicated that BMP use in lumbar, thoracic, and posterior cervical fusions was not associated with a greater frequency of inpatient complications. These findings confirm the results from smaller series yet indicate a lower complication rate than found in reports from case series.

A number of limitations exist in these data. First, the NIS database used for this analysis does not provide longitudinal data for individual patients and therefore cannot provide reoperation rates for individual patients according to BMP usage status. Within the literature, trends in the rates of revision procedures have not been evaluated since the introduction of BMP into clinical practice. Second, this analysis was of inpatient complications and does not include delayed complications in the outpatient setting; hence, length of stay is intrinsically associated with rate of complications. The local complications that have been described following BMP use in cervical fusion, such as edema, respiratory distress, and hematoma, have been described in both the postoperative hospitalization as well as the cause for readmission.\(^{12,15,19}\) In an effort to address this issue, length of stay was included in the analysis without a significant change in result. Furthermore, the validity of the application of administrative databases based on ICD-9-CM codes to the analysis of postoperative complications has been evaluated and has known limitations.\(^{34-36}\)

Previous examination of the validity of reporting of complication rates among patients who have had spine surgery using administrative data indicates that the specificity of complication reporting is high but that the sensitivity for complication detection is lower.\(^{35}\) These caveats suggest that our estimates may be viewed as a lower bound for the true rate of complication occurrence associated with BMP use and may also account for the lower complication rate reported in this study compared with prior case series. Furthermore, the actual amount of BMP used in the procedure is not coded and therefore cannot be analyzed. There is growing support for decreased complications with smaller doses of BMP, a result that would not be detectable in this analysis.\(^{11,16}\)

### Table 5. Association of Bone-Morphogenetic Protein Use With Length of Stay and Hospital Charges

<table>
<thead>
<tr>
<th></th>
<th>Anterior Cervical</th>
<th>Posterior Cervical</th>
<th>Thoracic</th>
<th>Lumbar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With BMP</td>
<td>Without BMP</td>
<td>With BMP</td>
<td>Without BMP</td>
</tr>
<tr>
<td><strong>Median length of stay, (IQR), d</strong></td>
<td>1 (1 to 2)</td>
<td>1 (1 to 2)</td>
<td>4 (1 to 7)</td>
<td>4 (1 to 7)</td>
</tr>
<tr>
<td>Increase % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.89 (1.46 to 6.38)</td>
<td>3.81 (-3.47 to 11.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>2.30 (0.35 to 4.29)</td>
<td>12.06 (-5.84 to 18.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median total charges, (IQR), $</strong></td>
<td>46112 (33,014 to 64,169)</td>
<td>31,179 (22,597 to 44,238)</td>
<td>70,868 (50,376 to 111,175)</td>
<td>52,073 (35,682 to 84,902)</td>
</tr>
<tr>
<td>Increase (95% CI), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>41.58 (38.04 to 45.21)</td>
<td>31.17 (22.05 to 40.97)</td>
<td>11.58 (5.40 to 18.13)</td>
<td>13.98 (8.19 to 20.07)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>36.37 (33.36 to 39.45)</td>
<td>37.24 (29.00 to 46.00)</td>
<td>13.98 (8.19 to 20.07)</td>
<td>20.02 (12.96 to 27.06)</td>
</tr>
</tbody>
</table>

Abbreviations: BMP, bone-morphogenetic protein; CI, confidence interval; IQR, interquartile range;
*Adjusted for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, medical comorbidities, levels fused, primary payer, and geographic location of hospital.
The association of BMP use during spine fusion with increased length of postoperative hospitalization has not been fully explored. A previous report of 151 patients treated with BMP reported prolongation of hospitalization in 8.6% of patients following BMP use in fusion. In the current report, BMP use was associated with a longer length of immediate postoperative hospitalization following multivariate adjustment for anterior cervical fusions, posterior cervical fusions, and lumbar fusions although the magnitude of the effect was small. The analysis of BMP use and length of stay is complex; it is well known that the length of stay can be influenced by multiple other factors unrelated to the medical condition such as hospital type, location, primary payer, and patient characteristics. Although we adjusted for several of these factors, there are likely many other factors that went unaccounted.

The economic implications of BMP use during spinal fusion have also had little formal analysis. In this report, BMP use was associated with higher total hospital charges for all categories of fusions after multivariate adjustment. Although hospital charges do not reflect the amount reimbursed to the hospital and are subject to interfacility and regional variation, higher charges were consistently seen in cases that used BMP. This is likely partially related to greater implant charges for cases that use BMP, which has been reported in smaller case series, although there may be other causes of the higher charges that cannot be evaluated in this study. The decision to use BMP to increase bony-fusion rates may decrease the need for a revision fusion procedure; therefore, cost-effectiveness analyses must include longitudinal outcomes that are not possible in this analysis. A recent report indicated that compared with lumbar fusions with iliac crest bone graft, the total costs including the first 90 days after hospitalization were less for procedures that utilized BMP. This effect was thought to be due to decreases in posthospitalization costs. An older study on the cost-effectiveness of BMP use indicated that from the payer perspective, the initial cost of BMP (estimated to be $4000), will be offset by the increased rate of fusion and decreased complications from iliac crest bone graft harvest resulting in an overall cost-neutral effect of BMP. The data presented in the current report only include in-hospital charges and do not account for differential charges after the hospitalization. As such, the effect of BMP on the rate of nonunion or number of revision surgeries a given patient undergoes cannot be directly determined.

In conclusion, this report highlights the robust nationwide application of BMP in spinal fusion procedures in the first 5 years of clinical usage since FDA approval. The association of BMP use with complication occurrence in anterior cervical fusion, as well as the increases in length of stay and hospital charges, illustrate the need to continue to develop refined guidelines for usage and to further study the long-term risks and benefits of usage.

**Author Contributions:** Dr Cahill had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cahill, Chi, Claus. Acquisition of data: Cahill, Day, and Drafting of the manuscript: Cahill, Claus.

**Critical revision of the manuscript for important intellectual content:** Cahill, Chi, Claus, Day.

**Statistical analysis:** Cahill, Claus.

**Obtained funding:** Day, Claus. Administrative, technical or material support: Day. Study supervision: Claus, Day.

**Financial Disclosures:** None reported.

**Funding/Support:** This work was supported by the Brain Science Foundation.

**Role of the Sponsors:** The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

**REFERENCES**

20. US Food and Drug Administration Public Health Notification. Life-threatening complications Associated with Recombinant Human Bone Morpho-


A civilization which develops only on its material side, and not in corresponding measure in the sphere of the spirit, is like a ship with defective steering gear which gets out of control at a constantly accelerating pace, and thereby heads for catastrophe.

—Albert Schweitzer (1875-1965)