Trends of Posterior Long Segment Fusion with and without Recombinant Human Bone Morphogenetic Protein 2 in Patients with Scoliosis

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Abstract

Study Design Retrospective study.

Objective Symptomatic scoliosis can be a source of severe pain and disability. When nonoperative treatments fail, spine fusion is considered as an effective procedure in scoliosis management. The purpose of this study was to evaluate the trends of patients with scoliosis undergoing posterior long segment fusion (PLSF) with and without recombinant human bone morphogenetic protein 2 (rhBMP-2).

Methods Patients within the orthopedic subset of Medicare database undergoing PLSF from 2005 to 2011 were identified using the PearlDiver Patient Records Database. Both diagnosis and procedural International Classification of Diseases, ninth edition and Current Procedural Terminology codes were used. The year of procedure, age, sex, region, and rhBMP-2 use were recorded.

Results In total, 1,265,591 patients with scoliosis were identified with 29,787 PLSF surgeries between 2005 and 2011. The incidence of PLSF procedures increased gradually from 2005 to 2009, decreased in 2010 (p < 0.01), and grew again in 2011. Patients over age 84 years had the highest incidence of PLSF. The lowest incidence of the procedures was in the Northeast, 5.96 per 100,000 patients. Sex differences were observed with a male-to-female ratio of 0.40 (p < 0.01). The use of rhBMP-2 for PLSF
Introduction

The incidence of adult scoliosis ranges from 2 to 32%. In 2005, Schwab et al reported the scoliosis prevalence of 68% in the healthy elderly adult population. Patients with adult scoliosis can suffer from a combination of low back pain, sciatica, and esthetic considerations related to disability. With the aging population rapidly increasing and more attention paid to quality of life, both physicians and elderly people consider this spinal deformity a considerable health care concern. There will most likely be an increase in surgical rates in the population with adult scoliosis because numerous studies have demonstrated that patients with symptomatic adult scoliosis achieved increased quality of life after the surgical treatment.

With abnormal spinal alignment in adult patients with scoliosis, achieving improved sagittal and coronal balance while appropriately decompressing the neural elements should be the goals of any surgical intervention. Unfortunately, poor local bone quality and quantity and the need to achieve a solid arthrodesis across multiple vertebral segments, coupled with the underlying medical comorbidities in this population, continue to pose a challenge for surgeons to achieve a successful posterior long segment fusion (PLSF). Alternatives to iliac crest bone graft have been pursued in hopes of avoiding the morbidity associated with its harvest. A series of clinical research on bone graft enhancement or graft substitutes led to the U.S. Food and Drug Administration (FDA) approval of recombinant human bone morphogenetic protein 2 (rhBMP-2), an iliac crest bone graft substitute, for anterior lumbar interbody fusion with an LT-CAGE (Medtronic, Minneapolis, Minnesota, United States). Due to the successful clinical effect, the off-label use of rhBMP-2 has been extended for posterolateral spinal fusion and achieved clinical success both in long and short fusion procedures. However, controversies continue because of the increased complication rates with rhBMP2 off-label use, concerns for underreported complications in the initial Investigational Device Exemption studies, and greater costs compared with other bone graft substitutes. Multiple case studies on rhBMP complications including ectopic bone formation, seroma, neck swelling, hematoma, and dysphagia have been summarized by Benglis et al and Ropper and Groff. The FDA issued a public health notification (July 2008) about the life-threatening complications of rhBMP-2/INFUSE (Medtronic, Minneapolis, Minnesota, United States) when utilized in cervical spine fusions. In addition, there are currently several lawsuits involving patients who have received rhBMP-2 in their surgeries.

The purpose of this study was to evaluate the demographic trend of posterior spine fusion for scoliosis and better understand rhBMP-2 off-label use for PLSF procedure.

Materials and Methods

A commercially available, searchable, online database comprised of patient insurance billing records was used (PearlDiver Patient Record Database, www.pearldiverinc.com; PearlDiver, Inc., Fort Wayne, Indiana, United States). The database is searchable by both the diagnosis ICD-9 (International Classification of Diseases, ninth edition) and procedure CPT (Current Procedural Terminology) codes. Our study was deemed exempt from Institutional Review Board review as all patient information was de-identified. We conducted a search using the orthopedic subset of the standard analytical files of Medicare database for all patients with scoliosis who underwent a PLSF procedure between 2005 and 2011. We included patients with an initial diagnosis of scoliosis as well as those who presented with progressive deformity in early adulthood. We identified patients based on the ICD-9 diagnosis codes (Table 1), CPT/ICD-9 procedure codes (Table 2), and inclusion or exclusion of ICD-9 code 84.52 (insertion of rhBMP; Table 1). Patients with ICD-9 code 81.62 for fusion or refusion of two to three vertebrae as short segment posterolateral fusion procedures were excluded. The incidence was calculated as the number of the elated code identified per every 100,000 patients searched in the database. Patients were stratified by the geographic region (Northeast, South, Midwest, and West), age group (less than 65, 65 to 69, 70 to 74, 75 to 79, 80 to 84, and greater than 84), year (2005 to 2011), and sex.

For our statistical analysis, we used the chi-square test and logistic regression. The chi-square test was used to determine the statistical significance of incidence between the groups for each variable (sex, age, and region in both rhBMP-2 and non-rhBMP-2 groups). Linear regression was performed to test the significance of trends over time. The level of significance was \( p < 0.05 \).

Results

In total, 1,265,591 patients were identified with a diagnosis associated to the ICD-9 codes listed in Table 1, among which 33,086 (2.35%) cases were PLSF procedures in the period between 2005 and 2011. Within PLSF cases, 63.4% (20,886)
had idiopathic scoliosis diagnosis, followed by 27% of the patients with scoliosis associated with other conditions (► Fig. 1).

The number of PLSF procedures increased significantly from 3,064 cases in 2005 to 5,563 cases in 2011 (p < 0.01). The incidence was calculated according to the number of searchable patients in the database each year resulting in an incidence of 7.21 cases in 2005 and 11.39 cases in 2011 per 100,000 patients, indicating a 0.6575 annual average increase during the 6-year period (p < 0.01; ► Fig. 2).

Sex
There were 21,019 female and 8,443 male patients. The male-to-female ratio of patients undergoing PLSF was 0.40, with 28.7% male and 71.3% female patients. A linear regression analysis showed that the incidence of surgery differed significantly between the male and female group (p < 0.05); female patients had a mean incidence of 6.11 per 100,000 higher than male patients (► Fig. 3).

Age
Patients were categorized into 5-year age groups and the PLSF trend and the incidence were calculated. There was a significant difference in surgery incidence between the different age groups (p < 0.05). The highest mean incidence of PLSF was observed in the group over 84 years old (47.76) and was followed by the group 65 to 69 years (31.03). The lowest incidence age group was <65 years, with a mean incidence of 6.36 (► Fig. 4).

Region
PLSF was performed less frequently in the Northeast compared with Midwest, South, and West (p < 0.05; ► Fig. 5). The mean incidence of PLSF cases per 100,000 patients searched for Northeast was 5.96. In comparison, the incidence was 10.83 in Midwest, 10.52 in South, and 10.69 in the West region. None of the pairwise comparisons were statistically significant in these three regions (► Fig. 5).

PLSF with or without rhBMP
The rhBMP-2 was used in 35.5% of PLSF procedures between 2005 and 2011 (10,498 rhBMP and 19,289 non-rhBMP cases). The average annual increase rate in the rhBMP-2 group was 15.8% and in the non-rhBMP-2 group was 8.5%, with no significant difference between the two groups (p = 0.398). A decrease in rhBMP-2 use for PLSF procedures was seen during 2010 (► Fig. 6).

The rate of rhBMP-2 use for PLSF changed with sex, with a statistically higher rate in male patients when compared with female patients (p < 0.05). Among all age groups, the groups of 65 to 69 years (36.3%) and 70 to 74 years (36.3%) had more procedures with rhBMP-2 compared with other age groups (p < 0.05). The group of age > 84 years had the lowest rhBMP-2 utilization in PLSF surgery (30.4%; ► Fig. 7).

rhBMP-2 was more frequently used in the West (39.7%) and Midwest (39.3%) compared with the other two regions. The Northeast was the most conservative region in rhBMP-2 consumption for PLSF procedure (24.9%, p < 0.05; ► Fig. 8).

Discussion
To our knowledge, this study is the first report on trends of PLSF in the treatment for adult scoliosis with and without rhBMP-2. The PLSF procedure can be an effective and safe solution for symptomatic scoliotic patients. A study done by McCarthy et al found that the surgical treatment for adult spinal deformity (ASD) is cost-effective after a 10-year period based on predicted deterioration in patient quality of life without a surgery. Although nonoperative treatment can demonstrate significant short-term improvements for certain patients, most of these patients struggle with disabilities and unsatisfied life. Compared with short segment

Table 1 ICD-9 procedure codes searched in the PearlDiver database

| ICD-9 code | Description |
|------------|-------------|
| 737.30     | Scoliosis (and kyphoscoliosis) idiopathic |
| 737.31     | Resolving infantile idiopathic scoliosis |
| 737.32     | Progressive infantile idiopathic scoliosis |
| 737.33     | Scoliosis due to radiation |
| 737.34     | Thoracogenic scoliosis |
| 737.39     | Other kyphoscoliosis and scoliosis |
| 737.43     | Scoliosis associate with other conditions |
| 754.2      | Congenital postural deformity: lordosis or scoliosis |
| 81.05      | Dorsal and dorsolumbar fusion, posterior technique |
| 81.63      | Fusion or refusion of 4–8 vertebrae |
| 81.64      | Fusion or refusion of 9 or more vertebrae |
| 84.52      | Insertion of recombinant BMP |

Abbreviations: BMP, bone morphogenetic protein; ICD-9, International Classification of Diseases, ninth edition.

Table 2 CPT procedure codes searched in the PearlDiver database

| CPT code | Description |
|----------|-------------|
| 22800    | Arthrodesis posterior for spinal deformity with or without cast; up to 6 vertebral segments |
| 22802    | Arthrodesis posterior for spinal deformity with or without cast; 7–12 vertebral segments |
| 22804    | Arthrodesis posterior for spinal deformity with or without cast; 13 or more vertebral segments |

Abbreviation: CPT, Current Procedural Terminology.
decompression and fusion procedures, the PLSF procedure requires more experienced spine surgeons and more detailed preoperative plans (considering the coronal plane, sagittal balance related to pelvic incidence-lumbar lordosis).\textsuperscript{20,21}

There are several reports on age correlation with the choices of treatment for patients with ASD. Smith et al showed that the postoperative improvement in elderly patients (65 to 85 years) was significantly greater when compared with younger patient groups (25 to 44 years and 45 to 64 years).\textsuperscript{22} In our study, the highest PLSF incidence was in the group with age $>84$ years, which could be due to the increase of degenerative disease with age. However, our study did not show a linear increase in posterior spine fusion with age. Some of the factors such as disorder type, disease duration, and Short Form-36 evaluation could contribute to our observations in nonlinear procedure increase.

Discrepancies based on geographic region have been described since the 1990s.\textsuperscript{23-25} Database studies, including

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**Fig. 1** Distribution of posterior long segment fusion by International Classification of Diseases, ninth edition (ICD-9) codes.

**Fig. 2** PLSF trend over time. Abbreviations: BMP, bone morphogenetic protein; PLSF, posterior long segment fusion.
Medicare analyses, commonly report the highest fusion procedure rates in the Midwest and South and lower in the Northeast.\textsuperscript{26–29} Consistent with previous data, we observed that the lowest PLSF incidence rate was in the Northeast region compared with the other three regions. Those regional variations can be potentially explained with differences in health care cost and surgeon training and experience attributing to the choice of fusion.\textsuperscript{30,31}

In our study, female patients had ~2.5 times higher incidence of PLSF procedures compared with male patients. Furthermore, 63.4\% of the patients in our study were diagnosed with idiopathic scoliosis. Previous studies have shown that the incidence of developing scoliosis is higher in female patients, both during maturity and later in life.\textsuperscript{32,33}

BMP, a member of the transforming growth factor β superfamily, plays an important role in bone and cartilage formation and repair of musculoskeletal tissues. Among multiple BMPs, BMP-2 has been the most extensively studied.\textsuperscript{10,34–37} Studies with short- and long-term follow-
up have shown that the use of rhBMP-2 yielded equal or superior fusion rates in long segment fusion surgery.\textsuperscript{11,38,39} Furthermore, rhBMP-2 outweighs iliac crest bone graft in several aspects, such as the potential of decreased blood loss, faster surgical time, and earlier hospital discharge, which in combination with stable fusion and elimination of donor site complications should result in better clinical outcomes.\textsuperscript{11,34,36,40–42} The present study demonstrates a steady increase in rhBMP-2 use for adult patients with scoliosis from 2005 through 2011, but no significant difference compared with the non-rhBMP-2 group, suggesting that rhBMP-2 did not completely replace the traditional bone graft as it did in other procedures after the FDA approval for anterior lumbar fusions.\textsuperscript{43} There was a decrease in rhBMP-2 use in 2010 according to our database, which is in accordance with previous literature.\textsuperscript{44} Possible explanations for this decrease were the studies that questioned the suitability of rhBMP-2 “off-label” use and whether it is really safe.\textsuperscript{45,46} There have been numerous reports on adverse effects associated with the off-label use of rhBMP-2 in spine surgery: heterotopic...
ossification, osteolysis, seroma, infection, increased neurologic deficits, dysphagia in anterior cervical surgery, and cancer. However, a multicenter study of 279 consecutive ASD surgeries suggested that rhBMP-2 did not increase acute major, neurologic, or wound complications. Furthermore, The Scoliosis Research Society retrospectively reviewed a database of 55,862 spinal fusion surgeries and found no statistical difference in the overall complication rates or the rates of deep or superficial wound infections and hematoma/seroma formation between the patients with or without BMP. Apart from the safety issues, the cost increase with the use of rhBMP-2 is the other relevant reason that this product cannot replace the traditional bone graft. In addition, Yale University Open Access Data meta-analyses found that the effects and harms of rhBMP-2 were under-reported, cancer risks were inconclusive, and rhBMP-2 had no existing advantage compared with the bone graft.

Furthermore, the Medicare database study done by Kelly et al found that BMP was not associated with the increase in cancer incidence. Even though the overall trend of rhBMP-2 use was not statistically significant, we found significant differences in rhBMP-2 use considering sex, age, and region, respectively. Similarly, Singh et al found that numbers of elderly patient who underwent spinal arthrodesis with rhBMP-2 nearly doubled from 2002 to 2011 according to their database analysis. Further studies capturing detailed patient information are needed to explain these differences.

Limitations of this study include that the database had a potential risk for inaccuracy in capturing the correct

![Fig. 7](image1.png)  
**Fig. 7** Posterior long segment fusion (PLSF) and bone morphogenetic protein (BMP) trends with age.

![Fig. 8](image2.png)  
**Fig. 8** BMP use for PLSF in different regions. Abbreviations: BMP, bone morphogenetic protein; PLSF, posterior long segment fusion.
The available data included only certain demographics; however, no clinical or radiographic information was available. The Medicare database predominantly consists of patients over the age of 65, thus patients < 65 years of age represent only a portion of this age cohort. Despite these limitations, we feel that the large number of patients in our study provides a representative sample of patients with adult scoliosis who have been treated with PLSF.

**Conclusions**

According to the PearlDiver Patient Record Database from 2005 to 2011, patients with scoliosis demonstrated a 0.6575 average incidence increase per 100,000 PLSF treatments annually. The age group over 84 years had the highest average incidence increase per 100,000 PLSF treatments 2005 to 2011, patients with scoliosis demonstrated a 0.6575 increase since 2005, but the number of patients with rhBMP-2 in the treatment of adult scoliosis with PLSF increased since 2005, but the number of patients with rhBMP-2 was not statistically different from the non-rhBMP-2 group. Significant differences of rhBMP-2 consumption were found when looking at sex, age, and region, respectively.

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