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Postoperative Complications Associated With rhBMP2 Use in Posterior/Posterolateral Lumbar Fusion

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Abstract

Study Design: Retrospective database review.

Objective: Posterior/posterolateral lumbar fusion (PLF) is an effective treatment for a variety of spinal disorders; however, variations in surgical technique have different complication profiles. The aim of our study was to quantify the frequency of various complications in patients undergoing PLF with and without human recombinant bone morphogenetic protein 2 (rhBMP2).

Methods: We queried the orthopedic subset of the Medicare database (PearlDiver) between 2005 and 2011 for patients undergoing PLF procedures with and without rhBMP2. Complication and reoperation rates were analyzed within 1 year of the index procedure. Complications assessed include: acute renal failure, deep vein thrombosis, dural tear, hematoma, heterotopic ossification, incision and drainage, cardiac complications, nervous system complications, osteolysis, pneumonia, pseudarthrosis, pulmonary embolism, radiculopathy, respiratory complications, sepsis, urinary retention, urinary tract infection, mechanical, and wound complications. Chi-square analysis was used to calculate the complication differences between the groups.

Results: Our data revealed higher overall complication rates in patients undergoing PLF with rhBMP2 versus no_rhBMP2 (76.9% vs 68.8%, $P < .05$). Stratified by gender, rhBMP2 males had higher rates of mechanical complications, pseudarthrosis, and reoperations compared with no_rhBMP2 males ($P < .05$), whereas rhBMP2 females had higher rates of pseudarthrosis, urinary tract infection, and urinary retention compared with no_rhBMP2 females ($P < .05$).

Conclusion: Our data revealed higher overall complication rates in PLF patients given rhBMP2 compared with no_rhBMP2. Furthermore, our data suggests that rhBMP2-associated complications may be gender specific.

Keywords

rhbmp2, posterior lumbar fusion, complications, gender, retrospective, PearlDiver

Introduction

The growing number of degenerative disc conditions seen in the aging population has contributed to the increased rates of posterior lumbar fusion (PLF) procedures.[1] Though surgical arthrodesis can provide symptomatic relief for a broad list of degenerative conditions, the concern for complications and non-union is prominent. Spinal fusion has historically involved iliac crest bone grafting (ICBG) for use as a structural nonimmunogenic scaffold. However, the harvesting of bone is associated with significant risk of morbidity, intraoperative complications, and donor site pain.[2-4] The ICBG adverse effects with its contraindications, such as osteoporosis, place

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a large limit on the potential in spinal fusion and necessitate the need to explore alternative techniques.

Human recombinant bone morphogenetic protein 2 (rhBMP2), a member of the transformation growth factor beta cytokine family, has been at the forefront of national discussion as one of the candidates to replace ICBG. Given rhBMP2's well-documented roles in osteoprogenitor cell recruitment, proliferation, terminal differentiation, and bone maintenance, the use of osteobiologics has gained considerable momentum as a novel solution to spinal fusion.[5] Procedurally, rhBMP2 is placed on an absorbable sponge synthesized from bovine collagen 1 and delivered either adjunctively to ICBG, femoral head allografts, or with other synthetic bone fillers.[6] Several early studies demonstrated the efficacy of rhBMP2 in surgical arthrodesis, with one PLF study reporting both superior fusion and decreased morbidity compared with the "gold standard," ICBG (88% vs 73%, $P = .051$).[7] With the benefit of increased fusion and the ability to spare ICBG harvesting, the Food and Drug Administration (FDA) approved rhBMP2 for anterior lumbar fusion in 2002.[8] After the initial approval, rhBMP2's role rapidly expanded into multiple on and off-label uses, including cervical, lumbar interbody, and posterior lumbar fusions.[8,9] However, in 2008, the FDA issued a Public Health Notification regarding rhBMP2's propensity to cause life-threatening complications in anterior cervical procedures.[9] Consequently, the investigation of the original industry-sponsored-research ensued and some authors have suggested that protocols were biased in favor of rhBMP2.[10,11] Both the FDA report and the criticism of the original research have caused considerable controversy in rhBMP2's PLF use may have contributed to the drop in rhBMP2 usage from 2010 to 2011.[12]

Several studies have attempted to characterize rhBMP2's PLF complication profile, but have generally been underpowered or pooled data with other surgical approaches, such as interbody fusion.[13] These limitations have made the assessment of rhBMP2's PLF complication profile difficult and thus warrants an extensive review. The primary objective of our study was to quantify the frequency of various complications seen in patients undergoing PLF with or without rhBMP2 using a national insurance database.

Materials and Method

Patients undergoing PLF with and without rhBMP2 were searched in the PearlDiver Patient Records Database (PearlDiver Technologies, Fort Wayne, IN, USA). PearlDiver is a national insurance database that provides information covering procedural data, reimbursements, and patient outcomes. We queried the Medicare portion of PearlDiver database for patients who underwent single-level PLF surgery with and without rhBMP2 utilization between 2005 and 2011. Patients were identified by Current Procedural Terminology (CPT) code 22612 ("Posterior, Posterolateral, or Lateral Transverse Lumbar Fusion") in combination with or exclusion of ICD-9 (International Classification of Diseases, Ninth Revision) code 84.52 ("Insertion of recombinant bone morphogenetic protein [rhBMP2]"), and were further paired with ICD-9 codes representing various complications commonly reported in literature (Table 1). Only complications that occurred on the same day or within 1 year of the index procedure were noted. Retrieved data was further stratified by gender and 5-year age groups (<65, 65-69, 70-74, 75-79, 80-84, ≥85 years) to assess their roles in complication occurrence. Finally, patients undergoing a revision surgery within 1 year were searched. Reoperation and complication rates were compared by chi-square analysis to identify statistically significant differences between the patient cohorts. PearlDiver database does not report an exact numbers when ≤10 records are retrieved, in these instances both low- and high-end complication rates were compared. The level of significance was defined as $P < .05$.

Table 1. ICD-9 and CPT Codes.

Pulmonary embolism	ICD-9-D-41511, ICD-9-D-41512, ICD-9-D-41513, ICD-9-D-41519
Deep vein thrombosis	ICD-9-D-45340, ICD-9-D-45341, ICD-9-D-45342, ICD-9-D-45389, ICD-9-D-4539
Cardiac	ICD-9-D-4100:4109, ICD-9-D-9971
Nerve complications	ICD-9-D-99700, ICD-9-D-99701, ICD-9-D-99709
Incision and drainage complications	CPT-10060, CPT-10061, CPT-10140 CPT-10160, CPT-10180, CPT-11000 CPT-97597, CPT-97598, CPT-11042, CPT-11043, CPT-11044, ICD-9-P-8622 ICD-9-P-8604
Wound complications	ICD-9-D-99811, ICD-9-D-99813, ICD-9-D-99812, ICD-9-D-99830, ICD-9-D-99831, ICD-9-D-99832 ICD-9-D-99833, ICD-9-D-99883, ICD-9-D-9985 ICD-9-D-9986, ICD-9-D-9987, ICD-9-D-9988 ICD-9-D-9989, ICD-9-D-9993
Sepsis	ICD-9-D-99591, ICD-9-D-99592
Pneumonia	ICD-9-D-480:486, ICD-9-D-99731
Urinary tract infection	ICD-9-D-5990
Respiratory complications	ICD-9-D-5185, ICD-9-D-51881, ICD-9-D-51882 ICD-9-D-7860, ICD-9-D-9973
Heterotopic ossification	ICD-9-D-72813
Urinary retention	ICD-9-D-78820
Pseudarthrosis	ICD-9-D-73382
Acute renal failure	ICD-9-D-5845: ICD-9-D-5849
Radiculopathy/Radiculitis	ICD-9-D-7292, ICD-9-D-7244
Dural tear	ICD-9-D-34931
Mechanical complications	ICD-9-D-99649
Postoperative hematoma	ICD-9-D-99812
Osteolysis	ICD-9-D-73399
Posterior lumbar refusion	CPT-22612

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; CPT, Current Procedural Terminology.

Results

There were 5051 patients undergoing PLF identifiable by CPT code 22612. Within this group, 1912 (39%) were male and

Table 2. Overall Complication Rates in All Patients Given rhBMP2 Versus No_rhBMP2.

Total Complications	rhBMP2 (%)	No_rhBMP2 (%)
Cardiac	2.48	3.06
Deep vein thrombosis	6.15	4.58
Dural tear	1.94	2.11
Hematoma	0.8-1.1	1.43
Incision and drainage	5.29	5.89
Mechanical	5.93	4.03
Nerve	0.5-1.1	1.26
Osteolysis	0.8-1.1	1.31
Pneumonia	8.74	7.93
Pseudoarthrosis	2.16	0.92
Pulmonary embolism	1.78	2.38
Radiculopathy	10.9	11.78
Renal	6.47	5.38
Reoperation	0.8-1.1	1.24
Respiratory	5.39	4.24
Sepsis	2.8	2.55
Urinary retention	9.39	6.81
Urinary tract infection	29.77	24.39
Wound	6.26	6.16
Any complication	76.91	68.84

Abbreviation: rhBMP2, human recombinant bone morphogenetic protein 2.

Table 3. Complications in Females Given rhBMP2 Versons No_rhBMP2.

Female Complications	rhBMP2 (%)	No_rhBMP2 (%)
Cardiac	2.37	2.52
Deep vein thrombosis	6.26	4.68
Dural tear	2.20	2.16
Hematoma	0.8-1.7	1.12
Incision and drainage	5.08	5.88
Mechanical	5.75	4.64
Nerve	0.8-1.7	1.36
Osteolysis	1.0-1.7	1.68
Pneumonia	8.29	8.28
Pseudoarthrosis	2.20	0.96
Pulmonary embolism	1.86	2.48
Radiculopathy	11.51	11.84
Renal	5.92	4.88
Reoperation	0.8-1.7	1.44
Respiratory	5.75	4.12
Sepsis	2.88	2.40
Urinary retention	6.43	4.16
Urinary tract infection	37.23	31.43
Wound	7.28	6.04
Any complication	79.86	72.05

Abbreviation: rhBMP2, human recombinant bone morphogenetic protein 2.

3092 (61%) were female. The most represented age group was 65 to 69 years (24%). Further combination with ICD-9 code 84.52 revealed that 927 (18%) of the patients received rhBMP2 whereas 4124 of patients underwent the procedure without it. Of the 927 patients receiving rhBMP2, 64% were female and 25% were aged 65 to 69 years. The incidence of PLF without rhBMP2 was more than 5 times greater than the incidence of PLF with rhBMP2 (0.16 and 0.03 cases per 100 000 patients, respectively). The highest rates of rhBMP2 use were in the Midwest and West, 20% and 21% of PLF cases, respectively; the Northeast and South utilized rhBMP2 less frequently at 14.2% and 17.9%, respectively.

Complications

Nineteen out of the twenty complications searched were observed in both the no_rhBMP2 and rhBMP2 cohorts with the results reported in Table 2. Of the patients undergoing PLF without rhBMP2, 68.8% suffered one or more complications compared with the 76.9% complication rate observed in the PLF rhBMP2 group ($P < .05$). The most common complication reported in both rhBMP2 and no_rhBMP2 groups was urinary tract infection (29.8% and 24.4%, $P < .05$). The following complications had significantly higher rates in patients who received rhBMP2 ($P < .05$): deep vein thrombosis (6.2% vs 4.6%), mechanical (5.9% vs 4.0%), pseudarthrosis (2.2% vs 0.9%), urinary retention (9.4% vs 6.8%), urinary tract infection (30.0% vs 24.4%). No significant differences were found in patients who developed cardiac, dural tear, hematomas, incision and drainage, nerve complications, osteolysis, pulmonary embolism, pneumonia, renal, radiculopathy/radiculitis, respiratory, sepsis, or wound complications ($P > .05$). Similarly, there was no significant difference in reoperation rates between the rhBMP2 and no_rhBMP2 groups.

Gender

Filtering the data by gender revealed the results shown in Tables 3 and 4 for females and males, respectively. Males undergoing PLF with rhBMP2 observed a total complication rate of 73.6%, while those without rhBMP2 saw a rate of 64.9% ($P < .05$). For female rhBMP2 and no_rhBMP2 groups showed rates of 80% and 72%, respectively ($P < .05$). The most common complication in both genders was urinary tract infection, which occurred more than 2 times more frequently in women. Interestingly, both male rhBMP2/no_rhBMP2 groups had higher rates of urinary retention when compared with females (rhBMP2 14.6% [males] vs 6.4% [female] and no_rhBMP2 11.1% [males] vs 4.2% [females], respectively); however, only rhBMP2 females had statistically higher rates of urinary retention vs no_rhBMP2 females ($P < .05$), though rhBMP2 males approached significance ($P = .07$).

When analyzed by individual complications, males who received rhBMP2 had higher rates of Mechanical complications (6.38% vs 3.16%, $P < .05$). Fewer than 11 events occurred in males receiving rhBMP2 for cardiac, dural tear, hematoma, nerve complications, osteolysis, pseudoarthrosis, pulmonary embolism, reoperation, and sepsis; rate ranges were calculated (Table 4). urinary retention also approached significance in the rhBMP2 male group (14.6% vs 11.1%, $P = .07$).

Females receiving rhBMP2 observed higher rates of the following complications ($P < .05$): pseudarthrosis (2.2% vs

Table 4. Complications in Males Given rhBMP2 Versus No_rhBMP2.

Male Complications	rhBMP2 (%)	No_rhBMP2 (%)
Cardiac	1.5-3	3.85
Deep vein thrombosis	6.08	4.55
Dural tear	1-3	2.08
Hematoma	1-3	1.96
Incision and drainage	5.78	6.06
Mechanical	6.38	3.16
Nerve	0.3-3	1.14
Osteolysis	0.6-3	0.69
Pneumonia	9.73	7.58
Pseudoarthrosis	1.8-3	0.88
Pulmonary embolism	1.2-3	2.27
Radiculopathy	10.03	12.00
Renal	7.60	6.32
Reoperation	2.1-3	0.95
Respiratory	5.17	4.55
Sepsis	1.8-3	2.84
Urinary retention	14.59	11.05
Urinary tract infection	16.72	13.64
Wound	4.56	6.51
Any complication	73.56	64.94

Abbreviation: rhBMP2, human recombinant bone morphogenetic protein 2.

0.96%), urinary retention (6.4% vs 4.2%), urinary tract infection (36.2% vs 31.4%) with respiratory complications approaching significance (5.8% vs 3.1%, $P = .08$).

Discussion

Controversy regarding the safety of rhBMP2 in PLF has long been a conversation with largely inconsistent results. One speculated advantage for rhBMP2 use involves the ability for surgeons to harvest less iliac crest bone thereby limiting operational length, blood loss and time under anesthesia; surgical variables well known to increase the risk of both intra- and perioperative complications.[14-17] While rhBMP2 may optimize surgical efficiency, its net effect may not meet the expectations of an improved safety profile. Our data revealed significantly higher complication rates in PLF patients given rhBMP2 compared with those who underwent the procedure without rhBMP2 (76.9% and 68.8%, $P < .05$).

The role of gender in PLF $\pm$ rhBMP2 has not been previously defined and may be an important factor in evaluating rhBMP2's safety. Both males and females receiving rhBMP2 had higher complication rates than those who did not receive rhBMP2; however, our data suggests that rhBMP2 may have more gender-specific complication profiles. While rhBMP2 was associated with a higher risk of mechanical complications, urinary retention, and urinary tract infections, each of these complications exhibited gender polarity. Interestingly, only the male_rhBMP2 group had higher rates of mechanical complications (6.38% rhBMP2 males vs 3.16% no_rhBMP2 males) as females saw similar rates to the no_rhBMP2 group. It is unclear why rhBMP2 males were at higher risk for mechanical complication, but possible explanations may include a male-specific anatomic susceptibility of the lumbar region and rhBMP2's pro-inflammatory effects on local tissues leading to mechanical compromise.[18,19]

Questions concerning the risk of urogenitary complications in PLF $\pm$ rhBMP2 have been raised due to the older demographics and high rates of urogenital complications in other lumbar fusion procedures. Our data showed that these concerns are more validated in females compared with males further highlighting gender as an important variable to consider for complication prevention. Compared with no_rhBMP2 females, those with rhBMP2 had a significantly higher risk for both urinary retention (6.4% vs 4.2%) and urinary tract infections (37.2% vs 31.4%); no significant difference was found in no_rhBMP2 males versus rhBMP2 males ($P = .07$). The increased risk of urinary complications may relate to rhBMP2's ability to induce renal arterial fibrosis leading to glomerular epithelial cell damage, stasis, and followed by infection.[20] Further investigation outlining the pathophysiology in rhBMP2-associated complications may merit better contraindication protocols and improve rhBMP2's complication profile; this would simplify the discussion of rhBMP2's clinical utility to one of fusion efficacy.

The risk for pseudarthrosis in lumbar fusion has been a challenging obstacle with conflicting data on whether rhBMP2 can improve outcomes.[21] Interestingly, we found a 2-fold higher rate of pseudarthrosis in the rhBMP2 group (2.16%) compared with no_rhBMP2 (0.92%), with both groups differing significantly from Singh's compiled study (rhBMP2 [6.3%] vs no_rhBMP2 [18.2%]).[22] While our data showed increased pseudarthrosis risk in both males (1.8-3%) and females (2.2%) given rhBMP2, it is possible that the etiologies of nonunion were different. Pseudoarthrosis in rhBMP2 males may have resulted from mechanical compromise evidenced by the higher rates of mechanical complications; this would explain why only rhBMP2 males were additionally associated with higher reoperation rates (2.1%-3% vs 0.95% no_rhBMP2 males, $P = .002$-$.067$) despite a similar frequency of nonunion to rhBMP2 females. Our analysis showed results similar to the data of Hoffman et al[23] data reporting both a 3.5% reoperation rate and male association in rhBMP2 patients. Though rhBMP2 may have a role in causing pseudarthrosis, the higher rates may also be explained by the tendency for surgeons to use rhBMP2 more frequently in populations at significant risk for nonunion (ie, smokers, patients with prior pseudarthrosis, osteoporosis).[24-26]

Variations in rhBMP2 complications may depend on directional approach, surgical technique, and spinal region under operation.[19] Both osteolysis and heterotopic ossification have been reported in other spinal fusion procedures with rhBMP2.[27] However, there is little data regarding rhBMP2's risk in PLF, though one case report described a single psoas ossification.[28] Our data showed similar rates of osteolysis for PLF (0.8%-1.1% rhBMP2 vs 1.31% no_rhBMP2) and interestingly, no instances of heterotopic ossification were recorded for either the rhBMP2 or no_rhBMP2 groups; this may lend evidence to rhBMP2-induced heterotopic ossification having little

occurrence or being of inconsequential clinical importance in posterior lumbar fusion.

Our data showed higher individual and total complications rates for both PLF groups than most numbers suggest in literature review. For example, Cahill[29] reported wound and total complication rates of 2.01%/6.97% for rhBMP2 and 2.15%/7.18% for procedures involving iliac crest bone grafting; these numbers differ significantly from our wound rhBMP2/no_rhBMP2 rates of 6.3%/6.2%. Glassman et al[30] reported a major complication risk of 4.5% with rhBMP2 and individual complications such as pneumonia (1.64%) and myocardial infarction (0.19%). For comparison, we saw a rhBMP2/no_rhBMP2 pneumonia and myocardial infarction frequency of 8.7%/7.9% and 2.5/3.1%, respectively. Our individual and total complication rates for both rhBMP2/no_rhBMP2 most closely resemble the numbers reported in the 2003 review of PLF cases by Carreon et al.[31] Several explanations may be given for the large variation seen in complication reporting. For one, most studies examining PLF $\pm$ rhBMP2 are severely underpowered and lead to large complication ranges when different studies are compared. Furthermore, some studies seek to resolve low power by pooling different lumbar fusion techniques, including transverse lateral interbody fusion, posterior lateral interbody fusion, and anterior lumbar fusion. This introduces complications native to different procedures (such as heterotopic ossification) into the PLF profile.[32] Finally, there is little consistency in the grouping of complications such as "nerve, wound, infection" as inclusion criteria differ significantly from article to article. The interstudy comparison of our data is difficult as many of the mentioned limitations apply. Nevertheless, our data reveals that complications may be underreported in PLF as a whole.

Limitations in our study include the lack of a control group given the retrospective design, as well as the limitations in using a database derived from Medicare billing records. For one, the Medicare sample may not serve as an accurate cross-section of the general population. In addition, database reviews have an inherent risk of errors related to ICD-9/CPT data extraction. Additional weaknesses include the inability to assess how surgical experience or regional preference in rhBMP2 use affect outcomes. Furthermore, our analysis does not account and statistically correct for the type of graft used, predisposing risk factors, or different rhBMP2 dosing regimens as individual records are not available. Finally, postoperative complication analysis using ICD-9 codes has been evaluated to show decreased sensitivity in spinal procedures.[33,34] Though the limitations in retrospective review are important to consider, the potential to report a comprehensive list of complications and frequencies is gained. Further research controlling for preexisting disease and risk factors will help clarify rhBMP2's role in posterior spinal fusion.

Conclusion

To our knowledge, this is the largest database study on PLF complications with rhBMP2 use. Our data demonstrated that the rhBMP2 group had significantly higher rates of complications compared with the no_rhBMP2 group. Patients with rhBMP2 may have higher rates of pseudarthrosis, deep vein thrombosis, mechanical complications (males), reoperations (males), urinary retention (females), and urinary tract infections (females). Furthermore, our data suggests that rhBMP2 does not contribute to increased rates of heterotopic ossification or osteolysis as suggested by some reports. Further research controlling for preexisting disease and risk factors will help clarify rhBMP2's role in posterior spinal fusion.

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