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Recombinant Human Bone Morphogenetic Protein–2 Use in Adult Spinal Deformity Surgery: Comparative Analysis and Healthcare Utilization at 24 Months' Follow-up

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Abstract

Study Design: Retrospective cohort study.

Objective: Recombinant human bone morphogenetic protein–2 (rhBMP-2) is used to achieve fusion in adult spinal deformity (ASD) surgery. Our aim was to investigate the long-term impact of rhBMP-2 use for clinical outcomes and health care utilization in this patient population.

Methods: We conducted an analysis using MarketScan to identify health resource utilization of rhBMP-2 use for ASD after surgical intervention compared to fusion without rhBMP-2 at 24 months' follow-up. Outcomes assessed included length of stay, complications, pseudoarthrosis, reoperation, outpatient services, and health care payments.

Results: Of 7115 patients who underwent surgery for ASD, 854 received rhBMP-2 and 6261 were operated upon without use of rhBMP-2. One month after discharge, the rhBMP-2 cohort had a nonsignificant trend in fewer complications (15.38%) than those who did not receive rhBMP-2 (18.07%), $P = .0558$. At 12 months, pseudoarthrosis was reported in 2.8% of cases with no BMP and 01.14% of cases with BMP, $P = .0048$. Average payments at 12 months were $120 138 for the rhBMP-2 group and $118 373 for the no rhBMP-2 group, $P = .8228$. At 24 months, payments were $141 664 for the rhBMP-2 group and $144 179 for the group that did not receive rhBMP-2, $P = .5946$.

Conclusions: In ASD surgery, use of rhBMP-2 was not associated with increased complications or reoperations at index hospitalization and 1-month follow-up. Overall payments, including index hospitalization, readmissions, reoperations, and outpatient services were not different compared to those without the use of rhBMP-2 at 12 months and 24 months after discharge.

Keywords

recombinant bone morphogenetic protein–2, BMP, adult spinal deformity, ASD, scoliosis, heath care utilization, spine surgery

Introduction

Adult spinal deformity (ASD) affects approximately 2.5% to 35.5% of the US population.[1] Its prevalence increases after 50 years of age[2] and may be present in 65% of adults over the age of 65 years.[3] Surgery is indicated for those who are at risk of progression, have intractable back pain, or radicular symptoms that have failed conservative management.[4-6] Several challenges confound the success of surgical treatment of ASD, including higher rates of complications in 26% to 55% of

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patients.[7,8] However, pseudoarthrosis remains the most commonly cited major complication of ASD surgery, occurring in up to 25% of cases.[9-12] It has been shown that there is a 21% lower fusion rate for ASD (70%) compared with surgery for degenerative disc disease (91%).[13]

Recombinant human bone morphogenetic protein–2 (rhBMP-2) has been shown to successfully augment traditional iliac crest bone graft (ICBG) in patients undergoing multilevel fusions for ASD.[14] rhBMP-2 has also been incorporated in lumbar fusion procedures as demonstrated by a meta-analysis showing increased fusion rate, decreased reoperation rate, and operation time in patients undergoing lumbar spine fusion.[15] However, the benefits of rhBMP-2 remain controversial with some studies reporting an increased rate of complications.[16-20] Significant costs associated with the use of BMP have also been widely reported.[21-23] Recently, Safaee et al[21] concluded that use of BMP reduced the need for revision surgery with 11% absolute risk reduction for pseudoarthrosis and that its direct in-hospital associated cost was not correlated to a net cost savings after 12 months due to reoperation. However, health care utilization metrics were not included in the analysis. Use of rhBMP-2 in patients with spine infections was cost-effective and associated with similar reoperation rates compared to those without rhBMP-2 use.[24]

A 10-year analysis of the Nationwide Inpatient Sample (NIS) database reported BMP use in ASD to be approximately 40% between 2002 and 2011.[25] In 2014, Bess et al[5] conducted a prospective, multicenter trial that demonstrated no significant increase in complications from rhBMP-2 in ASD in the acute perioperative setting. Other studies of ASD surgery with rhBMP-2 corroborate findings of few complications and fusion rates of 95%[14] and 93% to 100%[26] after 1- and 2-year follow-up, respectively. Health care utilization of rhBMP-2 use in patients undergoing surgery for ASD with long-term follow-up has not been extensively investigated.

In the present study, we evaluate the use of rhBMP-2 in ASD surgery regarding health care utilization metrics and trends of use and cost. We investigate index hospitalization metrics, including length of stay, complications, emergency room admissions, and health care payments. Additionally, we examine outpatient services at 30 days, 6 months, and 12 months follow-up. We report the first 24 months' follow-up with health care utilization with BMP and ASD. We hypothesize that the use ofrhBMP-2 is associated with increased savings, lower reoperation rates, and decreased health care utilization.

Methods

Data Source

We used the Truven Health MarketScan Research commercial claims and encounters, Medicare supplemental and Medicaid databases. This is a claims database containing information on healthcare resource utilization of included patients. Patients enter with enrollment with their insurance and exist with the end enrollment. As such, the MarketScan data captures a health care longitudinal snapshot of care. The database that we have is custom to neurological and neurosurgical conditions. In general, this database is available to researchers for a fee and health services and outcomes researchers have used it for decades.[27] Each patient has an encrypted ID that we use to link different files. We have inpatient, outpatient and medication files spanning the years of 2000 to 2016. This study is institutional review board approved and internally funded.

Patient Selection

We screened the inpatient tables for cases with diagnosis of spinal deformity that underwent fusion with or without rhBMP-2. Exclusion criteria are concurrent diagnoses of cancer, pregnancies, intraspinal abscess, inflammatory spondyloarthropathies, osteomyelitis, vertebral fractures, vehicular accidents, and patients <18 years of age. Details of claims codes used for inclusion/exclusion criteria are provided in Supplemental Table 1. For retained patients, the first occurring hospitalization satisfying the inclusion criteria was flagged as the index hospitalization and the beginning of follow-up. We also required patients in the analysis dataset to have at least 12 months postindex follow-up. For this project, we used records of 2003-2015 for patient extraction to account for a whole year after rhBMP-2 2002 approval by the Food and Drug Administration and to allow one full year of follow-up to everyone.

Baseline Characteristics

At the time of index hospitalization, age, gender, insurance type (commercial, Medicare, Medicaid) and comorbidities were noted. Comorbidities were captured through the Elixhauser comorbidity score[28] and computed using an adaptation to ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes developed by Quan et al.[29] At this time, we also calculated the enrollment time as the difference between the index admission date and the start enrollment date (preindex look-back) and the between the end enrollment date and the index discharge date (postindex follow-up).

Outcomes

We were interested in index hospital, 1-, 6-, and 12-month health care utilization, payment, complications, and reoperation.

Healthcare Resources Use and Costs. Healthcare utilization included index hospital length of stay, post discharge Emergency room admissions, hospital admissions, outpatient services and medication refills. In this project, the costs are from the payer's perspective. MarketScan is a claims database and all payments are captured, the payments from the insurance company, the copay any co-insurance. We

Table 1. IPTW-Weighted Demographics, Insurance, Elixhauser Index of Patients Who Underwent Fusion for Spinal Deformity.

	IPTW-weighted			
Variable	No BMP (n = 6263	BMP (n = 839)	*P*	Combined (n = 7102)
Demographics				
Age, years			.173	
Mean (SD)	51.5 (19.6)	52.4 (17.6)		51.6 (19.4)
Median (IQR)	57 (37, 65)	56 (41, 65)		57 (37, 65)
Range (min-max)	18-90	18-91		18-91
Gender: female, n (%)	4404 (70.32)	596 (70.98)	.6928	5000 (70.4)
Insurance, n (%)				
Commercial	4047 (64.61)	544 (64.81)	.9874	4591 (64.64)
Medicaid	616 (9.83)	83 (9.89)		699 (9.84)
Medicare	1600 (25.55)	212 (25.3)		1813 (25.52)
Elixhauser index, n (%)				
0	2284 (36.47)	268 (31.91)	.0772	2552 (35.93)
1	1819 (29.04)	266 (31.69)		2085 (29.35)
2	1188 (18.97)	168 (20.04)		1356 (19.10)
3+	972 (15.52)	137 (16.36)		1110 (15.62)

Abbreviations: IPTW, inverse probability of treatment weight; BMP, bone morphogenetic protein; IQR, interquartile range.

considered the overall payment which is inclusive of all payment made for the resource use. In the inpatient admission tables, the total payment is provided as a variable, which contains the amount paid for the overall hospitalization and all services received. In the outpatient and medication tables, the payment comprises the overall amount paid to the provider for the specific service or refill. We looked at payments for index hospitalization, medication refills, hospital readmissions, outpatient services, and cumulative payments at 6, 12, and 24 months postoperatively. Payments were inflated to 2016 US dollars using the medical component of the consumer price index, which can be accessed through the US Bureau of Labor Statistics website.[30]

Complications.. The presence of complication was noted as the occurrence of any of the following complication types: pseudoarthrosis, renal, cardiac, neural, deep vein thrombosis and/or pulmonary embolism (DVT/PE), pulmonary, infection, and wound (detailed claim codes are in Supplemental Tables 1 and 2). We looked at complications during the index hospitalization and within 1 month after discharge.

Reoperation.. Repeat surgery was either new fusion or repeat fusion (details in Supplemental Table 1).

Statistical Analysis

We summarized continuous variables using means and standard deviations, median and interquartile range as well as full range (minimum to maximum). Categorical variables were summarized using counts and percentages.

The main interest was to evaluate the effect of rhBMP-2 use in ASD surgery on health care utilization and expenditures. To eliminate bias due to observed confounders, we used the propensity score inverse probability of treatment weight (IPTW) method. The IPTW is one of the propensity score methods to balance the covariates among different groups in a comparison observational study. The propensity score was calculated as the probability of undergoing fusion with rhBMP-2 using logistic regression adjusting for all patient characteristics. Then, a weight was computed as the inverse probability of undergoing the treatment received to adjust for group sample size. This method has been used to correct for the patient characteristic imbalance.[31-35]

This weight was then included into comparison tests and models. Group health care utilization and outcomes were compared with weighted generalized linear models. All tests were 2 sided and were statistically significant if the *P* value was less than .05. We used the software SAS 9.4 (SAS Institute, Inc) for data analysis.

Results

Patient Population

A total of IPTW-weighted 7102 patients were identified using the MarketScan database (Table 1). A total of 839 received rhBMP-2 in the fusion procedure and 6263 underwent fusion without rhBMP-2. Mean age and female gender distribution were similar between the groups with 52.4 versus 51.5 years for rhBMP-2 and no rhBMP-2, respectively, and 70.97% versus 70.37% for rhBMP-2 versus no rhBMP-2. Elixhauser comorbidity index was also similar between groups. Insurance was similar between groups with commercial representing the largest percentage of both cohorts, with rhBMP-2 at 64.81% and without rhBMP-2 at 64.61%. Analysis at 24-month follow-up included a separate sample of patients totaling 4915 individuals, who had follow-up data available (Table 2). Comparison was also made between samples for the first 12-month and for the 24-month follow-up (Table 3).

Table 2. Demographics of Spinal Deformity Fusion Groups With 24+-Month Follow-up.

	IPTW-weighted values			
Variable	No BMP weighted n = 4342	BMP weighted n = 573	*P*	Combined weighted n = 4915
Demographics				
Age, years			.1668	
Mean (SD)	51.7 (19.6)	52.9 (17.3)		51.8 (19.3)
Median (IQR)	57 (37, 66)	56 (42, 66)		57 (39, 66)
Range (min-max)	18-90	18-91		18-91
Gender: female, n (%)	3067 (70.63)	407 (71.09%)	.8198	3474 (70.68)
Insurance, n (%)				
Commercial	2724 (62.74)	358 (62.43)	.985	3082 (62.7)
Medicaid	457 (10.53)	62 (10.73)		519 (10.55)
Medicare	1161 (26.73)	154 (26.83)		1315 (26.75)
Elixhauser index, n (%)				
0	1642 (37.82)	187 (32.58)	.1132	1829 (37.21)
1	1278 (29.43)	184 (32.18)		1462 (29.75)
2	803 (18.49)	114 (19.9)		917 (18.65)
3+	619 (14.26)	88 (15.33)		707 (14.39)

Abbreviations: IPTW, inverse probability of treatment weight; BMP, bone morphogenetic protein; IQR, interquartile range.

Table 3. Demographics of 12- and 24+-Month Follow-up Spinal Deformity Fusion Groups.

	IPTW-weighted values			
Variable	12 months (n = 2185)	24 months (n = 4845)	*P*	Combined weighted (n = 7031)
Demographics				
Age, years			.0003	
Mean (SD)	50.9 (18.9)	52.7 (17.9)		52.1 (18.2)
Median (IQR)	55 (36, 63)	56 (42, 66)		56 (41, 65)
Range (min-max)	18-89	18-91		18-91
Gender: female, n (%)	1535 (70.23)	3441 (71.02)	.4978	4976 (70.77)
Insurance, n (%)				
Commercial	1547 (70.80)	3005 (62.02)	<.0001	4552 (64.75)
Medicaid	134 (6.13)	560 (11.56)		694 (9.87)
Medicare	504 (23.07)	1280 (26.42)		1784 (25.38)
Elixhauser index, n (%)				
0	708 (32.38)	1636 (33.76)	.0454	2343 (33.33)
1	656 (30.04)	1513 (31.24)		2170 (30.86)
2	430 (19.67)	956 (19.72)		1385 (19.71)
3+	391 (17.91)	741 (15.28)		1132 (16.1)

Abbreviations: IPTW, inverse probability of treatment weight; IQR, interquartile range.

Outcomes

Index Hospitalization.. Length of stay (LOS) was similar between groups; index hospitalization complications were 26.9% for no rhBMP-2 and 24.02% for rhBMP-2 ($P = .0747$) (Table 4). Patients in rhBMP-2 cohort were likely to be discharged home compared to those without use of rhBMP-2 during surgery (81.98% vs 75.32%, $P < .0001$). Complications during index hospitalization were similar across the cohorts, $P = .0747$. Average payments were $92 699 for the rhBMP-2 cohort and $87 584 for the cohort that did not receive rhBMP-2, $P = .7579$.

Postdischarge 1 Month and 3 Months.. One month after discharge, those who did not receive rhBMP-2 had similar complications (18.06%) compared with those who received rhBMP-2 (15.38%), $P = .057$ (Table 4). Emergency room visits were 9.54% for no rhBMP-2 and 10.5% for those who received rhBMP-2, $P = .379$. At 90 days postoperative discharge, complications were 21.35% for the no BMP and 21.27% for the BMP group, $P = .991$.

Postdischarge 6 Months.. Reoperation rates were 32.2% for those who did not receive rhBMP-2and 31.12% for those who received rhBMP-2, $P = .5294$. Pseudoarthrosis was reported in 1.34% of cases with no BMP and 0.48% of cases with BMP, $P = .0355$. Hospital admissions were higher for no rhBMP-2 (15.79%) compared with BMP (13.45%), $P = .0781$. Number of outpatient services was higher for no rhBMP-2cohort (41)

Table 4. Outcomes at Index Hospitalization, 30 Days, 6 Months, 12 Months, and 24 Months of Patients Who Underwent Fusion for Spinal Deformity.

	IPTW-weighted values			
Variable	No BMP (n = 6263)	BMP (n = 839)	*P*	Combined cohort (n = 7102; 100%)
Index hospitalization outcomes				
Length of stay, days, median (IQR)	5 (3, 7)	5 (3, 6)	.0917	5 (3, 7)
Payment, $, median (IQR)	87 584 (52 380 149 187)	92 699 (56 921 152 767)	.7579	88 498 (53 063 149 966)
Discharge home, n (%)	4718 (75.33)	688 (81.98)	<.0001	5406 (76.12)
Complications, n (%)	1685 (26.9)	202 (24.02)	.0747	1886 (26.56)
30 days, postdischarge outcomes				
Complications, n (%)	1131 (18.06)	129 (15.38)	.057	1260 (17.75)
ER readmission, n (%)	598 (9.54)	88 (10.5)	.379	686 (9.66)
90 days, postdischarge outcomes				
Complications, n (%)	1605 (25.62)	199 (23.73)	.2381	1804 (25.4)
6 months, postdischarge outcomes				
Pseudoarthrosis, n (%)	84 (1.34)	4 (0.48)	.0355	88 (1.23)
Reoperation, n (%)	2017 (32.2)	261 (31.12)	.5294	2278 (32.08)
Hospital readmissions				
Admitted, n (%)	989 (15.79)	113 (13.45)	.0781	1102 (15.51)
Payments, median (SD)	25 629 (10 482, 67 866)	24 885 (9895, 68 868)	.9092	25 447 (10 414, 67 866)
Outpatient services				
No. of services, median (IQR)	41 (18, 77)	38 (19, 69)	.5264	41 (18, 76)
Payments, $, median (IQR)	4481 (1529, 9649)	4103 (1477, 8725)	.43	4446 (1519, 9544)
Medication refills				
No. of refills, median (IQR)	42 (6, 84)	35 (0, 75)	.063	42 (4, 83)
Payments, $, median (IQR)	1970 (32, 7057)	1313 (0, 5061)	.291	1875 (9, 6882)
Overall payments, $, median (IQR)	105 314 (65 328 176 542)	108 283 (68 440 173 362)	.5974	105 669 (65 706 175 919)
12 months postdischarge outcomes				
Pseudoarthrosis, n (%)	175 (2.8)	10 (1.14)	.0048	185 (2.6)
Reoperation, n (%)	2959 (47.24)	397 (47.33)	.9593	3356 (47.25)
Hospital readmissions				
Admitted, n (%)	1502 (23.98)	183 (21.77)	.1579	1685 (23.72)
Payments, $, median (IQR)	28 199 (11 206, 70 090)	22 648 (8413, 67 652)	.0482	27 305 (10 680, 69 967)
Outpatient services				
No. of services, median (IQR)	71 (35 130)	71 (36 123)	.5713	71 (35 129)
Payments, $, median (IQR)	7856 (3063, 16 205)	6857 (2966, 15 992)	.7778	7767 (3047, 16 184)
Medication refills				
No. of refills, median (IQR)	75 (12 152)	57 (0, 140)	<.0001	72 (9, 152)
Payments, median (IQR)	3824 (97, 13 891)	2577 (0, 10 592)	.174	3650 (60, 13 381)
Overall payments, $, median (IQR)	118 373 (74 070 195 930)	120 138 (76 035 192 687)	.8228	118 455 (74 350 195 150)
24 months postdischarge outcomes	No BMP (n = 4342)	BMP (n = 573)		Combined (n = 4915)
Pseudoarthrosis, n (%)	203 (4.68)	18 (3.14)	.0962	221 (4.5)
Reoperation, n (%)	2710 (62.41)	368 (64.14)	.4191	3077 (62.61)
Hospital readmissions				
Admitted, n (%)	1621 (37.32)	210 (36.56)	.7232	1830 (37.23)
Payments, $, median (IQR)	32 578 (12 837, 79 573)	25 153 (10 428, 73 103)	.2515	66 083 (100 903)
Outpatient services				
No. of services, median (IQR)	173 (177)	168 (166)	.4519	173 (176)
Payments, $, median (IQR)	14 578 (6029, 29 937)	12 826 (6041, 27 789)	.8656	14 385 (6032, 29 471)
Medication refills				
No. of refills, median (IQR)	147 (30 294)	115 (0, 282)	.1401	144 (27 293)
Payments, $, median (IQR)	9033 (558, 28 694)	5726 (0, 22 222)	.4147	8493 (460, 28 018)
Overall payments, $, median (IQR)	39 086 (13 199, 88 103)	32 634 (10 851, 74 697)	.2983	38 103 (12 949, 86 136)
Overall payments including index hospitalization (IQR)	144 179 (88 245 232 998)	141 664 (91 017 225 415)	.5946	143 816 (88 607 232 343)

Abbreviations: IPTW, inverse probability of treatment weight; BMP, bone morphogenetic protein; IQR, interquartile range.

Table 5. Comorbidities Associated With 12 Months' Reoperation.[a]

Variable	IPTW-weighted		
	No reoperation (n = 3747)	Reoperation (n = 3356)	P[b]
Diabetes	253 (6.77)	315 (9.39)	**<.0001**
Smoking	209 (5.57)	179 (5.34)	.6767
Obesity	165 (4.39)	205 (6.12)	**.0011**
Malnutrition	40 (1.08)	64 (1.89)	**.0044**
Intravenous drug use	18 (0.47)	29 (0.86)	**.0399**

Abbreviations: IPTW, inverse probability of treatment weight; IQR, interquartile range.
[a] Values are number (percentage).
[b] Boldfaced *P* values indicate statistical significance ($P < .05$).

compared with the BMP group (38), $P = .5264$. Any medication refills, including analgesics and all other medications, were also higher for no rhBMP-2 (42) compared with rhBMP-2 (35), $P = .063$. Overall payments were $105 314 for no rhBMP-2compared with $108 283 for rhBMP-2, $P = .5974$.

Postdischarge 12 Months.. At 12 months after discharge, reoperation rate was 47.24% for those who did not receive rhBMP-2 and 47.33% for those who received rhBMP-2, $P = .9593$. Pseudoarthrosis was reported in 2.8% of cases with no BMP and 01.14% of cases with BMP, $P = .0048$. Hospital admissions were higher for no rhBMP-2 (23.98%) compared with rhBMP-2 (21.77%), $P = .1579$. Payments were $28 199 for the no rhBMP-2 group and $22 648 for the rhBMP-2 group, $P = .0482$. Number of outpatient services were similar between groups, $P = .5713$. Medication refills were larger for the no rhBMP-2 group (75) compared with the rhBMP-2 group (57), $P < .0001$. Overall payments were $120 138 for the rhBMP-2 group and $118 373 for the no rhBMP-2 group, $P = .8228$. Risk factors associated with reoperation at 12 months included diabetes (present in 9.39% reoperation group vs 6.77% in the no reoperation group, $P < .0001$), obesity (6.12% reoperation vs 4.39% no reoperation, $P = .0011$), malnutrition (1.89% reoperation vs 1.08% no reoperation, $P = .0044$), intravenous drug use (0.86% reoperation vs 0.47% no reoperation, $P = .0399$), see Table 5.

Postdischarge 24 Months. Reoperation rate for the rhBMP-2 cohort at 24 months was 64.14% and for the no rhBMP-2 group was 62.41%, $P = .4191$ (Table 4). Pseudoarthrosis was observed in 4.68% of cases with no BMP and in 3.14% of cases with BMP, $P = .0962$. Hospital readmission rate was 36.56% for rhBMP-2 and 37.32% for the no BMP group, $P = .7232$. Readmission payments were $25 153 for the rhBMP-2 cohort and $32 578 for the no rhBMP-2 cohort, $P = .2515$. Number of outpatient services ($P = .4519$), number of medication refills ($P = .1401$), and payments associated with medication refills ($P = .4147$) were not different across the cohorts.

Trends in Use and Cost of rhBMP-2 in ASD.. There was a gradual increase in the use of rhBMP-2 during ASD surgeries between

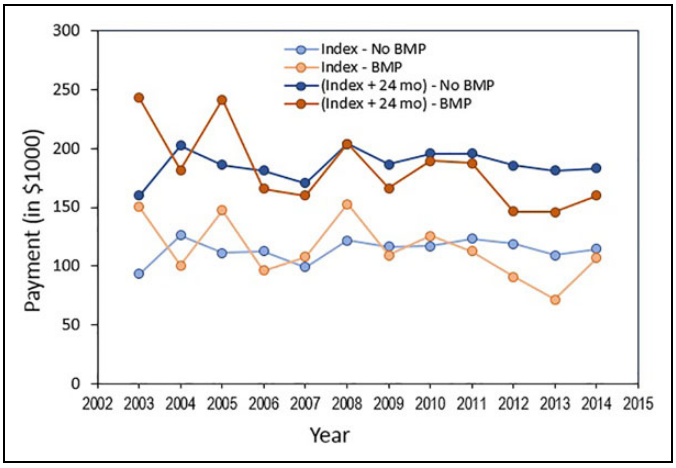

Figure 1. Trends in recombinant human bone morphogenetic protein–2 (rhBMP-2) use in adult spinal deformity (ASD) surgery from 2003 to 2014.

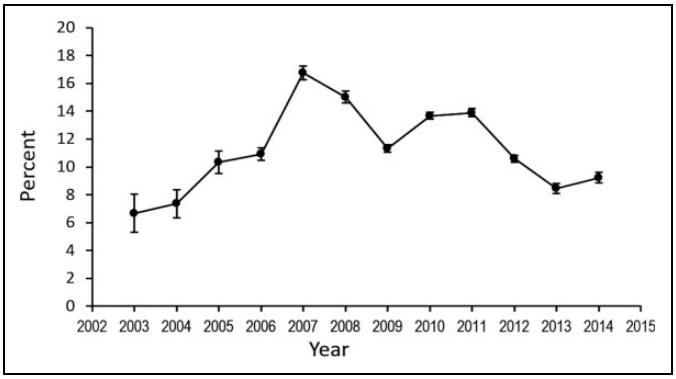

Figure 2. Trend of cost for recombinant human bone morphogenetic protein–2 (rhBMP-2) use in adult spinal deformity (ASD) surgery between 2003 and 2014.

2003 and 2007 with a peak in 2007 (16.7%), followed by a general decrease between 2007 and 2014 (Figure 1). Mean cost of ASD surgery with use of rhBMP-2 at index hospitalization was $126 400 in 2003 and $123 800 in 2014 (Figure 2). Peak cost occurred in 2008 for BMP use in ASD at $129 600. The cost of ASD surgery without BMP was $95 300 in 2003 and was $112 500 in 2014, with peak cost of $125 700 in 2004. Combined payments (index hospitalization and 24-month follow-up) for patients with rhBMP-2 use in ASD were $219 400 in 2003 and 199 200 in 2014, compared with $161 400 in 2003 and $177 800 in 2014 in patients without rhBMP-2 use. Peak cost was in 2004 at $201 000.

Between 2003 and 2014, percentage use of BMP for fusion of 2 to 3 levels was 14%, 4 to 8 levels was14%, and 9+ levels was 6.5% (see Table 6). Total number of fusions in 2003 was 120 and in 2014 was 379, with a peak of 680 in 2010. Use of BMP was highest in 2007 and 2008 for fusion of 2 to 3 levels at 11.2% and 11.7%, respectively.

At index hospitalization, use of BMP for 2 to 3 levels was associated with $83 491 compared to $81 756 without BMP for

Table 6. Trend of BMP Use by Number of Fusion Levels.

		2-3 levels		4-8 levels		9+ levels		BMP use (%)		
Year	Total fusions	No BMP	BMP	No BMP	BMP	No BMP	BMP	2-3 levels	4-8 levels	9+ levels
2003	120	47	5	18	N/A	47	3	4.2	N/A	2.5
2004	163	73	4	28	3	50	5	2.5	1.8	3.1
2005	203	93	17	26	1	63	3	8.4	0.5	1.5
2006	357	187	27	35	7	96	5	7.6	2.0	1.4
2007	376	190	42	31	10	92	11	11.2	2.7	2.9
2008	426	244	50	25	5	93	9	11.7	1.2	2.1
2009	592	348	53	47	8	130	6	9.0	1.4	1.0
2010	680	410	69	43	12	134	12	10.1	1.8	1.8
2011	612	350	63	54	12	123	10	10.3	2.0	1.6
2012	604	338	51	56	4	146	9	8.4	0.7	1.5
2013	414	214	26	36	5	129	4	6.3	1.2	1.0
2014	379	202	22	38	5	104	8	5.8	1.3	2.1
Total	4926	2696	429	437	72	1207	85	N/A	N/A	N/A

Abbreviation: BMP, bone morphogenetic protein; N/A, not applicable.

2 to 3 levels (see Table 7). Use of BMP for 4 to 8 levels was associated with $96 979 compared to $89 246 without use of BMP. For 9+ levels, BMP use was associated with $125 453 compared to $95 786 without use of BMP. Differences in payments for index hospitalization for use for BMP compared to no BMP were $1735 greater for 2 to 3 levels, $7733 greater for 4 to 8 levels, and $29 667 more for 9+ levels.

At 24 months, payments for those with use of BMP for 2 to 3 levels were $37 064 compared to $40 368 without BMP, use of BMP for 4 to 8 levels were $30 007 compared to $35 482 without use of BMP, and use of BMP for 9+ levels were $15 157 compared to $49 360 without use of BMP. Differences in payments at 24 months for use for BMP compared with no BMP were $3304 lower for 2 to 3 levels, $5475 lower for 4 to 8 levels, and $34 203 lower for 9+ levels.

Discussion

rhBMP-2 has been increasingly used in patients with ASD with 40% increase from 2002 to 2009.[25] Use of rhBMP-2 has been shown to reduce the incidence of pseudoarthrosis, which is associated with ASD surgery.[10,11] However, some studies report increased complications associated with rhBMP-2 use in spinal fusion.[17,18] Our comparative study is the first to analyze health care utilization, long-term outcomes at 24 months' follow-up, complications, and reoperation rates in patients undergoing surgery for ASD with and without use of rhBMP-2 in MarketScan.

Previous reports on rhBMP-2 suggested higher fusion rates with fewer complications in patients with ASD compared to those without rhBMP-2 use.[36] Paul et al[37] conducted a Nationwide Inpatient Sample (NIS) study of ASD patients undergoing surgery with BMP and reported a 28.9% reduction in incidence of pseudoarthrosis postoperatively. In 2008, Mulconrey et al[14] conducted a prospective 2-year follow-up study of rhBMP-2 use in ASD surgery and demonstrated a 95% fusion rate. Also, Bess and colleagues in a prospective study reported that patients who received rhBMP-2 did not show increased major neurological or wound complications, consistent with other prospective data.[5,38,39] In the present analysis, there was no increase in complications associated with BMP, with a non-significant trend in decreased complications with the use of rhBMP-2 in ASD at index hospitalization and 30 days post-operatively. Additionally, we demonstrated no increase in reoperation rate at 6, 12, and 24 months' follow up. We also find a general decrease in cost associated with rhBMP-2 use in ASD surgery between 2004 and 2014, consistent with previously reported trends regarding rhBMP-2 incorporation in spine surgery.[24] Additionally, use of BMP was associated with lower follow-up payments at 6, 12, and 24 months stratified by number of levels fused when compared with no use of BMP.

In 2018, De la Garza-Ramos et al[25] reported an increase in hospital charges of $53 023 for rhBMP-2 use in patients with ASD compared to those without rhBMP-2 use. Similarly, Dagostino et al[40] conducted an analysis of thoracolumbar and lumbar fusion procedures with rhBMP-2 and reported that total hospital charges increased by $13 326 for the rhBMP-2 use cohort. During the study period, $900 million additional hospital charges were associated with rhBMP-2 use in thoracolumbar procedures.[40] We demonstrate that use of rhBMP-2 was not associated with increased payments at 30 days, 6 months, 12 months, and 24 months. Additionally, we showed that there was no increase in complications or reoperations rates associated with rhBMP-2 from index hospitalization to 24 months' follow up. Outpatient services were decreased at 6 months in the rhBMP-2 group compared to the no rhBMP-2 cohort. Medication refills were also lower for the rhBMP-2 group (35) compared with the no rhBMP-2 group.

Safaee et al[21] showed that rhBMP-2 in ASD was linked to a reduction in reoperations, yet cost analysis showed no financial benefit with the use of rhBMP-2. The number needed to treat (NNT) with rhBMP-2 to prevent reoperation was 9.2 and amounted to $96 181 per NNT that was more than the cost of revision surgery at $52 153.[21] However, health care utilization

Table 7. Payments ($) Associated With Number of Levels With BMP.

	No BMP			BMP			
	2-3 levels	4-8 levels	9+ levels	2-3 levels	4-8 levels	9+ levels	P[a]
Index payment, median (IQR)	81 756 (49 475 147 266)	89 246 (50 654 140 978)	95 786 (56 701 171 351)	83 491 (52 258 147 963)	96 979 (75 131 163 213)	125 453 (84 012 164 077)	**<.0001**
Post 6 months payment, median (IQR)	10 329 (4422, 22 545)	8655 (2987, 21 196)	14 848 (4539, 31 922)	8133 (3486, 19 489)	5336 (3032, 16 442)	9979 (2746, 18 490)	**<.0001**
Post 12 months payment, median (IQR)	19 439 (8436, 44 124)	17 302 (5621, 39 992)	26 053 (8480, 54 146)	17 486 (6367, 38 722)	10 594 (5451, 44 560)	12 004 (5251, 42 791)	**<.0001**
Post 24 months payment, median (IQR)	40 368 (15 688, 88 615)	35 482 (10 381, 82 505)	49 360 (15 640 107 236)	37 064 (13 835, 75 599)	30 007 (10 098, 67 519)	15 157 (10 318, 80 143)	**.0005**

Abbreviation: BMP, bone morphogenetic protein; IQR, interquartile range.
[a]Boldfaced *P* values indicate statistical significance ($P < .05$).

metrics were not taken into consideration in this analysis. Cost effectiveness of rhBMP-2 may also be hospital dependent as it relates to cost of revision surgery, front-end cost of rhBMP-2, as well as the rate of complications expected, including pseudoarthrosis. At 24 months, we found that rhBMP-2 use was not associated with increased cost. Additionally, we reported that reoperation rates were also similar between groups. Health care utilization metrics showed similar payments between rhBMP-2 and the no rhBMP-2 group, indicating that there may not be an additional financial benefit in long-term follow-up with use of rhBMP-2. Procedures that involve multiple levels of fusion come with higher rates of pseudoarthrosis.[41] In 2014, Bess et al[39] also demonstrated no increased risk of complications for ASD using rhBMP-2 for fusion when compared with ICBG. Other studies also showed efficacy of rhBMP-2 in posterolateral-instrumented fusions using rhBMP-2 when compared with ICBG.[42,43] Advantages of rhBMP-2 use compared with ICBG include availability of large amount of graft and no donor site morbidity with similar incidence of complications and fusion rates. Similar advantages are seen with use of alternative allograft, fresh frozen, or other bone graft extenders.

Strengths and Limitations

The MarketScan database represents a substantial clinical population with longitudinal analysis capability. However, one limitation is the generalizability of study results because the cohort is a non-random sample and a retrospective observational study. The window of analysis is also limited given resources of the MarketScan search that does not include data beyond 2016. Selection of ICD-9 codes for diagnoses and procedures may misrepresent proper coding. The current investigation would have benefited from a more detailed subanalysis on the number of levels fused. Coding was not conducive to determine number of levels fused in ASD surgery as ranges were applied to number of levels that were also not consistent between ICD-9 and ICD-10 codes for analysis. Reporting of certain CPT (Current Procedural Terminology) codes during reoperation or readmission such as pseudoarthrosis was likely underreported without further method of verification or recording. Comparison groups of rhBMP-2 versus no rhBMP-2 were mismatched in sample size, as those with use of rhBMP-2 were roughly 1/8 of the size of the cohort with no rhBMP-2 use. The additional analysis at 24 months included only patients with available follow-up data, further limiting sample size and creating sample discrepancy between follow-up time points. Another limitation is that the MarketScan database does not include items such as radiographic measures and specifics of implants utilized, for example. Also, specific level of surgery in the cervical spine may be an informative covariate to include in future analyses that may detail clinically relevant findings.

Conclusions

In ASD surgery, rhBMP-2 use was not associated with increased complications or reoperation at index hospitalization

and 1-month follow up. Non-significant trends were observed for decreased complications associated with use of rhBMP-2 at index hospitalization and 30 days postoperative follow-up. Median overall payments, including index hospitalization, readmissions, reoperations, medications, and outpatient services, were not increased with the use of rhBMP-2 at 12 and 24 months after discharge. Reduction in payments for healthcare utilization associated with rhBMP-2 did not outweigh front-end index hospitalization payments. While use of rhBMP-2 was associated with increased payments at index hospitalization, payments at 6, 12, and 24 months postdischarge were lower for the cohort with use of BMP compared to the group without BMP for same number of levels fused. Our findings support the use of rhBMP-2 in ASD fusion procedures that may serve as an alternative to traditional methods of fusion.

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Supplemental Material

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