Spine

SPINE Volume 39, Number 3, pp 233-242

DEFORMITY

Does Recombinant Human Bone Morphogenetic Protein-2 Use in Adult Spinal Deformity Increase Complications and Are Complications Associated With Location of rhBMP-2 Use?

A Prospective, Multicenter Study of 279 Consecutive Patients

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Study Design. Multicenter, prospective analysis of consecutive patients with adult spinal deformity (ASD).

Objective. Evaluate complications associated with recombinant human bone morphogenetic protein-2 (rhBMP-2) use in ASD.

Summary of Background Data. Off-label rhBMP-2 use is common; however, underreporting of rhBMP-2 associated complications has been recently scrutinized.

Methods. Patients with ASD consecutively enrolled into a prospective, multicenter database were evaluated for type and timing of acute perioperative complications. Inclusion criteria: age 18 years and older, ASD, spinal arthrodesis of more than 4 levels, and 3 or more months of follow-up. Patients were divided into those receiving rhBMP-2 (BMP) or no rhBMP-2 (NOBMP). BMP divided into location of use: posterior (PBMP), interbody (IBMP), and interbody + posterior spine (I + PBMP). Correlations between acute perioperative complications and rhBMP-2 use including total dose, dose/level, and location of use were evaluated.

Results. A total of 279 patients (mean age: 57 yr; mean spinal levels fused: 12.0; and mean follow-up: 28.8 mo) met inclusion criteria. BMP (n = 172; average posterior dose = 2.5 mg/level, average interbody dose = 5 mg/level) had similar age, smoking history, previous spine surgery, total spinal levels fused, estimated blood loss, and duration of hospital stay as NOBMP (n = 107; $P > 0.05$). BMP had greater Charlson Comorbidity Index (1.9 *vs*. 1.2), greater scoliosis (43° *vs*. 38°), longer operative time (488.2 *vs*. 414.6 min), more osteotomies per patient (4.0 *vs*. 1.6), and greater percentage of anteroposterior fusion (APSF; 20.9% *vs*. 8.4%) than NOBMP, respectively ($P < 0.05$). BMP had more total complications per patient (1.4 *vs*. 0.6) and more minor complications per patient (0.9 *vs*. 0.2) than NOBMP, respectively ($P < 0.05$). NOBMP had more complications requiring surgery per patient than BMP (0.3 *vs*. 0.2; $P < 0.05$). Major, neurological, wound, and infectious complications were similar for NOBMP, BMP, PBMP, IBMP, and I + PBMP ($P > 0.05$). Multivariate analysis demonstrated small to nonexistent correlations between rhBMP-2 use and complications.

Conclusion. RhBMP-2 use and location of rhBMP-2 use in ASD surgery, at reported doses, do not increase acute major, neurological, or wound complications. Research is needed for higher rhBMP-2 dosing and long-term follow-up.

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Acknowledgment date: June 4, 2013. Revision date: October 1, 2013. Acceptance date: October 14, 2013.

The device(s)/drug(s) that is/are the subject of this manuscript is/are not FDA approved for this indication and is/are not commercially available in the United States.

DePuy Synthes Spine grant funds were received to support this work.

Relevant financial activities outside the submitted work: board membership, consultancy, grants, payment for lecture, royalties, payment for development of educational presentations, payment for lecture, stocks, patents, expert testimony, travel/accommodations/meeting expenses.

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DOI: 10.1097/BRS.0000000000000104

Key words: bone morphogenetic protein, rhBMP-2, complications, surgery, adult spinal deformity, deep wound infection, superficial wound infection, neurological complication.
Level of Evidence: 2
Spine 2014;39:233–242

Pseudarthrosis is the most common reported major complication after surgery for adult spinal deformity (ASD).[1–7] Despite advances in spinal fixation, pseudarthrosis rates after ASD surgery remain between 17% and 20%.[7] Recombinant human bone morphogenetic protein-2 (rhBMP-2) was approved for human use by the Food and Drug Administration in 2002 as an iliac crest bone graft (ICBG) substitute for single-level anterior lumbar interbody fusion. Initial clinical data reported rhBMP-2 to be superior to ICBG for anterior lumbar interbody fusion procedures, indicating higher fusion rates and no increase in adverse events.[8–10] However, rhBMP-2 use has expanded beyond the Food and Drug Administration–approved applications. A review of BMP usage (rhBMP-2 and rhMBP-7) in the United States indicated that the number of surgical procedures using BMP between 2003 and 2007 increased 4.3-fold (from 23,900 to 103,194), of which 85% of the procedures used BMP in an off-label application.[11] As off-label rhBMP-2 use has increased, the reported complications associated with rhBMP-2 have also increased. Several studies indicate that complications associated with rhBMP-2 correspond to the location of use including airway compromise when used in the anterior cervical spine, spinal cord compression and myelopathy when used in the posterior cervical spine, endplate resorption and implant subsidence when used in the interbody space, and heterotopic bone formation with associated radiculopathy when used in posterior and transforaminal lumbar interbody fusion.[12–20] A call for attention to rhBMP-2 associated complications was recently published *via* a series of articles by Carragee *et al*.[21–25] The authors concluded that further independent research is needed to evaluate the early- and long-term complications associated with rhBMP-2 use, including complications that require reoperation, readmission, infection, neurological deficit, and death.

Little data exist on rhBMP-2 use in ASD. Luhman *et al*[26] published the earliest single-center experience using rhBMP-2 for ASD. The authors reported high fusion rates (93%–100% and few complications [3 complications in 70 patients]). Recently, Williams *et al*[27] reported that use of BMP (rhBMP-2 and rhMBP-7) for adult scoliosis was associated with a higher rate of overall complications; however, when controlling for the effects of patient's age and revision procedure status, use of BMP for patients with adult scoliosis was not significantly associated with increased rates of overall complications.

The recent criticisms surrounding rhBMP-2 and the lack of prospective, multicenter data demonstrate that the complication profiles for rhBMP-2 use are poorly defined. The purpose of this study was to (1) compare the acute perioperative complications for patients with ASD treated with or without rhBMP-2 in a prospective, multicenter cohort of consecutive patients with ASD and (2) evaluate the complication profiles of rhBMP-2 when used in different locations of the thoracolumbar spine.

MATERIALS AND METHODS

Study data were obtained from a multicenter, prospective, database of consecutively enrolled patients with ASD. Eleven participating sites located in the United States contributed patients to the data set. Institutional review board approval was obtained at all participating centers prior to enrolling patients into the database. Patient enrollment and data collection is ongoing. Patient inclusion criteria for database entry is age more than 18 years and ASD, defined as minimum 1 of the following: degenerative or idiopathic scoliosis with a curvature of the spine measuring greater than 20°, sagittal vertical axis greater than 5 cm (SVA; distance from C7 plumb line to the posterior, superior corner of S1), pelvic tilt greater than 25° (PT; angle between the vertical and the line through the midpoint of the sacral plate to femoral heads axis[28]), and/or thoracic kyphosis greater than 60°. Database exclusion criteria are spinal deformities due to neuromuscular, post-traumatic, neoplastic, rheumatologic, and/or infectious disorders. In addition to the database inclusion criteria, the following criteria served as inclusion criteria for this study: operative treatment for ASD, spinal arthrodesis of 4 or more levels, and minimum 3 months of postoperative follow-up. Patients were divided into 2 treatment groups: those receiving rhBMP-2 (BMP) or no rhBMP-2 (NOBMP). The BMP group was analyzed on the basis of location of rhBMP-2 use: posterior spine only (PBMP), interbody only (IBMP), and interbody + posterior spine (I + PBMP). The I + PBMP group was evaluated by the approach used for the interbody fusion: anterior interbody (AI + PBMP) or posterior interbody (PI + PBMP). Total rhBMP-2 dose and rhBMP-2 dose/spinal level were noted. RhBMP-2 was dosed according to the discretion of the surgeon. The NOBMP group received a combination of ICBG, local bone, and allograft. The BMP group received a combination of local bone and allograft. No BMP patient received ICBG *via* a separate facial incision and dedicated ICBG harvest. Complications were categorized into cardiopulmonary, gastrointestinal, implant, infection, neurological, operative, renal, and wound. Infectious complications were classified as superficial wound infection (superficial to the fascia), deep wound infection (deep to the fascia), pneumonia, and urinary tract infection. Complications were labeled major or minor complications as previously recommended, complications requiring surgery were noted, and duration of complication onset from the time of surgery was recorded (Table 1).[2,29]

STATISTICAL METHODS

Descriptive statistics and univariate analyses were performed using JMP (JMP; version 8; SAS Institute Inc., Cary, NC, 1989–2009). Descriptive statistics were calculated for all study variables. Univariate analyses were used to evaluate differences of variables between the BMP and NOBMP groups and to determine relations from regression analyses.

TABLE 1. Major and Minor Perioperative Complications[14,26]

Major Complications	Occurrence (n)	Minor Complications	Occurrence (n)
Any complication requiring surgery	68	Cerebrospinal fluid leak	1
Blindness	1	Ileus	15
Cardiac arrest	0	Urinary tract infection	4
Congestive hart failure	4		
Death	3	Wound dehiscence–-no surgery	3
Deep venous thrombosis	4	Wound infection–-superficial	5
Instrumentation failure	13	Seroma or hematoma—no surgery	1
Myocardial infarction	1		
Neurological deficit	25		
Pneumonia	4		
Pulmonary embolism	4		
Sepsis	3		
Stroke	2		
Vascular injury	0		
Visceral injury	0		
Wound dehiscence–-surgery	2		
Wound infection—deep	13		
Seroma or hematoma–-surgery	2		

Distribution analysis was performed for each variable to determine whether distribution was normal and appropriateness of parametric or nonparametric tests. *P* values of less than 0.05 were considered significant. The adjusted r^2 statistic was used to assess the overall explanatory ability of the linear models. Multivariate regression models were constructed using Multivariate Adaptive Regression Spline Models (MARS). MARS was performed with R version 2.15.2 (2012-10-26) using package earth (earth: Multivariate Adaptive Regression Spline Models. R package version 3.2-3. http://CRAN.R-project.org/package=earth).

RESULTS

Demographic and Radiographical

Between 2008 and 2012, 279 of 353 consecutive surgically treated patients with ASD enrolled into the database met inclusion criteria and were evaluated for this study. BMP (n = 172) had similar age, body mass index, smoking history, and history of previous spine surgery as NOBMP (n = 107; Table 2). Mean BMP follow-up (31.3 *vs.* 24.8 mo), Charlson Comorbidity Index (1.9 *vs.* 1.2), and maximal scoliosis (43.0°*vs.* 37.9°) were greater than NOBMP, respectively ($P < 0.05$). I + PBMP (n = 62) was older (63.8 yr) than PBMP (n = 103; 54.6 yr) and NOBMP (n = 107; 56.8 yr; $P < 0.05$; Table 2). PBMP had longer mean follow-up, larger mean thoracic curve than I + PBMP and NOBMP, and smaller mean SVA than I + PBMP ($P < 0.05$).

Operative

Mean total rhBMP-2 dose (total dose) for all BMP patients was 31.0 mg (range: 2–96 mg). Mean posterior rhBMP-2 dose per level (PSF dose per level) for all BMP patients was 2.5 mg (range: 0.1–6.0 mg). Mean interbody rhBMP-2 dose per level (IBF dose per level) for all BMP patients was 5.0 mg (range: 0.6–18.0 mg; Table 2). Mean total dose was greater for I + PBMP (34.9 mg) than for PBMP (30.3 mg) and IBMP (8.8 mg; $P < 0.05$). Mean PSF dose per level was greater for PBMP (2.6 mg) than for I + PBMP (2.2 mg; $P < 0.05$; Table 2).

Total posterior spinal levels fused, estimated surgical blood loss (EBL), duration of stay in surgical intensive care unit, and hospital stay were similar for BMP *versus* NOBMP (Table 2). Mean operative time, number of spinal osteotomies per patient, and number of patients receiving combined anterior and posterior spinal fusion were greater for BMP *versus* NOBMP. Mean total posterior spinal levels fused were similar for PBMP (12.3), I + PBMP (11.9), NOBMP (12.0), and for IBMP (9.0; Table 2). I + PBMP had more mean interbody fusion levels (2.6) than PBMP (1.6) and NOBMP (1.0; $P < 0.05$). I + PBMP had greater mean EBL (2.8 L) than PBMP (1.5 L) and NOBMP (1.8 L; $P < 0.05$), and I + PBMP had greater mean operative time (514.4 min) than NOBMP (414.6 min; $P < 0.05$). Subanalysis of type of interbody fusion performed within the BMP group, including anterior lumber interbody fusion (n = 18), transforaminal interbody fusion/posterior lumbar interbody fusion (n = 34), and lateral

TABLE 2. Demographic, Radiographical, and Operative Data; (1) BMP *Versus* NOBMP, (2) According to Location of rhBMP-2 Use

	BMP (n = 172)	NOBMP (n = 107)	*P*	PBMP (n = 103)	IBMP (n = 7)	I + PBMP (n = 62)	NOBMP (n = 107)	*P*
Follow-up, mo (range)	31.3 (3.7–47.9)	24.8 (3.6–46.3)	<0.0001	33.0 (3.7–47.9)[1,2]	32.4 (20.7–41.6)	28.4 (4.2–46.6)[2]	24.8 (3.6–46.3)[1]	<0.0001[1], 0.0283[2]
Patient age, yr (range)	58.1 (19.0–81.5)	56.8 (18.7–82.2)	N/S	54.6 (19.0–81.3)[1]	60.2 (40.5–81.5)	63.8 (36.0–80.6)[1,2]	56.8 (18.7–82.2)[2]	0.0006[1], 0.0156[2]
BMI; mean (range)	27.9 (17.2–54.1)	27.9 (16.8–70.2)	N/S	27.5 (17.2–54.1)	28.6 (20.7–34.4)	28.6 (19.8–42.2)	27.9 (16.8–70.2)	N/S
Charlson Comorbidity Index; mean (range)	1.9 (0–8)	1.2 (0–7)	0.0004	1.8 (0–8)	0.9 (0–3)	2.2 (0–8)[1]	1.2 (0–7)[1]	0.0023[1]
ASA I; n (%)	9 (5.2)	13 (12.2)	0.0371	4 (3.9)[1,2]	2 (28.6)[1]	3 (4.8)	13 (12.2)[2]	0.0054[1], 0.0281[2]
ASA II; n (%)	85 (49.4)	55 (51.4)	N/S	55 (53.4)	2 (28.6)	28 (45.2)	55 (51.4)	N/S
ASA III; n (%)	75 (43.6)	38 (35.5)	N/S	43 (41.8)	3 (42.9)	29 (46.8)	38 (35.5)	N/S
ASA IV; n (%)	3 (1.7)	1 (0.9)	N/S	1 (1)	0	2 (3.2)	1 (1)	N/S
History of smoking; n (%)	20 (11.6)	7 (6.5)	N/S	16 (16)	0	4 (6.6)	7 (8.1)	N/S
Prior surgery; n (%)	53 (30.)	38 (35.5)	N/S	25 (24.3)	5 (71.4)	23 (37.1)	38 (35.5)	N/S
Maximum scoliosis; degrees (range)	43.0 (0–81.5)	37.9 (0–116.2)	0.0368	47.1 (0–81.5)[1,2]	39.4 (0–56)	36.6 (0–77.2)[1]	37.9 (0–116.2)[2]	0.0177[1], 0.0151[2]
SVA; mm (range)	60.1 (−84.1 to 288.6)	65.4 (−89.5 to 314.1)	N/S	45.7 (−84.1 to 288.6)[1]	68.6 (−44.4 to 168.0)	83.3 (−74.9 to 272.4)[1]	65.4 (−89.5 to 314.1)	0.0154[1]
Total posterior spinal levels fused; mean (range)	12.0 (4–18)	12.0 (5–19)	N/S	12.3 (4–18)	9.0 (4–16)	11.9 (4–18)	12.0 (5–19)	N/S
Interbody fusion levels; mean (range)	2.0 (0–14)	1.0 (0–7)	<0.0001	1.6 (0–6)[2]	2.6 (1–6)	2.6 (1–14)[1,2]	1.0 (0–7)[1]	<0.0001[1], 0.0045[2]
Total rhBMP-2 dose (mg); mean (range)	30.5 (2–96)	N/A	N/A	30.3 (2–72)[2,3]	8.8 (4–24)[1,2]	34.9 (12–96)[1,3]	N/A	<0.0001[1,2], 0.0412[3]
RhBMP-2 Dose (mg) per IBF level; mean (range)	5.0 (0.6–18)	N/A	N/A	N/A	4.8 (1–8)	5.0 (0.6–18)	N/A	N/S
RhBMP dose (mg) per PSF level	2.5 (0.1 -6)	N/A	N/A	2.6 (0.1–6)	N/A	2.2 (0.5–4.8)	N/A	0.0278
Total osteotomies per patient; mean (range)	4.0 (0–12)	1.6 (0–7)	<0.0001	4.1 (0–12)[2,4]	0.9 (0–4)[1,2]	4.2 (0–12)[1,3]	1.6 (0–7)[3,4]	0.0106[1], 0.0108[2], <0.0001[3,4]
Total PSO per patient; mean (range)	0.1 (0–4)	0.3 (0–2)	<0.0001	0.05 (0–1)[1,2]	0.4 (0–1)	0.2 (0–4)[2]	0.3 (0–2)[1]	<0.0001[1], 0.0364[2]

(*Continued*)

TABLE 2. *Continued*

	BMP (n = 172)	NOBMP (n = 107)	*P*	PBMP (n = 103)	IBMP (n = 7)	I + PBMP (n = 62)	NOBMP (n = 107)	*P*
APSF; n (range)	36 (20.9%)	9 (8.4%)	0.0057	26 (25.2%)[1]	1 (14.3%)	9 (14.5%)	9 (8.4%)[1]	0.0011[1]
Total operative time; minutes (range)	488.2 (181–1462)	414.6 (146–1140)	0.0008	474.6 (181–1462)	464 (240–727)	514.4 (217–1133)[1]	414.6 (146–1140)[1]	0.0038[1]
EBL; liters (range)	2.02 (0.2–12.2)	1.79 (0–7.5)	N/S	1.5 (0.2–10)[1]	2.2 (0.8–3.8)	2.8 (0.3–12.2)[1,2]	1.8 (0–7.5)[2]	<0.0001[1], 0.0002[2]
Total hospital stay; days (range)	9.2 (3–49)	8.8 (4–46)	N/S	8.3 (3–49)	9.4 (4–16)	10.6 (4–38)	8.8 (4–46)	N/S
Total SICU stay; hours (range)	63.2 (3–394.2)	46.1 (1–181)	N/S	50.5 (12–144)	79 (10–148)	71.0 (3–394.2)	46.1 (1–181)	N/S

BMP indicates patients receiving rhBMP-2; NOBMP, patients not receiving rhBMP-2; PBMP, patients receiving rhBMP-2 in the posterior spine only; IBMP, patients receiving rhBMP-2 in interbody fusion only; I + PBMP, patients receiving rhBMP-2 in interbody + posterior spine; N/S, not significant (P > 0.05), P < 0.05 = statistically significant; BMI, body mass index; ASA, American Society of Anesthesiologists Physical Status classification, SVA, sagittal vertical axis; N/A, not applicable; IBF, total interbody fusion levels; PSF, total posterior spinal fusion levels; PSO, pedicle subtraction osteotomy; APSF, anterior posterior spinal fusion; EBL, estimated blood loss; SICU, surgical intensive care unit.

transpsoas (lateral lumbar interbody fusion, n = 7), demonstrated that the subgroup sample sizes were not sufficiently large enough to draw meaningful statistical conclusions.

Complications

There were 304 complications in the 279 patients who met inclusion criteria for this study (Table 3). BMP had more total complications per patient (1.4 *vs*. 0.6), and more minor complications per patient (0.9 *vs*. 0.2) than NOBMP, respectively ($P < 0.05$). NOBMP had more complications requiring surgery per patient than BMP (0.3 *vs*. 0.2; $P < 0.05$). Major, wound, infectious, neurological, and renal complications were similar for BMP *versus* NOBMP. Complications occurring at 3 months or less after surgery per patient were greater BMP *versus* NOBMP (0.6 *vs*. 0.2; $P < 0.05$). Timing of all other specific complications was similar for BMP *versus* NOBMP (Table 3).

PBMP and I + PBMP had more total complications per patient than NOBMP (1.4 *vs*. 1.4 *vs*. 0.6, respectively; $P < 0.05$; Table 3). PBMP had more minor complications per patient than I + PBMP and NOBMP (1.0 *vs*. 0.7 *vs*. 0.2, respectively; $P < 0.05$). Major, implant, infectious, neurological, and wound complications per patient were similar for PBMP, I + PBMP, and NOBMP (Table 3). PBMP had more total complications per patient at 3 months or less than NOBMP (0.7 *vs*. 0.2; $P < 0.05$). AI + PBMP and PI + PBMP had similar major, wound, neurological, infectious, and implant complications, requiring surgery per patient as PBMP and NOBMP.

Linear regression analysis of total dose demonstrated significant correlations with total complications as well as major, operative, and infectious complications ($P < 0.05$); however, r^2 values indicated little to no demonstrable correlation, as per r^2 interpretation guidelines ($r^2 < 0.09$; Table 4).[30] Linear regression analysis of total PSF dose and total IBF dose demonstrated that total PSF dose significantly correlated with total, minor, major, neurological, operative, infectious, and deep wound complications ($P < 0.05$); however, r^2 values demonstrated little to no correlation ($r^2 < 0.09$). Linear regression analysis of PSF dose per level and IBF dose per level demonstrated that PSF dose per level significantly correlated with total complications ($P < 0.05$); however, r^2 values demonstrated little to no correlation ($r^2 < 0.09$).

Multivariate regression modeling (MARS) for specific complications using independent variables, including total PSF dose, total IBF dose, and other independent variables, demonstrated that SVA, total PSF dose, body mass index (BMI), EBL, and anterior spinal fusion levels (ASF) levels (in rank order using estimated variable importance methods) best modeled major complications; r^2 values demonstrated moderate correlation ($r^2 = 0.2$; Table 5). MARS analysis of deep infections demonstrated that SVA, BMI, and total PSF dose were the independent variables that generated the best-fit model; r^2 value showed moderate correlation ($r^2 = 0.2$). MARS analysis of wound complications demonstrated that operative time, SVA, BMI, and total anterior spinal fusion levels (ASF levels) provided the best-fit model; r^2 values showed moderate correlation ($r^2 = 0.11$).

TABLE 3. Perioperative Complications; BMP *Versus* NOBMP

	BMP (n = 172)	NOBMP (n = 107)	*P*	PBMP (n = 103)	IBMP (n = 7)	I + PBMP (n = 62)	NOBMP (n = 107)	*P*
Total complications	238	66	<0.0001	147[1]	6	85[2]	66[1,2]	<0.0001[1,2]
Total complications per patient	1.4 (0–7)	0.6 (0–3)	<0.0001	1.4 (0–7)[1]	0.8 (0–3)	1.4 (0–7)[2]	0.6 (0–3)[1,2]	<0.0001[1], 0.0012[2]
Total major per patient	0.5 (0–5)	0.4 (0–3)	N/S	0.4 (0–5)	0.3 (0–1)	0.7 (0–5)	0.4 (0–3)	N/S
Total major (% of total complications)	91 (38.2%)	40 (60.6%)	N/S	44 (29.9%)*	2 (33.3%)	45 (52.9%)*	40 (60.6%)	0.0015*
Total major (% of total patients)	56 (32.6%)	32 (29.9%)	N/S	24 (23.3%)[1]	2 (28.6%)	30 (48.4%)[1,2]	32 (29.9%)[2]	0.0009[1],0.0162[2]
Total minor per patient	0.9 (0–4)	0.2 (0–2)	<0.0001	1 (0–4)[1,3]	0.5 (0–2)	0.7 (0–3)[2,3]	0.2 (0–2)[1,2]	0.0000[1], 0.0092[2], 0.0452[3]
Total minor (% of total complications)	147 (61.8%)	26 (39.4%)	<0.0001	103 (70.1%)[1,2]	4 (66.7%)[1]	40 (47.1%)[3]	26 (39.4%)[2,3]	0.0018[1], <0.0001[2], 0.0068[3]
Total minor (% of total patients)	92 (53.5%)	23 (21.5%)	<0.0001	64 (61.1%)[1,2]	2 (28.6%)	26 (41.9%)[1,3]	23 (21.5%)[2,3]	0.0116[1],<0.0001[2], 0.0048[3]
Neurological per patient	0.23 (0–3)	0.12 (0–2)	N/S	0.3 (0–3)	0.5 (0–2)	0.2 (0–2)	0.1 (0–2)	N/S
Wound per patient	0.05 (0–1)	0.01 (0–1)	N/S	0.05 (0–1)	0.0	0.1 (0–1)	0.01 (0–1)	N/S
Infection per patient	0.14 (0–3)	0.06 (0–3)	N/S	0.1 (0–3)	0.1 (0–1)	0.1 (0–2)	0.1 (0–3)	N/S
Deep infection per patient	0.05 (0–2)	0.04 (0–3)	N/S	0.06 (0–2)	0	0.05 (0–1)	0.04 (0–3)	N/S
Superficial infection per patient	0.02 (0–1)	0.01 (0–1)	N/S	0.03 (0–1)	0	0.02 (0–1)	0.01 (0–1)	N/S
Sepsis per patient	0.01 (0–1)	0.01 (0–1)	N/S	0.01 (0–1)	0	0.02 (0–1)	0.01 (0–1)	N/S
Pneumonia per patient	0.02 (0–1)	0.0	N/S	0.01 (0–1)[2]	0.14 (0–1)[1,2]	0.03 (0–1)	0[1]	0.0107[1], 0.0205[2]
UTI per patient	0.02 (0–1)	0.0	N/S	0.03 (0–1)	0	0.02 (0–1)	0	N/S
Implant per patient	0.15 (0–2)	0.12 (0–2)	N/S	0.2 (0–2)	0	0.1 (0–1)	0.1 (0–2)	N/S
Cardiopulmonary per patient	0.24 (0–3)	0.06 (0–1)	0.0013	0.3 (0–3)*	0	0.2 (0–2)	0.1 (0–1)*	0.0008
Renal per patient	0.02 (0–1)	0.0	N/S	0.02 (0–1)	0	0.02 (0–1)	0	N/S
GI per patient	0.10 (0–2)	0.0	0.0008	0.1 (0–1)[2]	0	0.1 (0–2)[1]	0[1,2]	0.0084[1], 0.0320[2]
Operative per patient	0.3 (0–2)	0.1 (0–1)	0.0002	0.2 (0–2)[2]	0.1 (0–1)	0.5 (0–2)[1,2]	0.1 (0–1)[1]	<0.0001[1], 0.0017[2]
Complications requiring return to surgery per patient	0.2 (0–3)	0.3 (0–3)	0.0068	0.27 (0–3)	0.14 (0–1)	0.18 (0–3)	0.26 (0–3)	N/S
Complications at $t = 0$ per patient	0.4 (0–4)	0.1 (0–3)	0.0009	0.37 (0–4)	0	0.45 (0–4)*	0.14 (0–3)*	0.0155*
Complications ≤3 mo per patient	0.6 (0–5)	0.2 (0–3)	<0.0001	0.68 (0–5)[1]	0	0.61 (0–4)[2]	0.21 (0–3)[1,2]	0.0004[1], 0.0164[2]
Complications at 3–12 mo per patient	0.14 (0–3)	0.17 (0–1)	N/S	0.14 (0–2)	0.29 (0–1)	0.13 (0–3)	0.17 (0–1)	N/S

BMP indicates patients receiving rhBMP-2; NOBMP, patients not receiving rhBMP-2; PBMP, patients receiving rhBMP-2 in the posterior spine only; IBMP, patients receiving rhBMP-2 in interbody fusion only; I + PBMP, patients receiving rhBMP-2 in interbody + posterior spine; N/A, not applicable; N/S, not significant ($P > 0.05$), $P < 0.05$ = statistically significant; UTI, urinary tract infection; GI, gastrointestinal.

TABLE 4. Linear Regression Analysis for rhBMP-2 Use and Perioperative Complications*

BMP Correlations	r^2	P
Total rhBMP-2 dose *vs*. total posterior spinal levels fused	0.1364	<0.0001
Total rhBMP-2 dose *vs*. total minor complications	0.0091	N/S
Total rhBMP-2 dose *vs*. total major complications	0.0860	<0.0001
Total rhBMP-2 dose *vs*. total complications	0.0655	0.0007
Total rhBMP-2 dose *vs*. total operative complications	0.0507	0.0030
Total rhBMP-2 dose *vs*. total infections	0.0286	0.0265
Total rhBMP-2 dose *vs*. total deep infection	0.0546	0.0124
Total rhBMP-2 dose *vs*. total wound complications	0.0045	N/S
Total BMP *vs*. total neurological complications	0.0194	N/S
Total rhBMP-2 dose *vs*. return to surgery	0.0184	N/S
PSF rhBMP-2 dose *vs*. total minor complications	0.0237	0.0483
IBF rhBMP-2 dose *vs*. total minor complications	0.0000	N/S
PSF rhBMP-2 dose *vs*. total major complications	0.0713	0.0005
IBF rhBMP-2 dose *vs*. total major complications	0.00112	N/S
PSF rhBMP-2 dose *vs*. total complications	0.0770	0.0003
IBF rhBMP-2 dose *vs*. total complications	0.0007	N/S
PSF rhBMP-2 dose *vs*. total infections	0.0430	0.0075
IBF rhBMP-2 dose *vs*. total infection	0.0050	N/S
PSF rhBMP-2 dose *vs*. deep infections	0.0504	0.0178
IBF rhBMP-2 dose *vs*. deep infection	0.0006	N/S

**r^2 correlation strengths: 0 to 0.09 = weak; 0.09 to 0.49 = moderate; and 0.49 to 1.0 = strong.*

rBMP indicates recombinant human bone morphogenetic protein-2; PSF, posterior spinal fusion; IBF, interbody fusion; N/S, not significant ($P > 0.05$); $P < 0.05$ = statistically significant.

MARS analysis for specific complications using independent variables including PSF dose per level, IBF dose per level, and other independent variables demonstrated SVA, and total ASF levels best modeled major complications; r^2 value demonstrated moderate correlation (r^2= 0.13; Table 5). MARS analysis for deep infections demonstrated SVA and total PSF levels provided the best-fit model; r^2 values demonstrated moderate correlations (r^2= 0.10; Table 5).

DISCUSSION

RhBMP-2 has demonstrated efficacy in promoting higher and/or accelerated fusion rates for a number of applications.[8,31–38] As a consequence, the Food and Drug Administration has approved the use of rhBMP-2 for well-defined medical conditions.[11] However, the use of rhBMP-2 has extended beyond the approved indications, and, accordingly, so have the reported complication rates. Clear use guidelines and accurate complication profiles for rhBMP-2 must be established to promote responsible use and maximize benefits. To achieve these goals, researchers must investigate the complications associated with rhBMP-2 use with the same vigor that the efficacy for rhBMP-2 to promote fusion is evaluated. The purpose of this study was to evaluate the acute perioperative complication rates associated with rhBMP-2 use in a prospective, consecutive cohort of patients with ASD treated with rhBMP-2 compared with patients with ASD who did not receive rhBMP-2 and to evaluate the impact that location of rhBMP-2 use had upon perioperative complications. Our findings indicate that, at the reported rhBMP-2 doses, there were no consistent associations between use of rhBMP-2 and major, wound, or neurological complications; superficial or deep infections; and complications requiring surgery. When associations between rhBMP-2 use and specific complications reached statistical significance, linear regression and multivariate modeling demonstrated that the correlation coefficient values had small to nonexistent correlations.

Little data exist regarding complications associated with rhBMP-2 use in ASD. Williams *et al*[27] used the Scoliosis Research Society Morbidity and Mortality registry to compare complications between spinal fusion procedures performed with and without BMP (rhBMP-2 and BMP-7). Excluding anterior cervical fusion procedures, complications were similar between procedures performed with and without BMP. Despite the large study population, limitations to the study include retrospective analysis of a data set that is dependent upon volunteer data submission, with no method to ensure data accuracy or consecutive patient enrollment. Luhman *et al*[26] published the initial, single-center experience using rhBMP-2 for ASD. At mean follow-up of approximately 17 months, the reported fusion rates ranged from 93% to 100%. There were 3 complications noted; superficial wound dehiscence (n = 1), deep wound hematoma (n = 1), and deep wound infection (n = 1). Subsequently, Mulconrey *et al*,[39] published a longer follow-up on the same patient cohort. Reported fusion rates were again high, including 91% for anterior spinal fusion, 97% for posterior spinal fusion, and 100% for the high-dose posterior spinal fusion. One case of subfascial hematoma was reported. No other wound, infectious, or neurological complications were noted. Maeda *et al*[40] performed a comparative retrospective analysis of prospectively collected data on 55 consecutive patients with ASD who received multilevel fusion using either ICBG (n = 32) or rhBMP-2 without ICBG (n = 23). Pseudarthrosis rates were higher in the ICBG group (9 of 32 patients; 28.1%) than in the BMP group (1 of 23 patients; 4.3%). One perioperative complication was reported in the BMP group (renal complication; acute tubular necrosis attributed to antifibrinolytic use). No infections or neurological complications were reported. In this study, BMP patients had greater total complication

TABLE 5. Multivariate Adaptive Regression Splines (MARS) for Perioperative Complications

Dependent Variables	Complication Frequency	Rank Order of Independent Variable Estimated Importance; Modeling for Total PSF Dose and Total IBF Dose	Rank Order of Independent Variable Estimated Importance; Modeling for PSF Dose/Level and IBF Dose/Level
Total complications	304	A_1, C, E, M; r^2= 0.22	C, E, A_2, K; r^2= 0.20
Total minor complications	173	A_1, C, G, J, D, E, F; r^2= 0.27	A_2, C, E, G; r^2= 0.20
Total major complications	131	E, A_1, M, K, C; r^2= 0.18	E, K, C, L; r^2= 0.13
Total operative complications	59	K, A_1, E, B_1, C; r^2= 0.35	K, A_2, E, C; r^2= 0.29
Total infection	31	E, M, A_1, H, G, D; r^2= 0.26	E, A_2, G, D, H; r^2= 0.20
Total superficial	5	H, G, D, J; r^2= 0.27	H, G, D, J; r^2= 0.27
Total deep	14	E, M, A_1; r^2= 0.19	E, D; r^2= 0.10
Total sepsis	3	No variables identified	No variables identified
Total neurological	53	C, E, D; r^2= 0.15	C, E, D, F; r^2= 0.17
Total wound	10	J, E, M, C; r^2= 0.11	J, C, A_2, E, G; r^2= 0.14
Reoperation	68	E, C, K; r^2= 0.10	E, C, K; r^2= 0.10
Implant failure	13	G, K, J; r^2= 0.15	G, K, B_2; r^2= 0.14

PSF indicates posterior spinal fusion; IBF, interbody fusion; A_1, total PSF dose (mg); A_2, PSF dose (mg)/level; B_1, total IBF dose (mg); B_2, IBF dose (mg)/level; C, total anterior spinal fusion levels; D, total posterior spinal levels fused; E, sagittal vertical axis; F, Cobb; G, total osteotomies; H, total PSO; I, ASA grade; J, total operative time; K, estimated blood loss; L, age, M, BMI; r^2, correlation strengths: 0–0.09 = weak; 0.09–0.49 = moderate; 0.49–1.0 = strong.

rates and greater minor complication rates than NOBMP but similar wound, neurological, superficial, and deep infection complication rates as NOBMP. Reasons for greater total and minor complications in the BMP group are likely multiple. It is possible that an untoward side effect of rhBMP-2 could have played a role in generating greater total and minor complications in the BMP group. However, BMP also had greater Charlson Comorbidity Index, greater operative time, and greater rates of anterior and posterior spinal fusion, all of which are risk factors for perioperative complications.[41–44] These risk factors may have also accounted for the greater gastrointestinal, cardiopulmonary, and complications occurring less than 3 months per patient in the BMP group. It is also possible that discrepancies in complication reporting at the participating study sites may have accounted for the differences in complication rates between the groups; however, this error was attempted to be mitigated by the prospective, consecutive patient cohort study model with standardized complication reporting and standardized quality analysis of data.[45] NOBMP had more complications that required return to surgery and a greater percentage of complications occurring at the 3- to 12-month postoperative time frame than BMP. This in part is likely due to greater percentage of implant failures occurring at 3 to 12 months in NOBMP compared with BMP. There are several factors that could explain these findings; however, NOBMP had greater pedicle subtraction osteotomies per patient than BMP, and pedicle subtraction osteotomy procedures are a risk factor for rod fracture after ASD surgery.[46]

The greatest limitations to this study include (1) lack of long-term follow-up, (2) no analysis of spinal fusion rates, and (3) no reporting of patient health-related quality of life outcomes scores. The mean follow-up for all patients in this study was 28.8 months (range: 3.6–47.9 mo). However, the purpose of this study was to address concerns surrounding previous reports that failed to accurately assess short-term complications associated with rhBMP-2 use; therefore, the inclusion criteria for the analysis were patients with minimum 3 months of follow-up. We recognize the importance of long-term complication analysis for rhBMP-2 and anticipate that as this data set matures, we will report on long-term complications. No attempt was made in this study to evaluate the efficacy of rhBMP-2 in promoting spinal fusion or improving health-related quality of life outcomes for patients with ASD. The safety, efficacy, and cost-effectiveness of rhBMP-2 use in ASD must be demonstrated. As this data set matures, we will investigate fusion rates, patient outcomes, and cost-effectiveness of rhBMP-2 for ASD. Finally, the mean rhBMP-2 dose per level reported in this study (PSF dose/level = 2.5 mg, IBF dose/level = 5.0 mg) is below values previously reported for rhBMP-2 use in the spine.[26,34,36,39,47–50] This study is a prospective observational study; consequently, the dosages of rhBMP-2 reported in this study were chosen according to the discretion of the surgeon. The dosages of rhBMP-2 reported may account for our findings, and it is possible that if rhBMP-2 is used in higher doses, greater complication rates may arise.

In conclusion, this prospective, multicenter analysis of consecutive patients with ASD demonstrated that use of rhBMP-2 and the location of rhBMP-2 use, at the reported dosages, did not increase acute major, neurological, or wound complications or superficial or deep infections when used in multilevel

fusion for ASD. When associations between rhBMP-2 use and specific complications did reach statistical significance, linear regression and multivariate analysis demonstrated that the associated correlation coefficient values had small to no correlations. Future research on rhBMP-2 use must focus on long-term outcomes, evaluate outcomes at higher doses of rhBMP-2, and should consistently utilize advanced statistical techniques to quantify the strength of correlations between rhBMP-2 use and specific complications.

➢ Key Points

- ❑ Use of rhBMP-2 in ASD, at the reported dose per level, is not associated with increased major, neurological, wound, or infectious complications, or complications requiring surgery.
- ❑ Specific location of rhBMP-2 use in ASD surgery including posterolateral, posterior interbody, or anterior interbody, at reported doses, is not associated with increased major, neurological, wound, or infectious, complications, or complications requiring surgery.
- ❑ Linear regression and multivariate analysis demonstrated that when associations between rhBMP-2 use and specific complications reached statistical significance ($P < 0.05$), the correlation coefficient values had small to nonexistent correlations.

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