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Cost–Utility Analysis of rhBMP-2 Use in Adult Spinal Deformity Surgery

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Study Design. Economic modeling of data from a multicenter, prospective registry.

Objective. The aim of this study was to analyze the cost utility of recombinant human bone morphogenetic protein-2 (BMP) in adult spinal deformity (ASD) surgery.

Summary of Background Data. ASD surgery is expensive and presents risk of major complications. BMP is frequently used off-label to reduce the risk of pseudarthrosis.

Methods. Of 522 ASD patients with fusion of five or more spinal levels, 367 (70%) had at least 2-year follow-up. Total direct cost was calculated by adding direct costs of the index surgery and any subsequent reoperations or readmissions. Cumulative quality-adjusted life years (QALYs) gained were calculated from the change in preoperative to final follow-up SF-6D health utility score. A decision-analysis model comparing BMP *versus* no-BMP was developed with pseudarthrosis as the primary outcome. Costs and benefits were discounted at 3%. Probabilistic sensitivity analysis was performed using mixed first-order and second-order Monte Carlo simulations. One-way sensitivity analyses were performed by varying cost, probability, and QALY estimates (Alpha = 0.05).

Results. BMP was used in the index surgery for 267 patients (73%). The mean (±standard deviation) direct cost of BMP for the index surgery was \$14,000 ± \$6400. Forty patients (11%) underwent revision surgery for symptomatic pseudarthrosis (BMP group, 8.6%; no-BMP group, 17%; $P = 0.022$). The mean 2-year direct cost was significantly higher for patients with pseudarthrosis (\$138,000 ± \$17,000) than for patients without pseudarthrosis (\$61,000 ± \$25,000) ($P < 0.001$). Simulation analysis revealed that BMP was associated with positive incremental utility in 67% of patients and considered favorable at a willingness-to-pay threshold of \$150,000/QALY in >52% of patients.

Conclusion. BMP use was associated with reduction in revisions for symptomatic pseudarthrosis in ASD surgery. Cost–utility analysis suggests that BMP use may be favored in ASD surgery; however, this determination requires further research.

Key words: adult spinal deformity, cost-utility analysis, health economics, health utility, Monte Carlo simulation, nonunion, pseudarthrosis, recombinant human bone morphogenetic protein-2, reoperation, revision surgery.

Level of Evidence: 2

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Adult spinal deformity (ASD) surgery is associated with a high risk of complications,[1–3] including pseudarthrosis or nonunion[4,5] that can require additional surgery.[6,7] Since it was introduced in the early 2000s, recombinant human bone morphogenetic protein-2 (BMP) has been used to facilitate spinal fusion.[8–13] Several ASD studies have reported improved fusion rates with BMP use.[14–17] However, in addition to concerns about complications of BMP use,[18–20] the cost of BMP can be thousands of dollars.[21,22] To our knowledge, an economic analysis of BMP use in ASD surgery has not been reported. Our goal was to analyze the cost utility of BMP use in ASD surgery.

TABLE 1. Preoperative and Surgical Characteristics of Patients who Underwent Surgery for Treatment of Adult Spinal Deformity

Characteristics	No-BMP Group (n = 100)		BMP Group (n = 267)		P
	N (%)	Mean ± SD	N (%)	Mean ± SD	
Preoperative data					
Age, y		55 ± 17		60 ± 13	0.004
Female sex	76 (76)		208 (78)		0.641
Body mass index, kg/m^2		26 ± 6.0		28 ± 5.6	0.010
Previous spine surgery	50 (50)		144 (54)		0.489
Frailty index score		3.2 ± 1.7		3.5 ± 1.6	0.101
History of smoking	5 (5)		16 (6)		0.554
Surgical data					
No. of levels fused		12 ± 4		12 ± 3	0.711
Surgical invasiveness index score		94 ± 34		99 ± 36	0.135
Three-column osteotomy	33 (33)		56 (21)		0.021
Estimated blood loss, L		1.7 ± 1.4		1.9 ± 1.8	0.193
Intensive care unit stay, days		1.5 ± 1.4		2.1 ± 2.9	0.112
Hospital stay, days		7.9 ± 3.7		8.4 ± 4.8	0.264

BMP indicates recombinant human bone morphogenetic protein-2; SD, standard deviation.

METHODS

This study used a multicenter ASD registry of patients aged 18 years or older who were treated surgically between October 2008 and August 2013 at one of 11 participating institutions. Institutional review board approval was obtained at each institution. ASD was defined as major curve ≥20°, sagittal vertical axis ≥5 cm, pelvic tilt ≥25°, and/or thoracic kyphosis ≥60°. We excluded patients whose deformity was caused by infection, malignancy, or neuromuscular disease.

Study Population

We identified 522 ASD patients with five or more levels fused who were eligible for 2-year follow-up. Of these, 367 patients (70%) had minimum 2-year follow-up and were included in the analysis. The mean (±standard deviation) follow-up after surgery was 3.2 ± 1.1 years.

Patients were assigned to the BMP or no-BMP group according to whether BMP was used in the posterior spinal fusion during the index procedure. Preoperative patient characteristics (age, sex, body mass index, history of spine surgery, history of smoking, and ASD frailty index score[23]) and surgical characteristics (number of levels fused, ASD surgical invasiveness index,[24] performance of 3-column osteotomy, estimated blood loss, and duration of intensive care unit and hospital stays) were recorded (Table 1). Standard deformity-related radiographic measurements using 36-inch radiographs obtained preoperatively and at final follow-up were recorded (Table 2).

Pseudarthrosis Assessment

Records were reviewed to identify patients with clinical or radiographic evidence of pseudarthrosis during 2- to 7-year follow-up. Pseudarthrosis was defined as back pain with radiographic evidence of rod fracture, presence of nonunion on computed tomography scan, or subsequent revision surgery with intraoperative confirmation of nonunion.

TABLE 2. Radiographic Measures (Mean ± Standard Deviation) of Patients who Underwent Surgery for Adult Spinal Deformity

Measure	Preoperative			Final Follow-up		
	No-BMP Group	BMP Group	P	No-BMP Group	BMP Group	P
Thoracic curve,°	21 ± 34	16 ± 32	0.291	13 ± 25	9.1 ± 20	0.264
T2-T12 kyphosis,°	36 ± 20	35 ± 18	0.529	49 ± 17	52 ± 19	0.155
L1-S1 lordosis,°	43 ± 23	37 ± 22	0.117	54 ± 15	51 ± 14	0.093
Pelvic incidence,°	55 ± 14	55 ± 13	0.817	55 ± 14	55 ± 12	0.872
C7-S1 SVA, cm	5.6 ± 78	6.9 ± 76	0.168	2.7 ± 5.3	2.9 ± 5.5	0.755

BMP indicates recombinant human bone morphogenetic protein-2; SVA, sagittal vertical axis.

Inpatient Episode of Care Direct Costs

Index direct inpatient episode-of-care costs were available from five of the 11 institutions. For two institutions, itemized direct costs for all events in the inpatient episode-of-care were also available.

Itemized costs from the two institutions were averaged to obtain mean costs for each of the following cost centers associated with the inpatient episode of care: operating room (OR) (including fixed cost for disposable equipment and OR cost per unit time), hospital stay and intensive care unit (ICU) stay (cost per unit time), pharmacy/medications, radiology, inpatient therapy (physical, occupational, speech), phlebotomy/laboratory services, and consultation services (*e.g.*, internal medicine consultation). Implant costs were estimated by multiplying the number of units used by the mean cost of the implant type (screws, hooks, wires, set screws, interbody devices, rods, and cross-links). BMP costs were estimated by multiplying the number of INFUSE kits (Medtronic Sofamor Danek, Memphis, TN) used with the mean cost of the type of kit(s) used (X small, small, medium, large, large II).

For the six institutions that did not provide total direct inpatient episode-of-care costs, we calculated total inpatient episode-of-care costs by summing all individual estimates of costs based on resource utilization using the methods above. For example:

$$\begin{aligned}&\text{cost of OR time} \times \text{OR time} + \text{cost of ICU stay}\\&\quad \times \text{duration of ICU stay} + \text{cost of hospital stay}\\&\quad \times \text{duration of hospital stay}\\&\quad + \text{cost per pedicle screw}\\&\quad \times \text{number of pedicle screws} + \text{cost per rod}\\&\quad \times \text{number of rods} + \text{cost of large BMP kit}\\&\quad \times \text{number of large BMP kits used.}\end{aligned}$$

Internal validation of this method was performed by comparing the estimated versus reported inpatient direct costs for three of the five institutions that did not provide itemized costs but that shared the overall inpatient episode-of-care costs. Excellent agreement was found (Pearson correlation, 0.88).

Two-year Direct Costs

Two-year direct costs were estimated by adding the direct costs for the index inpatient episode of care (using the method described above) with the estimated cost of any subsequent readmission/reoperation episode. Readmission/reoperation episodes were assumed to be associated with a fixed cost. Estimates for the fixed costs for the various types of readmission/reoperation events were derived from previously reported mean cost data: reoperation for pseudarthrosis ($84,985), reoperation for proximal junctional kyphosis ($67,420), reoperation for infection ($76,422), reoperation for neurologic problem ($40,765), and readmission/reoperation for pain ($38,414).[25]

Health-related Quality-of-life Assessment

All patients completed health-related quality-of-life (HRQL) questionnaires preoperatively and at 1- and 2-year follow-up visits. The SF-36 item responses at each time point were used to calculate SF-6D (six-dimensional health state classification) health utility scores.[26] Cumulative quality-adjusted life years (QALYs) gained were calculated by adding the discounted incremental health utility changes between baseline and final follow-up SF-6D scores.

Monte Carlo Modeling

A decision-analysis model comparing BMP *versus* no-BMP treatment was developed with pseudarthrosis as the primary outcome (Figure 1). For the purpose of modeling, costs and benefits were discounted at 3%.

The decision-analysis model had seven inputs, including three cost variables (costs of index surgery, BMP, and revision surgery), two QALY variables (health utility of patients with and without pseudarthrosis), and two probability variables (incidence of pseudarthrosis with and without BMP use).

Each variable was represented as an independent statistical distribution to address the uncertainty in model input values. Cost and QALY estimates were sampled from normal distributions, and pseudarthrosis probability estimates were sampled from β distributions. Normal and β distributions used in the model were constructed with the mean centered at the mean estimates derived from our multicenter data and a relative standard deviation of 10% (Table 3).

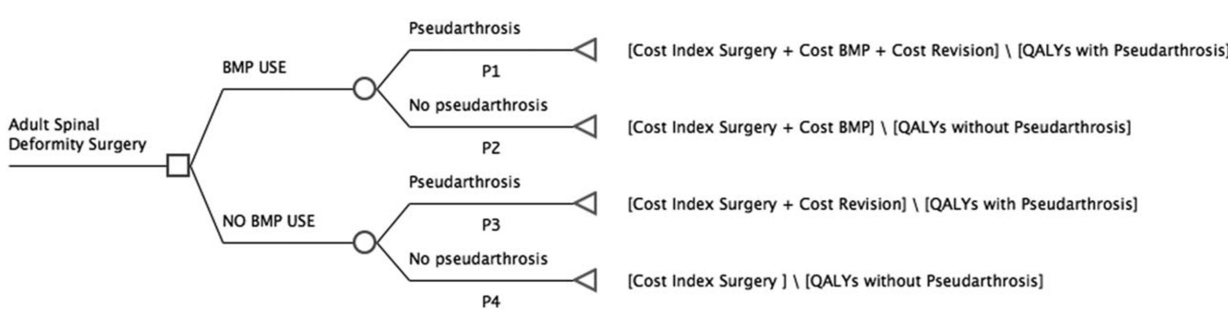

Figure 1. A decision-analysis model comparing recombinant human BMP use *vs.* no-BMP use in patients with adult spinal deformity treated surgically. BMP-2 indicates bone morphogenetic protein-2; QALYs, quality-adjusted life years.

TABLE 3. Input Values for the Mean ± Standard Deviation of the Probability Distributions used in the Monte Carlo Model

Model Input	Mean ± Standard Deviation
Cost, USD	
Index surgery	40,660 ± 8934
BMP use	14,178 ± 6423
Revision for pseudarthrosis	83,226 ± 7534
QALYs gained	
Patients without pseudarthrosis	0.646 ± 0.801
Patients with pseudarthrosis	0.311 ± 0.800
Probability of pseudarthrosis, %	
With BMP use	8.6 ± 0.9
Without BMP use	17 ± 1.7

BMP indicates recombinant human bone morphogenetic protein-2; QALYs, quality-adjusted life years; USD, United States dollars.

A mixed first-order and second-order Monte Carlo simulation model was executed for 1000 trials with simultaneous sampling from the corresponding probability distributions for each of the seven model input parameters to obtain random sets of model input estimates. One-way deterministic sensitivity analyses were performed by varying the seven model input parameters by ±50% to assess the effect of the variability in a given variable on the overall model.

Statistical Analysis

Analyses were performed using Stata/SE, version 12.0 (StataCorp, College Station, TX). Decision analysis and Monte Carlo modeling was performed using TreeAge Pro 2017 software (TreeAge Software, Williamstown, MA). $P < 0.05$ was considered significant.

RESULTS

Patient Characteristics

BMP was used for posterior/posterolateral fusion and/or interbody fusion during the index procedure in 267 of 367 patients (73%). The no-BMP group was significantly younger (mean ± standard deviation age, 55 ± 17 years) than the BMP group (60 ± 13 years) ($P = 0.004$). The groups were not significantly different in the proportion of women, mean ASD frailty index score, or proportion of patients undergoing revision surgery (Table 1).

Surgical and Radiographic Characteristics

The groups were not significantly different in the mean number of levels fused, ASD invasiveness index score, estimated blood loss, or duration of ICU or hospital stay (Table 1).

There was no significant difference between the groups in any of the key radiographic parameters at baseline or final follow-up (Table 2). Both groups showed excellent improvement between preoperative and final follow-up radiographs in key sagittal plane parameters, including pelvic incidence–lumbar lordosis mismatch (both groups, $P < 0.001$) and C7-S1 sagittal vertical axis (both groups, $P < 0.001$).

Pseudarthrosis Incidence

Patients in the BMP group had a significantly lower rate of pseudarthrosis (8.6%) *versus* patients in the no-BMP group (17%) ($P = 0.022$; Table 3). We found no significant differences between patients with *versus* without pseudarthrosis in mean age at surgery, sex distribution, number of levels fused, or ASD invasiveness index score.

Direct Costs

The mean direct cost for the index episode of care for the entire cohort was $55,000 ± $17,000. This cost was significantly higher for the BMP group ($60,000 ± $17,000) than for the no-BMP group ($41,000 ± $8900) ($P < 0.001$). The mean direct cost of BMP use was $14,000 ± $6400. In the BMP group, the mean amount of BMP used was 2.5 ± 0.5 mg/spinal level (commonly, two large kits were used with the graft for the posterior/posterolateral fusion and one large kit was used in conjunction with any interbody devices). The mean 2-year direct cost for patients with pseudarthrosis ($138,000 ± $17,000) was significantly higher than that of patients who did not develop pseudarthrosis ($61,000 ± $25,000) ($P < 0.001$).

HRQL Changes

HRQL scores improved significantly for the entire cohort from baseline to final follow-up: Oswestry Disability Index, 28.5 to 44.0; SF-36 mental component summary, 49.5 to 45.0; SF-36 physical component summary, 39.5 to 31.5; and Scoliosis Research Society-22r total score, 3.6 to 2.7 (all, $P < 0.001$). Mean cumulative QALYs gained for the entire cohort was 0.61 ± 0.81.

Mean cumulative QALYs gained for patients without pseudarthrosis (0.65 ± 0.80) was significantly higher than for patients with pseudarthrosis (0.31 ± 0.80) ($P = 0.013$). However, there was no significant difference in cumulative QALYs gained between the BMP group (0.66 ± 0.76) *versus* the no-BMP group (0.48 ± 0.91) ($P = 0.062$).

Monte Carlo Analysis

Probabilistic sensitivity analysis using a mixed first-order and second-order Monte Carlo simulation model for 1000 hypothetical patients showed that BMP use was favored (incremental cost-utility ratio <$150,000/QALY gained) in 52% of patients (Figure 2). Overall, BMP use was associated with incremental utility >0 in 67% of patients. In 10% of patients, BMP use was the dominant strategy (with incremental utility >0 and incremental cost <0). In 38% of patients, BMP use was favored because the incremental utility was >0, despite the incremental cost being >0. In an additional 4.6% of patients, BMP use was favored

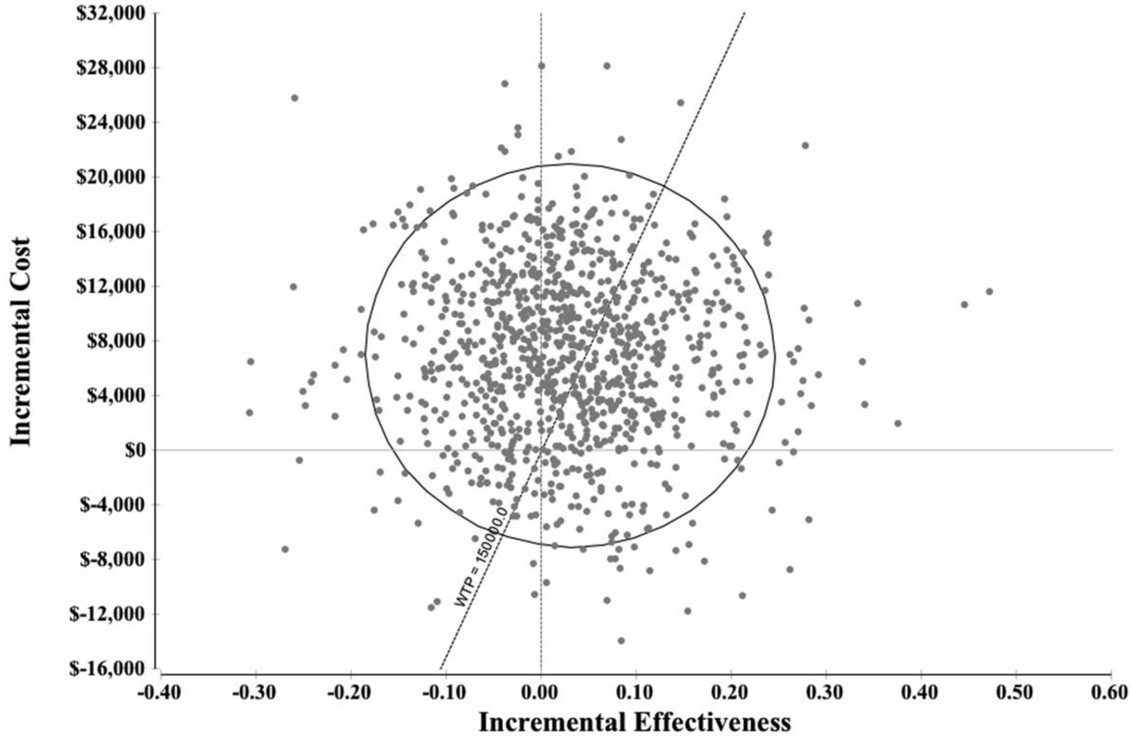

Figure 2. Scatter plot of incremental cost *vs.* incremental utility of recombinant human bone morphogenetic protein-2, ''(BMP)'' *vs.* no-BMP treatment for 1000 hypothetical patients (blue dots) undergoing surgery for adult spinal deformity. The ellipse represents 95% confidence interval. The dotted line represents the $150,000/quality-adjusted life year willingness-to-pay threshold.

because the incremental cost was <0, despite the incremental utility being <0.

In 28% of patients, BMP use was the inferior strategy (incremental utility <0 and incremental cost >0). In 19% of patients, BMP use was not favored because it was associated with incremental costs >0, despite incremental utility >0. In 0.6% of patients, BMP use was not favored because the incremental utility was <0, despite the incremental cost being <0. One-way deterministic sensitivity analysis showed that the two variables associated with the greatest variation in the model were the probability of developing pseudarthrosis with BMP use and cost of BMP. The remaining variables did not significantly impact the model ($P < 0.05$).

DISCUSSION

Our goal was to model the cost utility of BMP use in ASD surgery. Our analysis revealed that BMP use was associated with a significant reduction in the rate of symptomatic pseudarthrosis and associated revision surgeries. Probabilistic sensitivity analysis using Monte Carlo simulation showed that BMP use was favorable in >52% patients at a societal willingness-to-pay threshold of $150,000/QALY.

Since the results of the original clinical trials using BMP as a substitute for iliac crest bone graft (ICBG) in anterior lumbar interbody fusion in the early 2000s,[8] the spine community has been interested in ''off-label'' use of BMP for augmenting spinal fusion. BMP has been shown to be effective in treating high-risk patients, such as smokers,[27] and those undergoing short-segment posterior/posterolateral lumbar fusions for degenerative conditions[9,28] and posterior cervical fusion.[29]

Patients undergoing ASD surgery are at high risk for pseudarthrosis because of the high number of motion segments involved and the magnitude of spinal manipulation. Reported pseudarthrosis rates in this population are 17%[4] to 24%.[5] Symptomatic pseudarthrosis may require revision surgery, resulting in unanticipated morbidity in the form of pain and potential complications, and higher costs for the patient.[1,30] Because of the high risk of pseudarthrosis in ASD patients, some surgeons have recommended use of BMP in ASD surgery.[15,16,31,32] A recent study of elderly Medicare patients found that patients treated with BMP during fusion of eight or more levels were significantly less likely to undergo revision surgery than matched controls.[14] Similarly, we found that the rate of revision surgery for pseudarthrosis in the BMP group (9%) was almost half that of the no-BMP group (17%).

Some authors have recommended very high doses of BMP, such as 10 to 40 mg per level in ASD surgery.[15,32] However, BMP use carries risks, and many complications may be associated with BMP use in the spine, including postoperative radiculitis and root injury, ectopic bone formation, vertebral osteolysis, hematoma, and wound healing complications.[12,33,34] In our cohort, mean BMP use was 2.5 ± 0.5 mg per level, which is an order of magnitude lower than the 10 to 40 mg per level advocated by some authors. The relationship between BMP and pseudarthrosis may be dose-dependent, and our study did not account for this.

Few studies have focused on the cost of BMP use.[21,35,36] The difficulties of performing health economics studies in the field of spine surgery are, in part, caused by the challenges in obtaining cost data. Institutions are often reluctant to share cost data because of business and contractual concerns. We were able to obtain direct costs from five of the 11 institutions and were able to model the net costs for patients from the remaining six institutions. Although this method introduced an element of uncertainty in our analysis, we adjusted for this by using Monte Carlo simulation analysis to model the costs as independent probability distributions, from which data were randomly sampled for the analysis. Furthermore, post-hoc deterministic sensitivity analysis showed that the variation from the cost of index surgery did not significantly affect the cost-utility model.

We used a societal perspective for our analysis, assuming a willingness-to-pay threshold of $150,000/QALY, and found that BMP use was favorable. Of note, the willingness-to-pay threshold applies to the entire episode-of-care cost, with or without BMP, not just the incremental cost of BMP itself. There is debate regarding the appropriate threshold, and some health economics experts recommend using thresholds of $100,000 to $150,000, or approximately two to three times the per-capita annual income of the society.[37] Previous cost-effective analyses of ASD surgery have used thresholds of $140,000[38] and $150,000.[39] Assuming a patient perspective and accounting for only incremental utility (as measured in QALYs) irrespective of the cost, BMP use was associated with positive incremental utility in two-thirds of ASD simulation patients.

Our study has several limitations. First, we make various assumptions regarding the direct costs of the index episode of care and subsequent readmission and revision surgery associated with pseudarthrosis because direct cost data were unavailable from some centers. We tried to mitigate the uncertainty introduced by these assumptions via Monte Carlo simulation modeling. Second, pseudarthrosis assessment was inconsistent. Not all patients in our cohort received a computed tomography scan to rule out pseudarthrosis. It is possible that we missed some patients who developed pseudarthrosis but who were asymptomatic and did not undergo revision surgery. Thus, our conclusions may be relevant only for patients with "symptomatic" pseudarthrosis. Third, our Monte Carlo model was simplistic and did not account for other postoperative complications, such as infection, proximal junctional kyphosis, or medical complications[2] that may develop after ASD surgery and influence costs[25] and patient-reported outcomes. Off-label use of biologic agents such as BMP may cause complications, such as seroma formation, which may lead to additional hospitalization or reoperation and thus increase costs. Our study did not account for these factors. Fourth, only direct hospital costs were considered and nonhospital costs, such as for post-hospitalization rehabilitation and outpatient treatment, were excluded from analysis. Furthermore, we did not have true direct costs from all participating institutions, and we had to estimate some of the institutional costs using a resource consumption accounting model. Fifth, the mean age of the no-BMP cohort was significantly younger than that of the BMP cohort. We did not account for this potential confounder.

Although BMP use was associated with reduction in pseudarthrosis and reoperations, the link between BMP use and changes in QALYs was not linear. Any potential loss of QALYs is likely attributable to development of symptomatic pseudarthrosis, and not because of lack of BMP use. Thus, the next step to understand the utility of BMP in ASD would be to perform a cost minimization analysis. This will require standardized, time-driven, activity-based costing financial data from participating institutions.

CONCLUSION

BMP, although costly, was associated with a significant reduction in the rate of symptomatic pseudarthrosis in ASD surgery. Our model was built on various assumptions, most of which did not affect the overall model results in the sensitivity analysis. Future studies focusing on the economics of spine care in the ASD population are needed.

➢ Key Points

- ❑ BMP was used in the index surgery in 73% of ASD patients.
- ❑ The rate of pseudarthrosis was significantly higher in the no-BMP group (17%) compared with the BMP group (9%).
- ❑ Cost–utility analysis suggests that BMP use may be favored in ASD surgery; however, this determination requires further research.

References

1. Hassanzadeh H, Jain A, El Dafrawy MH, et al. Clinical results and functional outcomes of primary and revision spinal deformity surgery in adults. *J Bone Joint Surg Am* 2013;95:1413–9.
2. Jain A, Hassanzadeh H, Puvanesarajah V, et al. Incidence of perioperative medical complications and mortality among elderly patients undergoing surgery for spinal deformity: analysis of 3519 patients. *J Neurosurg Spine* 2017;27:534–9.
3. Sciubba DM, Yurter A, Smith JS, et al. A comprehensive review of complication rates after surgery for adult deformity: a reference for informed consent. *Spine Deform* 2015;3:575–94.
4. Kim YJ, Bridwell KH, Lenke LG, et al. Pseudarthrosis in adult spinal deformity following multisegmental instrumentation and arthrodesis. *J Bone Joint Surg Am* 2006;88:721–8.
5. Kim YJ, Bridwell KH, Lenke LG, et al. Pseudarthrosis in long adult spinal deformity instrumentation and fusion to the sacrum: prevalence and risk factor analysis of 144 cases. *Spine (Phila Pa 1976)* 2006;31:2329–36.
6. Pichelmann MA, Lenke LG, Bridwell KH, et al. Revision rates following primary adult spinal deformity surgery: six hundred forty-three consecutive patients followed-up to twenty-two years postoperative. *Spine (Phila Pa 1976)* 2010;35:219–26.

7. Hamilton DK, Buza JA III, Passias P, et al. The fate of patients with adult spinal deformity incurring rod fracture after thoracolumbar fusion. *World Neurosurg* 2017;106:905–11.
8. Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine (Phila Pa 1976)* 2002;27:2396–408.
9. Dimar JR, Glassman SD, Burkus KJ, et al. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine (Phila Pa 1976)* 2006;31:2534–9.
10. Dawson E, Bae HW, Burkus JK, et al. Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial. *J Bone Joint Surg Am* 2009;91:1604–13.
11. Jain A, Kebaish KM, Sponseller PD. Factors associated with use of bone morphogenetic protein during pediatric spinal fusion surgery: an analysis of 4817 patients. *J Bone Joint Surg Am* 2013;95: 1265–70.
12. Jain A, Hassanzadeh H, Strike SA, et al. rhBMP use in cervical spine surgery: associated factors and in-hospital complications. *J Bone Joint Surg Am* 2014;96:617–23.
13. Passias PG, Soroceanu A, Yang S, et al. Predictors of revision surgical procedure excluding wound complications in adult spinal deformity and impact on patient-reported outcomes and satisfaction: a two-year follow-up. *J Bone Joint Surg Am* 2016;98: 536–43.
14. Puvanesarajah V, Jain A, Cancienne JM, et al. BMP use and the risk of revision surgery after long posterolateral fusions in the elderly. *Clin Spine Surg* 2017;30:E931–7.
15. Maeda T, Buchowski JM, Kim YJ, et al. Long adult spinal deformity fusion to the sacrum using rhBMP-2 versus autogenous iliac crest bone graft. *Spine (Phila Pa 1976)* 2009;34:2205–12.
16. Kim HJ, Buchowski JM, Zebala LP, et al. RhBMP-2 is superior to iliac crest bone graft for long fusions to the sacrum in adult spinal deformity: 4- to 14-year follow-up. *Spine (Phila Pa 1976)* 2013;38:1209–15.
17. Poorman GW, Jalai CM, Boniello A, et al. Bone morphogenetic protein in adult spinal deformity surgery: a meta-analysis. *Eur Spine J* 2017;26:2094–102.
18. Cahill KS, Chi JH, Day A, et al. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. *JAMA* 2009;302:58–66.
19. Deyo RA, Ching A, Matsen L, et al. Use of bone morphogenetic proteins in spinal fusion surgery for older adults with lumbar stenosis: trends, complications, repeat surgery, and charges. *Spine (Phila Pa 1976)* 2012;37:222–30.
20. Singh K, Ahmadinia K, Park DK, et al. Complications of spinal fusion with utilization of bone morphogenetic protein: a systematic review of the literature. *Spine (Phila Pa 1976)* 2014;39:91–101.
21. Glassman SD, Carreon LY, Campbell MJ, et al. The perioperative cost of Infuse bone graft in posterolateral lumbar spine fusion. *Spine J* 2008;8:443–8.
22. Louie PK, Hassanzadeh H, Singh K. Epidemiologic trends in the utilization, demographics, and cost of bone morphogenetic protein in spinal fusions. *Curr Rev Musculoskelet Med* 2014;7: 177–81.
23. Miller EK, Neuman BJ, Jain A, et al. An assessment of frailty as a tool for risk stratification in adult spinal deformity surgery. *Neurosurg Focus* 2017;43:E3.
24. Neuman BJ, Ailon T, Scheer JK, et al. Development and validation of a novel adult spinal deformity surgical invasiveness score: analysis of 464 patients. *Neurosurgery* 2018;82:647–853.
25. Yeramaneni S, Gum JL, Carreon LY, et al. Impact of readmissions in episodic care of adult spinal deformity: event-based cost analysis of 695 consecutive cases. *J Bone Joint Surg Am* 2018;100:487–95.
26. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21: 271–92.
27. Glassman SD, Dimar JR III, Burkus K, et al. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. *Spine (Phila Pa 1976)* 2007;32:1693–8.
28. Glassman SD, Dimar JR, Carreon LY, et al. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. *Spine (Phila Pa 1976)* 2005;30:1694–8.
29. Crawford CH III, Carreon LY, McGinnis MD, et al. Perioperative complications of recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge versus iliac crest bone graft for posterior cervical arthrodesis. *Spine (Phila Pa 1976)* 2009;34:1390–4.
30. Pateder DB, Park YS, Kebaish KM, et al. Spinal fusion after revision surgery for pseudarthrosis in adult scoliosis. *Spine (Phila Pa 1976)* 2006;31:E314–9.
31. Luhmann SJ, Bridwell KH, Cheng I, et al. Use of bone morphogenetic protein-2 for adult spinal deformity. *Spine (Phila Pa 1976)* 2005;30:S110–7.
32. Mulconrey DS, Bridwell KH, Flynn J, et al. Bone morphogenetic protein (RhBMP-2) as a substitute for iliac crest bone graft in multilevel adult spinal deformity surgery: minimum two-year evaluation of fusion. *Spine (Phila Pa 1976)* 2008;33:2153–9.
33. Smucker JD, Rhee JM, Singh K, et al. Increased swelling complications associated with off-label usage of rhBMP-2 in the anterior cervical spine. *Spine (Phila Pa 1976)* 2006;31:2813–9.
34. Tannoury CA, An HS. Complications with the use of bone morphogenetic protein 2 (BMP-2) in spine surgery. *Spine J* 2014;14: 552–9.
35. Glassman SD, Carreon LY, Djurasovic M, et al. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: a randomized, controlled trial in patients over sixty years of age. *Spine (Phila Pa 1976)* 2008;33:2843–9.
36. Carreon LY, Glassman SD, Djurasovic M, et al. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion in patients over 60 years of age: a cost-utility study. *Spine (Phila Pa 1976)* 2009;34: 238–43.
37. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371:796–7.
38. McCarthy I, O'Brien M, Ames C, et al. Incremental cost-effectiveness of adult spinal deformity surgery: observed quality-adjusted life years with surgery compared with predicted quality-adjusted life years without surgery. *Neurosurg Focus* 2014;36:E3.
39. Raman T, Nayar SK, Liu S, et al. Cost-effectiveness of primary and revision surgery for adult spinal deformity. *Spine (Phila Pa 1976)* 2018;43:791–7.