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RESEARCH

Treatment of adult spine deformity: A retrospective comparison of bone morphogenic protein and bone marrow aspirate with bone allograft

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Abstract

Background The use of bone morphogenic protein (BMP-2) in adult spine deformity (ASD) surgery remains controversial more than two decades following its approval for clinical application in spine surgery. This study was performed to assess outcomes in patients undergoing ASD surgery with BMP application compared with a combination of bone marrow aspirate, cancellous bone chips and i-Factor.

Methods This was a retrospective cohort study. ASD patients were stratified by use of intra-operative BMP (BMP+) or not (BMA + I) and surveyed for the development of complications and mechanical failure. Quality of life gained following the procedure was evaluated using quality-adjusted life years (QALYs). Cost was calculated using the PearlDiver database and CMS definitions. Multivariable analyses (ANCOVA) and logistic regression were used to adjust for confounding.

Results 512 patients were included (60% BMP+). At baseline, BMP+ patients were older (62.5 vs 60.8 years, $p < 0.010$). Radiographic and quality-of-life metrics did not differ at follow up timepoints (all $p > 0.05$). BMP use was associated with higher supplemental rod use (OR: 7.0, 1.9 – 26.2, $p = 0.004$), greater number of levels fused (OR: 1.1, 1.03 – 1.17, $p = 0.003$) and greater neurological complications (OR: 5.0, 1.3 – 18.7, $p = 0.017$). Controlling for rod use and levels fused, BMP use was not associated with a lower risk of mechanical complications (OR 0.3, 95% CI: 0.2 – 3.0, $p = 0.353$), rod breakage (OR: 3.3, 0.6 – 18.7, $p = 0.182$) or implant failure (OR: 0.3, 0.04 – 1.51). At 2 years, the BMP+ cohort exhibited higher overall costs ($108,062 vs $95,144, $p = 0.002$), comparable QALYs (0.163 vs 0.171, $p = 0.65$) and higher cost per QALY ($p = 0.001$) at two years.

Conclusions In this analysis, BMP-2 application was not associated with superior outcomes when compared to a less costly biologic alternative (bone marrow aspirate + cancellous bone chips + i-Factor) following ASD surgery. The use of BMP-2 in ASD surgery appears to have reduced cost-efficacy at two years postoperatively.

Keywords Spine deformity · Spine fusion · Realignment · Recombinant human bone morphogenic protein-2 · Biologics · Bone marrow aspirate concentrate

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Introduction

The management of adult spine deformity (ASD) continues to evolve, with spine surgeons being increasingly able to provide surgical intervention for affected patients with a variety of techniques [38]. Despite the significant advances in ASD management, there is still concern for complications such as pseudarthrosis and mechanical failure. Even at present, the reported incidence of nonunion following ASD surgery is estimated in the range of 17—24% [31]. Achieving union is essential following spine deformity corrective surgery, and failure to do so results in early reoperation [21].

In the pursuit of enhancing fusion rates, supplementary biologic agents such as recombinant human bone morphogenic protein-2 (rhBMP-2) (INFUSE, Medtronic, Memphis, TN, USA) have been applied in ASD surgery. Recombinant human bone morphogenic protein 2 (rhBMP-2) is a biologic agent which functions to enhance bone fusion by inducing mesenchymal stem cells to differentiate into chondroblasts and osteoblasts [32, 39]. Although iliac crest bone graft (ICBG) remains the gold standard of fusion-enhancing agents, its efficacy is limited by concerns of donor site morbidity, increased operative time and a finite supply of graft [12, 24].

Despite its demonstrated benefits for improving the rate of fusion, the increased use of rhBMP-2 has also raised concerns due to higher associated costs and a potentially greater complication profile, including neurological deficits, ectopic bone formation, radiculopathy and wound complications [17, 18]. Given the greater risk of nonunion, and summarily higher effect of pseudarthrosis on outcomes in the setting of ASD surgery, the benefits of BMP application in these corrective surgery procedures may outweigh the downsides. This issue has not been effectively studied in a large population of ASD populations with sufficient clinical variation to enable the development of statistical models that would be considered translatable.

In this context, we sought to investigate the performance of rhBMP-2 compared with an alternative biologic combination (bone marrow aspirate [BMA] + cancellous bone chips + i-Factor) on postoperative outcomes, including complications, functional outcomes and costs, in patients undergoing ASD corrective surgery. To study this issue, we used a prospectively collected database that has been successfully employed in the past [26, 29, 30]. We hypothesized that the application of BMP would be associated with higher fusion rates, lower mechanical failure events, greater quality of life and consequently improved cost-effectiveness compared with BMA, bone chips and i-Factor.

Methods

Dara source and study design

This study was a retrospective review of a prospectively collected, single-center database of adult spinal deformity (ASD) patients enrolled from 2012 to 2020. This database has been used in previous work regarding the management of ASD [27, 29, 30]. Informed consent was gained from all patients, and Institutional Review Board (IRB) approval was obtained prior to patient enrolment.

We included patients undergoing thoracolumbar junction fusion-to-the-pelvis for ASD, and had complete demographic, clinical, radiographic and complication data up to at least two years postoperatively. Patients were stratified based on the intraoperative use of bone morphogenic protein. Those who received BMP application were defined as the "BMP" group, with a control group receiving a combination of bone marrow aspirate, cancellous bone chips and i-Factor (specified as "BMA + I"). Outcomes that we considered consisted of complication events up to two years postoperatively, patient-reported outcomes regarding health-related quality of life (HRQL) and post-operative healthcare costs. We also assessed radiographic outcomes including spinopelvic measurements associated with the treatment of ASD and spinal realignment [8].

RhBMP-2 usage

In the BMP group, the average used posteriorly was 83.7 mg (range 65.4 – 131.3 mg), with a mean rhBMP-2 per level of 10.4 mg. Whereas anteriorly, this was 37.3 mg (range 11.6 – 42 mg). When used posteriorly, rhBMP-2 was applied to the transverse processes and lamina of all instrumented vertebra. When used anteriorly, rhBMP-2 was applied into the intervertebral space, and also in and around the intervertebral cage.

In the BMA + I group, bone marrow aspirate (BMA) was obtained from the posterior iliac crests using an 11-gauge 5 side-hole Jamshidi needle and a 60 mL syringe flushed with heparinized saline. This mixture was then pooled into a bag containing Anticoagulant Citrate Dextrose Solution before placement into an aspirate concentrator for 15 min to a final volume of 10, 20, or 30 mL. This concentrated mixture was then combined with allograft cancellous bone chips (Royal Biologics, Hackensack, New Jersey, USA). The dose per level of this mixture was 6 mg. An additional 2.5 cc per level of i-Factor (Cerapedics, Westminster, Colorado, USA). I-Factor is a bone substitute material consisting of a bioactive peptide merged with anorganic bone material [36]. This mixture was then

applied anteriorly or posteriorly in a similar fashion to that described above for the BMP + group.

Data collection and radiographic assessment

We abstracted demographic data from all patients identified for inclusion, including age, gender, race, BMI, and frailty (as described using the Passias modified ASD Frailty Index) [25, 28]. Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI), which categorizes the severity of comorbidity burden into mild (CCI scores 1–2), moderate (CCI 3–4) and severe (CCI ≥ 5). Surgical details included estimated blood loss (EBL), operative time, number of levels fused, and the use of decompressions, osteotomies, or three-column osteotomies. HRQL metrics assessed included the Oswestry disability index (ODI, on a scale of 0 [no disability] to 100 [most severe disability]), the EQ-5D-5L (on a scale of < 0 [representing the worst possible health state] to 1 [best possible health state]) and Scoliosis Research Society 22-item revised questionnaire (SRS-22r, on a scale of 0 [worst possible score] to 5 [best possible score]). These were collected at baseline, as well as at 6 weeks, one-year, and two years postoperatively. The "best clinical outcome" (BCO) was defined using the criteria published by Smith et al. [37] with an SRS-22 score ≥ 4.5 and/or an ODI score ≤ 15. Lateral spine radiographs were used to assess radiographic parameters at baseline and follow-up. All images were analyzed with SpineView® (ENSAM, Laboratory of Biomechanics, Paris, France) [7, 33]. Fusion analyses were performed at the 2-year postoperative timepoint using the computed tomography imaging-based system proposed by Tan et al. [40]

Cost & utility calculations

Costs were calculated using the PearlDiver database, which encompasses a comprehensive information source concerning reimbursement charges (from Medicare and private insurance), outcomes reports, and trends [5]. CMS.gov definitions were used to determine mean costs associated with procedures based on adult spinal deformity diagnosis-related groups and procedural costs for cases [2]. Two-year reimbursement estimates were determined using regression analysis of Medicare pay-scales for all services rendered within a 30-day window, including costs of postoperative complications, outpatient healthcare encounters, revisions and medical related readmissions, as per previously published methods [5, 16, 34].

Utility data was calculated via ODI converted to SF-6D using published conversion methods [6]. The utilities were then transformed into Quality Adjusted Life Years (QALYs) using marginalized means controlling for baseline ODI score and characterized as QALYs gained. Quality adjusted life years were discounted at an annual 3% rate for each time point as recommended by the World Health Organization to account for decline in function associated with aging [41].

Statistical analysis

In all testing, we considered significance to be present for $p < 0.05$ with odds ratios, and 95% confidence intervals (CI) exclusive of 1.0. Means comparisons tests (T-tests and Pearson's Chi-Square) were used to assess differences between groups at baseline. Multivariable analyses (ANCOVA and logistic regression) were performed to assess postoperative outcomes, and any associated variables, factoring in differences in baseline and surgical characteristics between groups. Further logistic regression analyses were performed to analyze the association between BMP use and pseudarthrosis in subsets of patients with contributory demographic and surgical risk factors. All statistical analyses were conducted using SPSS, version 28.1.1 (Armonk, NY).

Results

Baseline cohort characteristics and comparisons

512 patients were included in the study. The mean age was 59.9 ± 14.4 years, mean body mass index was 27.0 ± 5.5 kg/m^2, and the mean Charlson Comorbidity Index was 1.64 ± 1.67. 81% (n = 415) of patients were female. 60% of patients had BMP-2 used during their surgery (60% BMP, n = 307). BMP patients were older (62.5 vs 60.8 years, $p < 0.010$). Otherwise, there were no other differences at baseline between both groups in demographic, disability or deformity severity parameters (Table 1). BMP had its highest frequency of use in 2018, while BMA + I had its highest frequency of use in 2021. BMP use was associated with higher supplemental rod use (OR: 7.0, 1.9 – 26.2, $p = 0.004$) and higher number of levels fused (OR: 1.1, 1.03 – 1.17, $p = 0.003$).

Perioperative and postoperative outcomes

BMP + patients underwent a higher mean number of levels fused (12.7 vs 10, $p = 0.047$). However other perioperative factors did not differ significantly between both groups, including operative time, estimated blood loss, length of stay, and osteotomy use (Table 2). Health-related quality of life (HRQL) metrics did not differ significantly between both groups immediately postoperatively, and at up to two years (Table 3). Similarly, deformity radiographic parameters did not differ (Table 4). Multivariable logistic regression analyses factoring age at baseline and surgical invasiveness (measured by levels fused) revealed that BMP use was not

Table 1 Baseline comparisons

	BMP	BMA+I	Sig
Patients, n	307	205	
Mean age, years (SD)	62.5 (12.8)	60.8 (16.0)	<0.010*
Mean BMI, kg/m^2, (SD)	27.9 (5.6)	27.3 (5.7)	0.219*
Mean CCI (SD)	1.81 (1.69)	1.61 (1.68)	0.184*
Smoker, n (%)	18 (5.9)	14 (6.8)	0.673†
Osteoporosis, n (%)	60 (19.5)	36 (17.6)	0.165†
Mean ASD-mFI (SD)	7.2 (4.3)	6.9 (4.7)	0.705*
Mean SRS-22r (SD)	2.74 (0.65)	2.73 (0.64)	0.704*
Mean ODI (SD)	45.4 (17.4)	45.1 (19.0)	0.662*
Mean EQ-5D-5L (SD)	0.74 (0.07)	0.74 (0.06)	0.517*
Mean SVA, mm (SD)	65.7 (68.7)	69.0 (74.4)	0.449*
Mean PI-LL, ° (SD)	16.7 (20.9)	15.0 (21.1)	0.915*
Mean PT, ° (SD)	24.6 (11.0)	23.1 (10.8)	0.523*

*Analysis of Variance

† Chi-squared test

ASD-mFI adult spinal deformity modified frailty index, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *EQ-5D* EuroQol five-dimension health questionnaire five-level, *ODI* Oswestry Disability Index, *PI–LL* pelvic incidence– lumbar lordosis mismatch, *PT* pelvic tilt, *SRS-22r* Scoliosis Research Society-22 item revised score, *SVA* sagittal vertical axis

associated with significantly better odds of achieving the best clinical outcome (OR 1.6, 95% CI: 0.7- 3.8, p = 0.063). At 2 years postoperatively, BMP patients demonstrated a higher overall mean cost of care ($108,062 vs $95,144, $p = 0.002$). Quality-adjusted life years (QALYs) at two years were not significantly different between BMP and BMA + I groups (0.163 vs 0.171, $p = 0.65$). BMP also had a $106,559 additional cost per QALY at two years ($p = 0.001$) compared TO BMA + I.

Complications

BMP demonstrated an overall higher rate of complications of by two years. Notable differences were seen particularly in proximal junctional kyphosis (9.8% [$n = 30$] vs 5.4% [$n = 11$], $p = 0.030$) and neurological complications (12.7% [$n = 39$] vs 7.8% [$n = 16$], $p = 0.049$). Of these neurological complications, BMP had 82.1% sensory [n = 32] and 17.9% motor types [n = 7], while BMA + I had 87.5% sensory [$n = 14$] and 12.5% motor types [$n = 2$]. BMP patients had a lower rate of mechanical complications (13.0% [$n = 40$] vs 20.5% [$n = 42$], $p = 0.009$) and reoperations (14% [$n = 43$] vs 21% [$n = 43$], $p = 0.017$) by two years (Table 5). Multivariable regression analyses factoring rod use and levels fused revealed that rhBMP-2 use was not associated with lower odds of mechanical complications (OR 0.3, 95% CI: 0.2 – 3.0, $p = 0.353$), including rod breakage (OR: 3.3, 0.6 – 18.7, $p = 0.182$) or implant failure (OR: 0.3, 0.04 – 1.51, $p = 0.353$). However, rhBMP-2 use was still associated with greater odds for neurological complications (OR: 5.0, 1.3 – 18.7, $p = 0.017$). Pseudoarthrosis rates at two years were generally low in the entire cohort and did not differ significantly between BMP and BMA + I groups (12.4% [$n = 38$] vs 14.6% [$n = 30$], $p = 0.210$).

Fusion evaluation

At 2-year follow up, grade I or II fusion was achieved in 83.4% of BMP [$n = 256$] vs 80.5% [$n = 165$] in BMA + I ($p = 0.132$). Grade I fusion was achieved in 77.2% of BMP [$n = 237$] and 74.6% of BMA + I, [$n = 153$] ($p = 0.113$). Pseudarthrosis (grade IV fusion) rates were 2.3% for BMP [$n = 7$] vs 4.4% for BMA + I [$n = 9$], ($p = 0.210$).

Table 2 Peri-operative factor comparisons

	BMP	BMA+I	Sig
Mean Surgical time, mins (SD)	354.7 (129.1)	324.7 (140.7)	0.231*
Mean EBL, ml (SD)	1469.0 (1404.1)	1327.0 (1345.5)	0.422*
Osteotomy performed intraoperatively, n (%)	224 (73)	137 (67)	0.083†
3CO performed intraoperatively, n (%)	62 (20.2)	48 (23.4)	0.302†
Mean Levels fused posteriorly, n (SD)	12.7 (5.1)	10.0 (4.3)	0.047*
Mean Interbody fusion levels, n (SD)	2.7 (1.7)	2.0 (1.4)	0.009*
Mean LOS, days (SD)	8.0 (4.4)	7.1 (4.2)	0.929*

*Analysis of Variance

†Chi-Squared test

3CO three column osteotomies, *EBL* estimated blood loss, *LOS* length of stay, *Osteotomy* any performed (all grades including 3CO)

Table 3 Health-Related Quality of Life metrics outcomes

	BMP	BMA+I	Sig
Mean 6W SRS-22r (SD)	3.04 (0.54)	2.99 (0.65)	0.553*
Mean Y1 SRS-22r (SD)	3.71 (0.71)	3.64 (0.79)	0.390*
Mean Y2 SRS-22r (SD)	3.69 (0.78)	3.56 (0.83)	0.111*
Mean 6W ODI (SD)	49.0 (17.2)	47.8 (19.9)	0.610*
Mean Y1 ODI (SD)	26.4 (18.4)	27.2 (20.3)	0.697*
Mean Y2 ODI (SD)	26.4 (19.9)	26.9 (20.8)	0.798*
Mean 6W EQ5D-5L (SD)	0.75 (0.07)	0.75 (0.07)	0.396*
Mean Y1 EQ5D-5L (SD)	0.81 (0.09)	0.83 (0.08)	0.127*
Mean Y2 EQ5D-5L (SD)	0.81 (0.09)	0.83 (0.09)	0.226*

*Analysis of Variance

6W six weeks, *EQ-5D* EuroQol five-dimension health questionnaire five-level, *ODI* Oswestry Disability Index, *SRS-22r* Scoliosis Research Society-22 item revised score, *Y1* Year 1, *Y2* Year 2

Table 4 Radiographic parameter outcomes

	BMP	BMA+I	Sig
Mean 6W SVA, mm (SD)	25.7 (45.5)	27.7 (43.8)	0.648*
Mean Y1 SVA, mm (SD)	20.4 (47.4)	29.2 (55.1)	0.085*
Mean Y2 SVA, mm (SD)	22.4 (48.3)	35.1 (55.2)	0.011*
Mean 6W PI-LL, ° (SD)	1.2 (14.4)	2.7 (13.2)	0.260*
Mean Y1 PI-LL, ° (SD)	2.0 (14.4)	2.2 (14.0)	0.884*
Mean Y2 PI-LL, ° (SD)	2.1 (14.4)	2.5 (13.9)	0.711*

*Analysis of Variance

6W six weeks, *PI–LL* pelvic incidence– lumbar lordosis mismatch, *PT* pelvic tilt, *SVA* sagittal vertical axis, *Y1* Year 1, *Y2* Year 2

Table 5 Complication outcomes

	BMP	BMA+I	Sig
Wound complication, n (%)	6 (2)	6 (3)	0.355†
PJK, n (%)	30 (9.8)	11 (5.4)	0.030†
PJF, n (%)	26 (8.5)	13 (6.3)	0.530†
Mechanical, n (%)	40 (13.0)	42 (20.5)	0.009†
Neurological, n (%)	39 (12.7)	16 (7.8)	0.049†
Reoperation, n (%)	43 (14)	43 (21)	0.054†
Pseudarthrosis, n (%)	38 (12.4)	30 (14.6)	0.210†
Reoperation for pseudoarthrosis, n (%)	4 (1.3)	7 (3.4)	0.176†

† Chi-squared test

PJK proximal junctional kyphosis, *PJF* proximal junctional failure

Sub-analyses by high-risk demographic and surgical components

The prevalence of smoking (5.9% [$n = 18$] vs 6.8% [$n = 14$], $p = 0.673$) and osteoporosis (19.5% [$n = 60$] vs 17.6% [$n = 36$], $p = 0.165$) did not differ at baseline for BMP vs BMA + I. Multivariable logistic regression analyses controlling for age, rod use and surgical invasiveness (levels fused), revealed that rhBMP-2 use was not associated with lower odds for pseudarthrosis in smokers (OR 0.82, 95% CI: 0.68–2.14, $p = 0.231$) or osteoporotic patients (OR 0.97, 0.84–1.86, $p = 0.059$). The incidence of index surgery being a revision procedure did not differ significantly between BMP and BMA + I (40% [$n = 123$] vs 38% [$n = 78$], $p = 0.660$). The use of rhBMP-2 in revision surgery was not associated with significantly lower odds for pseudarthrosis (OR 0.99, 0.74–1.45, $p = 0.074$). Three column osteotomy (3CO) use did not differ significantly between BMP and BMA + I (20.2 [$n = 62$] vs 23.4% [$n = 48$], $p = 0.302$). The use of rhBMP-2 in patients undergoing 3COs was not associated with lower odds for pseudarthrosis (OR 1.06, 0.96–1.25, p = 0.353). When assessing patients undergoing ≥ 10 levels fused, rhBMP-2 was associated with lower odds for pseudarthrosis (OR 0.89, 0.73–0.95, $p = 0.045$).

Discussion

ASD surgery can demand significant bone graft to accommodate large fusion constructs and thus frequently requires allograft or biologics alternatives, such as rhBMP-2, to support successful arthrodesis. In this context, we sought to compare the use of rhBMP-2 and an alternative biologic agent (bone marrow aspirate concentrate) in adult spinal deformity (ASD) surgery. In this retrospective cohort study, no significant difference was found for the primary outcome of radiographic or health-related quality of life (HRQL) metrics at each follow up timepoint. Furthermore, there was no significant difference in pseudoarthrosis or reoperation due to pseudoarthrosis at two years of follow up. Notably, at two years after surgery, patients who received rhBMP-2 had incurred a greater overall cost, similar quality adjusted life years (QALYs) and higher cost per QALY at two years.

Interest in the off-label use of rhBMP-2 grew following studies in the early 2000s that demonstrated its efficacy as a substitute for iliac crest bone graft in anterior lumbar interbody fusions [4]. Since then, studies on the off-label use of rhBMP-2 have demonstrated its effectiveness in improving fusion rates in short-segment posterior/posterolateral fusions and posterior cervical fusion [9, 11]. Most notably, rhBMP2

has been reported to improve fusion rates in smokers, who have a higher risk of pseudarthrosis [3, 14]. ASD patients undergoing posterior spinal fusion are at an elevated risk of pseudoarthrosis due to factors such as the significant amount of spinal manipulation across multiple motion segments and higher average age of most patients in this population [19]. Limitations with rhBMP-2 use include the notable costs and high complication rates (including osteolysis and subsidence secondary to known osteoclastogenic effects) [17, 23].

With the evolving technology in osteobiologic development, more novel materials have been developed to overcome the reported drawbacks of rhBMP-2 use, such as bone marrow aspirate (BMA). BMA contains mesenchymal stem cells (MSCs) which theoretically create an ideal regenerative environment that enhances fusion [13]. Its efficacy at promoting fusion has been evidenced by multiple studies, with one prospective randomized control trial by Hart *et* al. into 80 patients undergoing posterolateral fusion demonstrating definitively higher fusion rates when comparing BMA with allograft chips (80%) vs allograft chips alone (40%) [15]. Studies have also reported similar rates of fusion to those achieved with rhBMP-2 use, without the reported limitations of cost and complications [23]. Limitations to BMA use include age of patient harvested from (potential decrease in stem cell quantity with increased age), location for BMA sourcing and variability in how BMA is modified before implantation [1, 23].

Pseudarthrosis rates in ASD surgery may be as high as 17 to 24% [19]. Pseudarthrosis in ASD is a major cause of revision surgery and can lead to added morbidity, increased complications, and greater costs for both the patient and the health system. For this reason, the application of rhBMP-2 during ASD surgery has gained popularity, despite its limited FDA approval for single-level ALIF between L4 and S1. From 2008 to 2018, the use of rhBMP-2 in ASD surgery increased from 62.5% to 77%, with multiple studies investigating its off-label use [2]. Madeda et al. evaluated 55 patients who underwent ASD surgery using either iliac crest bone graft (ICBG) or rhBMP-2 [22]. The authors found that only 4.3% of patients in the rhBMP-2 group demonstrated pseudoarthrosis, and that this was substantially higher in the ICBG groups at 28.1%. Kim et al. evaluated fusion rates of 63 patients who underwent ASD surgery with either ICBG or BMP and found a significant lower rate of pseudoarthrosis in the BMP group (6.4%) than in the ICBG group (28.1%) [20].

Despite studies showing improved fusion rates amongst patients who received rhBMP-2 versus ICBG, it is less clear if utilization of rhBMP-2 translates to improved patient reported outcomes. In our study, there were no differences in HRQL outcomes between the BMP and BMA + I cohorts at all follow-up timepoints. This is mostly consistent with current literature evaluating ASD surgery outcomes based on graft type. The aforementioned work of Kim et al. did not find any differences between ICBG and rhBMP-2 groups in ODI or composite ODI scores at final postoperative time points [20]. However, patients in the rhBMP-2 cohort did report significant higher SRS self-image scores. Crawford et al. compared outcomes of patients who underwent extension of previous idiopathic scoliosis fusion with or without rhBMP-2, and found no difference in SRS and ODI scores between groups [10].

Our study found that the use of BMP had a higher overall mean cost of care. Quality-adjusted life years (QALYs) were similar between groups. Jain et al. conducted a retrospective cost-utility analysis that suggests a favorable view of rhBMP-2 use, albeit with certain caveats [16]. Their analysis indicated that BMP-2 could be considered cost-effective in over half of the modeled scenarios, especially when considering a willingness-to-pay threshold of $150,000 per QALY. The study however, acknowledged the complexity of determining the true cost-effectiveness of rhBMP-2, given the myriad of factors that influence outcomes in ASD surgery. The use of rhBMP-2, while beneficial in reducing pseudarthrosis rates, did not directly translate to a linear improvement in QALY. Safaee et al. conducted a cost–benefit analysis of using rhBMP-2 for preventing pseudarthrosis and reported that rhBMP-2 significantly reduces the rates of revision surgery due to pseudarthrosis by providing an 11% absolute risk reduction in reoperation rates [35]. However, the direct in-hospital costs of BMP use did not result in a net savings when compared to the costs of revision surgery. Specifically, the study found that the mean direct cost of the primary surgery was $87,653 ± $19,879, with rhBMP-2 costing an additional $10,444 ± $4,607 on average. Meanwhile, the mean direct cost of revision surgery for pseudarthrosis was $52,153 ± $26,985 [35]. This is largely in agreement with our findings that the cost of rhBMP-2 may be associated with higher mean cost of care, without improvement in QALY. As such, our results suggest a measured use of BMP-2 in ASD corrective surgeries and speak against the need for routine application. We do not, however, believe that BMP-2 application in ASD surgery should be proscribed in its entirety. Certainly, in the case of mitigating circumstances or glaring risk factors for pseudarthrosis (e.g. prior history of infection, revision surgery, poorly vascularized fusion bed, etc.) the use of BMP-2 may still be justified.

The retrospective nature of the study poses inherent biases such as selection, surveillance and recall bias. Additionally, while the sample size is relatively large, the disproportionately high representation of female patients (81%) may limit the generalizability of findings. There is potential for confounding from factors that are difficult to account for, such as surgeon biases, surgical team biases, and institutional biases. We also did not have granular data on the details surrounding implant and screw type and specifications.

There is potential for temporal bias as BMP was used more frequently earlier in the study period, whereas BMA + I was used more in the later part of the study period. Despite the implementation of multivariable analyses, we acknowledge that such variables may still have had residual effects on the study's findings. Moreover, the study's focus solely on BMP as a treatment variable neglects potential influences from other treatment factors on outcomes. In conjunction, the fundamental differences between both cohorts of patients makes the study's findings challenging to accept definitively with the retrospective design implemented. Additionally, the lack of more granular data regarding the details of the neurological deficits experienced limits the interpretation of our findings, as this data would have been of particular analytic interest. Furthermore, the relatively short follow-up time frame of two years may not adequately capture long-term effects, benefits, or complications associated with BMP use. Lastly, the utilization of secondary data from the PearlDiver database for cost assessment may not accurately reflect the actual costs borne by patients or the healthcare systems.

Conclusions

In conclusion, we encountered relatively equivalent outcomes between the use of bone morphogenic protein (BMP-2) and an alternative biologic agent (bone marrow aspirate concentrate + cancellous bone chips + i-Factor) in ASD corrective surgery. At the same time, in the cohort receiving BMP-2, there was a significantly increased risk of neurological complications. Despite widespread utilization, our results suggest that BMP-2 use does not offer superior radiographic or clinical outcomes at two years following surgery compared to the less-costly biologic alternative combination used in this study. We believe that these findings suggest tempering the routine use of BMP-2 in ASD corrective surgery, unless other mitigating circumstances or risk factors are present that justify its application.

Authors contributions OOO- Investigation, Resources, Data Curation, Investigation, Formal analysis, Writing—Review & Editing ACU- Resources, Writing—Review & Editing AS- Resources, Writing—Review & Editing MG- Resources, Writing—Review & Editing NL- Resources, Writing—Review & Editing SM- Resources, Writing—Review & Editing MRF- Data Curation, Investigation, Resources AY- Data Curation, Investigation, Resources PT- Data Curation, Investigation, Writing—Review & Editing LS- Investigation, Writing—Review & Editing TR- Writing—Review & Editing, Investigation RL- Methodology, Validation, Investigation JS- Methodology, Validation, Writing—Review & Editing PPJ- Methodology, Validation, Writing—Review & Editing ZMS- Methodology, Validation, Writing—Review & Editing CIS- Conceptualization, Methodology, Supervision VL- Conceptualization, Methodology, Supervision AJS- Conceptualization, Methodology, Supervision PGP- Conceptualization, Methodology, Formal analysis, Validation, Supervision All authors reviewed the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of NYU School of Medicine.

Informed consent Informed consent was obtained from each patient prior to enrollment.

Competing interests Peter G. Passias Cerapedics: Other financial or material support Cervical Scoliosis Research Society: Research support Globus Medical: Paid presenter or speaker Medtronic: Paid consultant Royal Biologics: Paid consultant Spine: Editorial or governing board Spinevision: Other financial or material support SpineWave: Paid consultant JNS Spine: Editorial Board JCM: Editorial Board.

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