Routine use of recombinant human bone morphogenetic protein–2 in posterior fusions of the pediatric spine and incidence of cancer

Christina Sayama, MD, MPH,^{1,2} Matthew Willsey, BS,^{1,2} Murali Chintagumpala, MD,³
Alison Brayton, RN,^{1,2} Valentina Briceño, RN,^{1,2} Sheila L. Ryan, JD, MPH,^{1,2}
Thomas G. Luerksen, MD,^{1,2} Steven W. Hwang, MD,^{4,5} and Andrew Jea, MD^{1,2}

¹Neuro-Spine Program, Division of Pediatric Neurosurgery, and ³Neuro-oncology Program, Division of Hematology-Oncology, Department of Pediatrics, Texas Children's Hospital; and ²Department of Neurosurgery, Baylor College of Medicine, Houston, Texas; ⁴Division of Pediatric Neurosurgery, Floating Children's Hospital; and ⁵Department of Neurosurgery, Tufts University, Boston, Massachusetts

OBJECT The aim of this study was to determine the safety of recombinant human bone morphogenetic protein–2 (rhBMP-2) use in posterior instrumented fusions in the pediatric population, focusing on cancer risk. In a previous study, the authors reported the short-term (mean follow-up of 11 months) safety and efficacy of rhBMP-2 in the pediatric age group. The present study reports their results with a minimum of 24 months' follow-up.

METHODS The authors retrospectively reviewed 57 consecutive cases involving pediatric patients who underwent posterior occipitocervical, cervical, thoracic, lumbar, or lumbosacral spine fusion from October 1, 2007, to June 30, 2011, at Texas Children's Hospital. Seven cases were excluded from further analysis because of loss to follow-up. Three patients died during the follow-up period and were placed in a separate cohort.

RESULTS The patients' average age at the time of surgery was 11 years, 4 months (range 9 months to 20 years). The mean duration of follow-up was 48.4 months (range 24–70 months). Cancer status was determined at the most recent encounter with the patient and/or caretaker(s) in person, or in telephone follow-up. Twenty-four or more months after administration of rhBMP-2, there were no cases of new malignancy, degeneration, or metastasis of existing tumors. The cause of death of the patients who died during the study period was not related to BMP or to the development, degeneration, or metastasis of cancer.

CONCLUSIONS Despite the large number of adult studies reporting increased cancer risk associated with BMP use, the authors' outcomes with rhBMP-2 in the pediatric population suggest that it is a safe adjunct to posterior spine fusions of the occipitocervical, cervical, thoracic, lumbar, and lumbosacral spine. There were no new cases of cancer, or degeneration or metastasis of existing malignancies in this series.

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KEY WORDS bone morphogenetic protein; pediatric spine; spinal instrumentation; cancer; complications; malignancy; neurosurgery; spinal fusion; rhBMP-2; oncology; technique

THE use of autograft bone to achieve a spinal fusion is the gold standard by which all other grafting materials are judged. Its dependable rate of incorporation leading to a successful spinal arthrodesis has been documented.¹¹ The potential benefits of using recombinant human bone morphogenetic protein–2 (rhBMP-2) over autograft or allograft bone are numerous. These may include decreased operative time, blood loss, donor-site morbidity,⁵ transmission of infection associated with use of al-

lograft,² and rate of pseudarthrosis.⁶ In addition, its unlimited quantity and immediate availability make rhBMP-2 useful in certain pediatric spine applications, although its cost may be prohibitive in some settings. There are concerns regarding the routine and “off-label” substitution or supplementation of autologous or allograft bone graft with rhBMP-2. Significant concerns involve the possibility of bony overgrowth, interaction with exposed dura, systemic toxicity, local toxicity, immunogenicity, osteoclastic acti-

ABBREVIATION rhBMP-2 = recombinant human bone morphogenetic protein–2.

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vation, and effects on distal organs; the most serious concern has been the implication of BMP in the development of new cancers.³¹

As a growth factor, BMP has the potential to affect processes regulating cell division. Consequently, there has been concern that BMP may contribute to tumorigenesis, tumor degeneration, and metastasis. During the premarket approval application for a higher dose of rhBMP-2 (40 mg) (AMPLIFY; Medtronic Sofamor Danek), the risk of cancer was greater in the rhBMP-2 group compared with the control group.¹⁰ The FDA consequently denied approval.

We previously reported our experience with the routine use of BMP in pediatric spine surgery.¹⁴ In that study, we focused on the early postoperative complications related to BMP use. The follow-up was short (mean 11 months) and did not afford us an opportunity to analyze complications such as incidence of new cancer in long-term follow-up. The purpose of the present study is to examine the long-term incidence of cancer after posterior occipitocervical, cervical, thoracic, lumbar, or lumbosacral spine fusion using rhBMP-2 in pediatric patients after a mean follow-up of 48.4 months. To the best of our knowledge, this is, to date, the largest pediatric study of outcomes with at least 2 years of follow-up following rhBMP-2 administration.

Methods

We retrospectively reviewed the charts of 57 consecutive pediatric patients who underwent posterior occipitocervical, cervical, thoracic, lumbar, or lumbosacral spine fusions with rhBMP-2 from October 1, 2007, to June 30, 2011, at Texas Children's Hospital. Seven patients were excluded from the analysis because they were lost to follow-up and we were unable to obtain current information about them, and 3 patients died during the follow-up period, thus leaving 47 cases for our primary analysis (Table 1). The 3 cases involving patients who died were analyzed separately (Table 2).

The study group included 24 girls and 23 boys, and their age at surgery ranged from 0 years, 9 months to 20 years, 0 months, (mean age 11 years, 4 months). The minimum duration of follow-up was 24 months (mean 48.4 months, range 24–70 months). We recorded patient demographics; perioperative data, including dose of BMP; and outcome, including the development of cancer and other complications related to BMP (Table 1).

Follow-up consisted of clinic visits (33 patients), and if the patient had not been seen in 12 months, a telephone call asking the patient and/or parents/caregivers whether there were any other medical problems, such as cancer, that had developed and been diagnosed between this encounter and the previous encounter (14 patients). The rationale for this method of cancer case detection is that it is simple, low cost, and does not entail increased radiation exposure to the child. We consulted the chief of the neurooncology program at Texas Children's Hospital (M.C.) to ask about screening CT or PET scans to look for cancer in this cohort, and as there is not yet any proven association between BMP and cancer, there is little justification for screening tests.

We repeatedly attempted to contact patients lost to follow-up via telephone calls, voicemail messages, and

emails. Moreover, we performed a Worldwide Web search on all the patients lost to follow-up to ensure that there were no obituaries that would indicate death; in 1 case, the patient's death was found in this manner.

Of the 3 patients who died during the follow-up period, 2 died within 13 months of surgery (at 13 months and 1.5 months postoperatively), and the third died 5 years, 9 months after surgery. None of these patients had developed cancer at the time of death. Their mean age at the time of death was 8 years, 8 months (range 1 year, 7 months to 20 years, 9 months). The cause of death, and autopsy findings if available, were recorded (Table 2).

Surgical Technique

The senior author (A.J.) was the attending surgeon for all spine surgeries. The surgery consisted of routine exposure of the spine over the entire length to be instrumented. Placement of segmental instrumentation, if performed, was done in standard fashion. Decortication of the laminae, spinous processes, and facet joints was performed using a matchstick bur after placement of spinal instrumentation.

BMP Dosing

Increments of small (2.8 mg), medium (5.6 mg), and large (8.0 mg) kits of rhBMP-2 were used in each case and applied on a collagen sponge (INFUSE, Medtronic Sofamor Danek). The collagen sponges were generally cut into 1-cm strips and placed in a single layer overlying the posterior elements after thorough decortication of the bone. The amount of rhBMP-2 was determined intraoperatively, depending on the surface area of the intended fusion levels.

Use of Bone Graft

The rhBMP-2 was applied as described above along with some form of bone graft autograft, morselized cancellous bone allograft, and/or demineralized bone matrix (MasterGraft Matrix, Medtronic Sofamor Danek). In 25 patients, the rhBMP-2 was used with only allograft (demineralized bone matrix and/or morselized cancellous allograft). The rhBMP-2 was applied with autograft and allograft in 14 patients. In 8 patients, it was used with autograft alone.

Local autograft was used whenever it was available. If the quantity of locally available autograft was insufficient to adequately cover the fusion area, it was supplemented with either allograft (most commonly) or demineralized bone matrix. We abandoned the practice of harvesting iliac crest (or rib) autograft due to the associated morbidities. Harvest of autograft from separate donor sites, such as the iliac crest or rib, was performed in only 2 patients in our cohort.

Follow-Up

Patients were seen in clinic at 2 weeks, 6 weeks, and 3, 6, and 12 months after surgery and annually thereafter. For the purposes of this study, patients and caretaker(s) were brought back to the clinic off schedule for assessment of the development of cancer, or were questioned via telephone follow-up by a clinical neurosurgery nurse.

TABLE 1. Demographic and perioperative data in 47 patients with a minimum of 24 months' follow-up

Case No.	Pt Age, Sex	Indications for Surgery	Procedure	BMP Dose (mg)	Graft Material/Extenders	Follow-Up (mos)	New Cancer	Other Complications
1	14 yrs, 2 mos, F	H/O lipoblastomatosis; epidural lipomatosis; progr myelopathy; spastic paraparesis	Decompressive laminectomies at T7–L3 & arthrodesis	36	Local autograft, morselized cancellous allograft	70	No	Sterile seroma; heterotopic bone formation secondary to BMP with restenosis of spinal canal necessitating reoperation
2	5 yrs, 8 mos, F	S/P fall; neck pain; os odontoidum; myelomalacia	Occiput–C3 PIF	4.2	Morselized cancellous allograft	68.5	No	At 1-wk postop had dysphagia (resolved at 3-mo visit; required temporary NG tube)
3	4 yrs, 5 mos, F	Os odontoidum, trisomy 21	Occiput–C2 PIF	12	DBM	66.5	No	None
4	11 yrs, 8 mos, F	Rapidly progr postlaminoplasty kyphosis	T4–8 PIF	36	Morselized cancellous allograft	65.5	No	Pneumothorax; distal junctional kyphosis necessitating reoperation to extend instrumentation
5	16 yrs, 7 mos, M	H/O Down syndrome; occipitocervical instability; myelopathy	Occiput–C4 PIF	12	Morselized cancellous allograft, iliac crest autograft	64	No	None
6	18 yrs, 2 mos, M	Unstable L-3 burst Fx; failed prior short-segment fusion L2–4	T12–L5 PIF; L-3 PSO	24	Morselized cancellous allograft, local autograft	64	No	None
7	13 yrs, 8 mos, M	H/O congenital scoliosis	T9–S1 PIF; L-2 resection of hemivertebra	24	Morselized cancellous allograft, local autograft	63	No	None
8	2 yrs, 7 mos, M	H/O VACTERL syndrome; congenital scoliosis	T8–12 PIF; T-10 hemivertebra resection	4.2	Local autograft	63	No	None
9	20 yrs, 0 mos, M	H/O T11–12 disc-osteophyte: spinal cord compression; spastic paraparesis	T11–12 discectomy; right T-12 transpedicular decompression; T11–L1 PIF	12	Local autograft	62	No	DVT/PE postop
10	9 yrs, 11 mos, F	Fixed C1–2 rotatory subluxation; BI	Closed reduction for C1–2 rotatory subluxation; occiput–C2 PIF	12	Morselized cancellous allograft	62	No	None
11	9 mos, M	Congenital scoliosis	L-1 hemivertebra resection; T12–L2 PIF	12	Local autograft	62	No	Continued progression of scoliosis necessitating reoperation for placement of growing-rod construct
12	10 yrs, 0 mos, F	Grade 2 spondylolisthesis/lysis L5–S1	L5–S1 PIF	4.2	DBM, local autograft	61	No	None
13	15 yrs, 5 mos, M	C-2 chordoma S/P transoral odontoidectomy & occipitocervical fusion; postop wound infection	Washout of occipitocervical wound w/ irrigation & debridement & by placement of BMP & new bone graft	24	Morselized cancellous allograft, local autograft, iliac crest harvest	61	No	Transverse myelitis resulting in complete thoracic-level paraplegia
14	13 yrs, 5 mos, F	H/O severe TBI; progr neuromuscular scoliosis	T4–lum PIF	12	Morselized cancellous allograft	59	No	None
15	10 yrs, 6 mos, M	Atlantoaxial instability; os terminale persists	C1–2 PIF	8.4	Morselized cancellous allograft	55	No	Superficial wound cellulitis

(continued)

TABLE 1. Demographic and perioperative data in 47 patients with a minimum of 24 months' follow-up (continued)

Case No.	Pt Age, Sex	Indications for Surgery	Procedure	BMP Dose (mg)	Graft Material/Extenders	Follow-Up (mos)	New Cancer	Other Complications
16	16 yrs, 1 mo, M	S/P recurrent L3–4 disc herniation	Decompressive laminectomy & facetectomy from L-3 to L-5 w/ discectomy at L3–4; L3–5 PIF	12	DBM, local autograft, morselized cancellous allograft	54	No	None
17	17 yrs, 5 mos, F	H/O juvenile-onset spondyloarthritis; atlantoaxial instability	C1–2 PIF	12	Local autograft, DBM	53	No	Superficial wound cellulitis
18	16 yrs, 9 mos, M	L5–S1 spondylolisthesis/-lysis	L5–S1 PIF	12	Local autograft, DBM	52	No	None
19	6 yrs, 8 mos, M	L2–3 Chance Fx	T12–L4 PIF	4.2	Local autograft, DBM	52	No	None
20	14 yrs, 0 mos, F	H/O MMC; progr neuromusc scoliosis	T2–ileum PIF, placement of distal femoral pins	24	Local autograft, morselized allograft	51	No	Impaired proprioception immediately post-op
21	10 mos, M	H/O skeletal dysplasia; C1–2 instability S/P failed arthrodesis at C1–2; progr quadriparesis	Suboccipital craniectomy & C-1 laminectomy; occiput–C4 PIF	12	DBM	50	No	None
22	14 yrs, 10 mos, F	H/O juvenile RA; BI; C1–2 instability; myelomalacia	Occiput–C6 PIF	12	DBM	50	No	None
23	2 yrs, 9 mos, F	Traumatic atlantooccipital dislocation	Occiput–C2 PIF	12	DBM	49	No	None
24	16 yrs, 3 mos, F	Ligamentous injury at C5–6	C5–6 PIF	12	DBM	47	No	Posterior neck swelling, resolved by time of discharge
25	9 yrs, 6 mos, M	S/P failed Gallie fusion at C1–2; progr cervical scoliosis	Occiput–T3 PIF	24	Local autograft	46	No	None
26	1 yr, 6 mos, F	Unstable odontoid synchondrosis Fx	C1–2 PIF	12	DBM	46	No	None
27	1 yr, 7 mos, F	Congenital kyphosis	T1–8 PIF; PSO	12	Local autograft	46	No	Prominent instrumentation necessitating reoperation for removal
28	17 yrs, 4 mos, M	Adolescent idiopathic scoliosis	T2–L3 PIF	24	Morselized cancellous allograft	45	No	None
29	1 yr, 9 mos, F	Pathologic Fx of odontoid secondary to multifocal histiocytosis	C1–2 PIF	12	DBM	45	No	None
30	11 yrs, 11 mos, F	Type II odontoid Fx	C1–2 PIF	8	DBM	44.5	No	None
31	10 yrs, 6 mos, M	S/P MMC; congenital kyphosis	Kyphectomy; T9–ilium PIF	20	Local autograft	36	No	Erosion of instrumentation through skin necessitating reoperation for removal; delayed deep wound infection from soft tissue defect
32	3 yrs, 10 mos, M	Traumatic atlantooccipital dislocation	Occiput–C2 PIF	16	DBM	36	No	None
33	13 yrs, 11 mos, F	H/O cervical dystonia; rapidly progr cervical kyphosis	C2–T2 PIF	12	DBM	36	No	None
34	11 mos, M	C-2 spondylolysis; myelomalacia	Occiput–C4 PIF	12	DBM	34	No	None
35	10 yrs, 2 mos, M	H/O Down syndrome; atlantoaxial instability; myelopathy	Occiput–C4 PIF	12	DBM	34	No	None

(continued)

TABLE 1. Demographic and perioperative data in 47 patients with a minimum of 24 months' follow-up (continued)

Case No.	Pt Age, Sex	Indications for Surgery	Procedure	BMP Dose (mg)	Graft Material/Extenders	Follow-Up (mos)	New Cancer	Other Complications
36	6 yrs, 1 mo, F	Traumatic atlantooccipital dislocation	Occiput–C2 PIF	12	DBM	34	No	None
37	12 yrs, 8 mos, M	H/O CM-I; platybasia; BI; occipitalization of C-1; syringomyelia	Suboccipital craniectomy & C-1 laminectomy; occiput–C2 PIF	8	DBM	32	No	None
38	13 yrs, 6 mos, F	H/O Down syndrome; os odontoides; myelopathy	Occiput–C4 PIF	12	Morselized cancellous allograft, DBM	31	No	None
39	17 yrs, 0 mos, F	S/P NF-2; large neurofibroma w/ cord compression	Redo T10–L2 laminectomy; resection of tumor; T11–L2 PIF	8	Morselized cancellous allograft; DBM	31	No	None
40	6 yrs, 8 mos, M	C1–2 rotary subluxation; BI; CM-I	Occiput–C2 PIF	12	DBM	30	No	None
41	3 yrs, 1 mo, F	H/O tuberculosis; Pott disease	T6–8 vertebrectomy; T4–10 PIF	12	Local autograft	29	No	None
42	2 yrs, 3 mos, F	Unstable odontoid synchondrosis	Occiput–C2 PIF	12	DBM	29	No	Acute deep wound infection
43	14 yrs, 0 mos, M	S/P cervical canal stenosis; failed C3–7 open door laminoplasty	C3–7 laminectomy; C3–7 PIF	12	Local autograft	29	No	Adjacent-level disease proximal & distal to instrumentation, necessitating reoperation C3–4 ACDF & extension of posterior instrumentation to T-4
44	16 yrs, 6 mos, F	Unilat cervical facet injury w/ subluxation	C5–C7 PIF	8	DBM, local autograft	29	No	None
45	14 yrs, 2 mos, F	H/O CP; progr neuromusc scoliosis	T2–iliu PIF	24	DBM, local autograft	28	No	Proximal junction kyphosis; acute deep wound infection
46	16 yrs, 1 mo, M	Unstable T-11 burst Fx	T7–L2 PIF	24	Morselized cancellous bone allograft	28	No	None
47	20 yrs, 0 mos, M	H/O MMC; congenital kyphosis	L1–2 kyphectomy; T9–iliu PIF	12	Local autograft, DBM	24	No	Misplaced T-9 pedicle screw necessitating reoperation for revision

ACDF = anterior cervical discectomy and fusion; BI = basilar invagination; CM-I = Chiari malformation Type I; CP = cerebral palsy; DBM = demineralized bone matrix; DVT = deep venous thrombosis; Fx = fracture; H/O = history of; MMC = myelomeningocele; NG = nasogastric; neuromusc = neuromuscular; NF-2 = neurofibromatosis Type 2; PE = pulmonary embolism; PIF = posterior instrumented fusion; progr = progressive; PSO = pedicle subtraction osteotomy; Pt = patient; RA = rheumatoid arthritis; S/P = status post; TBI = traumatic brain injury.

TABLE 2. Demographic and perioperative data from 3 cases involving patients who died during the study period

Age, Sex	Indications for Surgery	Procedure	BMP Dose (mg)	Graft Material/ Extenders	Time btwn Surgery & Death (mos)	Development, Degeneration, or Metastasis of Cancer	Cause of Death/Autopsy Findings
1 yr, 7 mos, M	H/O Pfeiffer syndrome Type 2, atlantoaxial instability; CMJ myelomalacia; myelopathy	Suboccipital craniectomy w/ C-1 laminectomy; occiput–T5 PIF	12.0	Morselized cancellous allograft	13	No	Serratia & Pseudomonas PNA leading to respiratory failure & cardiopulmonary collapse w/ CPR x4; no autopsy performed
9 yrs, 4 mos, F	H/O Morquio syndrome; odontoid hypoplasia; CMJ compression; myelopathy	Suboccipital craniectomy w/ C-1 laminectomy; occiput–T3 PIF	12.0	Morselized cancellous bone allograft	1.5	No	Baseline hepatomegaly associated w/ Morquio syndrome; hepatorenal syndrome secondary to propofol infusion syndrome (propofol administered as part of total IV anesthesia for purposes of intraop/neuromonitoring); cardiopulmonary arrest secondary to bacteremia (from prolonged hospitalization) & septic shock (w/o evidence of surgical site infection); autopsy showed multiorgan polymicrobial infection w/ <i>Candida</i> , gram-positive cocci, & <i>Ochrobactrum anthropi</i>
15 yrs, 1 mo, M	H/O CP, mild ID, w/ progr myelopathy & kyphotic deformity S/P failed operation for reduction of a kyphotic deformity at outside hospital	C2–L3 PIF, revision of previous T4–L3 construct w/ removal of T-4 laminar hooks, T1–3 laminectomies, T-4 PSO	24.0	Morselized cancellous bone allograft, local autograft	69	No	Presumed cardiac arrest, family declined autopsy

CMJ = cervicomedullary junction; CPR = cardiopulmonary resuscitation; ID = intellectual disability; IV = intravenous; PNA = pneumonia.

Results

There were no cases of new cancers, degeneration, or metastasis of existing malignancies in our cohort of patients (95% CI 0%–7.6%, Wilson score interval). The mean duration of follow-up was 48.4 months across the range of doses of BMP administered (4.2–36 mg, mean 14.4 mg). Three patients had preexisting tumors, including lipoblastomatosis (1 case), chordoma (1 case), and neurofibroma (1 case). Seven patients (12.3%) were lost to follow-up despite repeated attempts to contact them.

In the separate cohort of deceased patients, the cause of death was unrelated to BMP use and the development, degeneration, or metastasis of cancer. One patient with a history of Pfeiffer syndrome and restrictive lung disease died 13 months after surgery from pneumonia and respiratory failure.

A second patient, who had Morquio syndrome, baseline hepatosplenomegaly, and chronic hepatitis, died 1.5 months after surgery from propofol infusion syndrome. Propofol infusion syndrome is a rare and frequently fatal complication of propofol infusion at high doses; it is characterized by metabolic acidosis, rhabdomyolysis of both skeletal and cardiac muscle, arrhythmias (bradycardia, atrial fibrillation, ventricular and supraventricular tachycardia, bundle branch block, and asystole), myocardial failure, renal failure, hepatomegaly, and death. Our patient developed worsening metabolic acidosis, myocardial failure, hepatomegaly and hepatic failure, and renal failure over a 5-day course after surgery; she had been given significant doses of propofol as part of total intravenous anesthesia in a standard regimen for intraoperative monitoring of motor evoked potentials. She ultimately succumbed to multiorgan failure and sepsis after a prolonged 1-month stay in the intensive care unit.

A third patient had a history of cerebral palsy, developmental delay, and spinal cord injury secondary to a worsening kyphotic deformity. He was initially operated on at an outside hospital; the upper part of the construct failed, resulting in proximal junction kyphosis. We subsequently performed a pedicle subtraction osteotomy and extended his fusion to treat his deformity and stenosis. He died 5 years, 9 months after his initial surgery due to a presumed cardiac arrest. His parents reported no development of cancer in the period from surgery to his untimely passing, but they declined an autopsy.

Discussion

The osteoinductive role of rhBMP-2 is multifaceted, as it acts as a chemotactic agent, a growth factor, and differentiation factor.³⁸ The FDA has approved rhBMP-2 as the first complete bone graft substitute for anterior interbody fusions of the adult lumbar spine.¹⁵ In clinical trials, authors have demonstrated the usefulness of rhBMP-2 for single-level anterior interbody fusion of the adult lumbar spine, resulting in greater radiographic fusion rates, improved pain and function scores on the Oswestry Disability Index, and higher overall clinical success over traditional bone grafting techniques.^{3,5}

Although the FDA has only approved the use of rhBMP-2–soaked absorbable collagen sponges for use in adult anterior interbody lumbar fusion, “off-label” appli-

cations have been reported.^{9,27} We previously reported the early safety and efficacy of rhBMP-2 use for posterior spinal fusions in the pediatric population (mean follow-up of 11 months).¹⁴

Advantages

Biomechanically, the rhBMP-2–generated fusion mass is superior at 3 months, as compared with that generated by autograft.^{32,33} Findings have shown the fusion mass to be more mature, with more advanced remodeling and marrow formation, than that generated by autograft alone. In our previous study,¹⁴ we did not expect to find large mature fusion masses (Grade 4) in our posterior spine fusions in the early postoperative period, but this occurred in 2 patients (10.5%). Bone healing and remodeling may take up to 12–24 months.¹¹ However, we did expect to see advanced bone healing, at least in the form of bilateral stable bridging bone (Grades 3–, 3, 4–, and 4), across the segment of spine where we laid down rhBMP-2 and bone graft/graft extenders, and this was observed in 16 (84.2%) patients.

Another advantage of rhBMP-2 is its potential role in promoting fusion in very young children. Our present study included 8 patients younger than 3 years of age at the time of surgery; we found these patients to have a very limited amount of bone available for autograft harvest without adding morbidity. In these cases, the ability to promote fusion by adding rhBMP-2 is advantageous.

The historically published fusion rates achieved with autograft alone are similarly high when compared with fusion rates achieved with BMP and allograft in children. The use of BMP, however, has allowed us to avoid a separate site of surgery to harvest autograft. In a young child, harvesting rib graft or iliac crest graft is not without risk. In addition, the volume of the child's own bone that can be harvested for grafting is relatively small compared with the volume afforded by BMP and manufactured allograft. For instance, in long-segment scoliosis surgeries, it would be impractical to harvest from multiple autograft donor sites to obtain enough bone graft to cover the surface needed for fusion, which spans the entire construct.

Safety Concerns

There have been anecdotal reports of complications associated with rhBMP-2 use with compressive bone formation adjacent to neural structures.⁹ This is particularly relevant after decompressive laminectomy or foraminotomy, in which raw bone surfaces are exposed,³¹ as in one of our patients.¹⁴ There is evidence to suggest that rhBMP-2 may lead to laminar reconstitution and neuroforaminal stenosis if it is implanted directly into the laminectomy site.²⁹ Leakage of rhBMP-2 beyond the fusion area may lead to fusion of adjacent levels. Therefore, the key steps of safe rhBMP-2 usage are careful placement away from raw decompressed areas and retention of the rhBMP-2 within the fusion area by the carrier used.

It is well established that BMP plays a role in the regulation of coupled osteoblastic and osteoclastic activity.^{21,22} It is possible that large doses of BMP may lead to localized areas of bone resorption.⁴¹ This is not desirable in spinal fusion, and strategies to prevent this include careful control of BMP doses and controlled release from the carrier.

It is likely, however, that any observed radiolucencies are temporary and may represent accelerated healing patterns resulting from transient stimulation of osteoclasts.⁴¹

Several studies have reported adverse local events associated with the use of rhBMP-2. Facial edema, oral erythema, pain, and rhinitis have been reported in patients who received rhBMP-2 for maxillary floor augmentation.⁴ The use of higher than recommended doses of rhBMP-2 has been known to cause hematoma, dysphagia, and excessive edema after anterior cervical fusion.^{34,36} This may be due to the enhancement by rhBMP-2 of the initial inflammatory response that is seen during bone graft incorporation.²⁶ There was 1 case of dysphagia in our series after posterior cervical fusion with rhBMP-2; this probably was unrelated to the BMP itself and more likely related to complications in the technique of instrumentation at the craniocervical junction.

This same enhanced inflammatory response may produce a hyperinflammatory response causing wound problems, allergic reactions, or other complications.¹⁷ In our prior study,¹⁴ we did not find any deep wound healing complications, although there were 2 cases of superficial wound infection (among 19 patients). In the present long-term study, there were 2 cases of superficial wound cellulitis, 1 case of deep wound sterile seroma formation, 1 case of delayed deep wound infection from instrumentation erosion through the skin at about 2 years after surgery, and 2 cases (4.4%) of acute (≤ 12 weeks after surgery) deep wound infection associated with the administration of rhBMP-2. This rate of acute deep wound infection for a mixed cohort of idiopathic and nonidiopathic complex spine cases in the pediatric age group is consistent with the range of infection rates (3.7%–8.5%) reported in the literature.^{8,18,23,25,28,42} Moreover, there was 1 case of exuberant posterior neck swelling after posterior cervical fusion with rhBMP-2 that resolved at about 3 days after surgery.

Of note, we used rhBMP-2 in a patient with a deep wound infection in whom the initial surgery for occipitocervical fusion did not include BMP.¹⁴ We removed the infected bone graft and substituted it with rhBMP-2 and demineralized bone matrix. We hypothesized that the intense inflammatory reaction caused by rhBMP-2 would stimulate wound healing and antisepsis. Two case series have documented the use of BMP in the surgical treatment of vertebral osteomyelitis, with resolution of infection in all cases and no instances of recurrence.^{1,30} These studies provide evidence in support of the angiogenic abilities of BMP-2 and suggest that BMP, in combination with the ability of BMP to activate endothelial cells and stimulate vascular endothelial growth factor, may be the major mechanism coupling angiogenesis with osteogenesis.^{1,30} Theoretically, increased osteoinduction combined with increased blood supply may lead to increased local antibiotic concentrations and more rapid eradication of infection.^{1,30} In this way, we attempted to create an environment that strongly favors fusion, vascularity, antibiotic delivery, and eradication of infection, which occurred in our patient.

Cancer Risk

This BMP-based fusion technology has experienced a rapid increase in utilization in all types of routine spine fusion procedures including anterior cervical discectomy

and fusions, posterolateral lumbar and cervical fusions, posterior and transforaminal lumbar interbody fusions, and pediatric spine fusions.¹² Cahill et al.⁷ noted that the nationwide usage of BMP increased from 0.69% of all fusions in 2002 to 24.89% of all fusions in 2006, confirming the widespread application of this technology and its routine use in spine fusion surgery. Many patients received dosages well in excess of those studied in the FDA trials to date. There is little data available for analysis, particularly with respect to BMP dosing. Furthermore, BMP has been used in clinical practice beyond spinal fusion, including in the treatment of extremity long-bone nonunion and open fractures.¹²

Recent systematic reviews and meta-analyses of the literature^{12,16,35} suggest that the cancer risk associated with rhBMP-2 may be dose dependent. The cancer risk was similar in patients treated with lower doses (4.2–4.8 mg) of rhBMP-2 (0.7%) and control groups (0.7% and 0.9%). However, the cancer risk was 3.8% in the higher-dose (40 mg) rhBMP-2 study.¹³ Applying these risk estimates to our cohort of 47 patients treated with rhBMP-2, we should have seen 1 or 2 cases of cancer at 2-year follow-up, and maybe an even higher incidence with longer follow-up (mean, 48.4 months). It is also possible that because our cohort did not receive “high doses” (i.e., 40 mg) of rhBMP-2, these extrapolated estimates for cancer risk are too high for our cohort; however, the relationship between dose and cancer risk has not been previously studied in the pediatric age group, and our present study does not have the statistical power to stratify varying BMP doses and cancer risk.

A recent large retrospective database study by Lad et al.²⁴ looked at high-dose BMP and its relationship to cancer. The authors looked at BMP exposure and cancer risk at a national level by performing a retrospective cross-sectional study using a large MarketScan database with at least 24 months’ postoperative follow-up (mean postoperative follow-up between 49.7 and 55.6 months). Analysis showed a significant increase (31%) in benign tumors but not malignancies.²⁴ Moreover, there was a significantly higher number of benign tumors of the spinal meninges in the BMP group. In our study, our patients with comparable follow-up experienced neither new benign nor malignant tumor; in addition, there was no degeneration or metastasis of existing tumors.

Both BMP and BMP receptors have been isolated from human tumors. However, *in vitro* studies suggest that rhBMP-2 has an antiproliferative effect on human tumor colony-forming units taken from breast, ovarian, lung, and prostate cancers and embryonal cell carcinoma and cerebellar neuroectodermal tumor cell lines.^{19,20,37,39} Detailed data from manufacturers’ preclinical safety studies failed to demonstrate any proliferative effects of rhBMP-2 on human osteosarcoma, prostate, breast, tongue, and lung carcinoma cell lines; on the contrary, there was an inhibitory effect in all cases.³¹ In fact, rhBMP-2 was found to have no mutagenic activity.³¹ Given these available data, it seems unlikely that rhBMP-2 used to promote spinal arthrodesis has the potential to induce carcinogenesis.

Thawani et al.⁴⁰ reviewed basic science and clinical data to determine the possible role of BMP in cancer. They found no definitive association between BMP and the promotion of tumorigenesis or metastasis. Our long-term ex-

perience and clinical data with rhBMP-2 in the pediatric age group seem to support the conclusion of Thawani et al.

Risk-Benefit Balance

At the present time, the risk-benefit balance of BMP use during routine spinal fusion surgery is undetermined. Moreover, the scarcity of BMP studies in the pediatric age group makes the endeavor to establish clinical indications for BMP use in spine fusion surgery in children even more daunting. We routinely provide each patient and family with benefit and risk information, including the possibility of increased risk of future cancer with BMP use, as part of our informed consent process. We recommend that until the safety of BMP is firmly established with further study, our pediatric neurosurgery/spine surgery colleagues explicitly discuss the off-label use of BMP and its attendant risks in the pediatric age group with the patients' families and document these discussions.

We are currently analyzing BMP cost utilizing the KID database (unpublished data). The average cost of hospitalization was \$59,240 for patients receiving BMP and \$53,378 for those who did not receive BMP. The cost difference between these groups did not reach statistical significance ($p = 0.057$). Our surprising finding has implications for, and challenges, the commonly held belief that BMP use is cost prohibitive.

Limitations

Our retrospective study includes many inherent opportunities for bias, including recall bias. A significant number of patients were lost to follow-up (7 patients [12.3%]) or died (3 patients, [5.3%]) in our small cohort. It is conceivable that these patients may have developed a new malignancy or experienced degeneration or metastasis of an existing cancer, but this would have not been detected in our study. Without knowing the outcome in the cases of the 7 patients lost to follow-up, assuming all 7 of these patients developed cancer, the 95% CI would range from 6.4% to 24.4%. Because of the significant number of patients lost to follow-up, this means that the actual risk of cancer for the entire cohort could be anywhere from 0%–24.4%. In addition, there was no control group with outcomes that could be compared with those of our rhBMP-2 cohort.

The assessment of cancer was based on patient or caretaker report rather than screening laboratory studies or radiological examinations. Routine screening for cancer with full-body CT or MRI is not typically done in pediatric patients, nor is it practical. Therefore, it is possible that undetected cancer is present that has not yet manifested. We acknowledge that even 2-year follow-up may be insufficient and even longer-term follow-up is needed to fully address carcinogenicity of rhBMP-2 in the pediatric population. We intend to follow up this patient population prospectively and update the clinical outcomes at a minimum of 5, 10, and 20 years after surgery.

Conclusions

It is evident that rhBMP-2 is a valuable adjunct for achieving bone fusion in spine surgery. However, little has been published regarding the use of rhBMP-2 in the pediatric population prior to our studies. We previously dem-

onstrated that, in the early postoperative period, routine rhBMP-2 use is safe and efficacious, similar to its use in the adult population. A high rate of bony healing is evident with a low risk of wound healing complications; it may carry an antisepsis property as a result of its inherent ability to elicit a hyperinflammatory reaction. Judicious placement and choice of carrier is important in the setting of decompressive laminectomy to avoid unwanted bony overgrowth, restenosis, and compression of neural elements. Despite a fair number of published studies reporting an increase of cancer with use of rhBMP-2, our follow-up of at least 2 years (mean 48.4 months) in children who underwent posterior spine fusion with rhBMP-2 suggests a lack of carcinogenic potential for this agent; moreover, none of our patients had a malignant degeneration or metastasis of an existing tumor. Unfortunately, the exact incidence of cancer in our cohort of patients is uncertain due to a relatively high proportion of patients lost to follow-up. Furthermore, longer-term follow-up on the order of 5, 10, and 20 years is necessary to fully delineate the carcinogenic potential of rhBMP-2 in children.

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Author Contributions

Conception and design: Jea. Acquisition of data: Sayama, Brayton, Briceño, Ryan. Analysis and interpretation of data: Jea. Drafting the article: Jea, Sayama, Willsey. Critically revising the article: Jea, Sayama, Chingtagumpala, Luerssen, Hwang. Reviewed submitted version of manuscript: Jea. Approved the final version of the manuscript on behalf of all authors: Jea. Administrative/technical/material support: Jea, Ryan. Study supervision: Jea.

Correspondence

Andrew Jea, Neuro-Spine Program, Division of Pediatric Neurosurgery, Department of Neurosurgery, Texas Children's Hospital, Baylor College of Medicine, 6621 Fannin St., CCC 1230.01, 12th Fl., Houston, TX 77030. email: ahjea@texaschildrens.org