Complications associated with recombinant human bone morphogenetic protein use in pediatric craniocervical arthrodesis

Clinical article

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Object. Management of pediatric occipitocervical instability remains especially challenging. The off-label use of recombinant human bone morphogenetic protein (rhBMP)-2 for spinal fusion has increased with a well-documented increase in fusion rate in many case series. Unfortunately, recent reports have documented complications associated with rhBMP use in adult spinal fusions. Complications associated with the use of rhBMP in pediatric spinal surgery is less well understood. In this study the authors report on the fusion rate and complications associated with rhBMP in pediatric occipitocervical arthrodesis.

Methods. The authors reviewed the medical records of those patients 18 years old and younger who underwent dorsal occipitocervical fusion from January 2004 to December 2007 at the University of Iowa Hospitals and Clinics. Forty-eight patients were identified who received rhBMP-augmented fusion. The clinical outcome and complications of these fusions were analyzed.

Results. All 48 patients had fusion confirmed on lateral radiographs within 4–14 months with an average fusion time of 6.7 months. There were 6 complications, 5 of which included seroma formation. Two of 5 patients who developed postoperative seroma presented with symptoms suggesting brainstem compression and obstructive hydrocephalus requiring emergency reoperation. One patient developed heterotopic bone formation causing cervicomedullary compression requiring reoperation.

Conclusions. The use of rhBMP to augment autograft in occipitocervical fusion allows for a high rate of successful arthrodesis, but is associated with potentially life-threatening complications in pediatric patients.

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KEY WORDS • recombinant human bone morphogenetic protein • craniocervical arthrodesis • complication

Nineeen years after describing the ability of de-mineralized bone matrix to induce differentiation of bone,24 Urist23 isolated bone morphogenetic proteins. Since its discovery in 1984, the use of rhBMP to promote fusion in surgical patients has increased steadily.5 Although currently only FDA-approved for anterior lumbar interbody fusion (rhBMP-2) and revision of posterolateral surgery (rhBMP-7),7 there are increasing reports of the use of rhBMP for posterolateral lumbar interbody fusions, anterior and posterior cervical fusion, and thoracolumbar fusions.14 Between 2002 and 2007, Ong et al.14 reported a 4.3-times increase in the use of rhBMP with off-label fusion accounting for 85% of its primary use in fusions. This increase in use is driven by the clear efficacy of rhBMP to promote arthrodesis. A meta-analysis by Papakostidis and colleagues15 demonstrated a fusion failure rate of 14.5% versus 39% for rhBMP versus autologous bone graft in the setting of posterolateral spinal fusion, respectively.

Management of instability across the craniocervical junction is especially challenging in the pediatric population due to diminutive osseous and ligamentous structures and anatomical variations associated with syndromic craniocervical anomalies.1 Stabilization is achieved via instrumentation with placement of autograft producing varying fusion rates. Reports of increased rates of fusion...
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sion associated with the use of rhBMP compared with autologous bone graft alone suggest that these products may be beneficial for occipitocervical fusion as well.\textsuperscript{5,46,8} However, the increased fusion rate gained with the use of rhBMP has been recently shown to come at the cost of serious complications. Recent reports have described increased rates of seroma formation, tissue edema, and heterotopic bone formation, for example. There is now a warning regarding the use of rhBMP in the anterior cervical spine in adults. However, there is little information in the current literature reporting on the safety and efficacy of rhBMP in pediatric occipitocervical fusions. A recent report by Fahim et al.\textsuperscript{6} described their experience using rhBMP in a variety of pediatric spinal procedures. They report 1 case of ectopic bone formation and no evidence of seroma formation in any patient. However, only 3 of these procedures involved occipitocervical fusions. In this study we report on the fusion rate and safety of rhBMP when used specifically for occipitocervical fusion in the pediatric population.

Methods

With the permission of the Institutional Review Board, we retrospectively reviewed the medical records of patients 18 years of age and younger who had undergone dorsal occipitocervical fusions by the senior author (A.H.M.) between January 2004 and December 2007 at the University of Iowa Hospitals and Clinics. The patients’ demographic data, surgical details, and complications were recorded.

Patient Data

We identified 48 patients who had received rhBMP-2 to augment their fusion constructs. Twenty-seven patients were male and 21 were female. The average age at the time of surgery was 11.4 years (range 3–18 years). Patients treated with occipitocervical decompression and fusion were found to have a number of congenital and acquired defects. These defects included Chiari malformation in 17 patients, Down syndrome in 2, Klippel-Feil syndrome in 6, os odontoideum in 7, spondyloepiphyseal dysplasia in 1, congenital malformation of instability in 10, and basilar invagination in 4. Of the 48 patients treated, 10 had undergone previous posterior occipital cervical fusions. Twelve patients had first undergone transpalatopharyngeal resection of the inferior clivus and odontoid as necessary to decompress the cervicomedullary junction prior to posterior occipitocervical fusion.

Surgical Technique

All surgeries were performed by the senior author (A.H.M.). A meticulous dissection of the occiput and posterior cervical spine was performed. A suboccipital craniectomy and cervical laminectomies were performed as necessary to decompress the cervicomedullary junction. Titanium instrumentation was performed in all but 1 case to achieve immediate internal stabilization. One patient was treated with a plate and polyaxial screw construct, 35 with custom-contoured rod and titanium wire constructs, 11 with a rib autograft secured with titanium wires alone with no other instrumentation, and 1 with onlay fusion using autograft alone without instrumentation. Forty patients underwent fusion from the occiput to C-2, 5 to C-3, 2 to C-4, and 1 to C-6. A thorough decortication of the occiput, lamina, spinous processes, and facet joints was then performed with a matchstick bur. Five or 10 ml of Allomatrix (Wright) was used in conjunction with local autograft, rib graft, or cranial graft material and applied laterally along the construct. Calvarial autograft was used in 18 patients (37.5%), rib autograft in 28 (58.3%), and 2 patients (4.2%) received either morcellized spinous process or did not receive autograft. Over this graft, a small kit of rhBMP (4.2 mg, Infuse, Medtronic Sofamor Danek) was used with a 1-cm strip of collagen sponge placed on each side of the construct at the craniocervical junction. No surgical drains were placed intraoperatively. A meticulous multilayer anatomical closure was then performed.

Follow-Up

Postoperatively, patients were maintained in a halo vest or an Aspen cervicothoracic orthosis for 3 months and then transitioned to a cervical collar for an additional 3 months. Patients were assessed postoperatively at 6 weeks and at 3-month intervals during the first year and then yearly by the senior author. In some cases, follow-up imaging was obtained locally and sent for review. The integrity of the construct and the status of the bone fusion were assessed with static and dynamic lateral cervical radiographs by the senior author.

Results

We identified 48 patients who underwent posterior occipital decompression and fusion with rhBMP augmentation ranging from age 3 to 18 years (average 11.4 years). All patients achieved successful bone fusion (100%) as assessed by static and dynamic lateral cervical radiographs. There were a total of 107 levels fused with an average fusion of 2.2 levels and a range of 0–5 levels. No evidence of pseudarthrosis or hardware failure was encountered in any patient. The average duration to achieve fusion was 6.7 months with a range of 4–14 months. The average time to fusion was similar for both calvarial and rib autografts (6.6 and 6.7 months, respectively). Of the 48 patients, 39 (81.3%) received perioperative steroids after surgery (mean 104 hours, range 24–312 hours). The average hospital stay was 13.7 days (range 5–55 days). All patients have been followed up to date. The average follow-up duration was 53.2 months (range 34–75 months).

Postoperative complications included 1 persistent pseudomeningocele in a patient following duraplasty that resolved after treatment with a lumbar drain. There was 1 case of a superficial wound infection, which was treated with local wound care, and no cases of deep infection requiring reoperation. There was 1 case each of ventilator-associated pneumonia and aspiration pneumonia. One patient required a tracheostomy due to persistent inability to adequately protect the airway due to laryngeal dysfunction. One patient recovered slowly after surgery and imaging results suggested prominent ventricles, and therefore a
ventriculostomy was performed. The patient continued to recover slowly and the EVD was removed without need for permanent CSF diversion. Most concerning were 6 complications believed to be related to the use of rhBMP that had never been encountered by the senior author prior to the introduction of rhBMP into his practice. These complications included 5 incidences of postoperative seroma formation and 1 case of excessive ectopic bone formation, which will be discussed in more detail below.

Illustrative Cases

Postoperative Seroma Formation

Case 1. This 14-year-old boy complained of worsening diffuse headaches for 1.5 years. On examination, the patient had moderately decreased lateral neck flexion and rotation with normal flexion and extension. He was found to have normal strength and sensation, but was hypopreflexic throughout the upper and lower extremities. Magnetic resonance imaging revealed an upward, near-horizontal position of the clivus with a short basiocciput and a high-riding anterior arch of the atlas. The clivus-canai angle was abnormal at 95°–100°. There was hindbrain herniation and a holocord syringohydromyelia. The patient was taken to the operating room for a foramen magnum decompression and C-1 laminectomy, followed by dorsal Oc–C2 fusion with custom-contoured titanium-loop instrumentation using rib graft, AlloMatrix, and rhBMP. There was no evidence of durotomy during the procedure. The patient tolerated the procedure well with no new postoperative deficits. On postoperative Day 4, the patient began having apneic spells. Imaging revealed a large fluid collection in the operative site with extension into the epidural space within the posterior fossa, and obstructive hydrocephalus (Fig. 1A and B). During evaluation, the patient became increasingly somnolent and apneic. An emergency head CT scan demonstrated a large posterior fossa epidural fluid collection and hydrocephalus (Fig. 1C). The patient underwent an emergency right frontal ventriculostomy followed by wound exploration. Intraoperatively, clear yellow-stained fluid under high pressure was encountered. There was no evidence of postoperative hematoma or CSF leakage. Intraoperative cultures were negative. A hemovac drain was placed and the wound was closed. Postoperatively the patient recovered well with resolution of his ataxia. He was subsequently tapered off the EVD and discharged on hospital Day 14 in good condition with resolution of his neck pain.

Additional Cases. Three additional cases of postoperative seroma formation were encountered. A 6-year-old boy had undergone a foramen magnum decompression and C-1 laminectomy followed by a dorsal Oc–C2 fusion using custom-contoured threaded titanium-loop instrumentation using rib graft, AlloMatrix, and rhBMP. There was no evidence of durotomy during the procedure. The patient tolerated the procedure well with no new postoperative deficits.

Case 2. This 8-year-old boy, with a history of Apert syndrome and craniofacial dysostosis for which he had previously undergone craniofacial remodeling and cranial release procedures, presented with new onset neck pain. Physical examination revealed typical facial features of Apert syndrome and bilateral hand deformities. Flexion-extension cervical spine radiographs demonstrated atlantoaxial instability. The patient underwent a foramen magnum decompression followed by a dorsal Oc–C1–C2 fusion using custom-contoured threaded titanium-loop instrumentation with rib graft, AlloMatrix, and rhBMP. There was no evidence of durotomy during the procedure. The patient initially progressed well postoperatively. However, on postoperative Day 3 the patient developed worsening ataxic gait and somnolence. An emergency head CT scan demonstrated a large posterior fossa epidural fluid collection and hydrocephalus (Fig. 1C). The patient underwent an emergency right frontal ventriculostomy followed by wound exploration. Intraoperatively, clear yellow-stained fluid under high pressure was encountered. There was no evidence of postoperative hematoma or CSF leakage. Intraoperative cultures were negative. A hemovac drain was placed and the wound was closed. Postoperatively the patient recovered well with resolution of his ataxia. He was subsequently tapered off the EVD and discharged on hospital Day 14 in good condition with resolution of his neck pain.

Fig. 1. Case 1. An axial CT scan of the head obtained at the onset of apneic spells revealed epidural fluid in the posterior fossa and evidence of obstructive hydrocephalus (A). A sagittal MR image (B) revealed epidural fluid extending from the surgical site into the epidural space causing mass effect on the craniocervical junction. Case 2. An emergency axial CT scan of the head obtained at the onset of progressive somnolence revealed a large epidural fluid collection and obstructive hydrocephalus (C).
an 11-year-old girl who underwent an Oc–C3 fusion using custom-contoured loop instrumentation, rib graft, and rhBMP. She presented 2 weeks after surgery with a large fluid collection at the operative site. The patient denied any symptoms consistent with a pseudomeningocele, but was initially treated with a lumbar drain and acetazolamide. However, the fluid collection remained unchanged despite these interventions and they were subsequently discontinued. She was then treated conservatively and the fluid collection slowly resolved over several weeks. The final case involved an 11-year-old girl who had undergone a foramen magnum decompression and C-1 laminectomy, intradural lysis of adhesions, and shrinkage of the cerebellar tonsils, followed by an Oc–C2 fusion with custom-contoured loop instrumentation, rib graft, and rhBMP. She presented approximately 4 weeks after surgery with clinical and radiographic evidence of a fluid collection at the operative site. She did not complain of postural headaches. The fluid was aspirated and found to be serous and cultures were negative. It was believed that this patient might have also developed a seroma secondary to the use of rhBMP. She was then treated conservatively and the fluid collection resolved over several weeks.

Ectopic Bone Formation

Case 3. This 16-year-old boy initially presented to another facility with occipital headaches in December 2002. He was diagnosed with a Chiari malformation and underwent a posterior fossa craniotomy, C-1 laminectomy, and duraplasty. After the procedure, the patient continued to have severe headaches with nausea and vomiting. He also complained of dizziness and blurred vision. He presented to our facility in August 2005 with these complaints. At that time, physical examination revealed limited lateral neck rotation to 40° to the left and 50° to the right with normal flexion-extension. Hearing was diminished on the right, gag response was diminished on the right, and he was hyperreflexive throughout his upper extremities. Other signs included absent patellar and Achilles reflexes, normal strength in his upper and lower extremities, and subjectively better sensation in his face than the rest of his body. Magnetic resonance imaging revealed a hypoplastic clivus with compression of the medulla by the odontoid, tonsillar herniation, and a cervical syrinx. A 3D CT demonstrated the previous suboccipital decompression and C-1 laminectomy (Fig. 2A and B). The patient then underwent a transoral-transpalatopharyngeal approach to decompress the ventral medulla followed by a posterior approach for expansion of his previous suboccipital decompression, intradural exploration, lysis of adhesions, and dorsal Oc–C2 fusion with titanium loop instrumentation using calvarial bone graft, Allomatrix, and rhBMP. The hospital course was complicated by reintubation with anterior neck crepitus, which subsequently resolved. The patient responded well neurologically with improvement of his gag reflex and resolution of his headaches. However, by November 2006, the patient presented with weakness in his upper extremities and worsening neck pain. A 3D CT scan revealed excessive bone growth in the area of the previous decompression (Fig. 2C and D). In December 2006, the patient underwent posterior fossa and repeat C1–2 decompression, intradural lysis of adhesions, placement of a shunt from the fourth ventricle to the subarachnoid space, and duraplasty. The patient responded well postoperatively and showed improvement of his symptoms.

Discussion

From 2004 to 2007 we identified 48 patients with rhBMP-augmented occipitocervical fusion. There were a total of 107 levels fused with an average fusion of 2.2 levels and a range of 0–5 levels. These patients were followed for an average of 53.2 months with a range of 34–75 months. We obtained a 100% fusion rate with the use of rib or calvarial autograft and rhBMP augmentation. The average time to fusion was similar for both calvarial and rib autografts (6.6 and 6.7 months, respectively). Previous studies have reported success rates of 98.8% and 100% using rib or iliac crest grafts, respectively, without the use of rhBMP. Our results were similar to those reports in terms of successful fusion.

Of the 48 patients, 6 suffered postoperative complications believed to be related to the use of rhBMP. Four patients developed epidural fluid collections that were evident within 5 days of the operation, while 1 patient did not present until 1 month postoperatively for wound swelling as a result of a seroma. The incidence of seroma formation in this study was 10.4%, which may underestimate the true incidence of this condition. It is likely that more patients developed subclinical seromas because imaging was not performed unless the patient became symptom-
atic. Most concerning were the 2 patients who developed symptoms secondary to compression of the cervicomedullary junction and hydrocephalus. Of these 2 patients, 1 suffered numerous apneic episodes 4 days postoperatively, and was treated with exploration, ventriculostomy, and tracheostomy after imaging revealed a large posterior fossa fluid collection that tracked rostrally into the epidural space. The second patient became increasingly somnolent with gait difficulty 4 days postoperatively and was treated with wound exploration and EVD placement after a head CT scan revealed an epidural fluid collection and hydrocephalus. The remaining 3 patients who developed seromas did not develop neurological decline. These cases demonstrate the increased risk in using rhBMP in the pediatric patient following a posterior decompression of the craniocervical junction. As seromatous fluid collects at the surgical site, the fluid is able to track superiority within the epidural space. Obstructive hydrocephalus can occur with rapid neurological decline.

Recognition and awareness of this potentially life-threatening complication is critical for surgeons considering using rhBMP in their pediatric patients. Reports discussing rhBMP use in pediatric patients are very limited, particularly in regard to its use in occipitocervical fusions. A recent report by Fahim et al. described their experience using rhBMP in a variety of pediatric spinal procedures. Of these procedures, only 3 involved occipitocervical fusions. While 1 patient underwent suboccipital craniectomy, it is unclear if a suboccipital decompression was performed in the remaining 2 cases. In this same publication, however, the authors also observed a case of ectopic bone formation requiring reoperation and decompression due to progressive neurological decline. We observed a similar case of excessive ectopic bone growth resulting in compression of the cervicomedullary junction. Therefore, although somewhat rare, heterotopic bone formation does not need to be recognized as a serious possible complication associated with the use of rhBMP in the cervical spine.

We had not previously observed severe postoperative seroma formation or ectopic bone formation in our pediatric patients following posterior occipitocervical decompression and fusion. During the study period, 9 additional patients were identified who underwent posterior occipitocervical fusion without the use of rhBMP, and no significant complications were encountered (data not shown). Although this limited number of patients is not sufficient to directly demonstrate a statistically significant difference in complication rate associated with the use of rhBMP, it is consistent with our previously published experience. In a review including 24 patients with Down syndrome who underwent occipitocervical fusion for instability prior to the introduction of rhBMP to our practice, no cases of seroma formation or ectopic bone growth were observed. In a separate report including 102 patients under the age of 16 treated with occipitocervical fusion without rhBMP for instability secondary to os odontoideum, none were found to have developed postoperative seroma formation or ectopic bone growth. Together, these findings strongly imply an increased risk of postoperative complications associated with the use of rhBMP in pediatric occipitocervical fusions.

Unlike the limited evidence regarding rhBMP use in the pediatric spine, the risks associated with rhBMP use in the adult spine are much better understood. Larger doses of rhBMP have been associated with bone resorption, while ectopic bone formation has also been observed. Several studies have documented ectopic bone formation in animal models although neurological sequelae were not observed, even with mild cord compression. In human studies, McKay and Sandhu reported ectopic bone growth encroaching into the spinal canal following posterior lumbar interbody fusion without neurological deficit. Baskin et al. and Boakye and colleagues have also documented the formation of heterotropic bone with anterior cervical discectomy and fusion. Our findings and recent findings by others suggest that perhaps ectopic bone formation secondary to rhBMP use in the posterior thoracic or cervical spine places patients at increased risk of delayed neurological decline compared with other sites.

The development of painful seromas and excessive tissue swelling at the surgical site is also well recognized in adult patients. Garrett et al. reported a 4.6% incidence of seroma formation in the lumbar spine and suggest that this may be an underestimation of the true incidence due to underrecognition of this complication. In addition, Benglis et al. reported findings from a survey of surgeons who routinely use rhBMP in their practice that many had observed patients who developed painful seroma formation at the operative site. While seroma formation following rhBMP use in the lumbar spine may cause pain and difficulties with wound healing, seroma formation and tissue edema in the cervical spine can become life threatening. Use of rhBMP has been shown to cause hematoma, dysphagia, and excessive edema resulting in airway compromise after anterior cervical fusion. In addition, a recent report by Shahlaie and Kim described a patient who had undergone an rhBMP-augmented posterior cervical fusion and subsequently developed worsening numbness and weakness secondary to a large seroma at the operative site. The patient’s symptoms improved following evacuation of the fluid.

Because the majority of seromas following rhBMP use appear to occur during the first week after surgery, it is possible that leaving a drain in the operative site for several days may decrease the incidence of this serious complication. We did not leave a drain in any of our patients in this series. However, after recognition of this serious complication, we now routinely use postoperative drains whenever rhBMP is used.

It is also possible that the proper dose of rhBMP required to achieve the desired effect in pediatric patients is different from that in adults. We used the small rhBMP kit (4.2 mg) in our patients and placed half of the product on each side of the construct. It is possible that even smaller doses could be used in pediatric patients to decrease the rate of complications while preserving therapeutic efficacy. Recent evidence has supported this hypothesis. Boakye et al. reported a decrease in bone formation when only a fourth of a small Infuse kit was used. This was also supported by Baskin et al. who suggested that there was no statistically significant difference in complication rate when 0.4 ml of reconstituted
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rhBMP-2 solution was used compared with controls who received autograft for anterior cervical disectomy and fusion. Lack of consensus on the proper dosage has lead some authors to recommend against the use of rhBMP in occipitocervical fusion until proper dosage guidelines are developed. Thus, further studies are needed to determine the optimal dosing of rhBMP in pediatric patients. Although the exact mechanism of seroma formation with BMP use remains elusive, several authors have proposed that this formation is secondary to the intense inflammatory response to rhBMP. Although 38% of patients ultimately develop antibodies against rhBMP, the seroma formation within a few days is unlikely to be antibody-mediated. Rather, it is more likely secondary to the effect of rhBMP to activate endothelial cells and stimulate vascular endothelial growth factor. The coupling of osteogenesis with angiogenesis likely results in leaky, immature blood vessels that contribute to increased fluid in adjacent tissues. For these reasons it has been proposed that perioperative steroids may help prevent these complications. However, in our study, 39 patients (81.3%) received high-dose perioperative steroids. Of the 39, all 6 patients who developed a complication received perioperative steroids for durations ranging from 48 to 168 hours with an average of 84 hours. Unfortunately, despite the use of steroids, seroma formation was still observed.

Although the primary rationale for using rhBMP is to increase fusion rate, we find little benefit in this regard in posterior occipitocervical fusions in children. Our previous reports had described 98.8% and 100% fusion rates for pediatric occipitocervical fusions using rib or calvarial grafts, respectively. Thus, the use of rhBMP likely did little to augment fusion rates, but did increase the complication rate. Therefore, rhBMP is no longer routinely used in our practice and is now limited to patients undergoing repeat surgery for pseudarthrosis. We suggest that rhBMP use in pediatric occipitocervical fusions be avoided whenever possible and that these patients should be monitored extremely carefully when it is used.

Conclusions

The off-label use of rhBMP for fusion has been well documented in spinal fusion. The rates of fusion and complications of rhBMP-augmented fusion have not been clearly documented in the pediatric population. In this retrospective report, there was not a significant increase in the fusion rate or time to fusion with the use of rhBMP augmentation. A significant number of patients (10.4%) developed postoperative complications associated with the use of rhBMP. The most common complication was seroma formation observed in 5 patients and ectopic bone formation in 1 patient. The use of rhBMP during occipitocervical fusion in this population can create life-threatening complications and should therefore be avoided whenever possible.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Menezes, Lindley, Dahnale. Acquisition of data: Lindley, Abode-Iyamah. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Lindley, Abode-Iyamah. Administrative/technical/material support: Menezes.

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