The Use of Allograft and Recombinant Human Bone Morphogenetic Protein for Instrumented Atlantoaxial Fusions

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Key words
- Atlantoaxial allograft
- Cervical
- Fusion
- rh-BMP2

Abbreviations and Acronyms
CT: Computed tomography
rh-BMP2: Recombinant human bone morphogenetic protein-2

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■ BACKGROUND: **Iliac crest autograft is the historic gold standard for bone grafting, but is associated with a significant patient morbidity. Fusion rates of C1-C2 up to 88.9% using allograft and 96.7% using autologous iliac crest bone graft can be achieved when combined with rigid screw fixation. We sought to determine our fusion rate when combining allograft with recombinant human bone morphogenetic protein-2 (rh-BMP2) and rigid screw fixation.**

■ METHODS: **We reviewed our experience using allograft, bone morphogenetic protein (rh-BMP2) and screw fixation of C1-C2 in 52 patients and examined indications, surgical technique, fusion rates, and complications. In 28 patients, corticocancellous allograft pieces were laid along decorticated bone after a C2 neurectomy was performed. In 24 patients, unicortical iliac crest allograft was precision-cut to fit between the C1 lamina and C2 spinous processes.**

■ RESULTS: **Fifty-two C1-C2 fusions were performed with allograft, rh-BMP2, and rigid screw fixation. There were 25 female and 27 male patients ranging in age from 6 to 92 years (mean, 65.8 years). Operative indications included trauma (56%), degenerative disease (21%), rheumatoid arthritis (15%), congenital anomalies (6%), and synovial cyst (2%). The mean follow-up was 23.9 ± 2.1 months (range, 2—55 months). The mean dose of rh-BMP2 used for all patients was 4.5 mg (range, 2.2—12 mg). In patients who achieved sufficient follow-up, 100% achieved solid fusion: 45/50 Lenke A, 5/50 Lenke B. There were no known complications attributable to the use of rh-BMP2.**

■ CONCLUSIONS: **The use of small doses of rh-BMP2 added to allograft in addition to rigid screw fixation is a safe and highly effective means of promoting a solid fusion of the atlantoaxial complex and spares the patient the morbidity of iliac crest harvest.**

INTRODUCTION

The atlantoaxial complex presents a unique set of challenges for neurosurgeons who attempt a fusion at this level. The C1-C2 joint is highly mobile and accounts for more than 50% of the rotation and 12% of the flexion and extension movements of the head in relation to the thoracic spine (24). Stability at this joint is conferred by the dens and the ligamentous structures surrounding it including the transverse, apical, and alar ligaments (23). Instability at the atlantoaxial junction results from congenital (os odontoideum, odontoid aplasia, or hypoplasia), traumatic (ligamentous disruption or fracture), inflammatory (rheumatoid arthritis), neoplastic, and degenerative causes (4). Instability is associated with potentially disastrous neurological complications given the immediate proximity of the cervicomedullary junction. The unique anatomy and the inconsistent course of the vertebral artery lends to a limited set of operative interventions, as well as fusion rates that are lower than the subaxial cervical spine (5).

With the development of modern instrumentation techniques, historic methods, such as posterior graft/wiring techniques, have fallen out of favor. The ability to use transarticular screws (17) or a screw/rod construct (16, 19), as immediate internal fixators while bony fusion occurs, has lead to an increase in fusion rates for posterior atlantoaxial stabilization (10). The gold standard for bone grafting is still iliac crest autograft, which is associated with significant patient morbidity (3).

We have modified our technique of posterior bone grafting to incorporate iliac crest allograft used in combination with recombinant human bone morphogenetic protein (rh-BMP). In the present study, we investigated fusion rates and complications in 52 consecutive patients who underwent posterior atlantoaxial arthrodesis using allograft and rh-BMP2 to help understand the efficacy and safety of this technique.

METHODS

The present study was approved by the institutional review board of the University of Miami and the University of Virginia Health Systems. We identified a series of consecutive patients who underwent instrumented C1-C2 fusion with allograft and rh-BMP between July 2004 and June

2011. A total of 52 patients at the University of Miami Miller School of Medicine/Jackson Memorial Hospital (n = 24) and University of Virginia Health System (n = 28) underwent C1-C2 fusion with allograft and rh-BMP for C1-C2 instability from traumatic (odontoid fracture), congenital (os odontoideum), and inflammatory (rheumatoid arthritis) conditions. Patients with spinal instability from tumors were not treated with rh-BMP2. Preoperative symptoms, clinical findings, operations performed, and results were noted. The presence or absence of fusion as defined by radiographic analysis was analyzed, as were postoperative complications. Use of rh-BMP2 and instrumentation as adjuncts for posterior cervical fusion are off-label uses of these products.

Surgical Technique

All patients underwent C1-C2 instrumentation using C1 lateral mass screws and C2 pars/pedicle screw-rod technique described by Goel and Laheri (15) and Harms and Melcher (19). Six patients had bilateral transarticular screws placed, and one patient had a hybrid construct consisting of a unilateral transarticular screw and unilateral screw rod construct, the remaining 45 patients had screw/rod constructs. The mean amount of rh-BMP2 used for all patients was 4.5 mg (range, 2.2–12 mg). In earlier cases a slightly greater amount of rh-BMP2 was used and in one case 12 mg or one large kit was used. We modified our usage based on data from anterior cervical fusion with rh-BMP2 (7, 25) and subsequently used the amount of rh-BMP2 needed to cover the decorticated bone. In 24 patients (University of Miami), a piece of unicortical iliac crest allograft supplied by the University of Miami Bone and Tissue Bank was fashioned to fit tightly between C1 and C2. The posterior arch of C1 was decorticated, as well as the spinous process of C2. The graft was then notched to fit snugly between the posterior arch of C1 and the C2 spinous process, then cabled into place using a braided titanium cable passed beneath the screw-rod construct (Sonntag technique). The cable was then tensioned to 10 lbs and crimped into position. A small kit of rh-BMP2 was divided and placed at the interface between the decorticated bone and the allograft bilaterally (**Figure 1A**).

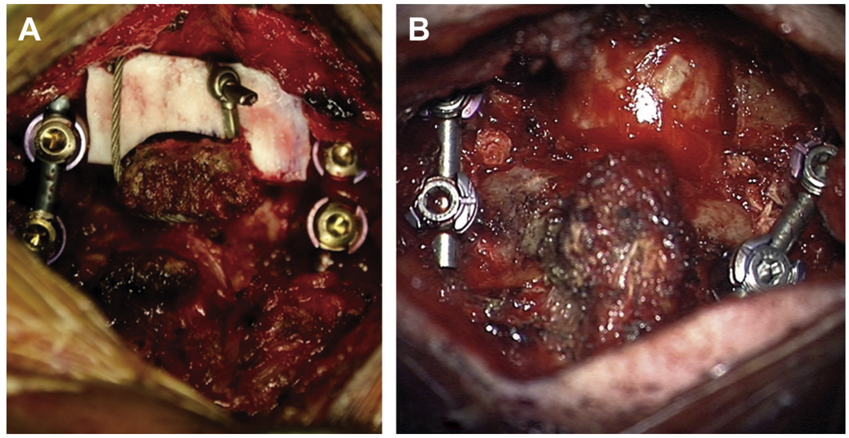

Figure 1. (**A**) Intraoperative photograph of screw rod construct with bi-cortical milled allograft cabled in. (**B**) Intraoperative photograph of screw rod construct after C2 ganglionectomy with chipped allograft on-lay.

In 28 patients (University of Virginia Health Systems), a screw-rod construct was placed after C2 neurectomy/ganglionectomy, as previously reported (18). The C1-2 joint space and posterior facet complex was decorticated as well as the spinous process and lamina of C2 and the posterior arch of C1. A small kit (4 mg) of rh-BMP2 was placed over the decorticated bone. Corticocancellous nonstructural allograft was then placed over the decorticated bone/BMP (**Figure 1B**). No cases of new onset postoperative C2 neuralgia occurred. Postoperatively, all patients were maintained in a rigid cervical collar (Miami J) for 8 weeks for additional bracing and to discourage activities that would jeopardize the fusion.

Assessment of Fusion

Fusion was defined by the classification of Lenke as determined on plain radiograph and computed tomography (CT) with coronal and sagittal reconstruction (A: definitely solid with trabeculated stout fusion mass; B: possibly solid with large fusion mass; C: probably not solid with small fusion mass; D: definitely not solid with bone graft resorption or obvious pseudoarthrosis), and dynamic radiographs

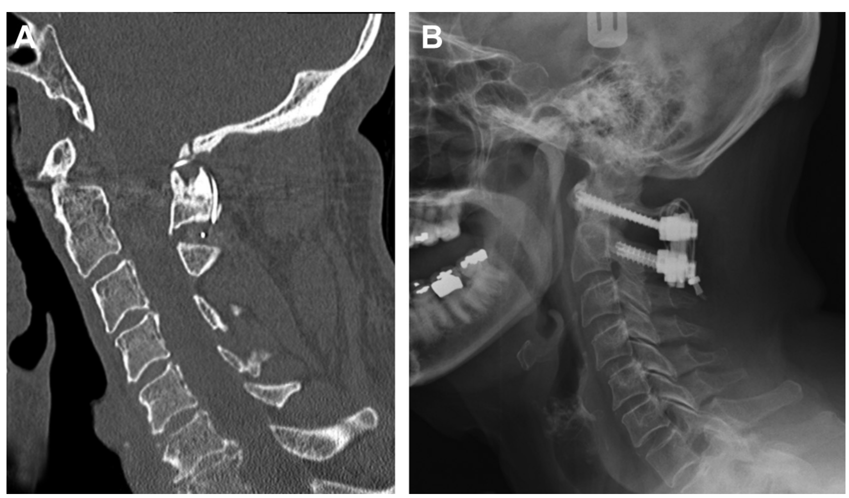

Figure 2. (**A**) Midsaggital reconstructed computed tomography scan obtained at 6 months demonstrating bridging bone. (**B**) Lateral cervical spine radiograph obtained at 6 months demonstrating the cabled allograft construct with no loosening of hardware.

in certain patients. In addition, fusion was determined by lack of hardware failure and the absence of motion on flexion-extension radiographs. We reviewed CT scans and anteroposterior, lateral, and dynamic (flexion-extension) radiographs obtained during routine follow-up (Figure 2A, B). Routine films were obtained at 3 months, then at 1 year as part of our standard practice. Twelve patients had less than 6 months of follow-up. All patients had plain films and several patients had CT imaging. Of this group, all patients appeared to developing bridging bone and had no loosening of hardware or motion on dynamic films.

RESULTS

The charts of 52 patients (25 women and 27 men) were reviewed. The patients ranged in age from 6 to 92 years with a mean age of 65.8 years (Table 1). Operative indications (Table 1) included trauma (56%), rheumatoid arthritis (15%), congenital (4%), degenerative (23%), and synovial cyst (2%). The mean dose of rh-BMP2 used for all cases was 4.5 mg (range, 2.2–12 mg). The mean (standard error of the mean) duration of follow-up was 23.3 months (range, 2–55 months). Complications included sustained postoperative tachycardia (n = 1), shock and respiratory failure (n = 1), hospital-acquired pneumonia (n = 1), and deep venous thrombosis (n = 1) (Table 2). There were no perioperative deaths, but there were two deaths unrelated to the procedure in patients of 92 years of age at the time of surgery who passed several years after the procedure from unrelated causes (age 94 years). There were no known complications directly attributable to the use of rh-BMP2 such as seroma, wound drainage, ectopic bone formation, or osteolysis.

Fusion analysis included data from all patients followed until fusion or at least 24 months after surgery. We began to see signs of fusion as early as 2 months after surgery. The rate of fusion appeared accelerated when compared to iliac crest autograft (personal experience). Two patients did not achieve sufficient radiographic follow-up. In the remaining patients, 100% achieved fusion, with 45/50 achieving Lenke A fusion criteria and 5/50 Lenke B. In patients not achieving 3 months of follow-up, all appeared to be progressing to fusion. There were no cases of pseudoarthrosis, screw loosening, or fracture.

Table 1. Characteristics of 52 Patients Who Underwent C1-C2 Posterior Instrumented Fusion and Completed Follow-Up

	Age	Gender	Follow-up (months)	Diagnosis
1	70	M	17	Fracture
2	92	F	3	Fracture
3	35	M	3	Fracture
4	49	F	27	RA
5	17	M	20	Congenital
6	70	F	28	Degenerative
7	6	M	25	Congenital
8	73	F	4	Degenerative
9	52	F	12	Fracture
10	92	M	2	Fracture
11	49	M	13	Fracture
12	74	F	10	Degenerative
13	38	M	10	Fracture
14	82	F	3	Synovial cyst
15	52	F	15	Degenerative
16	59	M	3	Fracture
17	69	F	11	Degenerative
18	36	M	9	Fracture
19	73	F	2	RA
20	88	M	2	Degenerative
21	63	F	2	Degenerative
22	64	F	2	Congenital
23	77	F	1	Degenerative
24	73	F	36	Fracture
25	4	M	46	Fracture
26	71	M	42	RA
27	84	M	34	Degenerative
28	84	M	33	Fracture
29	89	M	31	Fracture
30	10	M	29	Fracture
31	79	F	47	RA
32	21	F	38	Fracture
33	79	F	32	Fracture
34	61	F	27	RA
35	78	F	24	Fracture
36	88	F	20	Fracture
37	88	M	55	Degenerative
38	77	M	53	Fracture
39	74	M	45	Fracture
40	76	M	48	Fracture
41	77	F	43	Fracture
42	84	F	38	Fracture
43	81	M	27	Fracture
44	66	M	14	Fracture
45	65	M	17	Fracture
46	75	M	23	RA
47	65	F	22	Degenerative
48	86	M	13	Fracture
49	84	F	21	Fracture
50	73	M	19	RA
51	80	F	23	RA
52	71	M	28	Fracture
Mean	65.83		22.53	
SDEV	22.52		15.18	
SEM	3.12		2.13	

RA, rheumatoid arthritis; SDEV, standard deviation; SEM, standard error of the mean.

DISCUSSION

Posterior C1-C2 fusion was first mentioned by Gallie in 1939 (14). His method, described more completely by McGraw

Table 2. Complications

Complications	Number of Patients
Sustained postoperative tachycardia	1
Respiratory failure and shock	1
Hospital-acquired pneumonia	1
DVT	1

DVT, deep venous thrombosis.

and Rusch (22) and Fielding et al. (13) involved a structural piece of iliac crest autograft, which is secured between C1-2 with a sublaminar C1 wire that secures around the spinous process of C2. The midline wiring technique was modified by Brooks and Jenkins (8) by placing bilateral sublaminar wires at C1-2 with structural iliac crest autograft. Fusion rates using the Gallie technique reached 93% and with the Brooks Jenkins technique it reached 96%, with all patients requiring long-term rigid orthosis (5). In 1991, Dickman et al. (11) introduced a wire construct that avoided placing sublaminar C2 wires. By placing an iliac crest autograft held in compression with a loop wire, maintaining patients in a halo vest for 12 weeks, then a rigid Philadelphia collar for an additional 4–6 weeks, they (11) reported a 97% fusion rate.

Grob and Magerl (17) developed a fixation procedure involving the placement of transarticular screws as well as an autologous bone graft that is cabled into position. The combination of transarticular screws and a cabled autograft is biomechanically superior to wiring techniques and fusion rates between 87% and 100% have been reported (23). The technique of transarticular screw placement is demanding and aberrant vertebral artery anatomy precludes screw placement in 18%–23% of patients (2, 21).

In an effort to overcome the technical challenges of transarticular screw placement, yet achieve rigid internal immobilization, Goel and Laheri (15) introduced a method that used plate-screw fixation of the C1 lateral mass and the C2 pars. To facilitate passage of the plate and to enhance exposure for decortication of the joint and surface area for bone graft, Hamilton et al. (18) routinely sectioned the C2 ganglion. In a series of 157 patients, Goel and Laheri (15) reported a 100% fusion rate.

Harms and Melcher (19) introduced a similar technique of C1 lateral mass screws and C2 pars screws using polyaxial screws and rods. A special screw with a nonthreaded portion was used to avoid the C2 nerve root and facilitate connection to the C2 pars. In their series of 37 patients, 100% fusion was obtained.

Posterior instrumented screw constructs are biomechanically superior to cabled constructs, and with meticulous surgical technique a very high fusion rate can be achieved. However, when using the gold standard iliac crest autograft, significant patient morbidity related to the procedure may be encountered. Harvesting of iliac crest autograft increases operative time and blood loss and is associated with persistent postoperative pain, pelvic fractures, and infections (3).

In 2009, Hillard et al. (20) published their results of allograft bone for posterior C1-C2 fusion. In a prospective trial, they compared their fusion rates using posterior instrumentation and either iliac crest autograft or allograft. They also reviewed operative time, blood loss, and donor site complications. Forty-eight patients underwent fusion with allograft and 42 patients underwent fusion with autograft. The operative time was 50 minutes, shorter in the allograft procedure, blood loss was 50% lower in the allograft group, and the autograft group incurred a donor site complication rate of 16.7% including one pelvic fracture and two hernias (20). In their landmark article Hillard et al. (20) reported a fusion rate of 96.7% in the autograft group and 88.9% in the allograft group. They speculate that meticulous bone grafting and placement of an interpositional graft as opposed to an on-lay graft contributed to high rates of fusion in both groups.

Well-documented complications to rh-BMP2 include ectopic bone formation, bone resorption, and osteolysis, in addition to swelling, hematoma, and dysphagia in anterior cervical surgery (25). At present, there are multiple reviews that summarize our current knowledge of rh-BMP2, and major trials in animals and humans are available (6). However, recommended doses for specific procedures have yet to be established and increasing doses of rh-BMP2 do not necessarily result in higher fusion rates. Our investigation is the largest series to focus on the C1-C2 complex and reports fusion rates and dosages of rh-BMP2 required for a solid fusion. In addition, we have demonstrated that meticulous use of small amounts of rh-BMP2 appears to be safe in this location.

Due to concern for soft tissue swelling and airway compromise in the anterior cervical spine with rh-BMP (6, 9), the US Food and Drug Administration has issued a public health notice increasing scrutiny on the use of bone morphogenetic protein in the cervical spine (1). Because of the morbidity associated with harvesting autograft, we have routinely used banked allograft for anterior cervical surgery and have recently begun using allograft in the posterior cervical spine. In an attempt to increase fusion rates in the difficult-to-fuse patient population of rheumatoid arthritis, we began supplementing our atlantoaxial constructs with rh-BMP2. In our experience, no patient has had difficulties with postoperative seromas, heterotopic ossification, or bone necrosis. We attribute this, in part, to meticulous use of small doses of rh-BMP2.

In addition to Hillard et al. (20), we also believe that meticulous carpentry plays a role in achieving a high fusion rate. Properly crafting a piece of structural allograft and incorporating it as an interposition graft under compression (Wolff's law), prevents motion and encourages fusion. However, as further demonstrated, a high fusion rate can be achieved using allograft as an on-lay in combination with rh-BMP2, which can also achieve excellent fusion rates. We have demonstrated that combining the osteoinductive properties of rh-BMP2 with the osteoconductive properties of allograft can achieve a solid fusion using different surgical techniques. There was concern using rh-BMP2 off-label in pediatric patients and a long discussion was held with the family before surgery. A review of the literature found early support in the use of rh-BMP2 in its ability to develop stable bridging bone with maintenance of correction (12), but there were no data regarding long-term concerns, especially future neoplasms or extraskeletal effects.

The limitations of this study stem from its retrospective nature. On-lay grafting and structural interpositional grafting do not appear to affect the overall outcome with regard to fusion. Our technique also evolved in regard to usage of rh-BMP2. As it became more evident that small doses of rh-BMP2 were sufficient to achieve fusion, we decreased our dosage to the smallest amount needed to cover the decorticated bone. This worked out to be 4.5 mg or a small kit of rh-BMP2. In this difficult-to-treat anatomic region, the use of rh-BMP2 appears to achieve excellent fusion rates and limit patient morbidity from donor graft harvesting.

A high rate of fusion can be accomplished at the atlantoaxial joint using rigid internal fixation and iliac crest autograft; however, with a high potential for significant graft harvesting morbidity. In this series, we demonstrate that rigid instrumentation combined with allograft and low doses of rh-BMP2 also results in a high rate of fusion, nearing 100%.

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