Case Study

Adverse swelling associated with use of rh-BMP-2 in anterior cervical discectomy and fusion: a case study
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Abstract
BACKGROUND CONTEXT: The use of recombinant bone morphogenetic protein-2 (rh-BMP-2) is effective in augmenting lumbar spinal fusions. A safe, effective dosage of rh-BMP-2 in the cervical spine has yet to be determined. Use of rh-BMP-2 is currently being evaluated and is only indicated for use in the cervical spine on Investigational Device Exempt cases.

PURPOSE: To present a potentially serious adverse event that may occur when using rh-BMP-2 in cervical spine surgery.

STUDY DESIGN: An emergent sequence of events including physical examination, radiographic studies, intubation, and surgical exploration were performed upon arrival to the emergency department.

METHODS: We report a case of a 54-year-old male patient presenting with neck swelling and difficulty swallowing 5 days after anterior cervical discectomy and fusion (ACDF) using rh-BMP-2.

RESULTS: The patient was found to have massive neck swelling including the pharyngeal tissue. The patient was admitted to the intensive care unit where parenteral steroids were administered for 24 hours during monitored intubation. The patient was extubated on the second hospital day and discharged home on the fourth hospital day after swelling subsided.

CONCLUSIONS: Caution should be exercised with rh-BMP-2 use in ACDF surgery as the correct dose and technique for application is not yet determined. Respiratory distress and dysphagia may result secondary to rh-BMP-2 induced anterior neck swelling. © 2007 Elsevier Inc. All rights reserved.

Keywords: Cervical soft-tissue swelling; BMP (recombinant bone morphogenetic protein-2); Anterior spinal surgery

Introduction
The use of recombinant bone morphogenetic protein-2 (rh-BMP-2) has been shown to increase the success and recovery rate after lumbar spinal fusion. To date, rh-BMP-2 is not Food and Drug Administration–approved for use in the cervical spine. The success rate for a good clinical outcome after anterior cervical discectomy and fusion (ACDF) surgeries is high without use of rh-BMP-2, a costly osteogenic protein. There are, however, patient populations at higher nonunion risk in which augmenting bone fusion using rh-BMP-2 in cervical spine surgery may be desirable. Patients who have osteoporosis or chronic steroid dependency, cervical kyphotic deformity, revision fusion surgery, a smoking habit, cervical ankylosing spondylitis, or osteogenesis imperfecta are examples of cases where augmenting bone fusion with rh-BMP-2 use may be of benefit. We present a case in which rh-BMP-2 was used to augment an ACDF surgery which resulted in an adverse event of postoperative diffuse and intense soft-tissue swelling.

Case report
A 54-year-old male presented to the emergency room with a chief complaint of anterior neck swelling and difficulty swallowing. The patient was 5 days status-post...
removal of anterior cervical plate C5–C7 for a previous C5–C6 and C6–C7 ACDF, and underwent subsequent adja-
cent levels of ACDF at C3–C4 and C4–C5 with an applica-
tion of an anterior cervical plate fixation at C3 to C5. The
initial successful ACDF of C5–C7 was performed several
years earlier without any complications. A rigid cervical
collar was continuously worn for the 5 days after the most
recent surgery. No neck injury occurred postoperatively.
Diet, ambulation, and pain tolerance had improved in a nor-
mal progression for the first two days after surgery. At
home, postoperative days 3–5, the patient began noticing
increasing neck swelling and mild difficulty swallowing.
Although the patient was anxious secondary to his swallow-
ing difficulty, dysphonia and frank respiratory distress were
not encountered, nor were fevers or chills.

The patient’s past medical history was notably signifi-
cant for human immunodeficiency virus. However, the
CD4 count was 800, the viral load was negligible, and no
acquired immunodeficiency syndrome–defining illnesses
had ever been contracted. The additional medical history
included hypertension, gout, gastroesophageal reflux dis-
ease, depression, and anxiety. The only known medicine al-
lergy was to celecoxib which caused a generalized body
 rash. The list of medications includes allopurinol, zolpi-
dem, atenolol, lamivudine/zidovudine, losartan, hydromor-
phone, cephalexin, clonazepam, lamotrigine, levothyroxine,
escitalopram, ciprofloxacin, moxifloxacin, gabapentin, acet-
aminophen/hydrocodone, lansoprazole, valacyclovir, ne-
virapine, bupropion, and aprazolam.

Upon arrival to the emergency room on postoperative
day 5, the patient was complaining of gross anterior neck
swelling and difficulty swallowing. The patient was seen
and examined. The vital signs were normal with 98% oxy-
gen saturation on room air. The patient was in moderate
distress because of the difficulty swallowing. There was
no wound dehiscence or erythema. The incision was on
the right side of the neck, horizontal and in the typical lo-

cation for the Smith-Robinson anterior cervical spine surgic-
al approach. Massive neck swelling was readily noted
predominantly ipsilateral to the side of surgical approach.
The swelling extended from the mandible to the sternal
notch/clavicle border. The patient had mild vocal hoarseness.
There was no oral erythema or lesion noted. The neurologic
examination was without any focal deficits to bilateral upper
and lower extremities. Upper and lower extremity deep
tendon reflexes were normal at 2/4 and symmetrical on all
extremities. No signs of myelopathy were present.

Laboratory data were unremarkable. The urinalysis,
electrolytes, protime, and partial thromboplastin time were
all within normal limits.

Emergent cervical radiographs were obtained after the
physical examination. Massive soft-tissue swelling was ob-
vious by gross examination. This predominantly involved
the side ipsilateral to the surgical incision. Diffuse prever-
tebral soft-tissue swelling was noted on the lateral radi-
ograph (Fig. 1). On the anterior-posterior view, the trachea
was deviated to the contralateral side of the surgical ap-

The extent of soft-tissue swelling was readily identifiable on the
entire ipsilateral side of surgical approach (right side) (Figs.
3–6). For example, the sternocleidomastoid muscle on the
right was nearly twice the thickness of that on the left.
As a result of the swelling, the trachea and esophagus were
deviated to the contralateral side of the surgical approach.
The diameter of tracheal opening was remarkably narrowed
and in one image was less than 5 mm in cross-section. A
small fluid collection was evident on the ipsilateral side

Fig. 1. Anterior-posterior and lateral radiographs obtained on postoperative day 5, upon admission to the emergency department. Gas can be seen on both the
anterior-posterior and lateral images. Note the tracheal deviation to the patient’s left side, which is contralateral to the surgical approach. Note also the
extensive prevertebral soft-tissue swelling anterior to the cervical plate on the lateral radiograph.
of surgical approach. It was not clear whether this signal intensity was consistent with blood from a hematoma or edema from inflammation. This fluid extended from the anterior spine adjacent to the cervical hardware and tracked along the plane of surgical dissection to the level of the strap muscles. The air pockets that were visible on radiographs were determined to reside within this track of fluid. There were no signs of cervical hardware failure. The interbody grafts were intact without signs of fracture or displacement.

The medical records indicated that Cornerstone-HSR (Medtronic Sofamor Danek, Memphis, TN) 9-mm and 7-mm bioabsorbable implants were used for the ACDF at C3–C4 and C4–C5 interbody grafts. These implants are made from a noncrystalline polylactide copolymer, 70/30 poly (l-lactide-co-D,L-lactide) (PLa). Additionally, InFuse Bone Graft (Medtronic Sofamor Danek, Memphis, TN) was placed inside the Cornerstone-HSR implant to augment fusion. This graft contains rh-BMP-2 and an absorbable collagen sponge. Of note is that this is a novel use of a bioresorbable PLa cage combined with rh-BMP-2 in cervical ACDF surgery. A Blackstone Locking Plate 48 mm in length and six associated screws were used in the cervical instrumentation.

After the computed tomographic scan was completed and reviewed, the patient was urgently brought to the operating room and intubated under direct visualization using a flexible endoscope. The wound was opened using a scalpel for sharp dissection down to subcutaneous fat. The sutures reapproximating the platysma were released, and blunt finger dissection in the intermuscular plane was easily carried down the anterior spine. Approximately 15 cc of serous
fluid was aspirated. A discrete hematoma was not present. No active bleeding vessels were identified. No pus was identified. All tissues along the plane of dissection were firm and densely swollen from the skin deep to the prevertebral longus colli muscles. There was no evidence of injury (contusion, abrasion, or laceration) to the soft tissues.

The wound was irrigated with copious normal saline solution and closed in typical fashion. The patient was treated intraoperatively with 10 mg of decadron intravenously and given a similar administration of a tapering dose for 24 hours postoperatively. Finally, the patient was transported to the intensive care unit and, for 24 hours, remained intubated and on the ventilator for airway protection. After extubation, the patient had gradual resolution of swelling and improvement in swallowing. Continued improvement was observed over the subsequent 48 hours while support of oxygen was administered. He was discharged home on the third postoperative day.

**Discussion**

BMP use in the cervical spine is currently not Food and Drug Administration–approved. Rh-BMP-2 is an osteoinductive protein that induces a reliable fusion in the lumbar spine, but has only limited human experience in cervical spinal surgery. Few publications to date have examined rh-BMP-2 use in the cervical spine. Baskin et al. compared the InFuse (rh-BMP-2) bone graft to iliac crest bone graft when implanted within the Cornerstone-SR (Medtronic Sofamor Danek, Memphis, TN), a fibular allograft manufactured for use as an intervertebral bone graft in ACDF [1]. A total of 33 patients were enrolled in this study. An anterior cervical plate was used in all patients. The rate of fusion and all adverse events were recorded. All patients in both groups obtained a solid fusion by 6 months postsurgery, and there were no implant or device-related adverse events reported in either group.

In another study by Boakye et al. [2], ACDF surgeries were performed using polyetheretherketone (PEEK) implants filled with rh-BMP-2. This retrospective study on 24 patients looked at outcomes that included fusion rates and complications. Two patients experienced transient dysphagia, but the authors did not attribute this to rh-BMP-2 induced swelling. Of note in this study, the authors initially were packing the PEEK implant with half the total amount of rh-BMP-2 that comes in a small InFUSE kit (one of two sponges) per level. They found heterotopic bone formation in three patients and subsequently decreased the dose of rh-BMP-2 to one-quarter of a small InFUSE kit (one-half sponge of the two-sponge kit) per level. No heterotopic bone formation was documented in those patients receiving the lower rh-BMP-2 dosing. Additionally, the fusion rates in these patients remained at 100%. Thus, the adverse effects of rh-BMP-2 causing heterotopic ossification and diffuse soft-tissue swelling may be in part dose-dependent. The authors of this study suggested that the reports of soft-tissue swelling in the anterior neck in patients undergoing ACDF rh-BMP-2-filled PEEK spacers are likely a result of 1) placement of the rh-BMP-2 outside the PEEK cage and in direct contact with the soft tissue; 2) placement of the rh-BMP-2 in a cage that has perforations that allow migration of the rh-BMP-2; or 3) too high a dose of rh-BMP-2.

Bridwell et al. [3] suggest that the most likely cause of rh-BMP-2 induced postoperative hematoma and retropharyngeal swelling is a result of using too high a dose of rh-BMP-2 in the cervical spine. They recommend using fibrin glue to prevent the spread of BMP. The exact cause of postoperative soft-tissue swelling in patients who have undergone anterior spinal fusion surgery augmented with rh-BMP-2 is not known. It is known, however, that rh-BMP-2 induces a robust inflammatory reaction which is likely responsible for both the success in promoting bone formation as well as the adverse effects of soft-tissue swelling. This may very well be a dose-dependent phenomenon that still needs to be investigated for future use of rh-BMP-2 in the cervical spine.

One interesting consideration in the present case report is the effect of placing rh-BMP-2 within the bioresorbable PLa cage. Adverse tissue reactions have been observed when using bioresorbable devices in spinal and other orthopedic surgeries. Toth et al. [4] investigated PLa for use as a resorbable interbody fusion cage in a sheep model. The resorbable cage was combined with either rh-BMP-2 or autograft bone. They found the use of rh-BMP-2 with the bioresorbable cage did not decrease nor increase the rate of implant degradation. There was mild degradation at 12 months and significant degradation of the bioresorbable implant at 24 months by histological analysis. Although this degradation was associated with an increased inflammatory response, no adverse host responses were observed.

Lanman and Hopkins investigated the use of rh-BMP-2 placed within 70/30 PLa resorbable interbody cages in the human lumbar spine [5]. This study reported 98% solid fusion at 6 months and 100% solid fusion at 12 months. No device-related complications were reported. No adverse soft-tissue reactions were reported.

A second study by Lanman and Hopkins studied the efficacy of bioabsorbable interbody spacers used in conjunction with rh-BMP-2 in ACDF surgeries [6]. InFuse (rh-BMP-2) and local bone autograft were packed within the Cornerstone-HSR (Medtronic Sofamor Danek, Memphis, TN), a bioabsorbable interbody implant. They found 100% of the patients fused by 3 months postsurgery. In this study, again there were no reported implant- or device-related complications, nor adverse soft-tissue reactions.

Although there have been numerous reports demonstrating a local inflammatory reaction as the PLa resorbs, it is unlikely that this case represents an inflammatory response secondary to this degradation. PLa metabolizes into CO₂.
and H₂O, biologically inert within the human body. Additionally the 70/30 PLa does not significantly break down before 12 months, as has been shown by Toth et al. [4]. Vacarro et al. demonstrated a safe and effective use of a bioresorbable anterior cervical plate [7]. Nine patients underwent allograft interbody fusion in ACDF surgery. No patient had evidence of soft-tissue complications.

Another concern frequently raised with the use of rh-BMP-2 is the possibility of antibody formation. This may potentially occur if the immune system reacts to the external proteins, or antigens that are introduced. This response is said to be both concentration and duration dependent [8]. Proteins that are cleared quickly from the body are less likely to promote an antibody response as compared with proteins that have a longer clearance time. Data suggest that rh-BMP-2 clears rapidly from the circulation [9]. The patient in this case report had not been previously exposed to rh-BMP-2 during the first ACDF surgery. Therefore, a type IV or delayed hypersensitivity inflammatory reaction would not occur.

The patient in this case presented to the emergency department 5 days after his surgery with complaints of increasing neck swelling and eventually difficulty swallowing. The swelling was noticed on postoperative day 3 and progressively worsened over the next 3 days. There are no studies published which describe adverse postoperative soft-tissue swelling after rh-BMP-2 implantation. However, it is not surprising that an inflammatory response to rh-BMP-2 would manifest as a host tissue response beginning at 48 hours. This is a typical timeframe for an inflammatory host response.

The collagen-carrier for rh-BMP-2 that is currently used in the INFUSE kits may not be ideal for use in anterior cervical spine surgery. Kandziora et al. [10] reported on a sheep study which investigated the use of a biodegradable carrier system called poly(D,L-lactide) (PDLLA) which delivers rh-BMP-2, a thermolabile protein. The rh-BMP-2 is actually coated on the PDLLA biodegradable implant. As the implanted PDLLA polymer undergoes degradation, there is a sustained slow release of the rh-BMP-2. This is in contrast to the collagen-sponge carrier which may release a fast and uncontrolled amount of rh-BMP-2. This may in turn lead to uncontrolled and adverse soft-tissue inflammation.

This report is presented to illustrate a potentially serious adverse reaction with soft-tissue swelling in anterior cervical spine surgery when using rh-BMP-2. There are patients at risk for nonunion who may benefit from rh-BMP-2 induced osteogenesis. Therefore, the appropriate dose and delivery/carrier of rh-BMP-2 in anterior cervical spine surgery needs to be further investigated.

References