Acute renal insufficiency, supraventricular tachycardia, and confusion after recombinant human bone morphogenetic protein-2 implantation for lumbosacral spine fusion

Case report

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The authors report on a case of a patient who received recombinant human bone morphogenetic protein-2 (rhBMP-2) to augment spinal fusion for the first and third of 3 lumbosacral fusion surgeries. After receiving rhBMP-2 the first time, the patient became febrile and developed mild acute renal insufficiency and transient supraventricular tachycardia (SVT). The second operation was complicated only by perioperative fever. When the patient received rhBMP-2 again during the third operation, he developed fever, acute oliguric renal insufficiency, symptomatic SVT with hypoxemia, confusion, and joint pain. No clear cause of these problems was identified; however serum analysis revealed the presence of an antibody to rhBMP-2. The authors discuss potential mechanisms for the patient’s putative reaction to rhBMP-2, as the findings from a literature review suggest this is the first such reaction to be reported.

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Key Words • adverse reaction • arrhythmia • renal failure • rhBMP-2 • spinal fusion

Recombinant human BMPs are increasingly used as adjuncts to autologous bone or in conjunction with osteoinductive carriers to achieve bone fusion in instrumented spine surgery. In patients with diseased nerve root, spinal cord, or vertebral bodies, bone fusion performed with rhBMPs to eliminate instability or the potential for instability is at least equivalent, and perhaps superior, to the use of autologous bone graft alone.1,3,4 These higher fusion rates are of paramount importance in patients with systemic disease and poor or difficult to harvest autologous bone.

Clinical experience with differentiation factors at nonspinal sites predicts low rates of local and systemic adverse effects when these factors are used in spinal fusion surgery.13,15,18 When used appropriately, there is a low risk of ossification of adjacent soft tissue and disc spaces resulting in uncontrolled bone formation and neural impingement. There have also been few reported systemic toxicities from the use of rhBMP in human studies.15 Animal studies evaluating both acute toxicity from a single intravenous dose and chronic toxicity postimplantation also failed to demonstrate systemic toxicity. Retention of rhBMP in the implant site and its rapid circulatory clearance are thought to result in the observed low systemic toxicity.15

Several investigators who have measured serum antibodies to rhBMP before and after spinal fusion surgery report a low incidence of human antibody response to rhBMP. These studies demonstrated a rate of antibody formation to rhBMP-2 (0.7% of patients) that was lower than the rate of immune response to the allogenic or xenogenic collagen carriers that have been used to retain the BMP.1,3,7,10 Recombinant human BMP-7 more frequently produced detectable anti-BMP antibodies in trials in humans (38% of patients).1,3,7,10

Evaluation of the rates of rhBMP antibody formation was performed in rhBMP naive patients, allowing the possibility of immune-mediated toxicity with repeated use of rhBMP during additional operations. To date there have no
reports of systemic toxicity in patients who have been previously exposed to rhBMP and in whom the potential for a robust secondary immune response exists. In this article we describe a case of severe systemic toxicity after repeated use of rhBMP associated with a systemic immune response and highly elevated anti-rhBMP IgG levels.

**Case Report**

**History and Examination.** This 53-year-old man with obesity and a history of hypertension, gout, hepatitis C, and depression presented with a 3-year history of severe axial low-back pain and progressive bilateral radiculopathy that was refractory to conservative management. He had a 15-pack-year tobacco history, but had stopped smoking 6 years prior to his first admission. On physical examination he had intact strength and sensation and walked with an antalgic gait. His reflexes were diminished in the bilateral lower extremities.

**First Operation.** The patient underwent L5–S1 transfo-
raminal lumbar interbody fusion with PS placement. A 12-mm allograft Capstone spacer packed with rhBMP-2 (Medtronic) was inserted into his L5–S1 disc space. The patient lost 500 ml of blood during the procedure. Preoperatively the patient had a serum creatinine level of 0.6 mg/dl and a BUN level of 17 mg/dl. Postoperatively, on Day 2 the creatinine level rose to a maximum of 1.5 mg/dl and the BUN to 47 mg/dl. Levels dropped and stabilized to a creatinine level of 0.6 mg/dl and a BUN level of 35 mg/dl, in response to intravenous hydration.

On postoperative Day 1, the patient experienced SVT with a heart rate of 150–160 bpm for 3–4 minutes that resolved spontaneously. Despite a fever of 38.6°C, cultures of the patient’s blood, urine, and sputum did not show evidence of growth. The WBC count during this febrile episode never exceeded $10.9 \times 10^9$/L, which it reached on postoperative Day 2. On postoperative Day 5 the patient was transferred to an acute rehabilitation facility.

**Second Operation.** Throughout the course of the subsequent year, computed tomography failed to demonstrate a solid fusion mass, and the patient continued to report severe low-back pain. Imaging studies obtained at this time revealed lucencies around the screws consistent with pseudarthrosis. In a repeated operation, the fusion construct was extended to S-2, the PSs were revised, and autologous bone graft was used without rhBMP. The patient lost 2 L of blood during surgery and received a transfusion periopera-

tively.

During this admission, his creatinine and BUN levels remained within normal limits, reaching maximum levels of 1.2 mg/dl and 19 mg/dl, respectively. On postoperative Day 3, the patient developed a fever of 38.3°C. Blood, urine, and sputum cultures showed no evidence of growth. The WBC count during this febrile episode never exceeded $7.4 \times 10^9$/L, which it reached on postoperative Day 2. There were no episodes of SVT. The patient was transferred to an acute rehabilitation facility on postoperative Day 5.

**Third Operation.** The patient returned 5 months after the second operation with refractory axial back pain and radiographic indications of failed fusion. We performed an-
other exploration of the previous L5–S1 laminectomy defect and removed the ligamentum flavum, which was still partially intact. We also decorticated the interspace contralateral to the interbody graft and packed it with cancellous iliac crest autograft. We replaced the loose L-5 and S-1 PSs with larger screws and decorticated the transverse process of L-5 and ala of the sacrum, packing the lateral spaces with cancellous iliac crest autograft wrapped in collagen and hydroxyapatite sponges soaked with rhBMP-2 (Medtronic). The patient lost 1.5 L of blood and received 4 units of packed red blood cells and 2 units of fresh frozen plasma periopera-
tively.

The patient had preoperative serum creatinine and BUN levels of 0.8 mg/dl and 12 mg/dl, respectively. These levels increased to a maximum of 3.2 mg/dl and 53 mg/dl on post-operative Day 7. A renal echogram was performed to deter-
mine the cause of acute renal failure, and normal kidneys were revealed with no evidence of hydronephrosis. Levels dropped and gradually stabilized with a return to a normal creatinine level of 1.1 mg/dl and a BUN level of 25 mg/dl 3 months after surgery.

On postoperative Day 10, SVT developed. The patient’s heart rate was in the 160s and he became hypoxic as the oxygen saturation dropped to 70%. His temperature climbed to 38.5°C, and blood, urine, and sputum samples were obtained for culturing. Results from a Swan–Ganz catherization demonstrated hyperdynamic cardiac func-
tion and low systemic vascular resistance consistent with sepsis. He was started on a course of antibiotics prophyl-
actically. Anticoagulation therapy with heparin was initiat-
ed and continued until a ventilation–perfusion scan could be performed to rule out a pulmonary embolus. Results of the ventilation–perfusion scan demonstrated a low proba-
ability of pulmonary embolism and anticoagulation therapy was stopped.

After the first episode of fever, the patient intermittently developed both low- and high-grade fevers for a period of 3 weeks. Blood, urine, and sputum cultures were obtained multiple times that did not show evidence of growth. In addition, a transeosophageal echocardiogram was performed and revealed a normal ejection fraction and trace pericard-
dial effusion. The WBC count during these febrile episodes never exceeded $10.6 \times 10^9$/L (reached on postoperative Day 4).

Because of the lack of growth in cultures and the patient’s intermittent fevers and occasional episodes of altered mental status and confusion, MR imaging of the lum-
bar spine was performed to evaluate for a possible infect-
ious source on postoperative Day 14; no evidence of a surgical site abscess was revealed. A thin rim of enhance-
ment adjacent to the site of bone graft placement was evi-
dent on contrast-enhanced MR images (compare Fig. 1 to Fig. 1 right). An MR image obtained on postoperative Day 29 again showed no evidence of infectious disease.

Given the patient’s history of gout and an exacerbation of joint pain on postoperative Day 4, the patient underwent aspiration of fluid from the knee and elbow. The synovi-

al fluid contained uric acid crystals, but no organisms grew in culture. Aspiration and culturing was repeated 2 more times on postoperative Days 13 and 19 with no evidence of growth. The patient was subsequently started on a course of oral prednisone on postoperative Day 31 for a second exac-
erbation of gout.
The patient continued to have severe back pain limiting mobility for the first 6 postoperative weeks. He was then gradually able to increase his level of activity and was discharged to an acute rehabilitation center 7 weeks after the third fusion.

**Detection of BMP-2 Antibody.** The clinical picture of septic shock combined with the absence of a clear infectious source and lack of improvement after antibiotic therapy raised the concern of an immune response to the rhBMP. Blood was drawn from the patient 1 month after the third fusion, and a serum analysis for BMP-2 antibody was performed by immunoblotting. Unfortunately, a preoperative blood sample was no longer available for comparison analysis.

Various amounts of rhBMP-2 protein (0, 20, and 100 ng) were subjected to 15% sodium dodecyl sulfate polyacrylamide gel electrophoresis and then transferred to the membrane (Fig. 2). After blocking with 10% nonfat milk, the membrane (Bio Rad) was incubated with either the patient serum or a control serum (1:200 dilution) for 1 hour. After washing, the membrane was incubated with horseradish peroxidase–labeled anti–human IgG secondary antibody (1:1000 dilution; Santa Cruz Biotechnology) for another hour. The signal was detected using an ECL kit (Invitrogen). Serum taken from a random individual who had never been exposed to rhBMP-2 (Fig. 2 right) and serum from another patient who had received BMP-2, but did not have a reaction to it, were included as controls and yielded negative results when tested for the antibody. The control serum was found to be serologically viable for other proteins.

**Discussion**

Recombinant human BMP, sometimes used in conjunction with a collagen carrier, has been shown to promote bone growth and fusion in the lumbar spine and lead to improved clinical outcomes.\(^1,3,8,14\) Other than ectopic bone formation and postoperative cervical swelling, which appear to be avoidable by judicious placement, there have been few reported adverse effects associated with the use of rhBMP.\(^1,3,15,18\) Several studies have documented the formation of anti–rhBMP and anti–bovine Type I collagen antibodies in a small number of patients after surgery; however, these immune responses were not reported to be associated with any obvious clinical symptoms.\(^1,3,7,10\)

Authors of clinical trials evaluating the safety and feasibility of rhBMP use in spinal fusion surgery have reported elevation of anti–rhBMP and anti–bovine Type I collagen antibody titers after surgery.\(^1,4,15,19\) These trials were generally limited to initial operations, and did not address the second use of rhBMP during repeated operation for the rare instance of pseudarthrosis or adjacent segment degeneration. Antibody responses varied with the subtype of rhBMP used; a larger proportion of patients treated with rhBMP-7 formed anti–rhBMP antibodies compared to those that received rhBMP-2.\(^1,3,7,10\) An asymptomatic antibody response to bovine collagen carrier appeared to occur in a greater proportion of patients.

We describe here a patient who suffered severe and potentially life-threatening systemic immune toxicity after reexposure to rhBMP-2 and bovine collagen carrier. This case does not prove that exposure to rhBMP-2 resulted in our patient’s postoperative complications. Nevertheless, such a reaction is suggested and would be the first ever reported. In retrospect it appears that our patient had a mild version of systemic immune toxicity after first receiving rhBMP-2 and collagen and suffering from self-limiting SVT and mild renal dysfunction. The patient’s second operation serves as an internal control; despite substantial blood loss, the patient had an unremarkable postoperative course. After the third operation and readministration of rhBMP and bovine collagen carrier, acute renal insufficiency, hypoxemia, SVT, confusion, and delirium developed. These complications could represent a robust secondary immune response as evidenced by high levels of anti–rhBMP antibodies.

It is possible that our patient was having a reaction to collagen rather than BMP-2, but long-term collagen data suggest that it is relatively safe. Repeated injection of bo-
Vine collagen in humans desiring correction of soft-tissue contour irregularities has been performed without systemic reactions for many years, though some patients have developed a localized and self-limited hypersensitivity reaction. Circulating antibodies have been identified after repeated bovine collagen injection; however, there are no reports of severe life-threatening immunotoxicity. We suspect that, in our patient, the observed postoperative systemic complications were caused by a reaction to rhBMP-2.

The mechanism by which the rhBMP-2 could have provoked an arrhythmia and renal insufficiency is not known. Bone morphogenetic protein-2, like all members of the transforming growth factor-beta superfamily of proteins, has multiple functions, including roles in heart, neural, and cartilage development. One possible hypothesis is that the nonostogenic functions of endogenous BMP-2 were affected by the induced antibody response. Bone morphogenetic protein-2 has been shown to have a role in cardiac contractility in zebrafish and rats, provoking speculation that BMP-2 antibody could have directly affected the heart contractility in our patient. Renal insufficiency could have resulted from an increased immune-complex burden on the kidneys or from some other mechanism not yet elucidated.

The long-term significance of a patient’s development of anti-rhBMP-2 antibodies remains to be seen. If a patient generates antibodies to epitopes specific to the rhBMP-2 molecule that are not present in native human BMP, the duration of their effects will most likely be limited to the length of time that the rhBMP-2 is retained in the system. However, development of antibodies to epitopes specific to native human BMP-2 could theoretically impose the risk of an autoimmune disease that interferes with the endogenous functioning of BMP-2. The significance of such a theoretical condition will become clearer as the other nonostogenic roles of endogenous BMP are studied.

We report here the first putative systemic reaction to rhBMP-2, which in retrospect was mild and self-limited, occurring in a treatment-naive patient. Readministration of rhBMP-2 presumably resulted in a nearly life-threatening immune reaction. The clinical implications of our current case report suggest that unexplained fever, arrhythmia, or renal failure postoperatively in a patient receiving rhBMP-2 should raise the possibility of an immune reaction to the protein. Further study of this subject is necessary, but one might consider that prior to repeated operation in a patient who has already received rhBMP-2, it may be prudent to check for serum anti-BMP-2 antibodies or to perform a subcutaneous low-dose test injection before using rhBMP-2 again. Although it may be possible to use a different subtype of rhBMP, one could consider avoiding the use of rhBMP in these patients altogether.

Conclusions

Although the present study does not prove that the patient’s postoperative complications were caused by rhBMP-2 exposure, the protein appears to have provoked a systemic response that increased in magnitude after a second exposure. This is possibly the first potentially life-threatening adverse reaction to rhBMP-2 reported after its use in lumbar spinal fusion. It is possible that repeated use of rhBMP-2 may not be prudent in a patient who has had prior exposure to the protein with unexplained postoperative fever, renal insufficiency, or arrhythmia. Further study of this subject is warranted.
Reaction to rhBMP-2 after spinal fusion

References


