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Case Report

Off-label: The results of adjunctive bone morphogenetic protein for challenging femur fractures; a review of two cases

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ABSTRACT

Background: Although bone morphogenetic proteins (BMPs) are used as an adjunct to promote healing, they may have unintended effects such as heterotopic ossification (HO). The literature is limited regarding the effect of using off-label BMPs for femur fractures.
Case presentation: We report two outcomes after off-label use of BMPs for the treatment of femur fractures and propose a possible explanation for the difference.
Conclusions: BMPs are critical osteoinductive factors in injured bone and muscle that facilitate bony healing. However, it may be important to recognize the potentially negative effects of adding BMP to bone graft material in certain cases to stimulate bone repair. We hope this case series helps surgeons consider the risks and benefits of using BMP for femur fractures, and therefore to decide with caution when BMP is indicated.

Background

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor (TGFb) superfamily of proteins and are known to be active in multiple growth and differentiation processes [1,2]. Previous studies have cited that, in fractures, the concentration of BMPs at the non-union fracture site is a key factor for successful treatment [3,4]. With the use of recombinant DNA technology, high concentrations of single growth factors such as BMPs can be introduced for bone regeneration [5,6]. Although the use of BMP is currently only FDA approved for spinal fusion procedures and open tibial shaft fractures, off-label BMP use continues to be used for other orthopaedic injuries, specifically fractures of the tibia and humerus [7–9].

Although BMPs are often associated with positive outcomes, a reported complication related to the use of BMPs in the extremities is heterotopic bone formation [10–12]. Heterotopic ossification (HO) is the pathological formation of ectopic bone in soft tissues. It often occurs following severe trauma, and BMP signaling is believed to play a key role in the overall HO process [13]. We present two cases where off-label BMP was used for a femur fracture and led to two different outcomes.

Case 1

A 51-year-old African American female presented to our trauma service in 2009 following a high-speed motor vehicle collision (MVC). She suffered injuries including an open right tibia fracture, cervical spine fracture, and a complex left femoral neck and shaft

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fracture. Around 10–15 years prior, she had a previous injury that required an antegrade left femoral nail. Her femoral neck fracture from the MVC was around the proximal aspect of this pre-existing femoral nail. This nail had become ingrown within the femoral canal. For removal, the bent nail had to be transected and the proximal portion of the femur required an osteotomy to access the nail. The proximal portion of the nail was removed with anterior and lateral osteotomies, and the distal part was left in the femur. There was significant bone loss of the anterior and lateral proximal femur. The femoral neck and proximal femur were fixed with a proximal locking femoral plate that spanned the femoral shaft fracture. Then, cancellous bone allograft with one vial of BMP-2 was used to backfill the large defects in the anterior and lateral portions of the base of the femoral neck and shaft of the femur.

Postoperatively, she developed stiffness in her hip and knee. She was found to have extensive HO which nearly bridged the space between the trochanter and the ilium, and extended to her knee. Due to her stiffness, she required two surgeries for HO excision and manipulation. One surgery was for her left hip and the other for her left knee. This patient had over 10 years of documented follow-up. Most recently, she had 3–80 degrees of motion in her left knee. She had painless but limited external and internal rotation of her left hip, and normal intact sensation in her left lower extremity. However, she continues to have difficulty with ambulation (Fig. 1).

Case 2

A 64-year-old Caucasian female with severe polyarticular rheumatoid arthritis and a history of bilateral hip and knee replacements presented in 2011 after a fall. She sustained a left interprosthetic femur fracture. She underwent open reduction and internal fixation using a 6-hole large fragment AO locking plate along the medial side of the knee and a 10-hole lateral locking femoral plate with cerclage wires. Unicortical screws and 4-hole cloverleaf structures were applied around the femur to ensure stable proximal femur fixation. Cancellous bone allograft with one vial of BMP-2 was then placed at the fracture site in an area of vascularized bone to aid in

Fig. 1. A and B, AP of the left femur injury radiographs demonstrating a midshaft femur and femoral neck fracture with a bent intramedullary nail. C and D, AP of the left femur several months post operatively with HO formation forming around the hip to the midshaft femur. E and F, AP of the left femur with HO formation extending to the ilium.

healing. She had one year of postoperative follow-up documentation, and she had an uneventful and successful healing process with no HO formation in her left lower extremity (Fig. 2).

Conclusions

BMPs are promising growth factors that are involved in the enhancement of bone healing [14,15]. They can induce differentiation of mesenchymal stem cells into osteogenic cells capable of producing bone [16,17]. Although this can be beneficial in patients with orthopaedic injuries, BMPs also have the potential to lead to HO and stimulate bone growth in unintended areas. Our case series demonstrated two patients who were both treated with cancellous bone allograft with one vial of BMP-2, but had very different outcomes.

Certain patient-specific risk factors such as high energy injury, multiple medical comorbidities, and multiple previous surgeries have been cited to contribute to poor bone healing [18]. These risk factors may have impacted the healing of the two patients in our case study. The patient in case 1 had a prior surgery to the area and a high energy impact injury; the patient in case 2 had multiple lower extremity surgeries and a relevant comorbidity that may have impacted recovery. Patient risk factors may be important for a surgeon to consider when anticipating potential complications. We speculate that the risk factors of these respective patients led to the surgeon deciding to use BMP to promote healing.

The literature has documented that the complicated balance between BMPs and severe natural BMP antagonists represent one intrinsic source for pathologic fracture healing [19]. Additionally, a significant reduction in BMP expression has been found in the

Fig. 2. A and B, AP and lateral of the injury radiographs demonstrating left distal third femoral shaft periprosthetic fracture with lateral and posterior displacement. C and D, AP of the left femur post operatively several months following fixation without evidence of HO formation.

cartilaginous areas of non-healing fractures [20]. However, the physiologic nature of a traumatic injury has been shown to naturally induce osteoinductive factors such as BMP [21]. It may be important for a surgeon to understand this protein balance when considering which surgical patient should receive BMPs to promote positive outcomes and limit complications such as HO. The literature is limited regarding use of BMPs for femur fractures, and our case series adds to the available data on this topic.

Although the mechanism of acquired HO is still not fully understood, the literature has noted that more severe levels of muscular trauma can lead to an HO incidence as high as 64.6 % [22]. Therefore, we speculate that the patient in case 1 may have developed HO due to an intense natural upregulation of BMPs due to the severe nature of the trauma. The addition of more BMPs synthetically may have further upregulated this pattern and led to the debilitating postoperative HO. Although arthroplasty is also a risk factor for developing HO and the patient in case 2 previously had 4 of these procedures, the risk has been reported to be lower than intense trauma [23]. We believe that the extensive acute injuries experienced by the patient in case 1 may help explain their negative outcome.

The use of BMPs in orthopaedic surgery has grown in recent years, and surgeons may wish to continue using them to promote patient healing and bone growth. However, it may be important for surgeons to consider that most fractures heal without the use of osteoinductive factors [3]. Additionally, patient-specific factors and the mechanism of injury may have a crucial impact on their ability to heal and how they will respond to BMPs. It may be valuable for surgeons to consider that patients who sustain severe acute trauma already have a natural, acute upregulation of BMPs. Adding a high concentration of synthetic BMPs to the area may induce HO. Although BMPs are useful for healing when there is bone loss or when the patient has poor healing factors, they have the potential to lead to increased patient morbidity and should be used with caution. Overall, further investigation regarding the specifics of BMPs and their clinical indications may be warranted to elucidate the most appropriate cases that would benefit from their use. Additionally, it may be interesting to evaluate different subtypes of BMP for patients with femur fractures. Both patients in this study were treated with BMP-2, which has been shown to have a similar complication rate when compared with BMP-7 but a higher rate of radiographic healing and consolidation of nonunion for lower limb injuries [24,25]. Although the use of BMP-2 has been generally associated with positive outcomes, future research could focus on specific BMP subtypes that limit the formation of HO.

Ethics

The Prisma Health-Upstate Institutional Review Board reviewed the study and waived the need for IRB approval.

Consent to publish

IRB approval waived, no identifiable information was displayed in the study.

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Julia Anne Prodoehl: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft. **Yianni Bakaes:** Data curation, Investigation, Methodology, Project administration, Validation, Writing – review & editing. **Michael Tucker:** Conceptualization, Resources. **Frank Voss:** Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

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Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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