Recombinant Human Bone Morphogenetic Protein-2 (BMP-2): A Newer & Novel Osteoinductive Treatment Modality for Non-union of Bones.

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ABSTRACT

Background: The non-union of bones is a multifactorial phenomenon. In this study, it was emphasized to evaluate the efficacy and safety of bone morphogenetic protein-2 (BMP-2) as a bone-stimulating agent in the treatment of non-unions.

Methods: Fifteen patients [5 males, mean age 51.06 years (range: 21—75)] with sixteen non-unions were treated with BMP-2. There were eleven femoral non-union, three humerus, one ulna, one distal fibula non-union. The mean follow-up was 22.06 months.

Results: Both clinical and radiological union occurred in 15 (93.75%) non-unions cases. Radiological union achieved within a mean time of 15.75 weeks. The remaining one show incomplete union with recalcitrant formation was asymptomatic and having good pain free range of movement, declines further intervention. No complications or adverse effects from the use of BMP-2 were encountered.

Conclusion: In this study, it was observed that BMP-2 is a powerful adjunct and one of the safe armamentarium for the surgeon to handle difficult and challenging clinical conditions.

Keywords: Non-unions; BMP-2; Growth factors.

INTRODUCTION

Although there is a great advance in treatment of fracture and understanding of the fracture repair processes present today, impaired healing and non union continues to be one of severe complications of fracture, associated with pain and functional and psychological disability. Approximately 5% to 10% of the total 6.2 million fractures occurring annually in the United States are associated with impaired healing.¹

In the majority of aseptic non-unions the gold standard treatment is the mechanical stabilization with or without biological stimulation by using an autogenous cancellous bone graft.² However, the limited available quantity of autogenous bone graft, which is associated with donor site morbidity and complications, is a potentiate for further development and research to find out alternative methods of biological stimulation. The available alternatives, used either alone or in combinations, are the allergenic cancellous bone grafting, bone marrow injections, electrical, ultrasound, shock wave stimulation, bone graft substitutes,³ Bone morphogenic proteins (BMP) and platelet derived growth factors are biological response modifiers, which can also be used as a safe and efficacious alternative.⁴⁻⁶ BMPs are members of transforming growth factor-beta super family, which posses the great osteoinductive potential. They Induces Chondro-osteogenesis during bone formation by a sequential cascade of events resulting in fracture healing, chemotaxis proliferation of mesenchymal and osteoprogenitor cells and differentiation into the chondrogenic or osteogenic lineage.⁷⁻⁹

In this study, our purpose is to evaluate the safety and efficacy in the treatment of non-unions of various sites by using BMP-2 (off-label use).

MATERIALS AND METHODS

Duration of the study was from June 2010 to December 2014 in the orthopedic department of our...
tertiary care hospital. All the patients of non-union are treated with BMP-2 irrespective of their previous mode of treatment. Details such as demographic data location of non-union, initial and subsequent procedure performed, type of stabilization, methods of mobilization, applications of autologous bone graft, and postoperative complications were recorded.

Fifteen patients [5 males, mean age 51.06 years (range: 21—75)] with 16 non-unions were treated with BMP-2. There were eleven femoral non-unions, three humeral, one ulna and one distal end of the fibular non-union. One (6.25% of all fractures) was an open fracture (right supracondylar femur). However, prior to administration of BMP-2 of the skin condition of overlying non-union sites was completely healed. And there was no evidence of ongoing deep sepsis.

After discharge from the hospital, the patients were followed up in the outpatient orthopedic department with proper clinical and radiological assessment. The patient was declared to attend successful completion of treatment after both clinical and radiological unions at the fracture site. Clinical union was defined as the painless full range of motion, full weight bearing in the case of lower limb and no pain at the fracture site. Radiological union was defined as the presence of bridging callous of two cortices on two different X-ray views.

The mean follow up after the application of BMP-2 was 22.06 months (range: 6-49 months). Both clinical and radiological unions occurred in 15 (93.75%) non union cases. Radiological union achieved within a mean time of 15.75 weeks. The remaining one show incomplete union with recalcitrant formation was asymptomatic and having good pain free range of movement, declines further intervention. No complications or adverse effects from the use of BMP-2 were encountered. One of our patients developed redness & watering from the left eye, which was diagnosed as conjunctivitis by an ophthalmologist. Post operative superficial wound infection was observed in two patients, which was treated successfully with serial dressing and oral antibiotic in two of them.

**RESULTS**

Out of 51 patients, 41 (80.39%) were males and 10 The mean time of application of BMP-2 since injury was 8.87 months (range: 6-17 month). No further stabilization was performed in four non-unions as both pre-op radiograph & intra-op findings suggest a stable fixation. In rest twelve non-unions, further fixation was carried out at the time of application of BMP-2.

Both clinical and radiological unions occurred in 15 (93.75%) non union cases. Radiological union achieved within a mean time of 15.75 weeks. The remaining one show incomplete union with recalcitrant formation was asymptomatic and having good pain free range of movement in low demanding 52 yrs male. He was doing his daily routine activities and declines further intervention of any kind.

In our overall study, no systemic complications or adverse effects from application of BMP-2 were encountered.
Case-2: [Figure 5-8]
Supracondylar right femur fracture showing non union at the fracture site. It was treated with BMP-2 without implant removal or bone grafting. 3 month post-operative X-ray showing union.

Case-3: [Figure 9 & 10]
Shaft of humerus fracture (left) showing non union at the fracture site. It was treated with BMP-2 with exchange of implant without bone grafting. 3 month post-operative X-ray showing union.
Case-4: [Figure 11-14]
Subtrochanteric left femur fracture showing non union at the fracture site. It was treated with BMP-2 with implant exchange and autologous bone grafting. 3 month post-operative X-ray showing union.

Case-5: [Figure 15-18]
Distal humerus fracture (left) showing non union at the fracture site with implant failure. It was treated with BMP-2 with change of implant and autologous bone grafting. 3-month post-operative X-ray showing union.
DISCUSSION

Although there are great advances in treatment of fracture and understanding of the fracture repair processes present today, impaired healing and non union continues to be one of severe complications of fracture, associated with pain and functional and psychological disability.

As per the classification, different treatment methods or combination of methods are required. In case of hypertrophic non-unions, the provision of stable skeletal fixation generally results in union, as this type of non-union is well vascularised and usually reflects inadequate fixation. However, cases of atrophic non-unions are usually more difficult to treat, as they are indicative of a ‘poor biological environment’ of the non-union site. The probable causes may be inadequate vascularity of the fracture ends, poor bone-to-bone contact (bone loss, malposition, malalignment, soft tissue interposition, or distraction of the fracture fragments), or the existence of other contributing factors, such as malnutrition, smoking, NSAIDs, advanced age, medical co-morbidities; resulting in a very poor potential for bone regeneration.

The management requires a treatment strategy that employs both biological and mechanical augmentation, in order to maximize the regenerative response of such an impaired environment. The traditionally utilized gold standard biological stimulus is the autogenous cancellous graft, which contains osteogenic properties (osteo precursor cells), osteo-conductive properties (bone mineral and collagen), and osteo-inductive properties (growth and differentiation factors, including BMPs).

However the limited available quantity of autogenous bone graft, which is associated with donor site morbidity and complications, potentiate for further development and research to find out alternative methods of biological stimulation. The available alternatives, used either alone or in combinations, are the allogenic cancellous bone grafting, bone marrow injections, electrical, ultrasound, shock wave stimulation, bone graft substitutes, Bone morphogenic proteins (BMP) and platelet derived growth factors.

In this series of patients with upper limb and lower limb atrophic non-unions, recombinant BMP-2 was used for the stimulation of the ‘poor’ biological environment at the non-union sites. Depending on the adequacy or not of the existing method of mechanical stabilization at the fracture site. Fifteen patients [5 males, mean age 51.06 years (range: 21—75)] with sixteen non-unions were treated with BMP-2. There were eleven femoral non-union, three humerus, one ulna, one distal fibula non-union. The mean follow-up was 22.06 months. Both clinical and radiological union occurred in 15 (93.75%) non-unions cases. Radiological union achieved within a mean time of 15.75 weeks. The remaining one show
incomplete union with recalcitrant formation was asymptomatic and having good pain free range of movement, declines further intervention. No complications or adverse effects from the use of BMP-2 were encountered. In general, recombinant BMPs are components of the new biologically based strategies aiming to promote or facilitate the healing process. The development of such strategies was feasible because of the ongoing research in molecular medicine and molecular biology and our growing knowledge of fracture healing at the molecular and cellular level. New technologies in the field of tissue engineering, including stem cells genetically engineered to express BMPs & growth factors are also promising [12,13], showing to be capable of stimulating osteogenesis, but they still in their infancy with issues of Biosafety which need to be answered prior to clinical trials. Today, there is also a great deal of interest in the application of different types of BMPs and other growth factors, in a variety of complex orthopaedic conditions besides established non-unions. Such conditions embrace all those cases where the enhancement of bone repair is anticipated, including primary spinal fusion [14], acceleration of fracture healing, especially in patients at high risk for non-union [15], stabilization of implant devices [16,17], restoration of large segmental bone defects [18-20] and treatment of osteonecrosis of the femoral head. [21] It is expected that a lot of new developments are anticipated in the years to come regarding the treatment not only of fracture non-unions but also other complex orthopaedic conditions. As new advanced strategies are added to the surgeon’s armamentarium for the management of such difficult cases, continuous clinical studies presenting the results from their application are needed in order to evaluate continuously the efficacy and safety of these new treatment alternatives.

CONCLUSION

In this study, it was observed that BMP-2 is a powerful adjunct and one of the safe armamentarium for the surgeon to handle difficult and challenging clinical conditions.

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