Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

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

Vinod Agrawal[1], Saurav Narayan Nanda[2], Sanjay Tripathi[2], Munjal Satish Shah[2], Karmesh Lakhani[3], Aniruddha Agrawal[4], Himanshu Parmar[3]

[1]Consultant Department of Orthopaedics &Trauma, Lilavati Hospital and Research Centre Mumbai, India
[2]Resident, Department of Orthopaedics &Trauma, Lilavati Hospital and Research Centre Mumbai, India
[3]Fellow in Traumatology, Lilavati Hospital and Research Centre, Mumbai, India.
[4]Under graduate, Topiwala national medical college, Mumbai, India

Received: June 2016
Accepted: July 2016

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]

Name & Address of Corresponding Author
Dr. Saurav Narayan Nanda
Resident,
Department of Orthopaedics &Trauma,
Lilavati Hospital and Research Centre,
Mumbai, India.
E mail: saurav.scb@gmail.com

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 [3], 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.[4-6] Bone morphogenic proteins (BMP) and platelet derived growth factors are biological response modifiers, which can also be used as a safe and efficacious alternative. [7, 8]

BMPs are members of transforming growth factor-beta super family, which posses the great osteo-inductive potential. They Induces Chondro-osteo-genesis during bone formation by a sequential cascade of events resulting in fracture healing, chemotaxis proliferation of mesechymal and osteo-progenetor cells and differentiation into the chondrogenic or osteogenic lineage.[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.

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. 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.

Case-1: [Figure 1-4]

Supracondylar left 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.

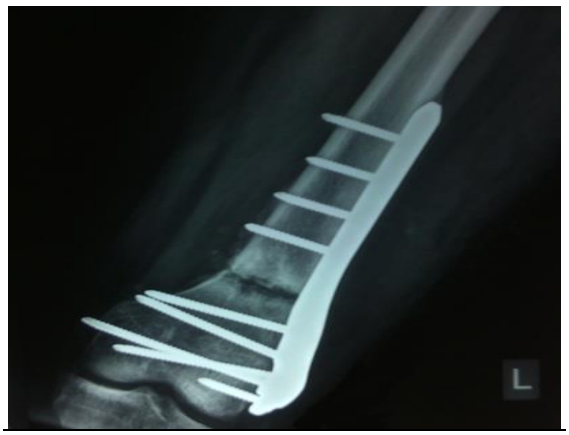

Figure 1: Pre- operative AP view.

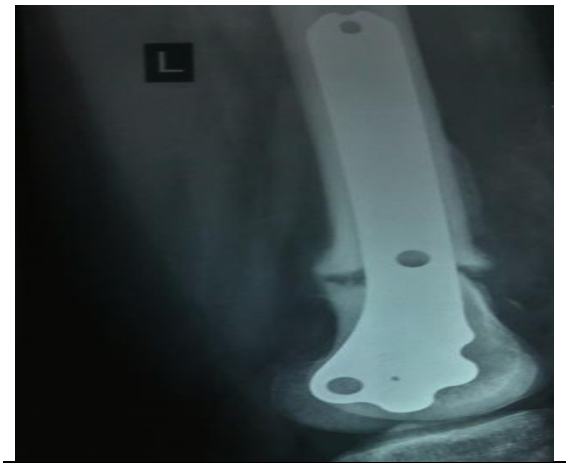

Figure 2: Pre- operative lateral view.

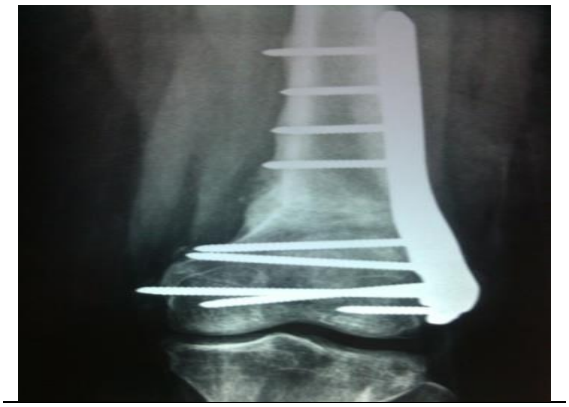

Figure 3: 3 month Post- operative AP view.

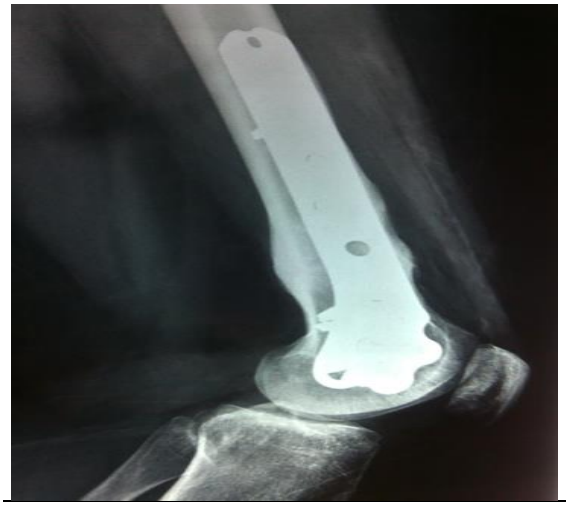

Figure 4: 3 month Post- operative lateral view.

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.

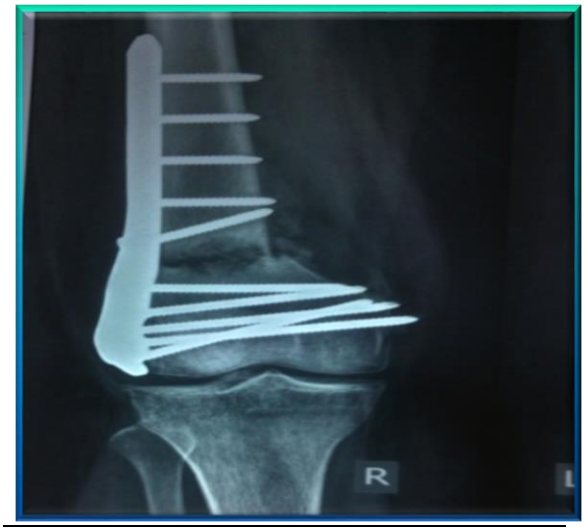

Figure 5: Pre- operative AP view.

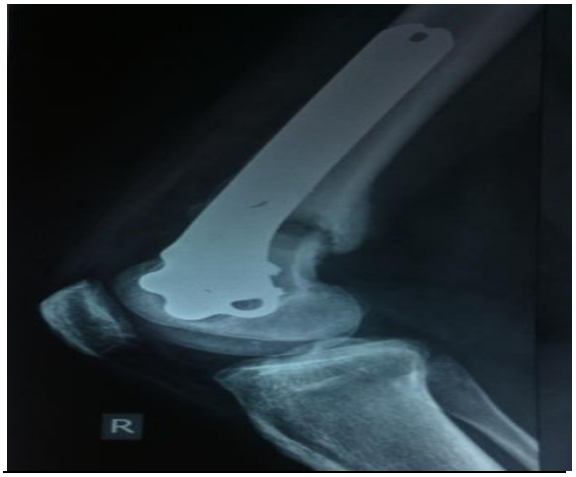

Figure 6: Pre- operative Lateral view.

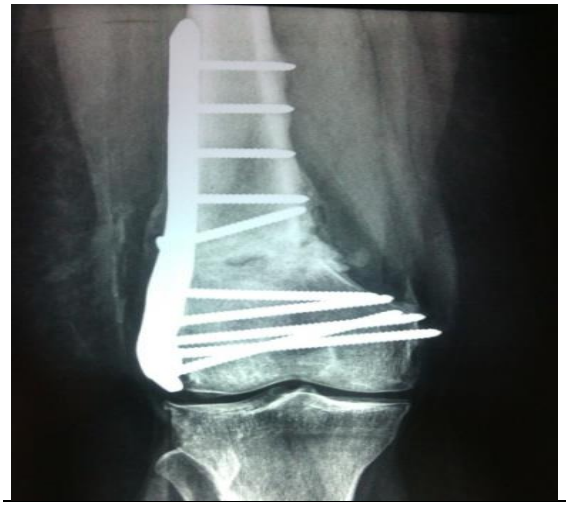

Figure 7: 3 month Post- operative AP view.

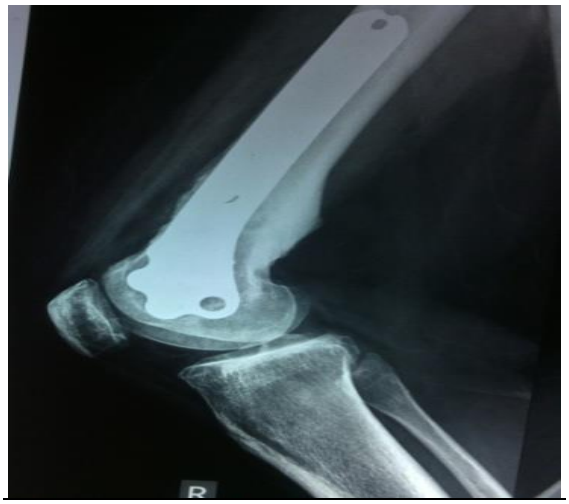

Figure 8: 3 month Post- operative Lateral view.

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.

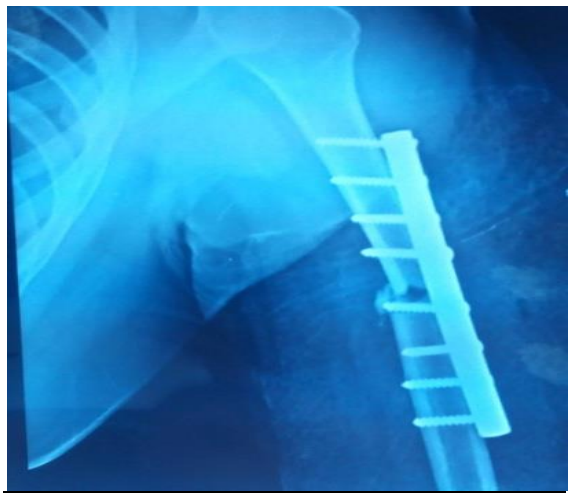

Figure 9: Pre- operative AP view.

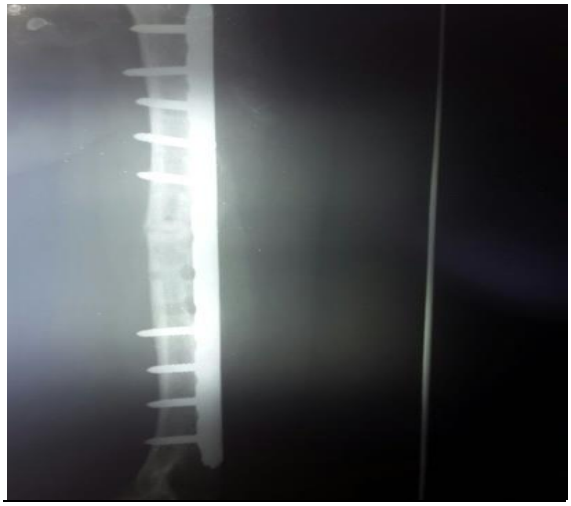

Figure 10: 3 month Post- operative AP view.

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 autologus bone grafting. 3 month post-operative X-ray showing union.

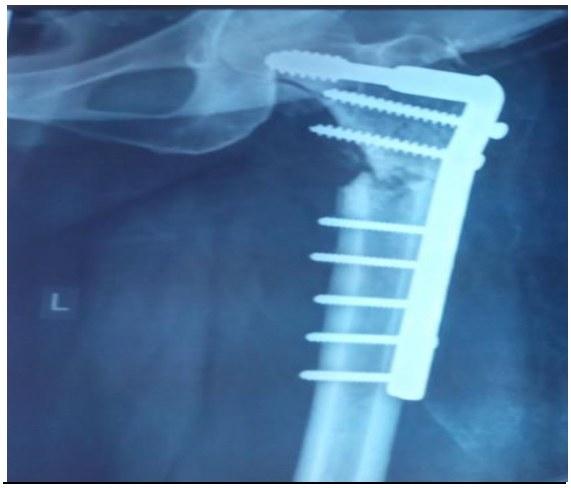

Figure 11: Pre- operative AP view.

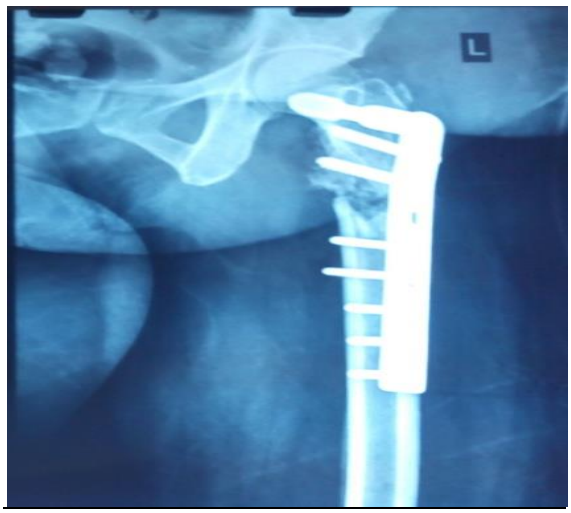

Figure 12: Pre- operative Lateral view.

Figure 13: 3 month Post- operative AP view.

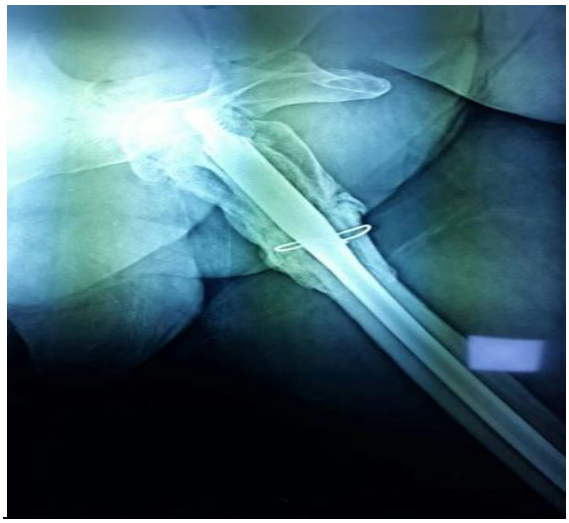

Figure 14: 3 month Post- operative Lateral view.

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 autologus bone grafting. 3-month post-operative X-ray showing union.

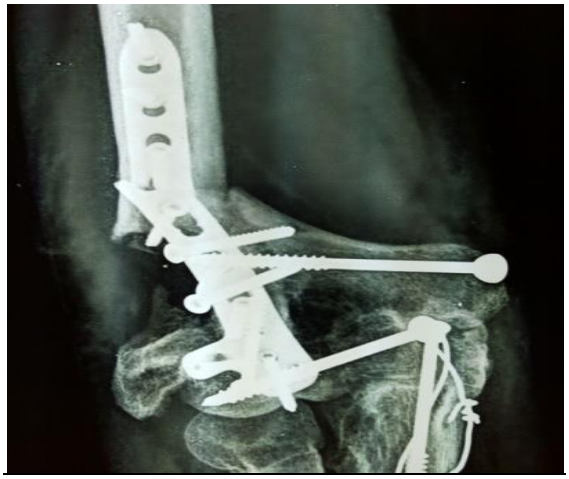

Figure 15: Pre- operative AP view.

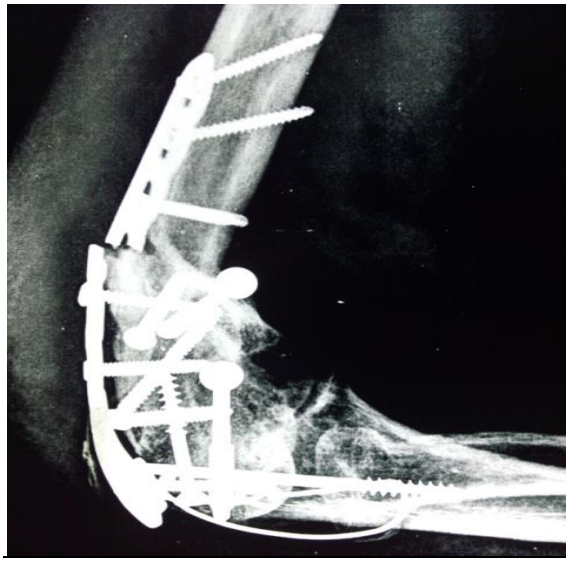

Figure 16: Pre- operative AP view.

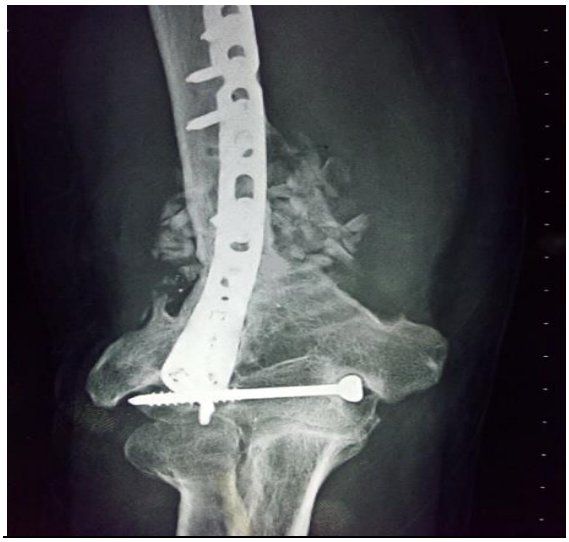

Figure 17: 3 month Post- operative AP view.

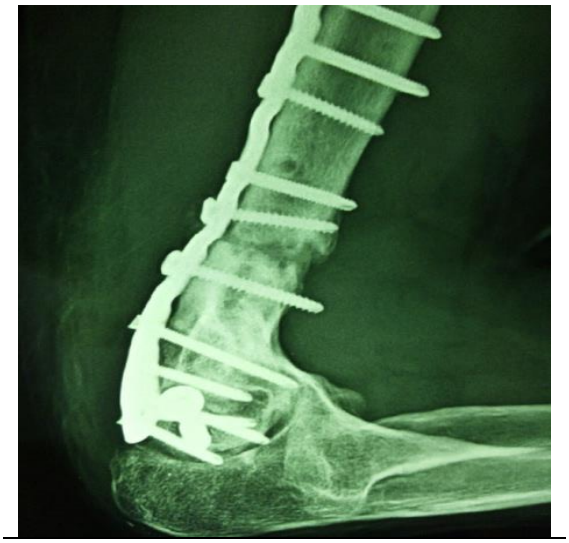

Figure 18: 3 month Post- operative Lateral view.

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.[2] 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.[2,10]

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).[11] However the limited available quantity of autogenous bone graft, which is associated with donor site morbidity and complications [3], 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 [4-6], Bone morphogenic proteins (BMP) and platelet derived growth factors.[7,8]

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.

Acknowledgements

No benefits have been received or will be received from any commercial party related directly or indirectly to the subject of this article in any form. No funds were received in support of this study in any form.

REFERENCES

1. Praemer A, Furner S, Rice DP. Musculoskeletal injuries. In: Musculoskeletal conditions in the United States. Park Ridge, IL: American Academy of Orthopaedic Surgeons. 1992 . pp. 85—124.
2. Brinker MR. Nonunions: evaluation and treatment. In: Browner BD, Jupiter JB, Levine AM, Trafton PG, editors. 3rd ed., Skeletal Trauma Basic science management and reconstruction, vol. 1, 3rd ed. Philadelphia: Saunders; 2003. p. 507—604.
3. Younger EM, Chapman MW. Morbidity at bone graft donor sites. J Orthop Trauma. 1989;3(3):192—5.
4. Bauer TW, Muschler GF. Bone graft materials. An overview of the basic science. Clin Orthop. 2000;371:10—27.
5. Brighton CT, Friedenberg ZB, Zemsky LM, Pollis PR. Directcurrent stimulation of non-union and congenital pseudarthrosis. Exploration of its clinical application. J Bone Joint Surg [Am]. 1975;57(3):368—77.
6. . Mayr E, Frankel V, Ruter A. Ultrasound——an alternative healing method for nonunions? Arch Orthop Trauma Surg. 2000;120(1—2):1—8.
7. Jimenez ML, Anderson TL. The use of allograft, plateletderived growth factors, and internal bone stimulation for treatment of recalcitrant nonunions. OTA 19th Annual Meeting; 2003 [abstract].
8. Johnson EE, Urist MR, Finerman GA. Bone morphogenetic protein augmentation grafting of resistant femoral nonunions. A preliminary report. Clin Orthop 1988;230:257—65.
9. Sakou T. Bone morphogenetic proteins: from basic studies to clinical approaches. Bone. 1998;22:591—603.
10. Giannoudis PV, MacDonald DA, Matthews SJ, et al. Nonunion of the femoral diaphysis. The influence of reaming and nonsteroidal anti-inflammatory drugs. J Bone Joint Surg [Br]. 2000;82(5):655—8.
11. Khan SN, Cammisa Jr FP, Sandhu HS, et al. The biology of bone grafting. J Am Acad Orthop Surg. 2005;13(1):77—86.
12. Musgrave DS, Pruchnic R, Bosch P, et al. Human skeletal muscle cells in ex vivo gene therapy to deliver bone morphogenetic protein-2. J Bone Joint Surg [Br]. 2002;84:120—7.
13. Peng H, Wright V, Usas A, et al. Synergistic enhancement of bone formation and healing by stem cell-expressed VEGF and bone morphogenetic protein-4. J Clin Invest. 2002;110: 751—9.
14. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27(23):2662—73.
15. Govender S, Csimma C, Genant HK, et al. BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) Study Group. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg [Am]. 2002;84-A(12):2123—34.
16. Bragdon CR, Doherty AM, Rubash HE, et al. The efficacy of BMP-2 to induce bone ingrowth in a total hip replacement model. Clin Orthop. 2003;417:50—61.
17. Zhang R, An Y, Toth CA, et al. Osteogenic protein-1 enhances osseointegration of titanium implants coated with periapatite in rabbit femoral defect. J Biomed Mater Res. 2004;71B(2):408—13.
18. Johnson EE, Urist MR, Finerman GA. Resistant nonunions and partial or complete segmental defects of long bones. Treatment with implants of a composite of human bone morphogenetic protein (BMP) and autolyzed, antigen-extracted, allogeneic (AAA) bone. Clin Orthop. 1992;277: 229—37.
19. Geesink RGT, Hoefnagels NHM, Bulstra SK. Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. J Bone Joint Surg [Br]. 1999; 81B: 710—8.
20. Salkeld SL, Patron LP, Barrack RL, Cook SD. The effect of osteogenic protein-1 on the healing of segmental bone defects

treated with autograft or allograft bone. J Bone Joint Surg [Am]. 2001;83-A(6):803—16.
21. Lieberman JR, Conduah A, Urist MR. Treatment of osteonecrosis of the femoral head with core decompression and human bone morphogenetic protein. Clin Orthop. 2004; 429: 139—45.

How to cite this article: Agrawal V, Nanda SN, Tripathi S, Shah MS, Lakhani K, Agrawal A, Parmar H. Recombinant Human Bone Morphogenic Protein-2 (BMP-2): A Newer & Novel Osteoinductive Treatment Modality for Non-union of Bones. Ann. Int. Med. Den. Res. 2016; 2(5):OR40-OR46.

Source of Support: Nil, **Conflict of Interest:** None declared