Original article

Long-term safety and efficacy of human bone morphogenetic protein (hBMP) in the treatment of resistant non-unions and failed arthrodesis

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ABSTRACT

The bone morphogenetic protein (BMP) has emerged as a suitable alternative to autogenous cancellous bone grafting and despite current knowledge about its mechanism; few studies provide evidence about the long-term safety of BMP. The aim of this investigation is to determine if BMP implantation is a safe and effective agent in a long-term setting for the treatment of patients with resistant non-unions and failed arthrodesis. This study is a retrospective case series study that was conducted on 55 patients who had received BMP. Collected data included all related surgical history, and clinical and X-ray data both pre-operatively and post-operatively. All patients were scheduled for follow-up evaluations at one week and 1, 3, 6, and 12 months post-operatively. Seven patients (13%) experienced adverse events related to their surgery with hBMP. Six patients (11%) experienced persistent non-union; five of these underwent further revision surgery. One patient (2%) developed an infected non-union. No patients experienced tumor induction, allergic reaction to hBMP. The remaining 48 patients achieved osseous union within six months of hBMP implantation. This study differs from previous studies that the use of hBMP is a safe and efficacious treatment method for resistant non-unions and failed arthrodesis in the long-term setting.

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1. Introduction

Long bone fusion and spinal arthrodesis both play an important role in the surgical management of degenerative orthopedic conditions, traumatic injuries, bony deformities, primary and metastatic bone tumors. Due to the high prevalence of non-union and mal-union associated with specific fracture patterns, a great deal of research has been geared toward finding methods to increase the rate of osseous union with the utilization of biological implants. One such implant that has received great attention over the past decades is bone morphogenetic proteins (BMP). BMP is an osteoinductive protein that was first discovered by Marshall Urist in 1965 and later extracted and synthesized through recombinant technology in 1979. BMP quickly gained favor due to its unique ability to induce chemotaxis of progenitor cells and induce differentiation and proliferation of mesenchymal cells into cartilage and bone-forming cells.^{1–5}

The landmark discovery of BMP by Urist marked a major turning point in the understanding of bone physiology, and has dually influenced the clinical management of resistant and delayed unions in orthopedic surgery. The current management for the majority of pseudarthrosis cases includes mechanical stabilization with various forms of internal or external fixation in addition to some form of a biological stimulation.⁶ Common methods of biological augmentation at the site of non-union include application of demineralized bone matrix, bone morphogenetic proteins, bone marrow aspirate, and the application of autogenous bone graft.⁷ BMP has emerged as a suitable alternative to autogenous cancellous bone grafting due to its ability to decrease the number of non-unions, risk of infection, and donor site morbidity. BMP is the only known inductive agent that will form De novo bone when experimentally implanted in an ectopic site in contact with mesenchymal stem cells (i.e. Hindquarter musculature of a rodent). This phenomenon was coined as “Osteoinduction” by Dr. Urist as noted in his seminal article entitled “Bone: formation by auto-induction.”¹ Since BMP is now being synthesized in the lab, there is unlimited supply of it in contrast to the finite autogenous bone graft.^{7–9} Furthermore,

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Table 1
Patients' demographics.

Demographic	Patients	Age (mean)	Sex		Type of non-union		Type of Received BMP		
			Male	Female	Aseptic	Atrophic	ICBG ^a & BMP ^b	BMP alone	
Number	55	47 (11–84)	23	32	55	55	23	55	
BMP implantation site	Femur	Humerus	Tibia	Carpal bone	Clavicle	Ulna	Radius	Phalanx	Spine
Number	33	5	4	4	1	2	1	1	4

^a Iliac crest bone graft.

^b Bone morphogenetic protein.

previous research has demonstrated the ability of BMP to augment the use of autogenous bone graft for fracture fixation in non-unions.¹⁰

The osteoinductive properties of BMP have been well documented to not only enhance the amount of new bone formed, but to increase the rate at which fracture healing occurs.^{2,11,12} As a result, the use of BMP in bone fusion and spinal arthrodesis continues to increase in volume. Despite substantial current knowledge about the mechanism of BMP, few studies provide evidence about the long-term safety of BMP. The aim of this investigation is to determine if BMP implantation is a safe and effective agent in the treatment of resistant non-unions and failed arthrodesis in a long-term setting. This retrospective study looks at the results of 55 patients with resistant non-unions and failed arthrodesis that was treated at UCLA with human bone derived BMP (hBMP).

2. Methods

2.1. Study design

An IRB approved retrospective case series was conducted on 55 patients who had received a combination of hBMPs in allograft bone that had been demineralized between 1987 and 1998 at UCLA Medical Center. The study data includes pre-operative and post-operative clinical data, radiographic data, and all related surgical history as collected by the four primary surgeons.

2.2. Study criteria

Patients included in the study had prior attempt at fracture fixation or spinal fusions with standard measures that resulted in aseptic, atrophic non-union, or pseudarthrosis at the fracture site. Non-union was determined by the surgeons, and was defined as (1) motion at the fracture site, (2) persistent pain at the fracture site, (3) absence of bridging bone in the long bones, or (4) lumbar spine X-rays on at least two views upon radiographic examination greater than six months after the initial operation. Patients with signs of active systemic infection and known sensitivity to collagen were excluded from the study.

2.3. Demographics

The 55 patients who received hBMP included 32 women and 23 men. The average age at time of hBMP use was 47 years (range: 11–84 years). The 51 cases of non-union included: 33 femurs, 5 humeri, 4 tibias, 4 carpal bones, 2 ulnae, 1 radius, 1 distal phalanx, and 1 clavicle (Table 1). All 4 cases of failed spinal arthrodesis included revision of posterior lumbar fusion. Patients with implants had the implants revised, if deemed necessary, during surgery with implantation of hBMP. The simultaneous use of autogenous iliac crest bone graft (ICBG) with the hBMP was determined at the surgeon's discretion.

2.4. Graft material

The Human Bone Morphogenetic Protein, non-collagenous proteins (hBMP/NCP) implants were prepared as described in previous studies.¹ All human bone tissues were harvested in accordance with the guidelines of the American Association of Tissue Banks and then used to prepare hBMP/NCP and Autolyzed, Antigen-extracted, Allogeneic (AAA) bone. AAA bone was then immersed in a solution of hBMP/NCP (5 mg hBMP/NCP per 1 g AAA), which adsorbed the solution. Then the implant as a whole was lyophilized. The implants were then sterilized using one cycle of ethylene oxide in accordance with the standards of the University Medical Center at which the studies were performed. Prior to adsorption to the AAA strips, each batch of hBMP was tested for bioactivity in the hindquarter muscle of rodents as previously described and validate. The non-inductive batches were not used in this experiment. The standard 10 cm in length prepared strips of implant were then cut to size or morselized in the operating room to meet the specific patient needs. HBMP/NCP capsules were also used in several cases by implantation in the bony defects as needed. Afterwards, 25 mg of hBMP was placed in each size 4 gelatin capsules and sterilized with one-cycle ethylene oxide fumes prior to implantation.

2.5. Post-operative course and outcomes

All patients in the study were scheduled for follow-up clinic evaluations at 1 week and 1, 3, 6, and 12 months post-operatively. After the evaluations, patients were instructed to return on a yearly basis or if they developed an adverse event related to the operation. The follow-up endpoint was determined by (1) the last time in which the patient was evaluated prior to discharge or being lost to follow-up or (2) the time (months) between surgical fixation with the utilization of hBMP and the development of an adverse complication. To assess the safety and efficacy of hBMP use, the following complications were identified at follow-up visits using clinical examination and radiographic assessment: (1) persistent non-union or failed spinal arthrodesis, (2) malignancy, (3) wound infection, (4) allergic reaction to hBMP, and (5) hematoma or seroma at the site of hBMP implantation.

3. Results

All of the patients participating in the study reached a minimum follow-up time of 12 months. The average follow-up time was 84 months (7 years; range = 12–256 months). All patients who reached only 12 months of follow-up were either lost to follow-up or experienced an adverse event related to their previous surgery. 23 of the 55 patients (42%) received iliac crest bone graft in addition to the hBMP (Table 2).

Of the 55 patients, seven (13%) experienced adverse events related to their surgery with hBMP; one patient (2%) developed an infected non-union, which was treated with removal of hardware, revision surgery, and a course of antibiotics; and six patients (11%)

Table 2
Adverse events.

Adverse event	Fracture Site	Procedure	Sex	Age (years)	Follow-up (months)
Persistent non-union	Scaphoid Bone	Open reduction and internal fixation of scaphoid non-union with implantation of ICBG and hBMP ^a	Male	31	12
	Femur	Removal of locked IM nail; femoral shaft lengthening using 16-hole 60 mm 95 fixed angled blade plate; implantation of ICBG ^b and hBMP	Female	38	12
		Removal of interlocking nail; debridement of devitalized bone; placement of 14-hole 70-mm fixed-angled blade plate; implantation of ICBG and hBMP	Male	27	12
	Clavicle	Removal of failed hardware and take down of clavicle non-union; retensioning and relengthening of clavicle non-union with plating using 8-hole AO pelvic reconstruction plate; implantation of ICBG and hBMP	Female	25	12
	Humerus	Proximal humerus removal of hardware; open reduction and internal fixation using AO eight hole T-plate with 6.5 screws, 4.5 screws, and tension band wiring; implantation of ICBG and hBMP	Female	58	12
Pseudoarthrosis of the tibia ^c	Tibia	Removal of plate from tibia; resection of non-union; Nonreamed rodding of tibia with implantation of ICBG and hBMP.	Male	11	12
Wound infection ^d	Ulna	Ulna hardware removal; excision of proximal ulna; total elbow replacement with cryopreserved osteoarticular elbow; olecranon osteotomy and extensor mechanism repair; implantation of ICBG and hBMP	Male	36	15

^a Human bone morphogenetic protein.^b Iliac crest bone graft.^c Requiring below-knee amputation.^d Requiring removal of hardware.

experienced persistent non-union. Five (9%) underwent further revision surgery with hBMP that subsequently resulted in successful union. One of the five patients required a below the knee amputation. In addition to pain and instability at the fracture site of these patients, persistent non-union was determined by absence of adequate bony callus on radiographic assessment. In this study, there were no patients that experienced tumor induction, allergic reaction to hBMP, or development of a hematoma or seroma at the hBMP implant site. Of the remaining 48 patients, all achieved successful osseous union at the fracture site within 6 months following surgery and implantation of hBMP (Table 2).

4. Discussion

This retrospective case series was conducted to provide further information about the long-term safety profile and efficacy of hBMP. Currently, the literature in regards to the safety of hBMP in a long-term setting is limited. We are able to add to the growing body of hBMP literature by providing information about the long-term outcomes of fracture fixation with hBMP supplementation by utilizing the fact that a great deal of the early research and use of hBMP took place at UCLA Bone Research Lab under the direction of Dr. Marshall Urist. The ability of bone morphogenetic proteins to improve the local biology at the site of atrophic non-unions through its osteoinductive capabilities has been ascertained in both animal^{13,14} and clinical trials.^{2,3,6,15} Several preclinical animal studies have demonstrated that hBMP can be used safely with few, if any, deleterious effects.^{13,16–18} This early work with animal models contributed to the progression of use of hBMP in clinical trials, which have also shown to be promising. As a growing strategy for the management for the treatment of resistant non-unions, it is essential to determine the efficacy and safety profile of hBMP.

It is important to note that hBMP used in this study represents a cocktail of various isotopes of the BMP family, which is a part of the TGF- β superfamily. More specifically, hBMP represents the two commercially available isotopes rhBMP-2 and rhBMP-7 along with various other BMPs present in the hBMP/NCP mixture produced at the UCLA Bone Research Lab. Furthermore, the patients who were selected for hBMP implantation had all failed one to two prior

surgeries which make it difficult to treat pseudarthrosis and signals failed arthrodesis.

Vaccaro et al.,¹⁶ showed that rhBMP-7 (recombinant human BMP) was safe in the intermediate term, with a mean follow-up time of 48 months. In this study there were no incidents of local or systemic toxicity, ectopic bone production, or other adverse events in patients being treated for degenerative spondylolisthesis with uninstrumented fusion and application of rhBMP-7.

Additionally, studies directed specifically at the use various recombinant BMPs have failed to show an association with the development of tumor induction, systemic toxicity, or allergic reaction to BMP in a short-term or intermediate-term follow-up period.^{2,6,8,10,12,14,16–19} Furthermore, several studies have shown that the use of hBMP in the treatment of non-unions and acute open fractures may be associated with a decreased risk of infection compared to control groups.^{7,12} Although the mechanism for this has not been fully elucidated, researchers suggest that this may be linked to the positive effect that BMPs exert on the local cellular environment and the vascularity by stimulating angiogenesis at the fracture site.

Despite being in accordance with previous studies in terms of the safety profile and efficacy of hBMP, this study differs by providing data that supports the notion that the use of hBMP is a safe, non-toxic, and efficacious method for resistant non-unions in the long-term setting. With a mean follow-up time of 84 months, this study stands alone in assessing the long-term potential sequelae associated with hBMP use. Furthermore, in our case series we did not see any evidence of tumor induction arising from the use of hBMP in our patients.

4.1. Limitations

The nature of this study being an observational, retrospective, uncontrolled study limits the level of evidence that is represented here. Other factors such as the mechanism of injury, extent of soft tissue damage, patient comorbidities, and other risk factors for poor healing of the patients in this study were not discussed. Having this information more readily available may prove to be useful in determining which patients are more likely to have a successful outcome and a lower risk of complications. In addition,

our study did not have the information for blood test and did not assess the functional outcome of patients after they attained union at the fracture site. This would have contributed to creating a more detailed picture of the clinical benefits associated with hBMP use.

5. Conclusion

In conclusion, this study reinforces the view that BMP is a clinically safe and effective implant to use with positive long term results without any evidence of tumorigenesis. The cornerstone of successful bone healing rests on improving current strategies aimed toward both the biomechanical stability of bone, and the biological vitality of bone, albeit in a safe manner. This study contributes to the latter. Although this osteoinductive material remains to be a costly implant, it has shown to have great clinical utility in patients with resistant non-unions and failed arthrodesis. Using hBMP in a judicious fashion can be an effective solution to avoid the limitations and co-morbidities associated with other bone grafts and bone graft substitutes.

Conflicts of interest

The authors have none to declare.

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