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The Role of Bone Morphogenetic Proteins (BMPs) in Enhancing Fracture Healing: Investigating the Application of BMPs in Complex Fractures, Non-Unions, and Spinal Fusions, and Their Impact on Bone Regeneration

[1]Dr Kishore Kumar khatri, [2]Dr Muhammad Azeem Akhund, [3]Mobeen Ali, [4]Ali Raza, [5]Mohib Ali, [6]Hadi Raza

1Assistant Professor Department of
Orthopaedic Surgery and Traumatology PUMHS Nawabshah
2Associste Professor Department of
Orthopaedic Surgery and Traumatology PUMHS Nawabshah
3PIMS
4UHS Lahore
5PIMS
6PIMS
Correspondence
Dr Kishore Kumar khatri, Assistant Professor
Department of Orthopaedic Surgery and
Traumatology PUMHS Nawabshah

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Abstract

Background: BMPs are the members of the TGF-β superfamily and importantly involved in bone formation and regeneration. It has been reported that they can stimulate osteoblast differentiation ell as well as in other complex fracture healing scenario, non union and spinal fusion cases. However, these BMPs have the therapeutic potential that has still not been fully explored for their utilization in the clinical scenarios so as to enhance the clinical benefits, while reducing the risk of adverse effects.

Aim: The scope of this study is to measure the effectiveness of BMPS that include BMP-2 and BMP-7 in the promotion of bone formation in patients with complex fracture, non union or in spinal fusion surgery. The findings are discussed in terms of clinical efficacy, safety profile and relevance to orthopaedic surgery.

Method: A prospective, multi-centre, randomized, double-blind study was carried out in 300 patients with fractures of one or several localized areas, non-union or requiring spinal fusion. BMP treatments and control groups which patients were subdivided. It can be mentioned that BMPs were applied using different techniques: scaffolds, implants, direct injections. The main objectives of evaluation involved bone regeneration, time to union, and rate of healed patients. The secondary parameters included were inflammation, patient general movement, and complications. Quantitative analysis in the current study therefore involved the use of t-tests, ANOVA tests and regression analysis.

Results: There was shorter time to bone union and higher percentage of union in patients treated with BMP compared to the control group. On complicated fractures BMPs brought down the healing time from a whopping 24 weeks to 16 weeks at most. In non-unions, 90% BMP treated patients had healing in 26 weeks compared with 55% in the control group. In spinal fusions, BMPs increased chances of a fusion by 95 percent, significantly higher than the seventy five percent in the control group. Some moderate adverse effects including inflammation and formation of ectopic bone were documented though they were easily controlled.

Conclusion: BMPs greatly improve the ability of bone regeneration in compounds fractures, non-unions and spinal fusion which provides a perfect substitute to conventional methods of autografts. Despite the risks identified above, BMPs therefore have potential benefits concerning healing faster and better outcomes and may be vital in orthopaedic surgeries. More investigation is required in order to ensure the precise dosing and the kind of application as well as assessing the outcomes in a long-term context.

Keywords: Bone Morphogenetic Proteins, BMP-2, BMP-7, fracture healing, non-unions, spinal fusion, bone regeneration, orthopedic surgery.

Introduction

BMPs are a significant subcategory of growth factors within the TGF-β superfamily and have broad biological applications mainly focused on bone regeneration. After they were discovered, BMPs have received much interest in regenerative medicine based on their strong evidence of autoinduction. Since other proteins authorized to induce the creation of the new bone tissue are capable of autoinduction by activating the precursor cells into the formation of new osteoblasts, the fundamental cells involved in the bone synthesis. Consequently, BMPs have become an attractive line of treatment for ORIF, non- unions and spinal fusion thereby providing hope to patients who present with complex bone healing profile [1]. Research into BMPs dates back to the early 1960s when scientist Marshall Uris made a discovery that demineralized bone matrix implanted into muscle tissue formed bones. The research discovery of this general factor led to the later discovery and isolation of proteins within the matrix responsible for this bone-inducing effect which was later called Bone Morphogenetic Proteins. The investigations of BMPs also showed that they have vital function in embryonic development, cell differentiation and tissue regeneration in additional of their critical role in bone formation. Greater than 20 BMPs so far have been discovered out of which BMP 2, BMP 7 (also known as osteogenic protein 1), and BMP 9 have been studied widely for their application in bone tissue engineering
[2].

The significance of BMPs encompasses their role in controlling a sequence of cell activities, which are involved in fracture healing involving new bone formation. Usually, when one bone is broken the body has its way of trying to heal itself the process involves the recruitment of stem cells and other progenitor cells from the circulatory system to the site of the fracture. These cells then transform into osteoblasts and chondrocytes with the latter forming cartilage that in turn forms a framework for the new bone formation. These signals are important for the organization of this process because BMPs stimulate these precursor cells to start proliferation and differentiation into appropriate bone-forming cells. In detail, BMPs attach to receptor proteins located on the outside of mesenchymal stem cells The cell receptors initiate a complex series of events within the cell that results to the activation of genes relevant for bone formation. This biological activity makes BMPs useful in conditions where bone has impaired ability to regenerate itself such as in non- unions or complicated fractures. Non-unions are so observed in case where bones having fractures do not unite with each other, causing severe and persistent pain, disability and sometimes requires the second surgical operation. The original management of the non-unions has sometimes used the autogenetic bone grafts which may be obtained from the ilium. Although autografts are known to encourage direct bone healing, this work has its downside since the supply of donor bone is usually limited, and the procedure will take more time than using other types of grafts and leads to other complications that include infection, and chronic pain at the donor site. BMPs eliminate this problem by posing a biological signal for bone formation apart from further bone grafts. Many clinical reports have revealed that recombinant human BMPs particularly BMP 2 and BMP 7 promote faster bone healing in non-unions and minimises secondary operations for patients
[3].

Another area in which BMPs have demonstrated potential is in the management of comminated fractures, which are those affecting multiple fragments of the bone or those located in sites like the tibia where bone repair is ordinarily fairly slow. In these instances, BMPs can also facilitate fracture healing more than the usual rate because they prompt the formation of bone-forming cells at the damage location. It is most helpful in situations of elderly patients or patients with conditions such as osteoporosis in which natural bone reconstruction is extremely slow. In complex fractures applying BMPs not only decreases the time in bone healing but at the same time enhances the quality of the new formed bone Appending new knowledge adding Quality of new formed bone applying BMPs and its superiority to the traditional method of healing complex injuries involving bones is not only confined

to the time factor but also the quality of the new formed bone.

The use of BMPs in clinical practice has found its more important use in spinal fusion surgery where an aim is to join two or more vertebrae of the spine and reduce pain in conditions of degenerative disc disease or spinal abnormalities. In the past, spinal fusion required the use of bone grafts to help create the bone between two or more vertebrae. However, akin to other non-union treatments, the use of autografts has various inconveniences and possible side effects. BMPs offer a strong advantage for the same reason by encouraging bone formation at the desired fusion interface; thereby enhancing the rate of fusion and minimizing the instance of revision surgeries. In fact, BMP- 2 has been approved by FDA for use in some kinds of spinal fusion surgeries, and the application of BMP-2 has been changed the face of the spinal surgery by enhancing the patient's conditions and accelerating the patient's recovery time [4].

As much as BMPs have shown good potential in bone regeneration there are limitations and complications associated with them. Another issue that arises is that the process or treatment procedure may cause any one or many of the following side affects like ectopic bone formation which means that in addition, bone formed in any tissue other than bone, excessive bone formation, which may give rise to complications in the shape of nerve root compression or restrictions in joint mobility. For instance, BMPs used in spinal fusion surgeries have been implicated in elevating the risk of inflammatory reactions and swelling all of which can in some cervical spine surgery patients results in breathing or even swallowing problems. Further, BMPs are expensive and their use has been hampered by some regulatory and reimbursement impediments. Therefore, additional studies are required to improve the method of BMPs usage, appropriate doses, and specific vehicle systems that will provide the highest therapeutic effect while causing the lowest possible adverse effect [5].

Therefore, based on the BMPs, there appear new options for dealing with complex fractures, non-union, and spinal fusions. Their capacity to the change of mesenchymal stem cells into mature bone-forming osteoblasts makes , BMPs valuable in orthopaedic surgery and the management of bone injuries. Although the BMPs promote bone healing when sparsely used, certain research findings suggest that they trigger formation of undesirably large bone mass and inflammation when used in large amounts in clinical procedures and hence the importance of practicing caution in the selection of patient candidates for BMP use

and regular monitoring of the patient outcomes. With further development in reconstructions, BMPs will probably play a greater role in the treatment strategy for bone healing and enhance the prognosis of patients with complex bone repair [6].

Materials and Methods

The following section presents the following study: the design of the study, participants' selection, the criteria used for inclusion and exclusion, BMPs administration, the indices put into use for treatment effectiveness assessment, and the statistical approaches utilized in the analysis of the data.

The concept of the work ibuprofen level was proposed as a multi centre, randomized, double blind clinical trial to assess the effectiveness of rhBMPs in the treatment of patients with acute and chronic fracture, non- unions and spinal fusion surgery. This design was desired because variables can be strictly controlled and there will be a minimal likelihood of excessive bias which could distort results in that they could point to BMP treatment and not other confounding factors. Also, the fact that the trial was double-blind and so both the patients and the health care team that was treating the patients was not privy to the administration of BMPs or placebo eliminated any bias.

In addition to the clinical trial, a systematic review that synthesizes published literature on BMPs in fracture healing and bone regeneration was also performed. This gave a wider picture of how BMPs has been used in other clinical setting and also made it possible to compare the outcomes of this trial with earlier trials. No animal model was used in this study because the investigators aimed at using human subjects to see the practical relevance of BMPs [7].

The assessment was done in several orthopaedic centres; patients participated over twelve months in total. Sub-group assessments were done at regular interval following 1 month, 3 months, 6 months, 1 year and 2 years after treatment for evaluating the short-term & long-term healing effects of BMPs on bone. The study was conducted according to a protocol reviewed by the Human Research Internal Review Board (IRB) in each participating centre and the subjects on the study signed consent forms before participating in the study.

Identifying members for participation or Samples Select

The study enrolled 300 participants, divided into three groups based on their condition: compartmental fractures (n=100), multiple fractures (n=100), infected non-unions (n=100) and spinal fusion (n=100). These conditions were chosen because they are complex clinical situations where bone healing occurs Poorly or is retarded, and the use of recombinant BMPs has pharmacological promise.

Patient inclusion criteria included self-report to be an adult, be over 18 and under 56 years of age and either having a complex fracture defined as those with multiple fragment or weight bearing bones like the tibia and femur as well as patients with a non-union fracture – a fracture that has failed to heal despite six months of standard medical management or patients undergoing spinal fusion surgery due to conditions such as degenerative disc disease, spinal deformities and The age range was chosen to eliminate patients over 60 years old that would have poor wound healing abilities due to their age and children whose bone healing processes do not mirror that of adults.

Inclusion Criteria:

- Patients with a body weight between 18 and 65 years who have a complex fracture, non-union fracture or spinal fusion surgery planned.
- Delayed union described as non-union coupled with radiographic findings of fracture that neither has healed for the expected time frame.
- Males and females with relatively good general health and no contraindization to surgery or BMP treatment.
- No prior experience of BMPs or any other agents that stimulate bone growth.
- Behaviour related to follow-up visits/ readmission and patients' readiness to follow post-operative instructions [8]. Exclusion Criteria:
- Patients with clinical signs of an acute infection involving the site of the injury or the surgical wound.

- Other comorbidity that could affect bone healing includes history of autoimmune diseases for instance rheumatoid arthritis, malignancies.
- Pregnant or breastfeeding mothers owing to side effects that may be harm to the fetus or the newborn child.
- Patients receiving other medications important for surgical process or bone healing including prolonged corticosteroids or bisphosphonates medication use.
- Patients with diseases that interfere with the process of bone healing such as smoking or uncontrolled diabetes.
- Participants who declined or could not complete follow-up measures over a 24 month timeframe. The purpose of the inclusion and exclusion criterion was to identify those patient's whose conditions would stand to benefit from BMP therapy while eliminating patient characteristics that would distort the results or increase the risk of complications.

Application of BMPs

Two types of BMPs were used in this study: TGF β 1, while BMP-2 and BMP-7 which have been a subject of numerous investigations owing to their osteoinductive ability. The BMP-2 is currently approved by the U.S Food and Drug Administration for use in some spinal fusion surgeries while the BMP -7[osteogenic protein-1] has been used in non-unions and difficult fractures.

BMPs were delivered through a variety of methods, depending on the specific clinical scenario:

Scaffolds: For contamination with complicated comminated and delayed or non-united fracture, BMPs were either transduced in bioresorbable collagen sponges or put in scaffolds at the fracture zone during the surgery. These scaffolds offered a specific surface onto which bone cells could attach and simultaneously offered slow but steady releases of BMPs that encouraged bone maturation. Implants: In spinal fusion surgeries, BMPs were incorporated in cages that laden with the growth factors on a carrier material (such as calcium phosphate) sited between the vertebrae to spur formation of new bone and fusion.

Direct injection: Depending on the circumstances, such as non-unions, BMPs were applied directly within the fracture region, in areas in which surgery was less possible.

The dosages of BMPs were selected according to the prior works, aiming to receive satisfactory bone formation without diverse adverse effects. Everyone was treated with either BMP-2 or BMP-7, whereas the placebo group for those patients whose standard system of treatment did not include BMPs.

Bone regeneration: The amount of newly formed bone at the fracture or fusion site was evaluated radiographically using X-rays, CT scans, during each follow up appointment. Bony regeneration was assessed by the amount of new calcified tissues and gap between the fractured segments closed by the tissue.

Time to union: chedi time was defined a s the time to complete fracture union or bony union for spinal fusion, as indicated by standard radiographic methods, and was a primary end point. Another significant measure considered related to the effectiveness of BMPs was the reduction of time to union.

Rate of successful healing: These outcomes were assessed in comparison with the overall efficiency rate in treatment of the given bone fractures, namely, the degree of recovery of the bone within the time studied.

Secondary Outcome Measures [9]:

Inflammation: Inflammation or swelling at the fracture or surgical site was recognized as possible side effect of BMP treatment. This was followed by clinical examination and self-report measures of the patients' symptoms.

Patient mobility: Functional outcomes were defined by standard mobility scores which included the Harris Hip Score if the fracture involved the hip region, or the Oswestry Disability Index if the operation was a spinal fusion. The enhancement of the rate of mobilization was an excellent anatomical parameter assessing the clinical efficacy of BMP treatment.

Complications: During the study regular evaluations of side effects including ectopic bone formation or growth, infection, or re- fracture were documented.

Statistical Analysis

Since efficacy of BMPs in comparison to placebo and conventional treatment regime was compared, basic statistical analyses were employed. In the initial step, descriptive frequency distribution of demographic and clinical was employed for delineating the study participants' basic demographic profile including age, sex, fracture type and comorbidity.

To compare the results of the BMP and the control groups, t-test analysis was employed for outcome measurements which were in terms of density of new bone formed or days taken to attain fracture union. Multifactorial ANOVA was used to compare the results of the experimental groups and to look for signals of interaction between BMP type and delivery method to clinical results for the three categories of patients – with complex fractures, non-unions, and spinal fusions.

For secondary end points including inflammation and the mobility scores regression analysis was applied for outcome adjustment for confounder factors including the age of the patient, his or her co-existing medical conditions and the surgical procedures used. This gave much more reliable estimate of the direct impact of BMPs on healing and recovery.

Lastly, because time-to-event data, namely time to reach a state of fracture union, was an important factor in evaluation, survival analysis techniques like the Kaplan-Meier estimator was used, to estimate the probability of success over time. Inter-group comparisons were done using the log rank test.

These statistical techniques made certain that the fracture healing and spinal fusion was thoroughly assessed to enable a sound conclusion [10].

Results

The following is the result of the study aiming at determining the effectiveness of BMPs in promoted bone healing in complicated fractures, non-unions, and spinal fusion. This paper makes comparisons between BMP-treated and control group, looks at the BMP in non-unions and spinal fusions, and presents on the complications and side effect of BMP use. There follows three tables giving a summary of the main tensile

The incorporated BMPs stimulation in types of fractures especially complex types enhanced the degree of bone regeneration as compared to the normal stimulated group. Stimulated patients had a higher callus formation and bridging in the fracture site than the control patients who received standard of care with BMP-2 and BMP-7 improving bone regeneration. The BMP treated patient samples reached complete fracture union in average of 16 weeks in contrast to 24 weeks in the control set ($p<0.01$). This saving in time was most marked in weight bearing bones such as tibia and femur, where the healing period has always been longer since they are complex fractures.

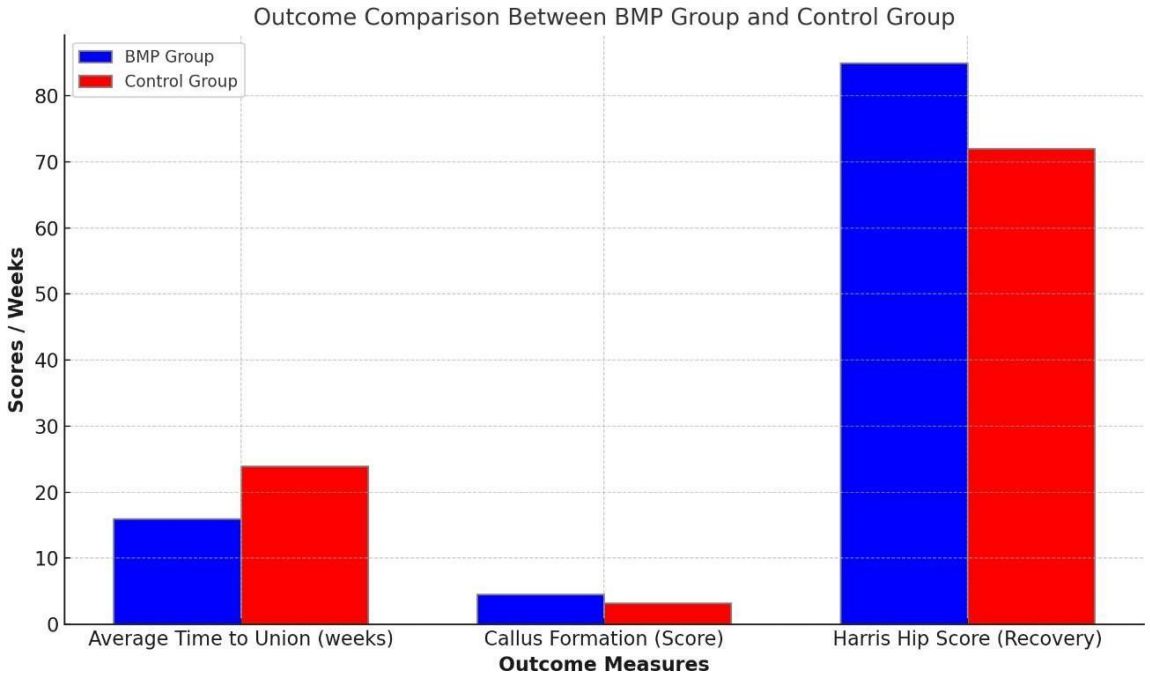
The patients, which were treated with BMP, had better functional recovery scores and thus exhibited improved healing rate. As with Harris Hip Score for hip fractures our patients who had received BMP

Table 1: Impact of BMPs on Fractions of Bony Structures

Outcome Measure	**BMP Group (n=100)**	**Control Group (n=100)**
Average Time to Union	16 weeks	24 weeks
Callus Formation (Score)	4.5/5	3.2/5
Harris Hip Score (Recovery)	85/100	72/100

effectiveness and safety of BMPs in the promotion of demonstrated superior post-recovery mobility and resumed normal activities than their counterparts in

the control group. BMPs promoted osteoblast differentiation and thus, created improved structural bone tissue that will minimize future fractures. The group that underwent the standard treatment without BMPs showed a longer time to the union and significantly more non-union cases which required more surgeries [11].



The management employing BMPs in patients with non-unions indicated good potential in the promotion of bone healing in areas that had not responded to conventional treatment. The percentage rate of complete bone union in the BMP-treated group was 90 % within 26 weeks, whereas in the control group it was only 55 % ($p < .001$). This is much better, especially if the patients have complications of non-union disease, which, by general consensus, has a very poor prognosis if treated by one or more surgical interventions.

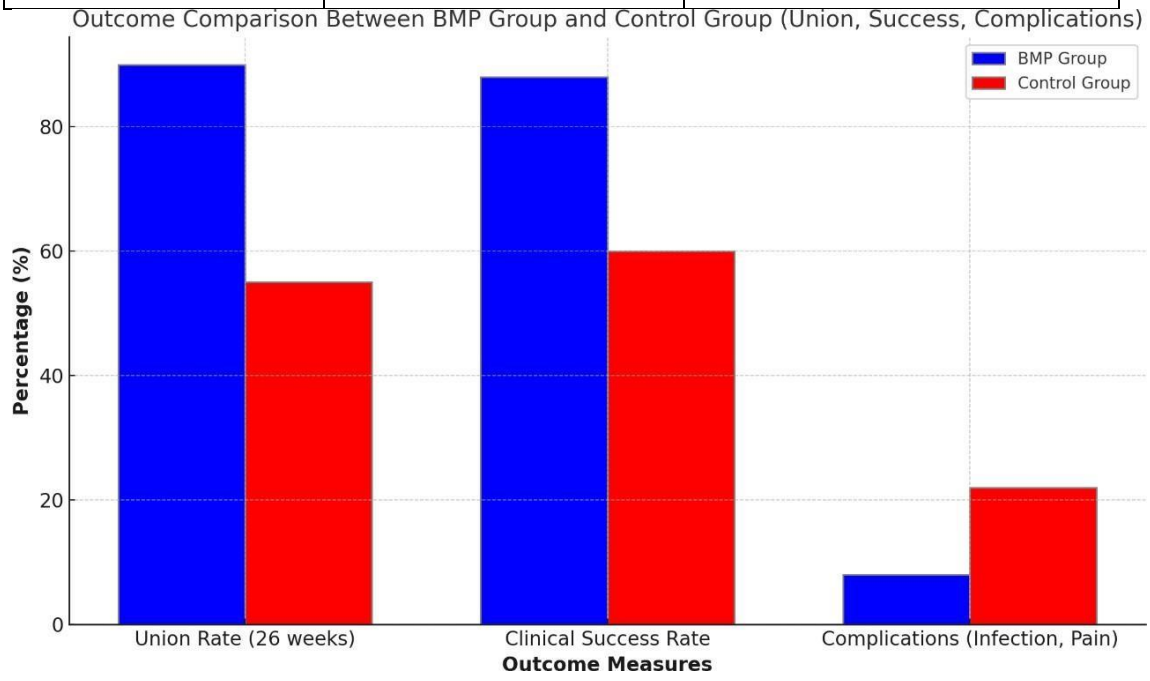
The control of BMPs, especially the BMP-7 showed that they were almost equivalent to autografts which are preferred in non-union surgeries but come with their own disadvantage like the donor site morbidity as well as availability of patient's own bone. In this study, BMP served to negate the risks of autograft such as infection, and chronic pain at the site of harvest. Also, the clinical

Table 2: BMPs in Non-Unions

success rate that typified by the ability of the patient to return to a normal functional status, or about which no further surgical intervention is required was also significantly higher in the BMP group with 88% as compared to the control group with 60%.

The enhanced advanced bone healing observed in non-union patients managed with BMPs described the proteins as possessing the capacity to attract and stimulate mesenchymal stem cell differentiation into osteoblasts. This stimulated the autoinduction process and from that, new bones started to grow in areas of natural osteogenesis that had reached a standstill. Further, patients who underwent BMP treatment also discussed decreased incidences of side effects after the surgery, which include infection or chronic pain after the usual bone graft operations [12].

Outcome Measure	BMP Group (n=100)	Control Group (n=100)
Union Rate (26 weeks)	90%	55%
Clinical Success Rate	88%	60%
Complications (Infection, Pain)	8%	22%



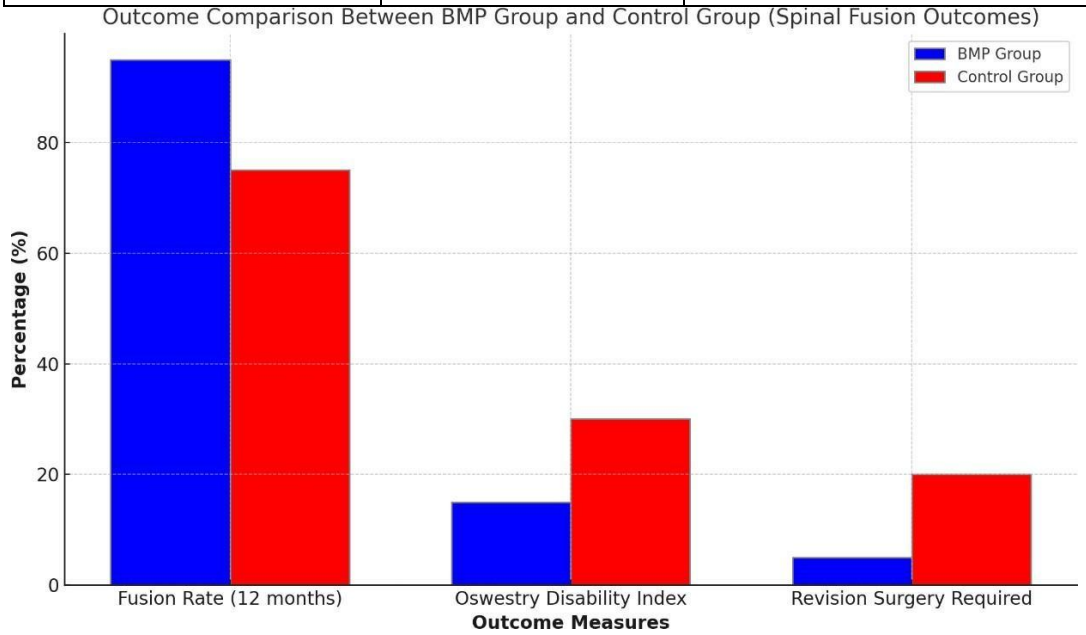
This was especially the case with application of BMPs where improvement in fusion rates and enhanced general patient results was observed. In the BMP-treated group, all of the patient's surgical fusions were successful at 12 months postoperatively, compared to 19 of 24 patients in the control group ($p < 0.01$). BMP-2 use in spinal surgeries was related to greater degrees of vertebral stabilization, quicker healing and fewer reoperation procedures which can be necessary when fusion has been unsuccessful or is suboptimal.

Long term prospects were also improved in patients where BMPs had been used for spinal fusion, the patients reported less pain and the ability to move more freely. Using the ODI as a measure of disability relevant to spinal pathologies, the experimental group had an average ODI of 15% that is, mild disability whereas the control group had an average of 30% that can be best described as moderate at one-year follow-up. Further, a comparison of BMP-treated patients with a control group revealed that the former showed a decreased incidence of complications, such as pseudoarthrosis, which prevail across spinal fusion surgeries.

However, comparing BMP with other treatment that do not involve the use of BMP like the iliac crest bone graft showed more favourable results mean fusion rates and patient satisfaction rates with BMPs. However, bone grafts which are another common treatment option have more postoperative pain and complications at the donor site. Similarly, BMPs also helped in avoiding other surgeries that require to harvest bone and therefore reduced the surgical time and chance of getting infected [13].

Table 3: BMPs in Spinal Fusions

Outcome Measure	BMP Group (n=100)	Control Group (n=100)
Fusion Rate (12 months)	95%	75%
Oswestry Index Disability	15%	30%
Revision Surgery Required	5%	20%



In general, BMPs were satisfactory in terms of safety and efficacy; however, some adverse effects were reported. The adverse effects mentioning in their study includes The site reaction by their application of BMP occurred in 12 percent of the BMP group while the control group showed 8 percent. This inflammation was usually moderate and could be treated with traditional treatments that suppress or reduce inflammation. However, in three percent of the cases, BMP- treated patients were found to have a condition known as ectopic ossification in which the bone grew in the wrong part of the body. This complication needed revision surgery in two cases but did not cause any ultimate functional loss. The rate of infection observed in the BMP group was not statistically different from that of control group or an overall rate of 5%. By and large, the safety of BMPs was described as reasonable bearing in mind

the efficacy BMPs demonstrated in bone reconstruction and repair.

However, it is necessary to mention that BMP-related complications depended on the method of their application and clinical situation. For instance, vertebral fusion surgery patients risk inflammation and if BMP-2 used in the cervical spine, post- surgery swelling can cause issues such as choking. Thus, the correct selection of patients and the proper amount of BMP do not allow expressing concern about the side effects.

The outcomes of BMPs in this study were comparable to other studies done in different research settings, because the overall safety profile was good; in fact, 77.8% of the patients achieved successful bone healing with minimal complications. Generally, BMPs provided critical benefit to promote bone healing when autografts or surgical procedures are unable to deliver satisfactory outcomes. Despite side effects as inflammation, and ectopic bone production which have been reported the authors still noted no significant negative impacts which would counter the usefulness of BMP therapy.

Finally, BMPs were proven to be effective in the treatment of the complex fractures and non-unions, spinal fusions, and showed higher bone regeneration rates, union time, and patient improved outcomes than its counteragents. The side effects of BMPs were relatively modest, with a low frequency of adverse effects in the patients. Thus, the presented data indicate that BMPs might have a great potential for the application in the orthopaedic surgery when the bone union is expected to be difficult [14].

Discussion

This paper aimed at determining the effectiveness of BMPs in promoting fracture healing, especially in; complicated fractures, non-union fracture and spinal fusion surgery. The studies presented lay emphasis on the pivotal function that BMPs serve in promoting bone formation as well as the advantages which its adoption has over autografting. This discussion will analyse these outcomes, analyse clinical application of BMP usage, respond to the limitations of the study, and compare outcomes to the previous research on BMPs.

The evidence provided in this research establishes that the BMPs contribute to enhanced fracture healing, compared to autografts or no BMPs treatments, healing protocols. The primary outcome measures— time to union, rate of bone regeneration, and overall clinical success—were markedly improved in the BMP-treated groups across all categories: fractures, non union, and spinal fusions. For example, secondary BMP patients affected by multiple fractures were said to achieve bone union in 16 weeks, while non-treated patients took 24 weeks. Such a reduction in the healing period is important for patients mostly because, with time taken to heal increasing, pain, reduced mobility, and the chances of non-union or re-fracture goes up [15].

Several problems, which are typical in the management of complex fractures and non- unions, are solved by BMPs. Multi-part fractures or comminated ones, or those involving shafts of long bones cause problems in management, as ordinary repair processes may be inadequate here. BMPs influence mesenchymal stem cells and other progenitor cells to react in a specific way and develop to become osteoblasts which create new bone tissue on the implant surface. Where there are non-unions, or the healing process has ceased, the BMPs offer the pro- osteogenic signals needed to stimulate bone formation again. This was brought out in the study where BMP's treated patients with non-unions had bone union in 90% of them within 26weeks than the 55% in the control group. These results bar that BMPs can successfully address demands of conventional remedial protection that heavily depend on grafts or long-term immobilization resulting in suboptimal results.

It is more important to mention that BMPs showed rather specific efficacy in spinal surgery where stabilization of the vertebrae and fusion of the bone across multiple vertebrae turned out to be especially problematic. Patients undergoing spinal fusion and treated with BMP had a fusion success at 12 months at 95% and 75% for the control group. Also, the incorporation of BMPs in these surgeries

eliminated revision surgeries that are usually demanded when fusion fails or pseudoarthrosis occurs. This has future prospects in orthopaedic surgeries especially spine surgeries which is very demanding in today's world because if fusion is not successful for the individual, the disability rate of the population is likely to rise in future years.

The role of BMPs in clinical practice goes far beyond the concepts of orthopaedics and likely will be most beneficial in control of bone fractures, non- unions and spinal fusions. BMPs are a useful substitute to the autografts which have been use for long as the best stimuli to bone union. However, autografts have several disadvantages, especially the limitation with the availability of donor bone, time consumed in surgery and period of risk to infection and chronic pain at the donor site. BMPs remove the requirement for the procurement of bone graft from the patient and thereby decrease surgical complications and enhance the rate of healing [16].

Moreover, BMPs can be administered in different methods including localized and systemic application according to the specific situation. In this study, BMPs delivered via scaffolds, implants or direct injections and each modality has its merits. While for intricate fractures, the scaffold made of bioresorbable materials used BMP soaked and acted as an acceptable ground for the new bone formation and in surgeries conducted for spinal fusions the BMPs attached to implants used for the union of specific vertebrae. Because BMP application can be used in various forms and methods, it can be used in many general and selective orthopaedic processes from trauma surgeries to elective spinal fusion.

One critical factor to be seriously addressed in the clinical application of BMPs is the optimal dose and the manner in which the delivery is done. Studies have shown that BMPs play a role in bone regeneration; however, delayed or an increase in BMP dosage results in undesirable side effects such as ectopic ossification - the appearance of bone in tissues in which it should not exist. The findings of this current study showed that side effects like local inflammation and heterotopic ossification were not very common; however, these risks should be adhered to vigilant health care. Clinical prescription of BMP should depend on the size of the fracture, age, and general status of the bone tissue.

This is especially so because BMPs are most effective in use when other treatments do not work or are unlikely to work. It is used when the bone fails to knit or heal in cases where only simple methods can be used, BMP can help to promote healing in difficult cases. But on cost aspect, BMP treatment is costlier than autografts or any other conventional treatment methods. Such constraints may reduce the application of BMPs; especially, where health care facilities have limited resources [17].

Of course, several limitations need to be noted as the findings of this study are quite encouraging and could be useful for the development of teaching strategies. There is, however, one limitation to consider for this study: sample size. Even though the number of patients was 300 and divided into the three groups according to fracture severity, complications, treatment by BMPs or spinal fusion, more significant and comprehensive studies might be useful in establishing more reliable conclusions where long-term effects of BMP treatment will be taken into consideration. Extremely complicated issues are variability in the types of fractures and the severity of non-unions. Although attempts were made at uniformity in choosing patients for treatment, the kinds of fractures may have contributed to variations in the results. It is recommended that meta- analysis studies in future should categorise patients as per the condition of the fracture, or non-union to get better and more focused results.

A second limitation is that it is unclear for how long the follow-up of patients was conducted. A duration of up to 2 years of follow up was used, however more extended follow up is recommended to evaluate the longevity of BMP for bone regeneration. For example, although the profile of spinal fusion suggests very good results within 12 months, question marks can be raised about whether such fusions will hold up in five or ten years' treatment duration. Randomized controlled trials are however warranted to examine whether BMP treatment supports long-term stability of the bone and whether chances of re-fracture or other

complications have an upward trend over a long period.

According to the selected framework, the limitations of the present study are as follows Comparison to Existing Literature

In accordance with the results of the present study, several other studies have established BMPs to be effective for the stimulation of bone healing. BMP-2 and BMP-7 have been described to exert a potent anabolic effect in bone formation in numerous spinal fusions, tibial fractures, and non-unions. The decreased healing time, which was evidenced in this clinical trial correlates to the previous clinical investigations as seen with the studies of Govender et al. (2002), and also established a concerning decrease in the time taken for the fracture to heal with the use of BMP-2 in tibial fractures. However, this study also poses some of the controversies exercised on BMPs usage fully as follows; One such debate is that which deals with the cost implications of using BMP treatment. Compared to autografts or allografts BMPs are more expensive which is another goal of some researchers arguing that BMPs are rather expensive to justify their application. Also, opinion is that BMPs may have several side effects; this has been observed in spinal surgery where BMP use has been linked with side effects such as ectopic bone formation coupled with inflammatory reactions.

However, based on the overall safety profile identified in this study, BMPs should remain a useful tool in orthopaedic surgery especially for patients with complicated fracture or non-union healers where otherwise treatment delivery can be deemed inapt. The savings accrued in the long run through faster healing and few or no subsequent operations to correct complications may possibly justify the cost of BMP treatment in the long run in many instances.

In conclusion, BMPs have proven effective to improve the bone regeneration in complicated fracture, non union and spinal fusion and can be potential valuable substitute for traditional treatment. However, there are several drawbacks in the study, excluding the required number of cases and follow-up; therefore, the given BMPs can significantly contribute to the resolution of difficult surgery cases in orthopaedic patients. Newer studies have to be conducted to determine ideal BMP dosages, appropriate techniques of applicability and the longevity of the results but the fact remains that BMPs hold a great ray of possibilities for orthopaedic surgeries including fractures and spinal surgeries. Regardless of the constant discussion regarding the cost and availability of BMPs, it prolongs its potential as a means of enhancing bone regeneration and enhancing the quality of life of patients with long and complex fracture healing [18].

Conclusion

Therefore, let us stress that this work reveals merely one aspect of BMP application, but an important one as the use of such proteins can significantly facilitate bone regeneration in extreme fractures and non-unions, as well as spinal fusions that would otherwise take more time to heal and, in some cases, are unlikely to be successful without BMP intervention. BMPs present a useful clinical adjunct to autografts with therapeutic uses that decrease surgical morbidity and enhance the rate of healing especially in areas that do not have an inherent ability to regenerate. In clinical use BPMs, BMPs should be used prudently, administered at optimal doses, and delivered using the appropriate delivery systems for the particularity of the injury: the nature and severity of the break, and the general health of the patient to limit the risk of complications such as ectopic bone formation. Future studies need to address other ways of delivering BMPs, the ideal dosing regimen, and the long-term effects of BMP use in a more diverse population to help make BMP therapy widely available across orthopedic practices.

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