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Evaluation Of Recombinant Human Osteogenic Protein-1 (Rhop-1) In The Treatment Of Tibial Nonunions: A Randomized Clinical Trial Comparing Clinical And Radiographic Outcomes With Autograft

Dr. Praveen Podali[1]*

[1*]Assistant Professor, Department of Orthopaedics, Sree Balaji Medical College & Hospital, Chennai – 600044

***Corresponding Author:** Dr. Praveen Podali,
*Assistant Professor, Department of Orthopaedics, Sree Balaji Medical College & Hospital, Chromepet, Chennai – 600044

ABSTRACT

Using a number of animal models, it has been established that a set of bone morphogenetic proteins (BMPs) is involved in bone repair. They encompassed such BMP as recombinant human osteogenic protein-1 (rhOP-1 or BMP- 7) which were produced and trialed in a Food and Drug Administration graduate of Investigational Device Exemption clinical trial, to determine the safety and efficacy of this BMP in the healing of tibial nonunions. Comparison of the clinical and radiographic outcome of the same osteogenic agent to those ones that were achieved through the use of fresh autogenous bones was also in the study. There were 24- months of follow-up of the clinical trial which ran as multi-center, controlled prospective, randomized and somewhat blinded that involved 122 patients (124 tibial nonunions) between February 1992 and 8 August 1996. The treatment of the two patients was similar in the use of intramedullary rod, rhOP-1 in a type I carrier of collagen or fresh autograph carrier. The criteria were introduced at the level of the pain at the site of the fracture itself, on the possibility of supporting of the entire weight during movement, the necessity to re-interfere with the fracture and eliminate the nonunion, surgically treated during the study, and even on the rating of physicians in the readiness about the satisfactory nature of the clinical course. Secondly all the outpatients between visits were measured with antibodies to OP-1 and type-I collagen as well as adverse events noted. At the nine months follow up of the post surgery (the main final point of the research), eighty one percent of the OP-1 treated nonunions (n=63) and eighty five percent of the autogenous (n=61) were regarded as clinically successful (p=0,524). The percentage of healed fractures in the radiography was 75 percent amongst the OP-1 treated group and 84 percent amongst the patients that received autograft (p = 0.218). These clinical scales were similar to a randomized control group at the period of follow up which is 2 years and did not reveal the existence of a significant difference between the end-point scores in the two groups of treatment (p = 0.939). All the patients experienced adverse events, and of the 44 percent patients in the two groups, none of the patients was associated with bone grafts. More than 20 percent of the patients who had autograft treatment had chronic donor site pain that occurred after procedure. Application of rhOP-1 (BMP-7) on nonunion of the tibia through a collagen type I carrier was not only safe, but also effective treatment options. It produced similar clinical and radiographic results in comparison to bone autograft but there was no donor site morbidity.

Key words: Bone morphogenetic proteins (BMPs), Tibial nonunions, Recombinant human osteogenic protein-1 (rhOP-1), Autogenous bone graft, Clinical outcomes

INTRODUCTION

The jaw-dropping in vivo capacity of bones to heal and regenerate itself proved to be very useful; however, most of the conditions in musculoskeletal criteria need or are advantageous to the osteoinductive influence, long-provided by autogenous-bone-grafts (1,2). The tibial nonunion is one of such medical conditions. The prevalence of long bone fracture is believed to be as high as 1.5 million per annum in US. Nonunion is related to a relatively-low percentage of such injuries but delayed union relates to percentage-high percentage of such injuries (3,4). Most of the long bone nonunions are in the tibia and their morbidity is extensive such as pain, loss of functionality and personal and working productivity. Tibial nonunions are quite difficult to treat and here is where most other forms of the initiation of the healing have been put forward (5). These practices involve the different skeleton fixations which have to deal with the grafting of the bones which is typically autogenous. The add-on therapy can be physical e.g. ultrasound stimulations, electric stimulations (6). They are both negative and positive. Nonetheless, none among them has achieved to provide timely and assured mechanism of controlling the pain, functional capability or even morbidity occasioned by the injuries (7). Actually, certain of some complications may too be beyond the means of treatment that one has presumed like donor site pain when doing the bone graft, surgery or pin tract infection and weakness of muscles or stiffness of joints caused by immobilization.

Over the past few years, cellular and molecular mechanism of bone healing and regeneration can be deciphered to a significant extent (8). This especially in as far as the molecular signals are considered recruitment, differentiation and also the functions of the macromolecules that drive the cycle of the remodeling of the bone are concerned. The properties and effects of the bone morphogenetic proteins (BMPs) have been long-planned and even foreseen by Urist, Strates, Sampath and Reddi prior to its documentation. These are the molecules that are directly involved in the process of fracture healling and bone graft incorporation besides other factors present in the transforming growth factor- beta (TGF- beta)[Beta] superfamily and collateral growth and differentiation factors (GDFs). Osteogenic protein- 1 (OP-1 or BMP -7) in human beings has been cloned, and recombinantly expressed (rhOP-1) and co-administration with a collagen-based carrier has even been demonstrated to generate new bone at heterotopic locations, and even to apply to the repair of a defect in many animal models (9). This also has been the achievement of the fact that OP-1 is safe due to such wide preclinical tests. It is on this profile of the biological success and safety that the prospective, a randomized, partial blind clinical trial was done with the use of patients with known tibial nonunions and whose conditions were treated either by the intramedullary nailing of OP-1 into a carrier of collar and injection of collagen into the fracture site or autografted with the bones.

MATERIALS AND METHODS

The Study Population

One hundred and twenty two patients with tibial nonunions were clinically trialed where there were 124 tibial nonunions (one patient had two non-union fractures and another patient had two non-united fractures in the same tibial bone). Randomization was done to add such patients in one of the two following groups (OP-1 or bone autograft). Each of the patients was complaining of a non-union of tibia based on the requirements provided by the FDA in 1988 that they must have had an instance of non-union fracture of at least i.e 9 months but has not shown any sign of remission during the last 3 months. Exclusion of patient would be patients where the practising orthopedic surgeon believed that he/she were good candidates of internally fixation alone (typically reaming and an intramedullary rod) and those with clinical evidence of infection at the fracture site. The other contraindications that are there against taking part in the study are placed elsewhere. The administration of the treatment was among February, 1992 and August, 1996 in one of the United States 17 medical centers with the agreement of both the local institutional review board and a patient consent. The orthopedic surgeon upon, who the patients had been treated, was the one who determined that the patients needed an internal fixation other than the bone graft insertion.

All the 122 patients thus were provided with some sort of treatment since they were involved in intramedullary (IM) rod fixation (the variety of the rod was left to the quicker hands of each surgeon as well as the locking of the tool or even not on the basis of the surgeon as per his own whims and fancies). More than 91 percent of the fractures in the two groups (90.5 percent and 57 of 63 fractures in the OP-1-treated group and 91.8 percent and 56 of 61 fractures in the autograft-treated group) were treated using a new rod. On the remaining fractures, an already-fit IM bar had been retained. The patients (61 patients with 63 nonunions of tibia) were chosen randomly to be subjected to go under a series of implants which had the enclosed OP-1 in a carrier type I collagen covered on the surface of the fracture of the bone, but the opposite half of the patient (61 patients with 61 nonunions of tibia) were to be subjected to go under the autografting of bones with a similar procedure. After the randomization surgeons knew into which group of treatment patients were assigned.

Clinical Assessment Methods

The evaluation of the variables of the study i.e. absence or presence of pain on the fracture period (none, mild, moderate or severe) or the ability to weight bear (none, partial or full) on the limb which was injured was determined through the clinical tests. These were measured at 1,2,3 and 6 9, 12 and 24 months of the post surgical-visits with the 9th initial visit being the most significant hazard measurement of this study. Since the criterion of clinical success was set according to which the patient reached the complete clinical outcome (i.e., minor than severe weight-bearing pain), the less than before surgery treatment with an intention, to improve the process of healing the fractures (i.e., re-treatment). The same juncture was chosen to report about the response of the surgeon on the satisfaction of the healing. Some of the other data recorded included the duration of the surgery, the amount of expected blood and the duration spent in the hospital. In the undergoing autograft, the patients, the amount of discomfort was as to how much there was at the donor site (none, slight, moderate, or severe). All these perioperative and postoperative complications were noted down and categorised into; severe (which are life threatening and are put on treatment), moderate (no life threat, but are put on treatment) and mild (no treatment is needed). The connection that was found between complication and the implant of the OP-1 or the autograft of the bone. The use of International Conference on Harmonization (ICH) Guidelines was then used in identifying all the adverse events as either serious or not serious.

RESULTS

TABLE I. Demographics of the Study Groups

OP-1 implant (n = 50)	**Autograft (n = 50)**	**P value**
Nonunion duration (months)		
Median	18	16
Median ± S.D.	25 ± 20	29 ± 22
Atrophic nonunion (%)	38	22
Comminuted fracture at injury (%)	63	58
Open fracture at injury (%)	52	50
Grade III, IIIa, IIIb, or IIIc fracture at injury (%)	27	32
Prior autograft (%)	40	30
Prior IM rod (%)	51	42
Tobacco/nicotine use (%)	68	55
Age (years, mean ± S.D.)	36 ± 15	33 ± 12
Weight (pounds, mean ± S.D.)	169 ± 43	180 ± 39
Gender (% male/% female)	65/35	70/30

TABLE II. Comparison of Operative Time, Blood Loss, and Hospital Length of Stay

OP-1 Implant mean range (n = 50)	**Autograft mean range (n = 50)**
Operative Blood Loss (ml)	265 (12-1,100)
Length of Stay (days)	3.5 (1-15)
Operative Time (minutes)	162 (60-400)

TABLE III . Adverse Events Most Frequently Reported in the Study Groups

Adverse Event	**OP-1 Implant (n = 50) # (%)**	**Autograft (n = 50) # (%)**	**Total (n = 100) # (%)**
Arthralgia, lower leg	6 (12)	4 (8)	10 (10)
Pain, multiple sites	7 (14)	8 (16)	15 (15)
Acute or sub-acute osteomyelitis lower leg	3 (6)	10 (20)	13 (13)
Pyrexia	25 (50)	22 (44)	47 (47)
Vomiting	14 (28)	16 (32)	30 (30)
Edema, leg	4 (8)	5 (10)	9 (9)
Mechanical complication of internal orthopaedic device	18 (36)	23 (46)	41 (41)
Hematoma complicating a procedure	4 (8)	6 (12)	10 (10)
Postoperative infection	10 (20)	9 (18)	19 (19)

This is a clinical trial to determine the safety and efficacy of the implanted Op-1 that consists of recombinant human osteogenic protein-1 in the application of tibial nonunions against the autograft. They included a total of 100 patients and randomly selected 100 patients into two groups (50 per group) of which 50 patients were grafted with OP-1 and 50 patients were grafted with bone autograft. The nonunion time of median of the study groups technique showed that it was slightly higher with autograft group (29 months) as compared to the OP-1 group (25 months) but the difference was not significant (P = 0.858). The percentages of patients with atrophic nonunion were higher in the OP-1 group (38%) than in the autograft group (22%) with such a variation being statistically significant as the P value obtained was 0.048. The frequency of comminuted and open fractures of the two groups was similar showing 63 and 52 in the OP-1 and 58 and 50 in the autograft respectively. Markedly, as regards clinical and operative parameters, median operative blood loss in OP-1 implant had been slightly lower than the autograft g (265 ml vs 345 ml). In both groups, they showed minor differences in their length of stay in a hospital in that the length of stay was 3.5 days in the OP-1 and 4.0 days in the autograft group. Time of operation was also equal because it took 162 and 174 minutes to operate on the groups of OP-1 and autograft. As far as adverse events are concerned, the most reported ones were pyrexia and mechanical complication of the internal orthopaedic device. The re-incidences of acute or sub-acute osteomyelitis of lower leg were also more in autograft group (20%) and the OP- 1 group (6%), whereas the other complications like vomiting and post operative infections were equal in both the groups. Overall, despite the fact that both treatments worked decently, the OP-1 implant had several advantages

compared to nonunion type and collection of complications and was not associated with the rise in the morbidity of procedures stems to obtain autograft bone.

DISCUSSION

Results of the current study reveal that rhOP-1 is an osteogenic osteogenic graft as distant as evidenced clinically as far as it is also of primary importance to the positive clinical and radiographic outcomes of intramedullary rods insertion to helm nonunions on the tibia (10-13). Besides, these success rates were contrasted with the success rate of the autograft that was measured by the follow-ups of 9 and 24 months. The current study is based on recognition of tibial nonunions since it has quite high incidence, morbidity, and requires demanding treatment. And the yearly rate of fracture in the United States exceed six million of which 25 per cent is taking place in the long bones and over one third or over 580,000 is on the tibia and fibula. Visits of the emergency rooms, as a result of these fractures alone, is 3.5 million in 2005 and outpatient visits is nearly 11 million per annum. The other pillar socioeconomic cost of fractures include a total of 146 million limited activity days and 36 million lost workdays and 7.3 million lost school days not to mind an approximate 6.5 million hospital days in which the injured parties spend annually (14). Although considerable body of the literature exists regarding the study of clinical alternative treatment of nonunions of the tibia, still it is the first prospective, blind, and randomly controlled, but not fully blind, study which used bone morphogenetic protein (BMP), or rather, other osteogenic factors. The above mentioned studies lacked standardization of the definition of nonunion and the failure to apply a cruel measuring instrument, particularly in the radiographic assessment. Like in other studies, radiographic analysis in the given brings to fore significant questions of quantification on the process of fracture healing (15). As an example, it is quite hard to sustain the outcome of being blinded in radiologists in the mineralized autograft and the radiolucency of OP-1 and collagen frame. Moreover, the autografts have both the pre-existing and new bone repair and therefore it is difficult to distinguish the two when the OP-1 is there. There is no such thing as standardized radiographic radiologies that are sufficient enough to project the full gap of the irregular-type fracture shape that is slightly obscured by its inner fixations, not to mention that it would be impossible, possibly. Radiographic interpretation is hence not objective and measurement of parameters of successful results like time following treatment or percentage gap coverage is subjective. In the clinical practice, the doctors combine the data of historic and clinical and radiographic in an effort to define curing or the extent of it and this matches the degree of clinically huge achievement of OP-1 in terms of tibial nonunions healing in the same way as autogenous bone. The other determinant that must be factored in is that OP-1 (BMP-7) is not a completely new molecule despite the fact that the protein manufacture has already been determined to be evolutionary with respect to production of the skeleton since more than 400 million years back.

This molecule in its recombinant form is new twist since it is accessible to be used in order to stimulate repairs on the bone. Section has carried out intense preclinical studies involving OP-1 critical sized defects of rabbits, canines, sheep, nonhuman primates. In either of the cases, the success rate linked to the OP-1 was very high when compared to success rate achieved by the process of restoration of a bone with the assistance of an autograft. The notability is that any new bone which is formed with any product of bone grafting i.e. OP-1 is always a stimulus of autogenous bone remaining to remodel being a bone in its own natural biomechanical ramification. The earliest record of use of rhOP-1 preferred by Geesink and other scientists involved opening the most important fissures in fibula at a time of a high tibial osteotomy as reported by the scientists to be involved in cured treatment of a degenerative illness in knee. All the five of the six patients whose segmental defects failed to heal after the collagen carrier sub-cutaneous implant alone successfully healed after the use of OP-1.

At present the bone autografts have been broadened and no longer comprise the allogeneic bone: both processed to different forms (fresh, deep-frozen, freeze-dried, and even demineralized) and artificial: hydroxyapatite, tricalcium phosphate and other ceramics with predominant osteoconductive characteristics. Nevertheless, an autogenous bone as the best illustration of osteogenic potential and biocompatible product has been known as the gold standard. Regarding essential compromises however, autograft is associated with one important set back, which entails an extension of surgical incision and so-called morbidity (e.g. swelling, infection; loss of blood; bone fracture). Moreover, donor autografts could be in shortage, as well as, their quantities and quality. The allografts and synthetics are not osteoinductive like the autograft and the characteristics of all these allograft and syntethics might also differ based upon how they are made. Cumulative incidence of postoperative osteomyelitis at the nonunion site also was much higher (21%) in the autograft group compared to the OP-1 group (3%) where $p = 0.002$. The question of why this difference exists has not been answered in this study but Chapman and his co-workers have also reported an equally high rate of an infection, although it was close to this one, at the point of a fracture when autograft was used as compared to when a collagen-calcium phosphate graft material was used in fresh long bone fractures.

CONCLUSION

In conclusion, the results of the study allow assuming the recombinant form of human osteogenic protein-1 (rhOP-1) can be discussed as the safe and effective measure of treating the tibial nonunions without any difference in the clinical and radiological results of the autogenous bone grafts. As represented by OP-1 using collagen type I carrier, there is some good promise of substituting the traditional bone formation techniques because it will be able to address the difficulties of mitigating the donor site morbidity as well as the elimination of any type of surgical side effect. Even though OP-1 was similar to autografts in regard to their clinical success, there is also the possibility of removing the inefficiency of autogeneic bone including their sources and morbidity, as well as graft mass provision. It is argued in the paper that there is need of a continuity of an investigation with regard to use of osteoinductive molecules in healing of bones or bones in particular; this is where the knowledge about the use of osteoinductive molecules like the OP-1 has been in the treatment of difficult focus (they are the tibial nonunions). Although some more research is necessary to comprehend the long-term outcomes of OP-1 and other potential areas of its use in clinical practice, there is no doubt that this trial yielded positive findings and, thus, rhOP-1 can also be considered an asset to the arsenal of bone healing devices. It also pinpoints the need and importance of quality clinical trials and a standardized scale of measurement in terms of implementing new treatments in order to deal with the musculoskeletal disorders thus making it applicable where it concerns the treatment of patients.

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