

Teriparatide in the Treatment of Infected Non-Union and Delayed Union – A Case Series.

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Abstract : There are not many pharmacological options available for infected non-union and delayed union subsequent to open fractures. The beneficial role of teriparatide (r PTH) in treating osteoporosis is well known but its use in delayed and infected non unions are yet to be explored. In our prospective case series, we explored the use of teriparatide to enhance fracture healing in such difficult scenario. Our case series includes 10 patients all of whom sustained grade II/ III compound fractures involving long bones at the initial trauma. Our first case, a 29 yrs male, presented to us with infected plating of proximal right tibia 1 ½ years later. We started him on teriparatide 20 mcg sc for 2 months. Encouraged by the improved bone stock and fracture healing we did an implant exit and bone grafting and continued teriparatide for 3 more months. In 9 other patients with tibial fractures, we adopted a similar protocol of initial treatment with external fixator till wound healing followed by cast application and progressive weight bearing supplemented by Teriparatide pharmacotherapy for 3-5 months monitored serially by radiographs. Complete fracture union with closure of pin sites was noted in 9 of the 10 tibial fractures. All 9 patients have walked unaided with full weight bearing within one year of injury without any need for second surgery. One patient with initial Grade IIIB compound tibial fracture did not unite despite 6 months post Teriparatide treatment required open reduction and fixation with interlocking nailing and bone grafting. **Conclusion:** Teriparatide, currently known only for improving bone stock in osteoporosis can be a viable option in infected and delayed unions of long bone fractures

INTRODUCTION

Teriparatide is a recombinant human parathyroid hormone that contains the amino acids 1-34 out of 84 of the hormone. Its beneficial role in osteoporosis is well known^{1,2}. It acts by preferentially stimulating osteoblasts when given intermittently for osteoporosis^{3,4}, as well as for fracture repair in laboratory animals^{5,6,7}. There are not many pharmacological options available for infected non-union and delayed union subsequent to open fractures. The beneficial role of teriparatide (r PTH) in treating osteoporosis is well known but its use in delayed and infected non unions are yet to be explored. In our prospective case series of 10 patients, we explored the use of teriparatide to enhance fracture healing in infected union and delayed union in compound fractures.

MATERIALS AND METHODS

Our case series included 10 patients who sustained a open fracture of the tibia and fibula at the initial trauma. Following is the illustration of 3 of our cases in detail.

CASE 1

A 29 year old male patient who sustained a grade IIIB compound fracture of tibia and fibula during a road traffic accident. Initially an external fixator was applied after wound debridement. As the wound settled external fixator was removed and plating was done three months later. But the implant got infected and he developed osteomyelitis. The patient was first seen in our OPD, one and half years after the initial accident with persistent infection and discharging sinuses with implant in situ. He was on weight relieving calipers with walking aid. Before the removal of the implant, we decided to improve his bone stock using teriparatide 20 mcg s.c. once daily for 2 months. There was marked improvement in bone stock and closure of the pin tracts which were evident on radiographs. Encouraged by our results we proceeded with implant exit, sequestrectomy and bone grafting. Sequestrum removed was of size 6x4x2 cm. The defect after sequestrum removal was filled with cancellous bone

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graft from iliac crest and fibular strut grafting as the infection was quiescent. The patient was continued on teriparatide for 3 more months along with linezolid 600 mg (Staph. Epidermis grown in culture). Following the use of Teriparatide there was an increase in the bone density observable on serial plain x rays. Further proof of benefit was obtained by the complete closure of screw holes left behind after implant exit. On further follow up the patient who was initially on non-weight bearing calipers was now able to walk without support. Good range of movements was obtained in the knee. There was bridging of the cortical bony defect despite infection. Our case may be the first documented case in which union using Teriparatide was obtained in the presence of infection. This case throws light on the yet to be explored use of teriparatide in nonunion



FIG 1: Infected tibial plating with Osteomyelitis with white arrows showing the sequestrum and unhealed pin tracts



FIG 2: Two months after teriparatide showing improved bone stock and arrows show the closing pin tracts despite infection



FIG 3: Immediate Postoperative X-ray after implant exit, sequestrectomy and bone grafting with arrow showing multiple screw holes



FIG 4: Two months after surgery white arrow showing closing screw holes



FIG 5: Six months follow up X-ray showing markedly improved bone stock and consolidation



FIG 6: At 2 years follow up



FIG 7: Infection settled and patient walking 2 years after injury

CASE 2

A 44 year old male who sustained a Grade IIIB compound comminuted fracture of his right distal third both bones leg was treated with wound debridement and ankle spanning external fixator at the time of injury. The wound settled in 8 weeks duration but no signs of fracture union was observed. He was prescribed Teriparatide 20 mcg subcutaneously for 1 month without removing the external fixator as the fracture was reasonably well aligned. On noting the improvement in bone stock in the follow up after a month, partial weight bearing with the external fixator was started for 1 more month. Noting signs of fracture healing, external fixator was removed and patellar tendon bearing (PTB) cast was applied. He was encouraged to walk with full weight bearing with the cast and continued on with teriparatide for 3 more months. We removed the PTB cast at 4th month and now the patient was walking with full weight bearing without any support from 5 months after the initial open injury without any additional surgery. (Fig:8, 9)



FIG 8: Preoperative X-ray, Immediate postoperative X-ray and at 3 months follow up X-ray



FIG 9: At 5 months follow up X-ray, fracture showing good consolidation and healing without any additional procedure

CASE 3

A 38 year old male sustained a similar high velocity compound fracture of his right proximal third both bones leg. He was treated in a similar fashion as the above case. He too had similar good result and the such high velocity comminuted open fracture healed without any adjunctive surgery after the initial debridement and external fixator. (Fig:10-12).



FIG 10: High Velocity Grade IIIB compound proximal tibial fracture managed initially with external fixator. Fract

FIG 11: Radiograph at 6 months follow up showing good fracture consolidation and healing without any form of internal fixation



FIG 12: At 6 months follow up, patient standing and walking unaided with full weight bearing

RESULT

The results were analyzed based on clinical and radiographic signs of union. Clinical Signs of union included absence of pain or tenderness at the fracture site with weight-bearing and on palpation of the fracture site and the ability of the patient bear full weight unaided. Radiographic signs of healing include bridging of the fracture site by bone, callus, or trabeculae in at least three cortices, Obliteration of the fracture line (cortical continuity). Adjuncts for fracture healing included closure of the pin tract holes and overall improved appearance of bone stock compared to previous radiographs.

Out of the 10 cases treated with teriparatide at a dose of 20 mcg daily after the initial wound debridement and external fixation, complete fracture union was achieved in 9 patients without any secondary intervention to achieve union within one year of initial trauma. All 9 patients are now walking unaided with full weight bearing. One patient with initial Grade IIIB compound tibial fracture, treated with 6 months of Teriparatide, did not show any clinical or radiographic signs of union. The case was considered a treatment failure and required a open reduction and fixation with interlocking nailing and bone grafting to achieve union. The fracture united 3 months later.

DISCUSSION

Teriparatide is a recombinant human parathyroid hormone (rPTH) containing 1-34 aminoacids Parathormone (PTH) is produced as an polypeptide chain containing 84 amino-acids (1-84) but the

N-terminal fragment, PTH 1-34, can reproduce the major biological actions attributed to full-length PTH. The primary action of PTH is to increase serum calcium levels by increasing bone resorption. Parathormone is one of the important regulators of the calcium, phosphate, and vitamin-D levels in blood and cellular activity in bone. However, Intermittently administered PTH can increase bone mass through preferential stimulation of osteoblasts. Hence it is currently approved for use in treating osteoporosis. This action has led to investigation of possible effects of teriparatide in fracture healing in lab animals^{3,4,8}. In our case series, we identified the use of teriparatide, to enhance fracture healing in open tibial fractures.

Only a few cases have reported the use of teriparatide in fracture management in humans. The theoretical role of teriparatide in healing of fresh fractures, as well as fractures with delayed healing has been proposed in literatures^{8,9,10}. To our knowledge, there has been only one internet article which published the delayed Unions and non-unions of long Bones managed with teriparatide in a case series of 16 patients but all the cases in the study were delayed unions and non-unions after adequately surgically stabilized fractures¹¹. However, our study includes delayed and infective nonunion after the initial high velocity open tibial fractures which is the first of its kind. We have observed early and abundant callus formation in our cases within 1 month of injectable Teriparatide. To our knowledge, however, no study has yet been published that investigates the use of teriparatide in open long bone fractures.

Non-union is described as the absence of union following a fracture requiring an additional treatment for healing to occur¹². The exact time for determining a non-union and delayed union after a fracture is not well defined. But both are quite common after temporarily stabilized open fractures. Numerous surgical treatments like dynamic compression plating, reamed intramedullary nails, dynamic external fixators augmented with or without bone grafting have been known for a long bone delayed union and non-union^{13,14,15}. However a standard medical treatment regimen which augments fracture healing consistently is yet to be devised. Iliac crest autograft is the gold standard for managing delayed union and non-union but its complications include infection, haematoma, hernia, pain, etc. These complications have always led to a continued search for alternatives in fracture healing like allografts which has its own complications like infection, graft rejection, etc.,

Bone morphogenetic proteins (BMPs) have no donor site morbidity but it also requires a surgical procedure for placement at the non-union site¹⁶⁻¹⁸. Recombinant human osteogenic protein 1, Gene therapy and Stem cell therapy has also been tried in delayed and non-unions with unpredictable results. These options are still being evaluated in trials and are not widely used. Electrical stimulation and low-intensity pulsed ultrasound stimulation are not standard therapies worldwide, but reflect the desire of orthopaedicians to have a non surgical way of addressing the issue^{19,20}. There are currently no approved drugs to enhance healing of non-unions with systemic application.

Encouraged by its effects on osteoporotic patients, we decided to use teriparatide in long bone non-unions and delayed union in open injuries. We administered it to our patients for a maximum period of 6 months to explore its peak effect. We see that injectable teriparatide has the potential of influencing the normal process of fracture repair in the first case. So we did not wait several months

in the subsequent cases for a established nonunion to settle in. Our innovative treatment with teriparatide in the these patients yielded a good result.

Injectable teriparatide has the theoretical increasing the risk for osteosarcoma especially in patients with Paget's disease of bone or people who had radiation treatment involving the bones.

CONCLUSION

Teriparatide, the recombinant PTH is known only for its use in osteoporosis. Teriparatide can be a effective pharmacological agent in the treatment of infective nonunion and delayed union in open fractures but a large clinical trial and long term follow up is required to explore its complete advantages.

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