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TERIPARATIDE IN MANAGEMENT OF NONUNION OF FRACTURES: A CASE SERIES

Orthopaedics

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ABSTRACT

Introduction: Nonunion of fracture remains a therapeutic challenge to orthopedic surgeons worldwide despite improved surgical techniques with a huge impact on quality of life. Previously, various animal and human studies have found that teriparatide, a parathyroid hormone (PTH) analogue, induces fracture healing in those with nonunion. **Material and methods**: We gave teriparatide injection (20mcg/day subcutaneously) in 9 patients with nonunion of fracture in combination with surgical intervention. Patients were followed up each month. The endpoint was clinical and radiographic evidence of union. **Results:** 8 of 9 fractures were united both clinically and radiologically. The average time for the union was 14.5 weeks after the start of medication. No adverse effects were recorded following the use of teriparatide. **Conclusion:** Teriparatide combined with stable fixation results in a satisfactory outcome for the challenging cases of nonunion of the fracture.

KEYWORDS

Teriparatide, Nonunion

INTRODUCTION:

Nonunion is a grave complication that affects nearly 10 % of fractures. (1,2) The U.S. Food and Drug Administration defined nonunion as a fracture that has not united after 9 months from injury or a fracture that does not show progression in the union over 3 consecutive months.(3) Nonunions are routinely associated with high energy trauma, wound infection and, significant soft tissue injury. Nonunion is often a consequence of inadequate stability or reduction or poor choice of an implant or poor biology affecting fracture healing.(4) Nonunion often require admission for surgical management, thereby increasing the economic burden.(5) Despite improved surgical techniques, the high prevalence of nonunions has encouraged research efforts towards the evolvement of novel treatments to increase fracture repair.

Teriparatide is currently approved by the US Food and Drug Administration for use in patients who are at high risk for osteoporotic fracture. (6)Teriparatide is the 1-34 amino acid segment of the full-length 84 amino acid human parathyroid hormone (PTH) molecule and is a systemic bone anabolic agent that increases osteoblastic activity and reduces osteoblast apoptosis. (7) Teriparatide has been investigated in various animal models(8–10) and in humans(11) as a potential adjuvant to enhance fracture repair with varying degrees of success. We present a prospective series of patients treated for nonunion of fractures to evaluate the efficacy of teriparatide on fracture healing and union.

METHODS:

We conducted a prospective study in patients presenting with nonunion of fracture of long bones at Assam medical college and hospital, Dibrugarh between June 2019 and June 2021. Patients aged between 18 to 65 years, presenting with nonunion, were considered for inclusion in the study. Non-union was defined as per the FDA definition as a fracture that has not united after 9 months from injury or a fracture that does not show progression in the union over 3 consecutive months, assessed clinically and radiologically. Patients who did not have regular follow-up were excluded. Patients with active liver disease or presence of clinical jaundice; or positive history of symptomatic nephrolithiasis or urolithiasis within 2 years were excluded from the study. Patients with known allergic history to teriparatide or any form of PTH hormone or analogue, Paget's disease of bone, a history of a malignant neoplasm in the preceding 5 years were excluded. At the time of surgery, all nonunions were confirmed to be aseptic according to intraoperative microbiology samples and also the clinical profile of each case. The standard treatment protocol consisted of subcutaneous administration of teriparatide, 20 mcg per day, plus calcium and vitamin D. The duration of teriparatide administration was targeted not less than 12 weeks and not more than 2 years. Medication was stopped if the patient refused to continue for any causes including adverse reactions and financial burden. Patients were followed up each month to evaluate any adverse response and necessity of teriparatide continuation. Progression of union was assessed radiographically at each visit. The fracture was considered to be united based on radiological and clinical evaluation. The pain-free ambulation was considered as a clinical union. Cortical continuity of atleast three cortices on anteroposterior and lateral plain radiographs was regarded as a complete radiologic union which was considered the endpoint and the drug was discontinued. The intervals between the start medication and the endpoint were recorded.

RESULTS:

We identified 9 patients aged 23 years to 45 years(6 male and 3 female) who fulfilled the inclusion criteria.4 had nonunion of fracture shaft of femur, 2 with nonunion of fracture tibia,1 each with nonunion of fracture distal femur, subtrochanteric fracture, fracture shaft of ulna respectively. All 4 cases of fracture shaft of the femur had previously undergone unsuccessful IM nailing. Nail removal followed by application of Limb Reconstruction System (LRS) was done in all 4 cases. Structural allograft was performed in 3 cases (distal femur fracture, subtrochanteric fracture, fracture ulna). Dynamization was done in 2 cases of tibia non-union. (Table 1)

Table 1: Patient clinical characteristics and response to teriparatide treatment

Patient	Age/Sex	Mode of injury	Fracture pattern	Fixation device /procedure	Time to union(weeks)
A	23Y/M	MVA	Femur Shaft	L.R.S.	16
B	45Y/F	Low energy fall	Subtrochanteric	Plate and allograft	12
C	28Y/M	MVA	Femur shaft	L.R.S.	12
D	32Y/M	MVA	Tibia	Dynamisation	20
E	33Y/M	Low energy fall	Distal femur	Plate and allograft	12
F	30Y/F	Low energy fall	Ulna	Plate and allograft	16
G	45Y/F	MVA	Femur shaft	L.R.S.	16
H	26Y/M	MVA	Tibia	Dynamisation	Did not unite
I	35Y/M	MVA	Femur shaft	L.R.S.	12
MVA, Motor vehicle accident; L.R.S, Limb Reconstruction System					

No adverse effects were recorded and teriparatide was well tolerated in all patients. Clinical and radiological evidence of union was seen in 8 out of 9 patients. The average time for completion of union was 14.5 weeks after starting on teriparatide. 1 case (fracture tibia) did not show any sign of union even after dynamisation and 24 weeks of teriparatide therapy. (Table 1)

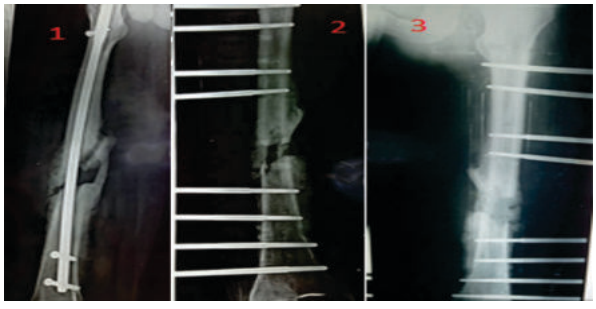

Figure A: Pretreatment and post treatment radiograph of patient A. Preoperative AP View(1) showing nonunion following fixation with IM Nail. Immediate post operative AP view (2) after nail removal and fixation with L.R.S. AP view at 16 weeks (3) showing union.

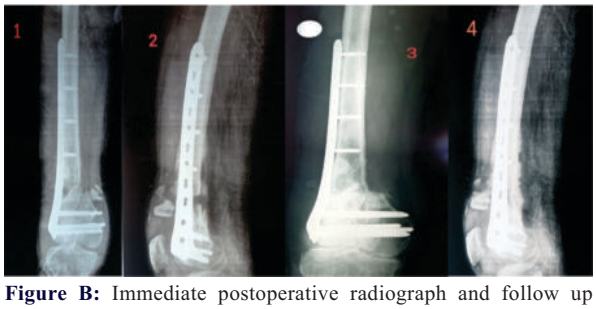

Figure B: Immediate postoperative radiograph and follow up radiograph of Patient E. Immediate postoperative AP view (1) and lateral view (2) after plate and allograft application following freshening up of fracture margins in a case of nonunion of distal femur. AP view (3) and lateral view (4) at 12 weeks showing radiological union.

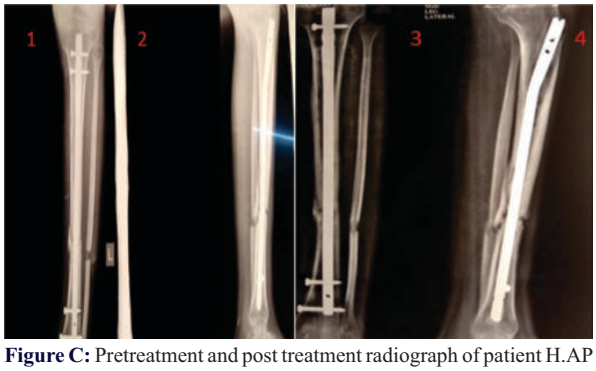

Figure C: Pretreatment and post treatment radiograph of patient H.AP view (1) and Lateral view (2) showing no signs of union following fixation with IM nail. AP (3) and Lateral (4) view showing still no sign of union at 24 weeks following dynamisation and teriparatide therapy.

DISCUSSION:

Regardless of the recent advances, the management of nonunion still remains a challenging topic. Fracture healing is complicated by both mechanical and anatomical factors. Undiagnosed metabolic disorders of calcium, vitamin D, and PTH are considered as a few predisposing factors in non-union which are often neglected. Autologous bone grafting still remains the gold standard in the management of atrophic nonunions, but is associated with complications of postoperative pain, surgical site infection, nerve or vascular injuries, and donor site morbidity.(12)

Our case series of 9 patients showed that teriparatide at a dose of 20 mcg/day facilitated early clinical and radiological union in 8 patients of nonunion with the average time for union being 14.5 weeks. These observations are similar to previous published clinical reports and small studies mentioned below, that suggest that teriparatide promotes fracture healing.

Studies	Patient profile	Time to union after initiation of teriperatide
Case Reports:		
Chintamaneni et.al (2009)	67 year old male with sternal fracture nonunion	Union at 9 months.
Oteo-A´lvaro et al. (2010)	32 year old male with humerus diaphysial nonunion previously treated with treated using 2 flexible nails.	Union at 5 months.
Ochi et al. (2013)	74 year old male with nonunion of periprosthetic femoral fracture after total knee replacement, associated rheumatoid arthritis. He was previously treated with a periarticular locking plate and hydroxyapatite graft and additionally daily low-intensity pulsed ultrasound was given.	Union at 6 months.
Ciurlia et al. (2017)	38 year old male with nonunion of diaphyseal humerus fracture previously treated with osteosynthesis with bridge plating followed by revision surgery with antegrade intramedullary nailing and autologous bone graft.	Union at 6 months.
Case Series:		
Lee et al. (2012)	3 patients with nonunion of the femur after the initial surgical intervention.	1st case united after 15 months (TPDT given for 9 months). 2nd case after 11 months. 3rd case after 15 months (TPDT given for 3 months in 2nd and 3rd case).
Mancilla et al. (2015)	6 patients aged 19 to 64 years with nonunion of tibial (2), femoral (2), subtrochanteric (1), both tibial and femoral (1) fractures.	5 patients had complete union within 3 to 9 months. Patient with both tibial and femoral fracture failed to unite.
TPDT, Teriparatide.		

Among 9 patients in the current study, 1 patient had failed to achieve union with adjuvant teriparatide (patient H; figure C). He underwent dynamization after 36 weeks of initial surgery with adjuvant teriparatide for 16 weeks. Though the literature predicts around 50% success rate with dynamisation,(19) it has a limited role when performed late as so with our case.

Most clinical trials and case reports in humans have employed PTH doses that are approved by FDA to treat osteoporosis: 20 mcg per day teriparatide.(20) Our series suggests that the standard dose of teriparatide of 20 mcg per day appears to be effective in the

management of cases of nonunion. A few recent studies have shown positive outcomes with weekly subcutaneous teriparatide(21,22), thus an alternative protocol may also be fruitful in cases of nonunion.

One of the major apprehensions towards the use of teriparatide is the concern of adverse effects associated with it.(20) A study by Vahle et al. raised concerns about the development of bone tumours especially osteosarcoma following the use of teriparatide.(23) No adverse effects were encountered in our study. The use of teriparatide seems entirely safe, however long-term follow-up is essential to rule out long term consequences.

Our study has several limitations. First, as a case series was an observational study without a control group. These made our study prone to bias. Second, other factors like comorbidities that affect the union were not taken into account. Third, our study included only a few patients.

CONCLUSION:

Adjuvant teriparatide was tried in 9 challenging cases of nonunion. Our case series indicated that teriparatide is a promising anabolic treatment for nonunion of fractures. No adverse effects were encountered in our series. This present study of 9 cases warrants further large, randomized placebo-controlled trial studies for the positive role of adjuvant teriparatide in nonunion and to determine its safety.

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