

A clinical study on role of short course teriparatide injection in management of delayed union of fractures

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Abstract

Background: Delayed union, is when healing has not advanced at required rate and has been prolonged for the location of fracture and involved bone in the expected time (usually 3-6 months) after initial trauma. Teriparatide is a synthetic analogue of the PTH Intermittent teriparatide subcutaneous injection can accelerate fracture healing by improving bone mass and skeletal architecture in non-union and delayed union and increase bone volume. **Methods:** A clinical study on role of short course teriparatide injection 20 mcg in management of delayed union was conducted on 40 patients. The patients were given daily 20 mcg injection teriparatide for 6 months and were evaluated for radiological and clinical signs of union at 6, 12, and 24 weeks of followup. **Result:** Humerus and tibia was the most common bone involved each constituting 32.5%. 70% patients did not have any underlying comorbidities. 14 patients were addicted to smoking, serum calcium subsequently increased from weak 0 to week 24 (p=0.001). Moreover, the mean serum alkaline phosphatase also significantly increased from 74.85 (SD: 11.68) in week 0 to 81.50 (SD: 12.32) in week 24 (p<0.01). The VAS (pain) score was 3.95 (SD: 1.08) at 0 week which decreased to 1.90 (SD: 1.23) at 6 Weeks. 82.5% patients did not have any complications during the study, while 17.5% of them suffered from non-union of fracture. **Conclusion:** It was observed that teriparatide has a significant effect on increasing callus formation, increase in calcium levels, and a significant improvement in the clinical signs of union.

Keywords: Delayed union, teriparatide, management, RUST score

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Introduction

Musculoskeletal injuries have become the most common cause of disability all over the globe[1]. The bone heals by a process identical to foetal skeletogenesis including enchondral ossification and intramembranous ossification without showing any signs of scar tissue[2]. However, bone regeneration can be impaired in large bone defects, osteoporosis, and avascular necrosis[3]. One of these impairments is delayed union, an prolongation of union in a bone after the completion of an appropriate time (usually 3-6 months) after initial trauma[4,5]. It is caused due to lack of blood supply, distraction, inadequate reduction, poor fixation or splintage, inadequate mobilization, infections, smoking and primary hyperparathyroidism[6]. Delayed unions are often the cause of increased financial and functional problems to the patients including increased length of hospital stay, blood loss, pain, stiffness and other complications[7-9]. According to United States Food and Drug Administration, if a fracture fails to unite after 8 months from trauma by conservative treatment,[10] Currently most orthopaedic surgeons follow standard care of established local intervention guidelines with a goal to enhance bone formation. Parathyroid gland produces parathyroid hormone (PTH) which deals with homeostasis

of phosphates and calcium levels in the body. Previously, exogenous PTH administration was thought to increase stem cell pool by acting on osteoblasts and increasing their population for bone regeneration[11]. Teriparatide is a synthetic analogue of the PTH approved by the Food and Drug Administration (FDA) for managing osteoporosis. It has also been effective in treating non-union of fractures by increasing the life span of osteoblast, formation of callus and mechanical strength and thereby stimulating bone formation by boosting the micro and macro architecture of the bone[12,13,9,14]. Intermittent teriparatide subcutaneous injection can accelerate fracture healing by improving bone mass and skeletal architecture in non-union and delayed union and increase bone volume in sternum, humerus, radius and femur[15-17]. Some case reports have shown that teriparatide injection can rectify this condition with minimal adverse effects[18]. However, there is a lack in evaluation of healing of fractures among clinicians[19]. Many of them have differences in opinion about the regimen and dosage of teriparatide. Clinicians are also concerned with two major adverse effects of teriparatide including hypercalciuria and hypercalcemia[20]. This study evaluates the role of short course teriparatide injection 20 mcg in the management of delayed union of fractures. Further, we assess the functional outcome of teriparatide on the basis of radiological and clinical evaluation, pain, abnormal mobility, bony crepitus and regaining function.

Materials and Methods

The study was conducted in the Orthopaedic Surgery Department of Rohilkhand Medical College and Hospital, Bareilly, India for a period of one year, from September 2018 to September 2019. Patients aged 20 years and above with delayed union of fracture

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and willing to take the injection were selected for this study. Moreover, any patients with underlying conditions like inflammatory disease of the knee, hypercalcemia, Paget's disease, increased alkaline phosphatase, osteogenic carcinoma, unfused epiphysis, neoplasm of bone, PTH allergy as well as pregnant or lactating women were excluded from the study. Forty patients fit the selection criteria. They were given injection teriparatide 20 mcg on the abdomen, 2 cm lateral to the umbilicus after taking necessary disinfection precautions. The same dosage was repeated every day at the same time for a period of 3 to 6 months. Each patient was followed up at 6, 12 and 24 weeks after the first injection and 6 months after the last injection. On each follow up visit, patients were evaluated using VAS Score and Rust Score. The analysis was conducted on SPSS 16.0 version (Chicago, Inc., USA). Results were determined using frequencies, percentages, mean and standard deviation (SD). The mean change in continuous variables from week 0 to subsequent time periods was compared using t-tests whereas, the changes in dichotomous variables from week 0 to subsequent time periods was compared using McNemar's test (p value < 0.05 was considered significant).

Observations and Results

A total of 40 patients were analysed, of which 12 were under 40 years of age, 13 between 40 to 50 years and 15 over 50 years with a mean age of 46.50 (SD: 11.52) ranging from 24 to 65 years (Fig 1). There were 19 males (47.5%) and 21 females (52.5%) (Fig 2). 40% of the patients were housewives, 20% of patients were farmers and private jobs each whereas 15% of them had government jobs. 19 patients belonged to a low socio-economic status (SES) and rest were from a middle SES. Humerus and tibia was the most common bone

involved each constituting 32.5%. Femur was the second most common bone involved (22.5%). Ulna and radius, and ulna each involved in 2.5% patients (Fig 3). 70% patients did not have any underlying comorbidities, while 17.5% of them were diabetic and 12.5% of them suffered from hypertension (Fig 4). Moreover, 14 patients were addicted to smoking, 15 to alcohol and 11 were addicted to both smoking and alcohol. The mean serum calcium of all patients at week 0 was 7.8 (SD:0.46), which increased to 7.99 (SD: 0.41) at 6 weeks, 8.18(SD: 0.45) at 12 weeks and 8.50 (SD: 0.50) at 24 weeks. Therefore, serum calcium subsequently increased from week 0 to week 24 (p=0.001) (Fig 5). Moreover, the mean serum alkaline phosphatase also significantly increased from 74.85 (SD: 11.68) in week 0 to 81.50 (SD: 12.32) in week 24 (p<0.01) (Fig 6). The VAS (pain) score was 3.95 (SD: 1.08) at 0 week which decreased to 1.90 (SD: 1.23) at 6 weeks, 0.80 (SD: 1.01) at 12 weeks and 0.05 (SD: 0.31) at 24 weeks. The comparison of mean change showed VAS significantly (p=0.0001) decreased from week 0 to subsequent time periods (Fig 7). Abnormal mobility was observed in 32.5% patients at week 0, which decreased to 20% at week 6, 2.5% at week 12 and was nil at 24 weeks. There was a significant change in abnormal mobility (p=0.0001) from 0 week to 6 weeks and 0 weeks to 12 weeks. Bony crepitus was observed in 22.5% patients at week 0 which became nil at 6 weeks till 24 weeks. Moreover, at 0 weeks a mean of 5.38 (SD: 1.25) patients showed signs of union of radiological evaluation, which increased to 7.75 (SD: 1.75) at 6 weeks, 10.22 (SD: 2.04) and 11.30 (SD:1.62) at 24 weeks. Furthermore, 82.5% patients did not have any complications during the study, while 17.5% of them suffered from non-union of fracture.

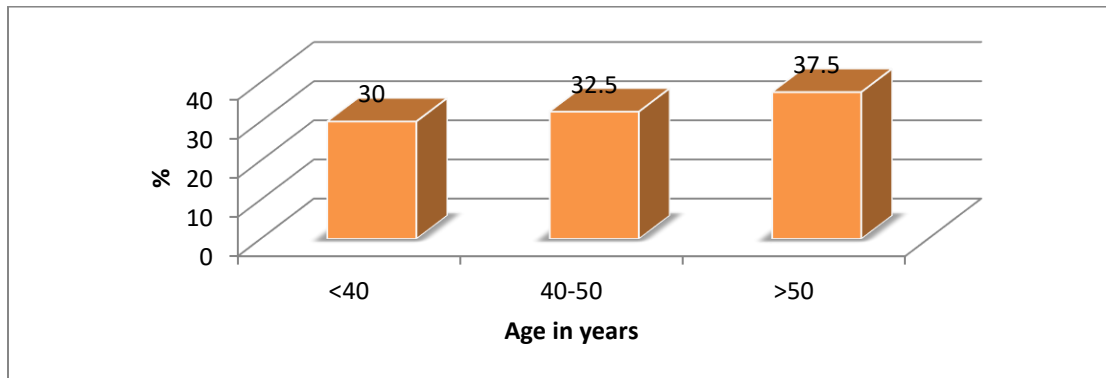


Fig. 1: Distribution of patients as per age

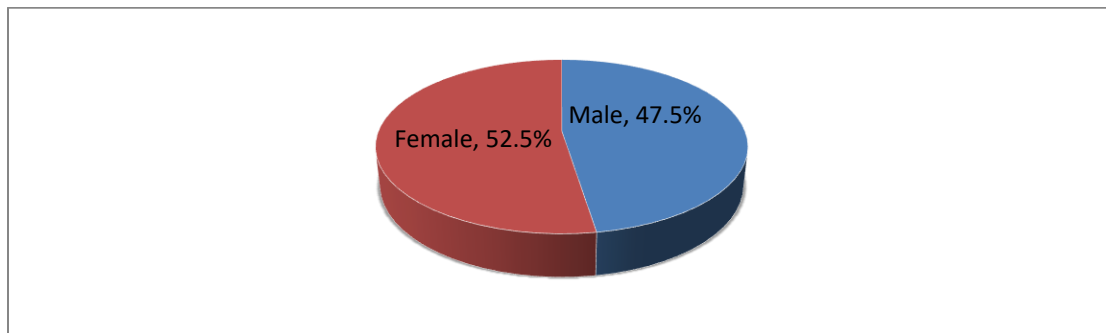


Fig. 2: Distribution of patients as per gender

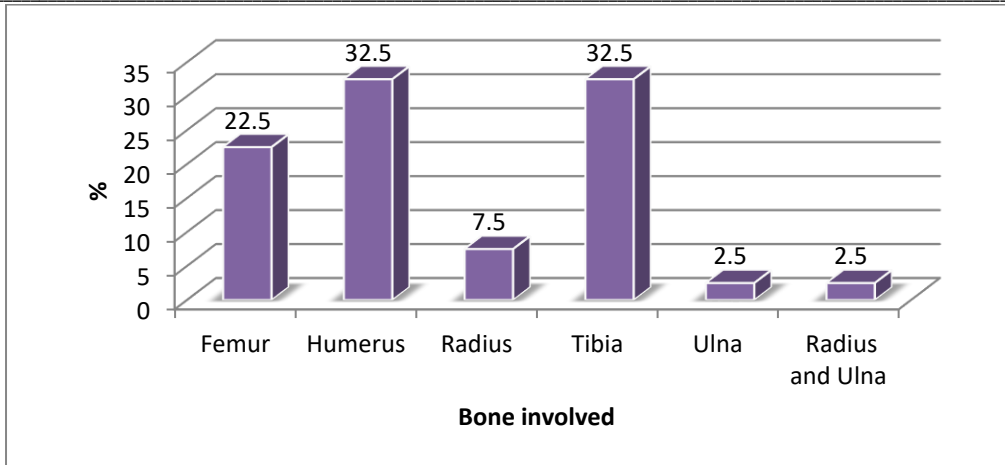


Fig. 3: Distribution of patients according to the involved bone

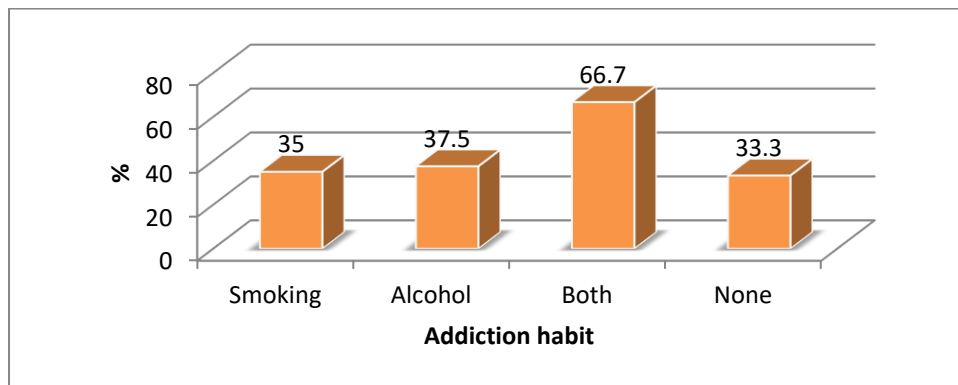


Fig. 4: Distribution of patients as per addiction habit

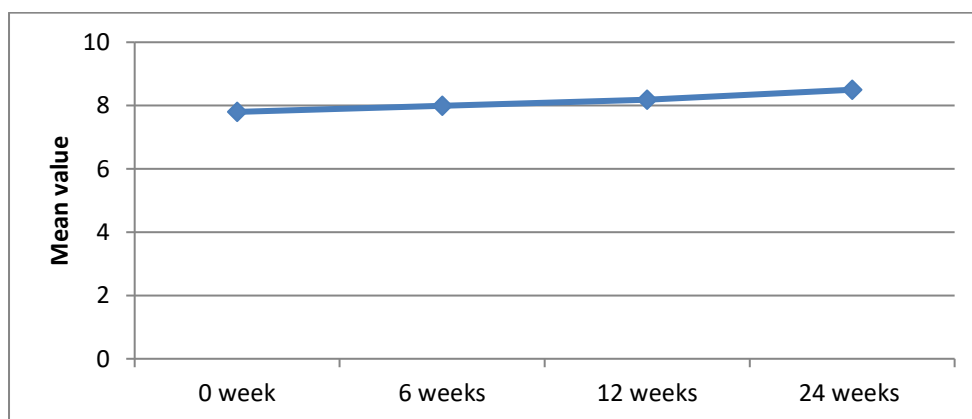


Fig. 5: Comparison of mean change from baseline serum calcium from 0 week to subsequent time periods

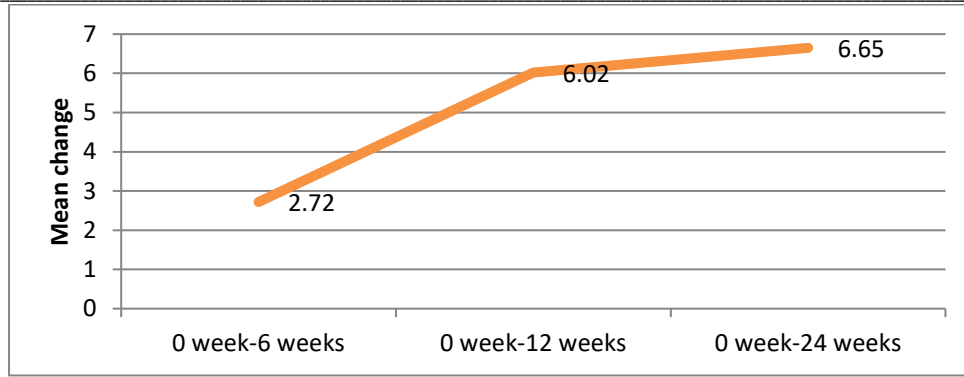


Fig. 6: Comparison of mean change from baseline serum alkaline phosphatase from 0 week to subsequent time periods

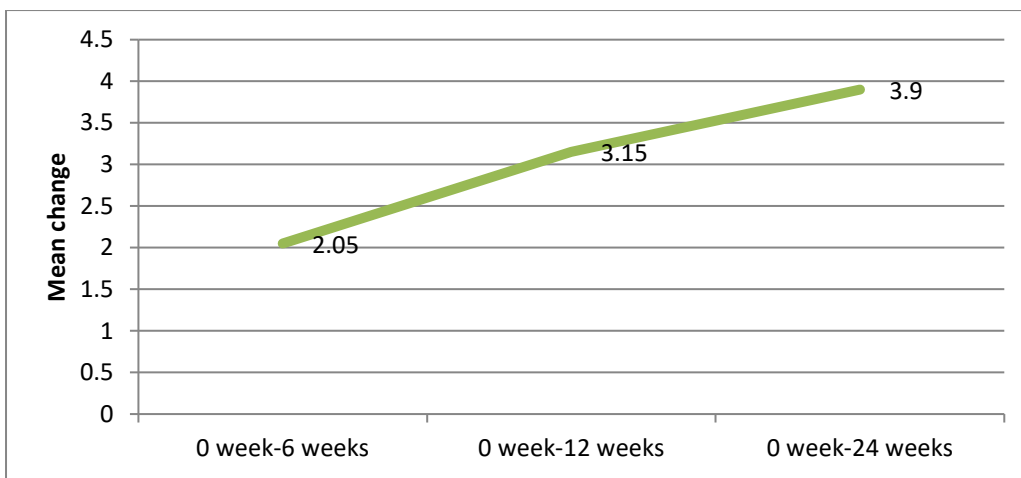


Fig. 7: Comparison of mean change from baseline VAS (Pain) from 0 week to subsequent time periods

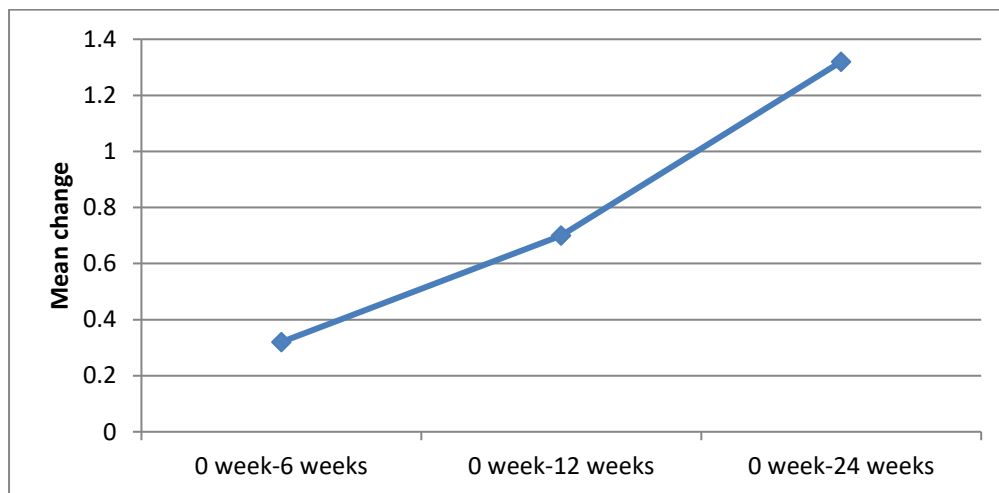


Fig. 8: Comparison of mean change from baseline Regaining of function from 0 week to subsequent time periods

Discussion

Systemic and local factors regulate healing of fractures by many pathways. Teriparatide promotes healing by these pathways including osteoclast production, multiplication of mesenchymal stem cells, chondroprogenitors, BMP formation, osteoprogenitors and maturation of chondrocytes. Teriparatide activates protein matrix and produces osteoclast facilitating callus remodelling and production. Any abnormality in this process can cause impaired healing leading to delayed union or non-union[21-23].

Teriparatide dosing promotes the Wnt/Beta catenin pathway which manages type 10&2 collagen that is associated with the volume of callus. Many studies have shown radiological and clinical union in non-union, delayed union and in primary union[24,25]. Moreover, some studies revealed that daily administration of teriparatide improved microarchitecture of bone followed by enhanced bone formation. Aspenberg *et al.* did a study on postmenopausal women which showed rectification of pelvis ring fracture and distal radial fracture on daily teriparatide administration.²² Tachiri *et al.* reported quicker healing in two cases of metatarsal fracture.²⁴ Rubery *et al.* reported delayed union in 3 odontoid fractures[26] and Oteo-Alvarez and Moreno showed atrophic non-union of humerus in one case following the use of teriparatide[27]. Lee *et al.* stated that teriparatide has the potential to be used as an alternate to surgical management of non-unions[23]. The present was carried out in the Orthopaedic Surgery Department, Rohilkhand Medical College and Hospital, Bareilly with the objective to assess role of short course of injection teriparatide in the management of delayed union of fractures. 40 patients were assessed in this study, greater than one third of patients were over 50 years (37.5%) followed by 40-50 (32.5%) and 30% were less than 40. The mean age of patients was 46.40 years (SD:11.52) ranging from 24-65 years (Fig 1). Mishra *et al.* showed that mean age of patients with delayed union of fractures was 43 years (ranging 28 to 54 years)[28]. Saraf and Munot evaluated that the mean age of patient with delayed union of fractures to be 48.43 years[29]. In this study greater than half of patients were females (52.5%). In contrast to a study by Mishra *et al.* in which majority of patients with delayed union were males (66.7%) (Fig. 2). However, Saraf and Munot had an equal number of both men and women in their study[30]. More than half of the patients in this study belonged to middle class SES (52.5%). Moreover, more than one third of patients were housewife (40%), followed by farmer and private jobs (20%) and government job (15%). Further, it was observed that humerus and tibia was the most common bone involved, followed by femur, ulna & radius and ulna.(Fig.3) Saraf and Munot reported the commonly involved bones in a fracture were humerus, radius, femur and tibia[29]. Among all patients 17.5% and 12.5 were suffering from diabetes mellitus and hypertension respectively while 37.5% of them were alcoholics and 35% smokers.(Fig.4)

At week 0, the mean serum calcium was 7.80 (SD: 0.46) which gradually increased to 8.50 (SD: 0.50) at 24 weeks (Fig.5). The mean serum alkaline phosphatase was 74.85 (SD: 11.68) at week 0 and 81.50 (SD:12.32) at 24 weeks (Fig.6). In a case study, the serum levels of alkaline phosphatase increased during the first nine months of therapy with teriparatide which reversed back to normal after 3 months of cessation of teriparatide administration[7].

The present study demonstrated that the VAS score gradually reduced over 24 weeks from 3.95 (SD:1.08) to 0.05 (SD: 0.31) (Fig.7). Mishra *et al.* (2019) found that pre-therapy was score was 8.3 (SD: 0.67), which reduced to 2.2 (SD: 0.91) after therapy. Bukata and Puzas reported irrespective of fracture site, 141 people reported rectification of pain within 12 weeks of therapy and fracture reunion was noted in 93%. Moreover, studies comparing the role of teriparatide to a control group showed substantial improvement of VAS score in teriparatide group[30,31,22,19]. In this study the abnormal mobility was present in 32.5% patients at the beginning of the study, which reduced to nil at 24 weeks. It

was also observed that regaining of function improved from 0.48 (SD:0.50) to 1.80 (SD: 0.40) during this time period (Fig.8). Furthermore, bony crepitus was observed in 22.5% at week 0 and became nil at 6 weeks till 24 weeks in this study. The radiological signs of union rose to 11.30 (SD: 1.62) from 5.38 (SD: 1.25) in 24 weeks. Non-union complications were seen in 17.5% patients. Mishra *et al.* also stated that one in nine patients could not respond to teriparatide injections and developed non-union.²⁸ Saraf and Munot concluded that some patients experienced mild adverse effects including dizziness, nausea, vomiting and leg cramps.²⁹ No other major or minor adverse effects were reported in these studies[28,29]. The limitation of this study was the small sample size, lack of control group and short duration of study period. More studies with larger sample size and long duration of study are required to paint a clearer picture about teriparatide.

Conclusion

The present study, conducted in Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh (India) on 40 patients with delayed union found that a significant effect of teriparatide on bone healing and callus formation.

There was also a significant rise in levels of serum calcium during the study and a drastic reduction in pain over the 24 weeks period. The abnormal mobility reduced with a significant gain in function overtime as the union progressed. However, 17.5% patients suffered from complication in the form of non-union. Hence, a short course of daily injection teriparatide can be considered as a useful treatment modality for delayed union of fractures.

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