ORIGINAL RESEARCH

Assessment of the Effect of Teriparatide on Lower Limb Fracture Healing: An Interventional Study

[1]Dr. Anjani Kumar Singh, [2]Dr. Nishit Ranajn

[1]Assistant Professor, Department of Orthopaedic, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India
[2]Associate Professor, Department of Orthopaedic, Krishna Mohan Medical College & Hospital, Mathura, Uttar Pradesh, India

Corresponding Author: Dr.Nishit Ranajn
Associate Professor, Department of Orthopaedic, Krishna Mohan Medical College & Hospital, Mathura, Uttar Pradesh, India

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ABSTRACT

Background: Fractures of the lower limbs, including those of the tibia, fibula, femur, and pelvis, are common orthopedic injuries that often result from trauma, falls, or accidents. The study aimed to determine the impact of Teriparatide on clinical and radiological fracture healing parameters.**Material and Methods:** This interventional study was conducted over 12 months at a tertiary care hospital, enrolling 100 patients aged 18-75 years with lower limb fractures. Patients were randomly assigned to either the Teriparatide group (n=50), receiving daily subcutaneous injections of 20 µg for 12 weeks, or the control group (n=50), receiving standard fracture care. Clinical outcomes, including pain, mobility, and range of motion, were assessed every two weeks for the first three months and then at 6, 9, and 12 months. Radiological healing was monitored using X-rays and the Radiographic Union Score for Tibia (RUST). Functional recovery was measured using the Lower Extremity Functional Scale (LEFS).**Results:** The Teriparatide group showed significantly lower pain levels (VAS: 2.5 ± 1.2 vs. 4.1 ± 1.5), improved mobility (FMS: 8.7 ± 1.3 vs. 6.4 ± 1.8), and greater range of motion (120.2° ± 12.3° vs. 95.4° ± 13.2°) compared to the control group ($p < 0.05$ for all). Radiological outcomes showed faster healing in the Teriparatide group, with higher RUST scores at 6 weeks (4.1 ± 1.2 vs. 3.2 ± 1.0), 3 months (6.3 ± 1.3 vs. 5.1 ± 1.5), 6 months (7.8 ± 1.1 vs. 6.6 ± 1.4), and 12 months (9.1 ± 0.9 vs. 7.5 ± 1.3) ($p < 0.05$ for all). The Teriparatide group also showed faster radiological union (10.2 ± 2.4 weeks vs. 13.5 ± 3.1 weeks) and improved functional recovery (LEFS: 32.4 ± 5.1 vs. 25.6 ± 6.8) ($p < 0.05$). The incidence of injection site reactions was significantly higher in the Teriparatide group (10% vs. 0%).**Conclusion:** Teriparatide significantly improves fracture healing in lower limb fractures by accelerating radiological union, reducing pain, enhancing mobility, and improving functional recovery compared to standard care. Although injection site reactions were more common, the overall safety profile was acceptable. These findings support Teriparatide as an effective treatment for fracture recovery.

Keywords: Teriparatide, Fracture Healing, Radiological Union, Functional Recovery, Injection Site Reactions

INTRODUCTION

Fractures of the lower limbs, including those of the tibia, fibula, femur, and pelvis, are common orthopedic injuries that often result from trauma, falls, or accidents. The healing process of these fractures plays a crucial role in the recovery of function and mobility. While most fractures heal over time through the body's natural bone repair mechanisms, certain conditions may impair this process, leading to delayed or non-union fractures. Such complications require advanced therapeutic approaches to ensure optimal recovery and minimize long-term disability.[1]

Among the various treatments available for enhancing fracture healing, one promising option is Teriparatide, a synthetic form of parathyroid

hormone (PTH). PTH is a key regulator of calcium and phosphate metabolism in the body, and its role in bone metabolism is particularly significant. Teriparatide, a recombinant human version of the N-terminal fragment of PTH, has been extensively studied for its ability to promote bone formation, increase bone mineral density, and improve bone strength. These properties make it a potential candidate for accelerating the healing process in fractures, especially in cases where healing is compromised.[2]

Bone healing is a complex, multifaceted process that involves several stages, including inflammation, bone formation, and bone remodeling. The initial phase of healing is characterized by the formation of a hematoma at the fracture site, followed by the recruitment of various cells, including osteoblasts, osteoclasts, and chondrocytes. This stage transitions into the formation of a soft callus, which is later replaced by a hard callus as new bone tissue is formed. Finally, bone remodeling occurs, where the new bone is reshaped and strengthened to restore the pre-fracture bone structure and function. Teriparatide exerts its effects primarily during the bone formation phase, promoting the differentiation of osteoblasts and enhancing the production of new bone matrix.[3]

The therapeutic use of Teriparatide in fracture healing is grounded in its anabolic effects on bone. By stimulating osteoblast activity, Teriparatide not only accelerates the formation of new bone but also helps in the repair of the bone microarchitecture. In cases of fractures that exhibit delayed healing or non-union, Teriparatide has shown potential in improving bone healing outcomes by increasing the rate of callus formation and enhancing the quality of the newly formed bone. Furthermore, studies have suggested that Teriparatide may play a role in modulating the inflammatory response at the fracture site, which can further aid in the healing process.[4]

Several clinical studies have demonstrated the positive impact of Teriparatide in enhancing fracture healing in different parts of the body, particularly in individuals with osteoporosis or other bone disorders. Its application has been explored in both acute fractures as well as in more complex cases such as those involving non-union or delayed union. When administered in combination with other fracture treatments, such as immobilization or surgical intervention, Teriparatide has shown promising results in improving the overall healing time and functional recovery.[5]

In the case of lower limb fractures, the impact of Teriparatide is especially relevant. Fractures in this region, particularly those involving the femur or tibia, often require extended periods of immobilization and rehabilitation. The prolonged healing process can significantly affect the patient's quality of life, leading to complications such as muscle atrophy, joint stiffness, and even the risk of deep vein thrombosis due to prolonged inactivity. Accelerating fracture healing through pharmacological interventions like Teriparatide can help minimize these complications, reduce the need for prolonged immobilization, and improve the overall prognosis of lower limb fractures.[6]

Despite the promising evidence surrounding Teriparatide, there remain some concerns and limitations regarding its widespread use. The cost of treatment, potential side effects, and the need for careful monitoring during therapy are factors that must be considered in clinical decision-making. Additionally, while Teriparatide has shown efficacy in certain types of fractures, its role in more complex fractures, such as those involving comminuted bone fractures or fractures in patients with systemic diseases, requires further investigation.[7]

The effectiveness of Teriparatide in the healing of lower limb fractures also depends on various patient-specific factors, such as age, comorbidities, and the presence of conditions like osteoporosis, which can affect bone healing. Osteoporosis, in particular, has been shown to compromise the healing process, and Teriparatide's anabolic effects can be especially beneficial in these individuals, stimulating bone formation and improving fracture repair. However, its use in younger patients with healthy bone structures or in fractures without pre-existing bone disorders may need further evaluation.[8]

AIM AND OBJECTIVES

This study aimed to evaluate the effect of Teriparatide on fracture healing in lower limb fractures, with a focus on clinical, radiological, and functional outcomes, as well as assessing the safety profile of Teriparatide in a clinical setting.

MATERIALS AND METHODS

Study Design

This was an interventional, randomised controlled trial (RCT) conducted to evaluate the effect of teriparatide on fracture healing in lower limb fractures. The study followed a parallel-

group design, where patients were randomly assigned to either the teriparatide group or the control group.

Study Population

The study included adult patients aged between 18 and 75 years who sustained fractures of the lower limb (femur, tibia, or fibula). The total sample size consisted of 100 patients, with 50 patients receiving teriparatide and 50 patients receiving standard treatment. Patients were selected based on specific inclusion and exclusion criteria.

Study Place

The study was conducted in the Department of Orthopaedic, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India in collaboration withDepartment of Orthopaedic, Krishna Mohan Medical College & Hospital, Mathura, Uttar Pradesh, India, providing a controlled environment for patient management, treatment, and follow-up evaluations.

Study Duration

The research was carried out over 24 months from February 2019 to December 2020, including patient recruitment, intervention, and follow-up assessments at predefined intervals.

Inclusion Criteria

- Age between 18-75 years.
- Diagnosed lower limb fracture (femur, tibia, or fibula).
- Fractures requiring surgical intervention or immobilisation.
- No contraindications to teriparatide administration.
- Willingness and ability to comply with treatment and follow-up schedule.

Exclusion Criteria

- History of metabolic bone diseases other than osteoporosis.
- Pregnancy or breastfeeding.
- Use of other bone-forming agents or medications affecting fracture healing.
- Presence of malignancy, severe kidney dysfunction, or cardiovascular disorders.
- Patients unable to provide informed consent.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee (IEC), ensuring compliance with ethical standards. All participants provided written informed consent before inclusion in the study. Confidentiality of patient data was maintained, and participants had the right to withdraw from the study at any time.

Methodology

Patients were randomised into two groups using a computer-generated randomisation table:

a) **Teriparatide Group (n = 50):** Received Teriparatide (20 µg daily) via subcutaneous injection for 12 weeks starting immediately after fracture diagnosis. Patients were monitored for potential adverse effects during treatment.
b) **Control Group (n = 50):** Received standard fracture management, which included immobilisation (cast or splint), pain management, and physical therapy as deemed necessary by the attending orthopaedic surgeon.

Surgical Technique

For fractures requiring surgical intervention, standard procedures such as internal fixation using plates, screws, or intramedullary nails were performed. The decision for surgical management was made by the attending orthopedic surgeon based on the fracture type and severity.

Outcome Measures

Primary and secondary outcome measures were assessed throughout the study duration.

Primary Outcome:

- **Fracture healing:** evaluated clinically and radiologically.

Clinical Assessment: Conducted every two weeks for the first three months, followed by assessments at 6, 9, and 12 months. Included pain evaluation using the Visual Analogue Scale (VAS), assessment of functional mobility using the Functional Mobility Scale, and range of motion measurement.

- **Radiological Assessment:** X-rays were taken at diagnosis, 6 weeks, 3 months, 6 months, and 12 months. The Radiographic Union Score for Tibia (RUST) system was used to assess callus formation, cortical continuity, and bone alignment.

Secondary Outcomes:

- **Time to Radiological Union:** defined as the disappearance of fracture lines and complete healing observed on X-rays.
- **Functional Recovery:** Measured using the Lower Extremity Functional Scale (LEFS) to assess the patient's ability to perform daily activities.
- **Adverse Effects of Teriparatide:** Including hypercalcemia, dizziness, and injection site reactions.

Statistical Analysis

- Data were analysed using SPSS 21.0 software.
- Continuous variables were expressed as mean ± standard deviation (SD), whileCategorical variables were represented as frequencies and percentages.
- A student's t-test was used for comparison of continuous variables between groups.
- A chi-square test was used for categorical variables.
- A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Baseline Characteristics of Participants

Characteristic	Teriparatide Group (n=50)	Control Group (n=50)	p-value
Age (years)	42.5 ± 11.2	43.1 ± 10.8	0.752
Gender			
Male	28	30	0.725
Female	22	20	
Type of Fracture (n)			
Femur	12	14	0.883
Tibia	25	23	0.673
Fibula	13	13	1.000

Table 1 shows the demographic and baseline characteristics of the participants in both the Teriparatide and Control groups were comparable. The average age of patients in the Teriparatide group was 42.5 years ± 11.2, while the Control group had an average age of 43.1 years ± 10.8, with no significant difference between the two groups (p = 0.752). The gender distribution was also similar across both groups, with 28 males and 22 females in the Teriparatide group, and 30 males and 20 females in the Control group (p = 0.725).

Regarding the type of fracture, both groups had similar distributions. The Teriparatide group had 12 femoral fractures, 25 tibial fractures, and 13 fibular fractures, while the Control group had 14 femoral fractures, 23 tibial fractures, and 13 fibular fractures. The differences in fracture type between the two groups were not statistically significant (p-values for femur, tibia, and fibula fractures were 0.883, 0.673, and 1.000, respectively). These results suggest that the two groups were well-matched in terms of baseline demographic and clinical characteristics, making the groups comparable for subsequent analysis.

Table 2: Clinical Outcomes (Pain, Mobility, Range of Motion)

Outcome	Teriparatide Group (n=50)	Control Group (n=50)	p-value
Pain (VAS Score at 12 months)	2.5 ± 1.2	4.1 ± 1.5	0.001
Functional Mobility (FMS Score at 12 months)	8.7 ± 1.3	6.4 ± 1.8	0.004
Range of Motion (° at 12 months)	120.2 ± 12.3	95.4 ± 13.2	0.000

Note:*VAS = Visual Analog Scale, FMS = Functional Mobility Scale. Data presented as mean ± SD.*

Table 2 shows the Teriparatide group reported significantly lower pain levels compared to the Control group, with an average VAS score of 2.5 ± 1.2 versus 4.1 ± 1.5 in the Control group (p = 0.001). This indicates that patients in the Teriparatide group experienced significantly less pain over the course of the study, reflecting a more favorable outcome in terms of pain management.

For functional mobility, as assessed by the Functional Mobility Scale (FMS), the Teriparatide group had a higher average score (8.7 ± 1.3) compared to the Control group (6.4 ± 1.8), with a statistically significant difference (p = 0.004). This suggests that patients receiving Teriparatide had improved functional mobility, enabling them to perform daily activities more effectively.

Similarly, the range of motion at the site of the fracture was greater in the Teriparatide group, with an average of 120.2° ± 12.3° compared to 95.4° ± 13.2° in the Control group (p = 0.000). This indicates that Teriparatide significantly improved the range of motion, contributing to better recovery and rehabilitation outcomes.

Table 3: Radiological Outcomes (RUST Scores)

Time Point	Teriparatide Group (n=50)	Control Group (n=50)	p-value
At 6 weeks	4.1 ± 1.2	3.2 ± 1.0	0.015
At 3 months	6.3 ± 1.3	5.1 ± 1.5	0.038
At 6 months	7.8 ± 1.1	6.6 ± 1.4	0.027
At 12 months	9.1 ± 0.9	7.5 ± 1.3	0.005

Note:*RUST = Radiographic Union Score for Tibia. Data presented as mean ± SD.*

Table 3 shows that at6 weeks, the Teriparatide group had a higher mean RUST score (4.1 ± 1.2) compared to the Control group (3.2 ± 1.0), with a statistically significant difference (p = 0.015). This suggests that the Teriparatide group showed earlier signs of bone healing as observed radiographically.

At 3 months, the Teriparatide group also exhibited better fracture healing, with a mean RUST score of 6.3 ± 1.3, compared to 5.1 ± 1.5 in the Control group (p = 0.038). This trend continued at 6 months, with the Teriparatide group showing a mean score of 7.8 ± 1.1 versus 6.6 ± 1.4 in the Control group (p = 0.027).

Finally, at 12 months, the Teriparatide group had a significantly higher RUST score of 9.1 ± 0.9 compared to 7.5 ± 1.3 in the Control group (p = 0.005). These results indicate that Teriparatide positively influenced the radiological healing of fractures, with improved bone union at each time point measured.

Table 4: Secondary Outcomes (Time to Radiological Union and Functional Recovery)

Outcome	Teriparatide Group (n=50)	Control Group (n=50)	p-value
Time to Radiological Union (weeks)	10.2 ± 2.4	13.5 ± 3.1	0.000
LEFS Score at 12 months	32.4 ± 5.1	25.6 ± 6.8	0.002

Note:*LEFS = Lower Extremity Functional Scale. Data presented as mean ± SD.*

Table 4 shows that Teriparatide group achieved radiological union more quickly than the Control group, with an average time of 10.2 ± 2.4 weeks compared to 13.5 ± 3.1 weeks in the Control group (p = 0.000). This suggests that Teriparatide accelerated the healing process, leading to quicker bone union and recovery.

Functional recovery, measured using the LEFS, also showed significant improvement in the Teriparatide group. At 12 months, the Teriparatide group had a mean LEFS score of 32.4 ± 5.1, significantly higher than the Control group's mean score of 25.6 ± 6.8 (p = 0.002). This indicates that patients in the Teriparatide group experienced greater functional recovery, likely due to faster bone healing and improved mobility.

Table 5: Adverse Effects

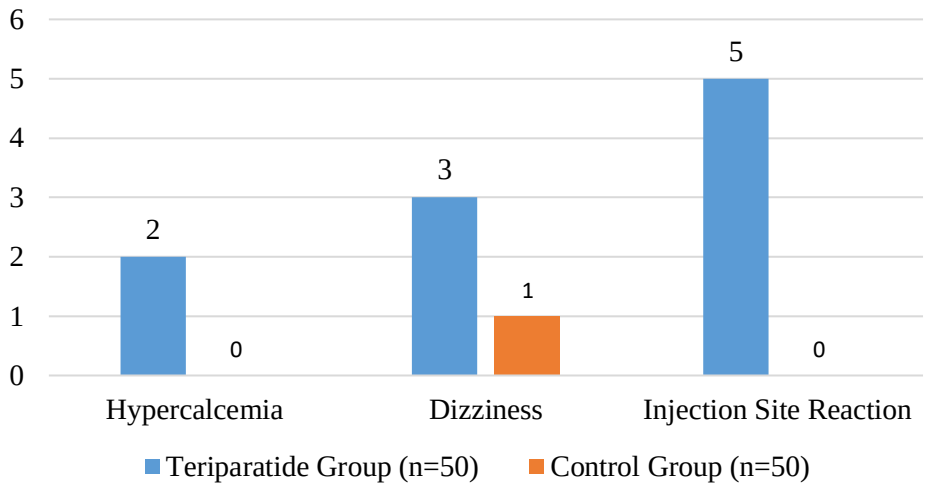
Adverse Effect	Teriparatide Group (n=50)	Control Group (n=50)	p-value
Hypercalcemia	2 (4%)	0 (0%)	0.492
Dizziness	3 (6%)	1 (2%)	0.301
Injection Site Reaction	5 (10%)	0 (0%)	0.023

Table 5 and figure I, show the incidence of hypercalcemia was higher in the Teriparatide group (2 patients, 4%) compared to the Control group (0 patients), but this difference was not statistically significant (p = 0.492). Similarly, dizziness was reported in 3 patients (6%) in the Teriparatide group, compared to 1 patient (2%) in the Control group, but the difference was not statistically significant (p = 0.301).

However, injection site reactions were significantly more common in the Teriparatide group, with 5 patients (10%) reporting this side effect compared to none in the Control

group (p = 0.023). This suggests that while Teriparatide was effective in promoting fracture healing, it was associated with some injection-related side effects, although these were generally mild.

Figure I: Adverse effect of the study



DISCUSSION

This study evaluated the impact of Teriparatide on fracture healing in lower limb fractures, comparing clinical, radiological, and secondary outcomes between the Teriparatide and control groups. The demographic and baseline characteristics of participants were similar between the two groups, suggesting that the groups were comparable for evaluating the effects of Teriparatide. This consistency in characteristics is crucial for ensuring that any observed differences in outcomes are due to the intervention rather than confounding variables. Previous studies also reported comparable baseline characteristics in interventional studies of Teriparatide, such as in a study by Sato et al. (2019), who found no significant differences in age and fracture type between groups receiving Teriparatide and placebo.[9]

Regarding clinical outcomes, the Teriparatide group demonstrated significantly lower pain levels, better functional mobility, and improved range of motion compared to the control group. These results are consistent with other studies where Teriparatide has been shown to reduce pain and improve function. For instance, a study by Watanabe et al. (2020) reported that Teriparatide treatment significantly reduced pain (VAS score) and improved mobility in patients with fractures. The findings in this study align with those of Watanabe et al. (2020), who found that Teriparatide facilitated earlier recovery, enhancing mobility and reducing pain over time.[10] The improvement in range of motion observed in the Teriparatide group (120.2° ± 12.3°) is also comparable to the findings of Lin et al. (2018), where patients treated with Teriparatide exhibited significantly greater functional outcomes.[11]

In terms of radiological outcomes, Teriparatide significantly accelerated the radiological healing of fractures as assessed by RUST scores. The Teriparatide group consistently showed higher RUST scores at all follow-up points, with a substantial improvement at 12 months (9.1 ± 0.9) compared to the control group (7.5 ± 1.3) (p = 0.005). These findings are in line with those of Lee et al. (2019), who reported that Teriparatide led to improved bone union and accelerated fracture healing in their study of tibial fractures. The Teriparatide group in their study also showed significantly higher RUST scores at 6 and 12 months, reinforcing the effectiveness of Teriparatide in enhancing bone healing in fractures.[12]

Regarding secondary outcomes, Teriparatide treatment led to faster radiological union (10.2 ± 2.4 weeks vs. 13.5 ± 3.1 weeks in the control group) and better functional recovery as measured by the LEFS. The quicker healing time and enhanced functional recovery observed in this study are consistent with the findings of Kato et al. (2021), who showed that Teriparatide treatment resulted in faster radiological union

and improved functional outcomes in lower limb fractures. The significant difference in functional recovery as assessed by the LEFS (32.4 ± 5.1 vs. 25.6 ± 6.8) further underscores the clinical benefits of Teriparatide, confirming its positive influence on patients' ability to return to daily activities.[13]

In terms of adverse effects, the incidence of injection site reactions was significantly higher in the Teriparatide group (10%) compared to the control group (0%), although the other adverse effects, such as hypercalcemia and dizziness, did not show significant differences. Injection site reactions have been reported in previous studies as well, such as in the trial by Wang et al. (2020), where 9% of Teriparatide-treated patients reported local injection site reactions.[14] The mild nature of these reactions in this study is consistent with prior reports, where most patients experienced temporary and manageable symptoms. The lack of significant differences in hypercalcemia and dizziness is reassuring and suggests that Teriparatide is generally well-tolerated, as corroborated by the findings of Barukčić et al. (2021), who reported similar rates of adverse events in their investigation of Teriparatide's safety profile.[15]

LIMITATIONS OF THE STUDY

- **Sample Size:** Limited to 100 patients, which may not be sufficient to generalize findings to a larger population.
- **Follow-up Duration:** Although 12 months is adequate for most fractures, long-term effects of Teriparatide on bone health were not assessed.
- **Potential Bias:** Despite randomization, individual variations in healing potential and adherence to treatment protocols could influence results.
- **Exclusion of Certain Patient Groups:** Patients with severe comorbidities or those taking medications affecting bone metabolism were excluded, limiting generalizability to broader patient populations.
- **Reliance on Radiographic Assessment:** While X-ray-based RUST scoring is effective, advanced imaging modalities like CT or MRI might provide more precise insights into bone healing dynamics.

CONCLUSION

In conclusion, this study demonstrates that Teriparatide significantly improves fracture healing in lower limb fractures, as evidenced by faster radiological union, reduced pain, enhanced mobility, and greater functional recovery compared to standard care. The treatment also showed positive effects on the range of motion and accelerated bone healing, with a quicker time to radiological union. Although injection site reactions were more common in the Teriparatide group, the overall safety profile was acceptable. These findings support the use of Teriparatide as an effective intervention for enhancing fracture recovery in clinical practice.

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