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Research Article

TO STUDY THERAPEUTIC USE OF TERIPARATIDE WITH FRACTURES THAT DELAY HEALING OF THE LOWER LIMBS: UPDATE

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ABSTRACT

According to the Food and Drug Administration (FDA), a fracture is considered persistent if it lasts for at least nine months without showing any indications of healing for three months. The biggest difficulty now facing orthopedic surgeons is delayed bone healing and nonunion. The failure of the body to mend a fracture is known as nonunion of bone. The aim of the study was to Therapeutic use of teriparatide with fractures that delay healing of the lower limbs: update The current prospective interventional study was carried out on patients attending our tertiary care Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, Orthopaedic Emergency and Outpatient Department over a one-year period.A total of 160 patients were initially enrolled and then after meeting inclusion criteria total 124 patients were selected for study. They were divided by randomisation by 1:1 method into two groups- Group A was test group of 62 cases; in which subcutaneous injection TPH 20 mcg daily up to six months was given along with calcium 500 mg and vitamin D 25 mcg, while in 62 cases in Group B (control group) only calcium 500 mg and vitamin D 25 mcg were given. Injection TPH was started within 10 days of fracture and given for six months. No placebo injection was given in control group. A 42 (67%) cases presented within 24 hours of injury, 32 (52%) cases reported between 24 to 48hours and 30 (48%) cases came after 48 hours of injury. All patients in test group were started with TPH within 10 days of fracture. A 38/62 (61.2%) cases of test group while 37/62 (60%) cases of control group were treated by surgical methods by open reduction and internal fixation by interlocking nailing (42/85; 49%) and plating (33/85; 39%). All those 85 patients 2 needing surgery in both test and control groups were operated within 2 to 7 days of presentation. TPH 20 mcg subcutaneously administered daily for six months at a regular dose may accelerate clinical and radiographic fracture union, encourage early weight bearing, and improve the alleviation of pain. As a result, improved functional outcomes and pre-fracture ambulatory status are possible without experiencing any serious side effects.

Keywords: -Teriparatide, Parathyroid Hormone, Radiological union, strontium ranelate.

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INTRODUCTION

According to the Food and Drug Administration (FDA), a fracture is considered persistent if it lasts for at least nine months without showing any indications of healing for three months. [1-2]The biggest difficulty now facing orthopedic surgeons is delayed bone healing and nonunion. [1]The failure of the body to mend a fracture isknown as nonunion of bone. The pace of fracture healing is influenced by a number of variables, which are categorised into general and local components.

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The first group of factors includes the patient's age, the type of bone involved, nutritional status, drug therapy, and bone pathology. Many medications and pre-existing bone pathology, such as corticosteroids, NSAIDs, or osteogenesis imperfecta, have a negative impact on fracture healing. The speed of the fracture's union also decreases with skeletal maturity and if the patient is not in good nutritional status and others metabolic disease of bone.

Separation of bone ends, disruption of blood supply, infections, characteristics of the involved bone, and type of fracture are all local factors. Bone ends must not be separated or with soft tissue interposition, blood supply is essential and its interruption may result in necrosis, pathogens interact with reparative cellular activity, resulting in a prolonged inflammatory phase, and finally, any type and localization of fracture heal according to their intrinsic characteristics.

Parathyroid Hormone (PTH) is considered to be a potential treatment option in fractures with impaired healing.[3] It is deemed as a key regulator of calcium metabolism in the body. Although hyperparathyroidism is associated with bone loss, intermittent administration of PTH has lead to increased bone mass, which may be due to the more dominant anabolic effects than the catabolic effects in PTH. [4] Teriparatide, a synthetic PTH analogue containing the 1e34 amino acid (PTH 1e34) is often used for treating osteoporosis. In recent years, the efficacy of teriparatide in promoting fracture healing has been reported in numerous animal models and clinical studies.[5]

The purpose of this study was to compare function, pain, and the need for analgesics before and after fracture treatment with TPH evaluated at regular intervals and to determine whether TPH enhances fracture healing in cases of lower limb fractures since it is still not regularly used as a supplement to calcium and vitamin D in lower limb fracture cases in India. The aim of study therapeutic use of teriparatide with fractures that delay healing of the lower limbs: update

MATERIAL AND METHODS

The current prospective interventional study was carried out on patients attending our tertiary care Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, Orthopaedic Emergency and Outpatient Department over a one-year period.Sample size was calculated keeping in consideration, the number of lower limb fracture cases being treated at our institute over last two years using software G Power 3.1, effect size of 0.65 was taken. Ethical committee approval was taken and valid written consents from patients were taken. Inclusion criteria for study were fractures in lower limbs, age equal/more than 50 years, communited fractures or fractures with presence of osteopenia or osteoporosis, closed fractures. All women included were postmenopausal.

Patients with age less than 40 years, open fractures, altered biochemical markers (calcium less than 8.6 mg/dL and/or vitamin D levels less than 20 ng/mL), presence of any metabolic bone disorder or malignancy and patients already taking TPH, patients having known malignancy, multiple injuries,head injury, joint disease and addiction to drug/alcohol were excluded from study.
A total of 160 patients were initially enrolled and then after meeting inclusion criteria total 124 patients were selected for study. They were divided by randomisation by 1:1 method into two groups- Group A was test group of 62 cases; in which subcutaneous injection TPH 20 mcg daily up to six months was given along with calcium 500 mg and vitamin D 25 mcg, while in 62 cases in Group B (control group) only calcium 500 mg and vitamin D 25 mcg were given. Injection TPH was started within 10 days of fracture and given for six months. No placebo injection was given in control group.

Time taken for radiological union, time to clinical union, and complete weight bearing time were among the criteria considered. Clinical union was defined as the lack of pain with ordinary loading, the absence of aberrant movement or crepitus, and the absence of tenderness at the site of the fracture. On an X-ray, radiological union is the creation of at least three of the four cortices. [6]

At regular intervals of one month, three months, six months, and 12 months following therapy, pain ratings by VAS on a range of 0-100 mm were also reported.[7] Additionally, DASH score, which computes scale scores ranging from 0-no disability to 100-most severe disability, was used to evaluate functional outcome. The DASH score questionnaire was mentioned as an extra tool since it highlights several everyday tasks that call for flexibility and stability in the lower limbs, as well as linked diabetes mellitus and hypertension.[8]

Statistical Analysis

Data collected were entered into MS-Excel 2013 spreadsheet. The collected data were analysed using IBM SPSS version 22.0 software. Mann-Whitney U Test was used to calculate p-value. Significant p-value was taken as p-value <0.05 and data presented as mean and Standard Deviation (SD).

RESULTS

Group A had 42 (68%) females and 20 (32%) males. Group B had 38 (61%) females and 24(39%) males. All patients in both the groups were of more than 40 years age [Table-1].

Table 1 Group wise distribution

	Group-A	Group -B
Females	42 (68%)	38 (61%)
Male	20 (32%)	24(39%)

Table 2 Age Wise Distribution

Age	Group-A		Group -B	
	F	M	F	M
40-50	7	3	9	5
51-60	26	12	13	16
61-70	5	3	10	2
>71	4	2	6	1

Table -3 Patients and fracture related characteristics in both groups.

Characteristic	Group-A	Group -B
Osteopenia or osteoporosis	23(37%)	20(32%)
Surgically treated cases	49(79%)	45(73%)
Communited fractures	17(27%)	15(24%)
Postmenopausal women	27(64%)	18(75%)

A total of 17(27%) cases in test group and 15(24%) cases in control group had communited fracture.

All fractures were of long bones i.e., femur, tibia and fibula and closed in nature.

Table 4: Long bone involved in injury in both groups

Bone	Group-A	Group -B
Femur	29(47%)	28(45%)
Tibia	15(24%)	14(22%)
Fibula	11(18%)	13(21%)
Both tibia and fibula	7(11%)	7(11.2%)

A 42 (67%) cases presented within 24 hours of injury, 32 (52%) cases reported between 24 to 48hours and 30 (48%) cases came after 48 hours of injury. All patients in test group were started with TPH within 10 days of fracture. A 38/62 (61.2%) cases of test group while 37/62 (60%) cases of control group were treated by surgical methods by open reduction and internal fixation by interlocking nailing (42/85; 49%) and plating (33/85; 39%). All those 85 patients 2 needing surgery in both test and control groups were operated within 2 to 7 days of presentation.

Weight Bearing, Clinical Union and Radiological Union

Average time period for full weight bearing with support, for test group was 16±2.7 weeks and 19±1.8 weeks in control group (p=0.001). Below knee pop cast was given in 9 cases of communited fractures of tibia/fibula. Average time to clinical union in test group was 14±1.9 weeks and in control group 18±2.2 weeks. Average time to radiological union was 15±1.4 weeks in test group while 25±2.2 weeks in control group (p-0.001).

Pain Score and Function Outcome

Decrease in pain is supposed to be an important indicator of fracture healing. On VAS from 0 to 100 mm, there was significant reduction in pain scores, especially on activity, in test group as compared to control group on first follow-up at one month, at three months and at six months follow-up needing fewer analgesics (p=0.001). Final follow-up at 12 months had comparable results in both groups; p>0.05.

DASH score was used to evaluate functional outcome. Patients treated with TPH, calcium and vitamin D had better functional outcome than those with calcium and vitamin D alone (p=0.001).None of the patients were lost to follow-up due to regular and rigorous follow-up and good patient compliance. Regular treatment and follow-up resulted in good callus formation along with less adverse effect.

Adverse effects such nausea (two in each group), sweating (none in either group), headaches (one in each group), and hypercalcemia (one in each group) did not differ significantly between the two groups. Within the first month of treating the fractures, every negative impact materialised. There were only two incidences of minor bruising at the injection site in the test group and none in the control group. In neither group were there

any fracture-related additional problems that were statistically significant.

DISCUSSION

In the present study authors have used 20 mcg of daily subcutaneous TPH for six months in lower limb fracture cases and achieved statistically significant benefits in time to clinical and radiological fracture union along with decreased pain score, better functional outcome with no significant adverse effects. Significant reduction of clinical and radiological union time ($p<0.05$) was achieved in present study. which is correlated with Yoon B and Kim K reported a study about radiographic features of TPH induced healing in femoral insufficiency fractures. [9]It was observed that callus was formed at very early stage, in some cases as early as two weeks. There was abundant callus formation. Normal bone remodeling was observed after one year in TPH treated cases.

In present study better pain control ($p=0.001$) was obtained similar to Kim SJ et al., [10] VAS pain scores ($p=0.008$). Almirol EA et al., also did not report any significant adverse effects with use of TPH used in fracture healing in bones of lower limb [11]shows adverse effects of present study compared to other studies. Kim SJ et al., in a retrospective study observed less postoperative surgery related complications in TPH treated group.

Lower limb fractures cause significant handicap, which causes people to lose their independence and become dependent on other family members and relatives. Consequences for society's economy include being absent from work and relying on others, sometimes even for simple household tasks. Age and fracture healing have a detrimental relationship, according to Giannotti S et al. [12] Therefore, in senior patients, it is crucial to achieve prompt clinical and radiological union. The several stages of callus production during fracture healing are influenced by a variety of variables, including patient-related and treatment method-related aspects.

The rate of fracture union can be accelerated by TPH treatment, although the ideal dose, dose interval, timing, and duration of TPH treatment for fracture healing are yet unknown. The goal of the current investigation was to determine how TPH affected the healing of lower limb fractures. According to Bhandari M et al., [13] TPH is still an option for treating hip fractures in older patients who are at high risk for subsequent fractures because there is less stress in these circumstances. Results supporting the use of strontium ranelate (SR) in fracture healing and non-union were published by Shin YH, et al.[14]SR was compared to calcium and vitamin D in a controlled experiment with individuals who were over 60 and receiving conservative care. SR did not improve fracture healing when administered in the acute periods. In the current trial, TPH was administered to patients who were older than 50 and who were receiving both conservative and surgical treatment.

CONCLUSION

Each example had a stable fracture repair and an acceptable reduction. Daily injection compliance must be assured; as an alternative, a biweekly dosing schedule may be explored.TPH 20 mcg subcutaneously administered daily for six months at a regular dose may accelerate clinical and radiographic fracture union, encourage early weight bearing, and improve the alleviation of pain. As a result, improved functional outcomes and pre-fracture ambulatory status are possible without experiencing any serious side effects.

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