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To Determine the Efficacy of Strontium Ranelate in the Healing of Surgically Fixed Tibial Diaphyseal Fractures Using Intramedullary Devices (Nails) in Tertiary Care Hospital

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ABSTRACT

Introduction: Strontium ranelate is a strontium salt of ranelic acid that enhances the bone healing by increasing deposition of new bone forming osteoblasts and reduces function and number of the bone resorbing osteoclasts. Strontium ranelate acts via a dual mode of action with both bone-forming and bone-resorbing properties, and may therefore be beneficial in fracture healing. It is therefore promoted as a "dual action bone agent.

Objective: To determine the efficacy of strontium ranelate in the healing of surgically fixed tibial diaphyseal fractures using intramedullary devices (nails) in tertiary care hospital.

Material and Methods: This descriptive case series study was done at department of orthopaedic surgery, Chandka medical college Larkana and conducted for six months between 1st of July 2021 to 31st of December 2021. Total 184 patients with closed diaphyseal tibial fracture were included. All patients were undergone closed reduction and internal fixation using nail. Strontium ranelate as single dose for duration of three months was given. Final outcome i.e. efficacy was measured on the basis of clinical and radiological criteria. Descriptive statistics were calculated using SPSS. Stratification was done and post stratification chi square test was applied. P-value ≤ 0.05 was taken as significant.

Results: There were 118 were male and 66 were female. Mean age of study subjects was 34.18±9.80 years. Mean duration of fracture was 5.78±3.29 days. 49.5% were caused fracture due to road traffic accident. Efficacy of strontium ranelate was found in 67.9%. The significant association of efficacy of strontium ranelate was observed with age and duration of fracture.

Conclusion: Significant efficacy of strontium ranelate in healing of surgically fixed tibial diaphyseal fractures on clinical and radiological assessment was observed.

Key Words: Efficacy, Strontium Ranelate, Fixed Tibial Diaphyseal Fractures, Nails, Bone healing, Radiological union

INTRODUCTION

The tibia is the most commonly fractured long bone.[1,2] Diaphyseal fractures of tibia are the most common. Minor trauma can lead to fractures of tibia because the tibia by its location is exposed to frequent injuries as one third of its surface is subcutaneous.[3]

Tibial diaphyseal fractures are usually treated surgically procedures like external fixation, open reduction internal fixation using dynamic compression plate (DCP) and screws and intramedullary (IM) nailing but still have complications such as delayed union or non-union.[3,4] The treatment of delayed unions, nonunions, malunions and bone loss pose great challenges for orthopedic surgeons.[5]

Fracture healing disorders negatively affect the patient's quality of life and result in high healthcare costs, as a second surgery is necessitated to stabilize the fracture and stimulate bone biology. In most cases, successful union will be achieved by restoration of the alignment and stable fixation of the fracture.[6] There are several factors influencing the fracture healing process.[7] Different modalities have been looked into to enhance union.[8]

Strontium ranelate acts via a dual mode of action with both bone-forming and bone-resorbing properties[9] and may therefore

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be beneficial in fracture healing. Strontium ranelate is a strontium salt of ranelic acid that both increases deposition of new bone osteoblasts and reduces the resorption of bone by osteoclasts. It is therefore promoted as a "dual action bone agent".[10]

Strontium ranelate (SrR) is an approved drug for treating osteoporosis and is thought to have anti-resorptive as well as bone anabolic properties. There is some evidence of its effect on the enhancement of healing of fractures.[11]

Several case reports on strontium promoting fracture healing have been reported in the literature.[6] Strontium ranelate accelerates filling of the bone defect and improves the properties of bone healing.[12] Strontium nucleus is almost similar in size to that of calcium, the body easily absorbs it, incorporating it into the bones and tooth enamel instead of calcium.[13] In a study, efficacy of strontium ranelate in the healing of surgically fixed tibial diapyseal fractures was 20(62.5%) .[11]

In all previous studies efficacy of strontium ranelate in bone healing has been assessed in the Tibial diaphyseal fracture which were fixed with absolute fixation using extramedullary dynamic compression plate (DCP) and in this study its efficacy will be assessed in the diaphyseal Tibial fracture fixed with relative fixation using intramedullary devices (nails). Both types of fixations have different mechanism of healing. In relative fixation bone healing occurs with callus formation, whereas in absolute fixation callus is not formed it heals with osteon and cutting cone formation.

The aim of the study is to determine the efficacy of strontium ranelate in the healing of surgically fixed tibial diaphyseal fractures based on clinical and radiological assessment. If we will find high efficacy so we would develop management guideline and treatment protocol to promote strontium ranelate for bone healing in surgically fixed diaphyseal tibial fracture.

MATERIAL & METHODS

This descriptive case series study was conducted from 1st of July 2021 to 31st of December 2021, after getting approval from hospital ethical review committee. The patients with closed diaphyseal tibial fracture visited to the department of Orthopaedic, Chandka medical college Larkana and fulfilled the inclusion criteria were included in the study. Patient demographics and clinical history was taken by the principal investigator.

By taking efficacy of strontium ranelate in the healing of surgically fixed tibial diapyseal fractures using P=62.5%,11 d=7% the calculated sample size is 184 patients with the help of WHO software for sample size calculation taking 95% confidence level. Non-probability consecutive sampling technique was used for the study.

All patients of either gender, age between 18 to 60 years with closed diaphyseal tibial fracture less than 30 days old on the basis of history, clinical examination and radiological examination of x-ray Tibia antero-posterior (AP) and lateral views were included in study, whereas exclusion Criteria were Patients with undisplaced, open fractures with metaphyseal on the basis of clinical history/examination, patient with previous surgery on same limb on the basis of clinical history, patient who will require bone graft on the basis of clinical history, pregnant women on the basis of clinical history, renal impairment on the basis of clinical history.

All patients were undergone closed reduction and internal fixation of the Tibial diaphyseal fracture using intramedullary, interlocking devices (nail). All surgeries were performed by a consultant orthopaedic surgeon having experience of more than 15 years. Strontium ranelate 2 gm per day as a single dose for duration of three months were given after surgery as oral medication with identical instructions on its use in healing of fracture. Patients were followed at one month, two months and three months after supply of drug of strontium ranelate postoperatively for clinical and radiological evaluation. The final outcome was assessed at follow up after 3 months. Clinical examination was taken as per operational definition. Patients were sent to radiology department for radiological evaluation. The x-ray films were analyzed and final comments were given by the experience consultant radiologist having experience more than 5 years. Final outcome of efficacy of fracture healing of strontium ranelate was measured on the basis of clinical and radiological criteria after three months as per operational definition. The effect modifiers and biasness were controlled by strictly following the inclusion and exclusion criteria.

Patient's data were compiled and analyzed through statistical package for Social Sciences (SPSS) Version 21. Frequency and percentage were computed for qualitative variables like gender, educational status, economic status, mechanism of injury, findings of clinical examination, findings of radiological investigations and efficacy. Mean±SD were calculated for quantitative variable i.e. age and duration of fracture. The stratification was done on gender, age, duration of fracture, educational status, economic status, and mechanism of injury to see the effects of these modifiers on outcome using Chi-square test. $P \leq 0.05$ was considered as significant.

RESULTS

Total 184 patients of either gender with age 18-60 years meeting inclusion criteria of study were evaluated to determine the efficacy of strontium ranelate in the healing of surgically fixed tibial diaphyseal fractures using intramedullary devices (nails). Descriptive statistics were calculated using SPSS version 21. Qualitative variables were presented

by frequency and percentages. Quantitative variables were presented by mean±SD. Stratification was done and post stratification Chi square test was applied to observe the effect of modifiers on outcome. P value ≤0.05 was considered as significant.

Out of 184 study subjects, 118 were male and 66 were female, overall mean age of study subjects was 34.18±9.80 years, overall mean duration of fracture was 5.78±3.29 days. It was observed that 35.9% patients got education till secondary. Among 184 study subjects, 19.6% patients belonged to lower class, 43.5% from middle and 37% from upper middle class, among total study subjects 49.5% were caused fracture due to road traffic accident. The detailed frequency distribution of mechanism of fracture is presented in Table-1.

Efficacy of strontium ranelate was determined by clinical and radiological findings. Frequency distributions of Investigations of fracture healing by clinical and radiological criteria are presented in Table-2 and Table-3.

In our study, efficacy of strontium ranelate was found for 67.9% study subjects as presented in Table-4.

Stratification with respect to gender, age, duration of fracture, educational status, economic status and mechanism of injury was done to observe effect of these modifiers on efficacy of strontium ranelate. P-value ≤0.05 was considered as significant.

The results showed that there was significant association of efficacy of strontium ranelate with age (p=0.005) and duration of fracture (p=0.032) while no significant association was found with gender (p=0.702), educational status (p=0.734), economic status (p=0.911) and mechanism of injury (p=0.190).

DISCUSSION

Efficacy of strontium ranelate in fracture healing can be defined on the basis of both clinical and radiological criteria. Low-intensity ultrasound were tried for fracture healing in a double-blind placebo-controlled study and showed significantly increased healing and union rates in terms of number of days.[12]

However, Emami et al. failed to show any shortening of healing time with low-intensity ultrasound treatment in fresh tibial fractures treated with a reamed and statically locked intramedullary (IM) nail.[13] A Cochrane systemic review by Griffin XL et al.[14] concluded that the currently available evidence for usage of ultrasound is insufficient to support the routine use of this intervention in clinical practice. Antiresorptive and anabolic drugs have been evaluated for healing. Parathyroid Hormone (PTH) is known to stimulate bone formation, has potent anabolic effects in both animals and human models.[15,16] and promotes fracture healing. Anti-catabolic agents, such as bisphosphonates, did not seem to interfere with initial union or to increased callus size. However, they are known to affect both bone resorption and formation, raising the possibility of decreasing the callus remodelling.[17]

The interest in use of SrR for fracture healing was initiated by Cebesoy et al.[18] Li et al. [19] in a paper, used systemic treatment with SrR on ovariectomised rats with fractured tibiae. Callus quality was assessed by radiographical, histological, micro-computerised tomography, and biomechanical examinations at 4 and 8 weeks after fracture. Results revealed that systemically applied SrR promoted osteoporotic fracture healing. Maimoun et al. found that SrR improves implant osteointegration and it increased pullout strength. It improved microarchitecture of bone around implant and thus implant bone contact increased. SrR had a significant beneficial effect on parameters of bone biomaterial properties at both cortical and trabecular areas.[20]

This was also supported in another study that showed improved mature bone formation and mechanical strength of bone treated with SrR compared to placebo in rats.[21] It was shown that SrR not only increases fracture healing radiologically, but also relieves pain with improved functional outcomes. Results showed good healing even in non-unions and delayed unions.[22] Similarly, a case series of 4 patients showed improved fracture healing in patients treated with SrR.[9]

In a study there were 39(61.9%) males and 24(38.1%) females. Overall mean age was 31.2±11.8 years and the mean duration of fracture was 10±9.3 days. In terms of age, gender and duration of fracture there was no statistically significant difference between the drug group and placebo group two groups (p=0.998, p=1.000 and p=0.220 respectively). Radiologically at 90 days, there was highly significant difference between SrR group (n=23; 71.9%) and placebo group (n=10; 32.3%) (p=0.002).[11]

In our study, there were 64.1% were male and 35.9% were female. Mean age of study subjects was 34.18±9.80 years. Age of 65.0% patients was ≤35 years and age of 35.0% patients was >35 years. The overall mean duration of fracture was 5.78±3.29 days. Duration of 31.0% patients was ≤3 days and duration 69.0% patients was >3 days. Main cause was road traffic accident which was 49.5%. Efficacy of strontium ranelate was found for 67.9% study subjects and there was significant association of efficacy of strontium ranelate with age (p=0.005) and duration of fracture (p=0.032).

Currently, there is no single scale that can measure fracture healing efficacy other than looking at X-ray evidence. Important parameter for fracture healing may be defined clinically as absence of pain during weight-bearing and radiologically by bridging of fracture with callus formation. As

strontium is a heavy metal, there have been concerns that SrR may be retained in the body for long duration of time. Animal studies have shown that once treatment is stopped, strontium is cleared from the body and its concentration in bone was found to be decreased. The clinical significance of these findings in humans are yet unknown.[11]

Study Limitations: The present study has some limitations. This study was a single hospital-based study. The main imitations of the present study include nonrandomized study design. It was conducted with small sample size therefore; the results might not be generalizable to larger populations.

CONCLUSION

The results of our study conclude a significant efficacy of strontium ranelate in healing of surgically fixed tibial diaphyseal fractures based on clinical and radiological assessment. This may open up new avenues to look at pharmacological stimulation of fracture healing, thus potentially reducing the long-term morbidity associated with fracture healing, delayed unions and non-unions. This also has significant economic implications by reducing not only the high costs associated with delayed unions and non-unions, but, by potentially accelerating fracture union, ensuring early return to full function and work.

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PERMISSION

It was taken from ethical review committee of the institute with letter no: CMCHL/3.2020/09

CONSENT

Informed consent was taken from every participant of study

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CONFLICT OF INTERSET

None

AUTHORS CONTRIBUTION

Soomro Saifullah

1. Conceived and designed the analysis
2. Collected data
3. Performed Analysis
4. Wrote the paper
5. Corresponding the queries

Soomro Zamir A

1. Collected Data
2. Contributed analysis tools

Chandio M Shuaib

1. Conceived and designed the analysis
2. Collected data

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Table 1: Frequency Distribution of Mechanism of Fracture

(n=184)

	Frequency (n)	%
Fall from Height	44	19.6
Road Traffic Accident	91	49.5
Sports	16	8.7
Other	33	17.9
TOTAL	**184**	

Table 2: Frequency Distribution of Investigation of Fracture Healing (Clinical Criteria)

(n=184)

	Yes	No
Absence of pain at the fracture site with weight-bearing	141(76.6%)	43(23.4%)
Absence of pain on palpation	126(68.5%)	58(31.5%)
Absence of pain on examination of the fracture site	70(38%)	114(62%)
TOTAL	**184**	

Table 3: Frequency Distribution of Investigation of Fracture Healing (Radiological Criteria)

(n=184)

	Yes	No
Absence of pain at the fracture site with weight-bearing	84(45.7%)	100(54.3%)
Absence of pain on palpation	140(76.1%)	44(23.9%)
Absence of pain on examination of the fracture site	127(69%)	57(31%)
TOTAL	**184**	

Table 4: Frequency Distribution of Efficacy of Strontium Ranelate

(n=184)

	Frequency (n)	%
Yes	125	67.9
No	59	32.1
TOTAL	**184**	