ORIGINAL ARTICLE

Significance of strontium ranelate in healing of surgically fixed tibial diapyseal fractures treated with strontium ranelate vs placebo; a randomised double blind controlled trial

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Abstract

Abstract: To assess the effect of strontium ranelate, an approved drug for treating osteoporosis, on the healing process of tibial fractures.

Methods: The randomised double-blinded placebo-controlled clinical study was conducted at the Indus Hospital, Karachi, from August 2011 to August 2013. Patients were randomised to receive placebo or strontium ranelate postoperatively after surgical fixation of tibial diaphyseal fractures. Assessment of fracture healing was done clinically and radiologically at 30, 60 and 90 days. SPSS 21 was used for statistical analysis.

Results: Initially, 76 patients were enrolled, but 63(82.9%) completed the study. Out of 63 patients, 32(50.8%) were randomly assigned to group A and 31(49.2%) to group B, which was administered the placebo. Overall enhancement of fracture healing efficacy of strontium ranelate group was 20(62.5%) versus 9(29%) of the placebo group.

Conclusion: Strontium ranelate was effective in enhancing fracture healing based on clinical and radiological assessment. Hence, it can be considered an effective therapeutic agent for accelerating fracture healing.

Keywords: Strontium ranelate, Fracture healing enhancement. (JPMA 64: S-123 (Suppl. 2); 2014)

Introduction

Fractures of the long bones are very common which are usually treated surgically but still have complications such as delayed union or non-union. Different modalities have been looked into to enhance union.[1,2] Tibial fractures are among the commonest of the adult long bone fractures, usually in young adults, and as a result of motor vehicle accidents or firearm injury. Though tibial fractures may be treated with operative fixation as well as conservatively, there is a significant rate of delayed union and non-union. Many different modalities have been tried to enhance the union of tibial fractures and decrease the risk of delayed union and non-union. Preventing delayed union in tibial fractures has remained a focus of intense study and debate.

Modalities like electrical stimulations,[3,4] pulse ultrasound,[5,6] bone morphogenic proteins (BMPs),[7-9] platelet-derived growth factors (PDGF), vascular endothelial growth factors (VEGF) and growth hormones,[10,11] have been showed to promote fracture healing.

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. We hypothesised that SrR would promote bone healing in surgically fixed diaphysealtibial fracture compared to a placebo. The current study was planned to evaluate the hypothesis.

Patients and Methods

The randomised double-blinded placebo-controlled clinical study was conducted at the Indus Hospital, Karachi, from August 2011 to August 2013 after approval by the institutional review board.

Eligible patients were identified in the emergency room (ER). Adult patients in between 18 and 60 years of age with closed diaphysealtibial fracture less than 30 days old were recruited after informed consent was obtained from each of them. Patients with un-displaced, open fractures, with metaphyseal or periarticular comminution, with previous surgery on same limb, requiring bone graft, pregnant women and those with renal impairment were excluded.

Demographic data, including age, gender, and socio-economic status, was collected. As our hospital is a free-of-cost health facility, so all patients belonged to poor socio-economic status.

All surgeries was performed by a consultant grade orthopaedic surgeon. All patients underwent open reduction and internal fixation of the tibial fracture with a

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Dynamic Compression Plate (DCP).

Groups were randomised and allocated on the basis of a draw method into group A (treatment group) and group B (placebo group). The groups were blinded and neither the surgical/medical team nor the patient knew which group contained the study drug or the placebo. Once a study arm had been allocated, the patients were provided with one-month supply of drug with identical instructions on its use. The patients was called in at postoperative day 15 for surgical wound assessment and instructed to bring the sachet for a packet count. Subsequently, the patient revisited the outpatient department (OPD) on day 30, 60, and 90 post-operation for clinical and radiological evaluation.

Outcome measures included callus and its status, ability to bear weight, tenderness and pain on palpation and weight-bearing, radiological efficacy, clinical efficacy and both radiological and clinical efficacy.

Efficacy was measured in terms of fracture union on clinical and radiological criteria.Clinical criteria included absence of pain or tenderness at the fracture site with weight-bearing, absence of pain or tenderness on palpation or examination of the fracture site and the ability to bear weight. Radiological criteria included fracture site bridging of the dense mass (callus), bridging of the fracture seen at three cortices in anterio-posterios (AP) and lateral view and obliteration of the fracture line (cortical continuity). Efficacy of fracture healing was defined as any 2 of the above radiological criteria achieved at any follow-up. Efficacy of fracture healing was defined as any 2 of the above clinical criteria achieved at 90-days.[12] Outcomes were measured at 30, 60 and 90 days for all clinical and radiological parameters.

Data was analysed using SPSS 21. Mean and standard deviation (SD) was computed for both age and duration of fracture. Frequency and percentage were computed for all the categorical variables like gender, callus and its status, tenderness and pain on palpation and weight-bearing, bear weight, radiological efficacy, clinical efficacy and both radiological and clinical efficacy. Independent sample t-test was used to check significant differences in the mean of age and duration of fracture between the two groups. Chi-square, likelihood ratio and fisher-exact tests were used to check association of various categorical variables with the groups. P <0.05 was considered significant.

Results

Initially 76 patients were enrolled, but 7(9.2%) had to be excluded due to protocol deviation, and 6(7.9%) were lost to follow-up. As such, 63(82.9%) patients who completed 90-day follow-up represented the final sample. Of the total, 32(50.8%) were randomly assigned to group A and 31(49.2%) to group B, which was administered the placebo. Overall, 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 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) (Figure-1).

Clinically at 90 days, 23(71.9%) in Sr R group and 17(54.8%) in the placebo group attained clinical efficacy. However, it

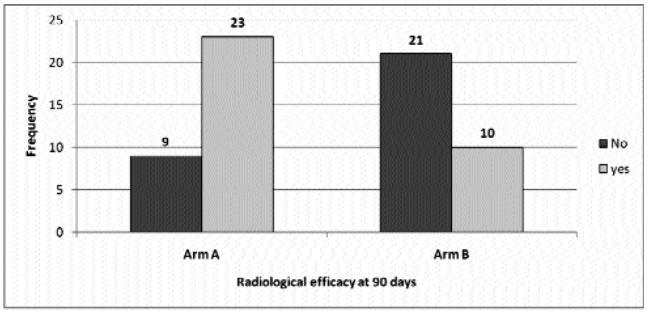

Figure-1: Frequency distribution of radiological efficacy at 90 days according to arms.

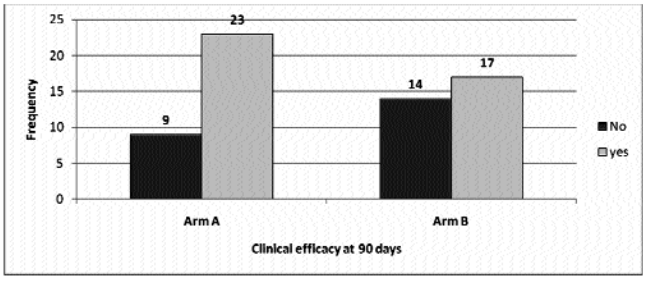

Figure-2: Frequency distribution of clinical efficacy at 90 days according to arms.

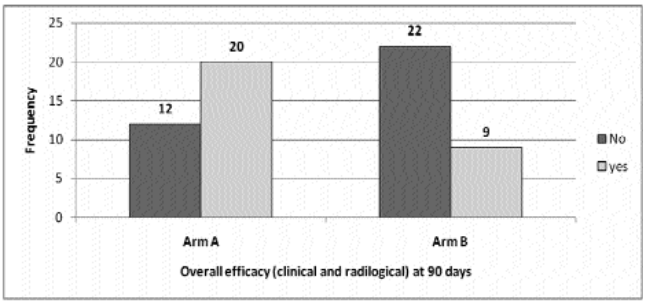

Figure-3: Frequency distribution of overall efficacy (radiological and clinical) at 90 days according to arms.

was not statistically significant (p=0.196) (Figure-2).

Overall enhancing of fracture healing efficacy of group A was 20(62.5%) and 9(29%) in group B (p=0.011) (Figure-3). Overall efficacy was more in males (n=23; 59%) compared to females (n=6; 25%) (p=0.010). Socioeconomic status, duration of fracture and age in years were not significantly associated with the overall efficacy (p=1.000; p=0.576 and p=0.442 respectively).

Overall the efficacy in the treatment group was 20(62.5%) and 9(29%) in the placebo group (p=0.011).

Discussion

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.[13]

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.[14]

A Cochrane systemic review by Griffin XL et al[15] concluded that the currently available evidence for usage of ultrasound is insufficient to support the routine use of this intervention in clinical practice.

Anti-resorptive 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,[16,17] 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.[18]

Denosumab is a relatively new anti-resorptive drug that works by inhibiting osteoclast formation and function. Studies on mice by inducing the femur fracture treatment with denosumab (10mg/kg) or alendronate (0.1mg/kg) biweekly for 6 weeks have shown increased mineralisation of callus and callus formation, but remodelling was found to be delayed.[19]

SrRis an approved drug for treating osteoporosis and is thought to have bone anabolic properties. SrR stimulates osteoblastic proliferation and synthesis of collagenous matrix.[20-22] It is also known to reduce osteoclastic activity,[23,24] and to induceosteoclasticapoptisis.[25]

The interest in use of SrR for fracture healing was initiated by Cebesoy et al[26] who failed to show any beneficial or harmful effect in rat tibia. However, Li et al,[27] in a later paper, used systemic treatment with SrR on ovariectomisedrats 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 osteo-integration 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.[28]

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.[29]

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.[30]

Similarly, a case series of 4 patients showed improved fracture healing in patients treated with SrR.[31]

Currently, there is no single scale that can measure fracture healing efficacy other than looking at X-ray evidence. We wanted to look at clinical as well as radiological criteria, and, therefore, resorted to using standard combination of clinical and radiological criteria. 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.

Our study showed that at 90 days, SrR promoted overall bone healing in surgically fixed diaphysealtibial fracture patients in comparison to those given a placebo. The overall effect on fracture healing was 62.5% versus 29% in the placebo group.

Conclusion

This is the first prospective, randomised, double-blinded, placebo-controlled clinical trial in humans that has conclusively shown a beneficial role of SrR in promoting fracture healing in surgically fixed diaphysealtibial fracture. This opens 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. Further research should be based on looking into the long-term outcomes of SrR on fracture healing.

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