ORIGINAL ARTICLE

Role of strontium ranelate in healing of surgically fixed long bone fractures after delayed/non-union: A double blind randomized controlled trial

Ijaz Ahmad, Ashfaq Ahmed, Muhammad Imran Javed, Ahsan Atta, Ammar Dogar, Rizwan Akram, Amer Aziz

Abstract

Objective: Delayed union, mal-union, non-union and bone loss after long bone fractures have remained a significant predicament in orthopedic practice. To enhance bone union after surgical fixation drugs such as strontium ranelate have shown a promising role. This study aims to assess the effect of strontium ranelate in closed diaphyseal long bone fractures that were managed with intra-medullary nailing and have undergone delayed/non-union.

Material and Methods: A randomized clinical trial was conducted at the Department of Orthopedics and Spine Centre, Ghurki Trust Teaching Hospital, Lahore from December 2016 to January 2018. Patients with non-union of long bone fractures were included after taking informed consent. They were randomized to receive placebo or strontium ranelate after non-union of closed diaphyseal fractures of long bones that were managed with intra-medullary nailing. Fractures were assessed clinically in form of Pain reduction as well as general feeling of wellbeing and radiologically at day 7, 14, 30, 60 and 90. SPSS Version 23 was used for statistical analysis.

Results: Of the 101 patients, 50 were randomly assigned to treatment group and 51 were randomly assigned to placebo group. Clinically enhanced fracture healing efficacy of treatment group was 86% (n=43) and radiologically it was 84% (n=42). Clinically enhanced fracture healing efficacy of placebo group was 60.8% (n=31) and radiologically it was 68.6% (n=35). General feeling of wellbeing significantly improved after treatment with strontium ranelate.

Conclusion: Systemic strontium ranelate has an exciting and promising role in management of fractures that have undergone non-union/delayed union in non-osteoporotic long bones and should always be considered in such patients.

Keywords: Bone fractures, delayed, fracture healing, double blind study, non-union, strontium renelate

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Ghurki Trust Teaching Hospital, Lahore
I Ahmad
A Ahmed
A Atta
A Dogar
R Akram
A Aziz

Hamdard University Hospital, Karachi.
MI Javed

Correspondence:
Dr. Ashfaq Ahmed, Department of Orthopaedics and Spine Centre, Ghurki Trust Teaching Hospital, Lahore.
Cell No:+92 333-9881342
email: ashfaqjadoon40@yahoo.com

Introduction:

For orthopedic practitioners, fracture non-union has always topped the list of most dreaded and ruinous surgical complications.[1] Delayed union, mal-union, non-union and bone loss after long bone fractures have remained a significant predicament in orthopedic practice of both developed[1] as well as developing countries.[2] In Pakistan, road traffic accidents pose the most common risk of fractures with lower limb bones being the most frequently fractured ones, according to a local survey.[3] Long bone fractures may be managed operatively or conservatively; there is a significant rate of delayed/non-union.[4] Disruptions in long bone fracture healing process negatively influence the patient's quality of life, increases treatment cost and duration and results in unnecessary consumption of healthcare facilities with frequent un-rewarding outcomes.[5]

The clinical and radiological progress of a healing fracture towards union greatly depends on apposite integration of the bio-materials into

the bone tissue. This integration occurs through adhesion, proliferation and then differentiation of osteoblastic cells. It is then followed by production of mineralized matrix directly on the surface of the bio-material. In order to enhance this osseo-integration, bio-materials are associated with molecules that stimulate osteoblastic adhesion, proliferation, and differentiation, thereby, enhancing the interaction of cells with the bio-material and ultimately the quality of the tissue interface.6

Such molecules maybe anabolic or anti-catabolic drugs commonly used in management of osteoporosis. Among these, antiresorptive agents such as bis-phosphonates (BPs) may form a larger callus and suppress the osteoclastic activity resulting in delayed remodeling of woven to lamellar bone. BPs may also develop an atypical fracture and further delay fracture healing.7 On the other hand, anabolic agent such as parathyroid hormone (PTH), although, has substantial role in bone defect healing,8 it increases cortical porosity, which has adverse effects son bone strength in the long term.9

In contrast, the ana-bolic and anti-catabolic agent strontium ranelate has shown a more promising dual mechanism of action. It increases bone formation by amplifying pre-osteoblastic and pluri-potent mesenchymal cell replication via directly interacting with calcium sensing receptor and triggering mitogenic signals. Simultaneously, strontium ranelate diminishes bone resorption by decreasing osteoclast differentiation and bone resorbing activity; the net result is improved bone strength.10 Moreover, systemic administration of strontium ranelate strengthens the micro-architecture of the bone tissue surrounding implants, thereby, enhancing implant fixation and osseo-integration.6

The role of strontium ranelate in fracture healing has only been studied once in Pakistan.11 Aslam et al conducted a randomized double blind controlled trial to assess the effect of Sr-Ron the healing of tibial fractures managed by open reduction and internal fixation with Dynamic Compression Plate. However, this study takes their work one step forward and aims to assess the effect of strontium ranelate in closed diaphyseal long bone fractures that were managed with intra-medullary nailing either with local implants or using SIGN Nail and have undergone delayed or non-union.

Material and Methods:

This randomized, double-blinded, placebo-controlled, clinical trial was conducted at the Department of Orthopedics and Spine Centre, Ghurki Trust Teaching Hospital, Lahore from December 2016 to January 2018 after approval by the institutional review board.

In this study, such patients were included who were of 18-60 years of age, suffered from closed diaphyseal fractures(Fractures of shaft) of long bone more than 3 months back, were managed with intra-medullary nailing either with local implants or using SIGN Nail (an intra-medullary nail named after its founder Kewa-nis SIGN) and then presented with delayed or non-union. Delayed or non-union was diagnosed on radiological and clinical grounds.

Patients with allergy to strontium salt, renal insufficiency, pathological fractures, pregnant patients and patients who either did not maintain follow up or did not give written informed consent were excluded from the study.

Patients were randomized with random allocation software version 1.0. Patients in Group A (active/treatment group)were given sachet of strontium rantelate (brand name: ONITA) and those of Group B(placebo group) were given placebo sachet once daily. All patients were also given non-steroidal anti-inflammatory drugs (NSAIDs) for pain management and proton pump inhibitors (PPIs) for gastric protection. All other medications were stopped to reduce the bias. Once a study arm had been allocated, the patients were provided with drug quantity (strontium ranelate ONITA/placebo, NSAIDs, PPIs)on monthly basis, for 3 months, free of cost. All patients were given identical instructions of use.

Table 1: Clinical features of patients with non-union of bone (n= 101)

Variable	Value n (%)
Age in years (Mean ± SD)	31.46 ± 13.9
Gender	
Male	87 (86.14)
Female	14 (13.86)
Fracture Location	
Humerus	11 (10.89)
Femur	35 (34.65)
Tibia	55 (54.46)
History of fracture (Delayed / non union)	(Mean 4.7 ± 1.3) Months
Smokers	23 (22.8)
Diabetes Mellitus	6 (5.9)
Glucocorticoid usage	3 (3)

Table 2: Radiological and clinical efficacy among patients with Delayed/ Non-Union after 90 days of treatment

Radiological Efficacy	**Active (n=50)** N (%)	Placebo (n=51) **n (%)**	P value
Union	42 (84.0)	31 (60.8)	<0.03*
Improvement	4 (8.0)	11 (21.6)	
Non-union	4 (8.0)	9 (17.6)	
Clinical Efficacy			
No pain	43 (86.0)	35 (68.6)	<0.037*

**Chi2 test was applied between the groups*

Table 3: General feeling of Wellbeing score during treatment (n=101)

Score	Active (n=50) Mean ± SD	Placebo (n=51) Mean ± SD	P value
Before treatment	1.38 ± 0.69	1.25 ± 0.74	0.385*
After 90 days of treatment	8.16 ± 0.79	5.57 ± 0.60	<0.001*
No pain	43 (86.0)	35 (68.6)	<0.037*

**Independent sample t test was applied between the groups*

The patients were followed at post-operative day 7, 14, 30 , 60 and 90 for assessment and instructed to bring the sachet for a packet count. On the last visit of the study (i.e. end of 12 weeks), clinical and radiological evaluation, drug accountability and side effect monitoring was conducted.

Non-union was diagnosed on the basis of clinical as well as radiological criteria at the end of 12 weeks. Clinical criteria included absence of pain or tenderness at the fracture site with weight-bearing, status of callus and adequate active and passive movements. Radiological criteria included fracture site bridging of the dense mass (callus), bridging of the fracture seen at three cortices in anterio-posterior (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 60-days. Patients who still did not show any signs of union on radiology or clinical grounds were considered as non-union and then managed accordingly. Pain was assessed using three point likert scale.

Data was analyzed using SPSS V. 23. 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 test was used to check significant differences in the mean of age and duration of fracture between the two groups. Chi-square tests were used to check association of fracture healing with the groups. Student t-test was used to find different in patient general satisfaction with the treatment during the study period. P <0.05 was considered significant.

Results:

A total of 101 patients met the inclusion criteria of this study and were included. Of these patients, 87(86.14%) were males and 14(13.86%) were females with male to female ratio of 6.21:1. Mean age of the patients was 31.46 ± 13.9 years. Group-A (ONITA group) consisted of 50 patients and group-B (placebo group) included 51 patients. Their socio demographic and clinical features are summarized in Table I.

The radiological and clinical efficacy of group-A and group-B after a follow up of 90 days are summarized in table 2. It was seen that in the active group, 84% (n=42) patients achieved radiological union of fracture with daily use of strontium ranelate and 86% (n=43) patients reported no pain. However, in the placebo group only 60.8% (n=31) achieved radiological fracture union and

68.6% (n=35) reported no pain at the end of the study, which are statistically significant $p<0.05$

General feeling of wellness (scale of 1-10) was compared between the two groups pre and post treatment, it was significantly improved. In the treatment group, mean score of well being improved from 1.38±0.69 to 8.16±0.79 after treatment, while in the placebo group it only improved from 1.25±0.74 to 5.57±0.60. The difference is statistically significant $p <0.005$. (Table 3)

Placebo group did not experience any side effects however, in the active group 2% (n=1) reported nausea and 16% (n=8) patients reported constipation. Laxatives were advised to these patients. No other side effect of strontium ranelate was reported in our study population.

Discussion:

The study reports significant role of strontium ranelate (Brand name: ONITA) in healing of long bone fractures that have undergone non-union/delayed union. The overall rate of fracture healing was 84% in treatment group vs. 61% in placebo group. The study indicated improved fracture outcome both radiologically and clinically. Patients also experienced a general feeling of well being which was related to recovery from fracture and resumption of everyday routine. Our patients reported constipation and nausea as side effects of strontium ranelate.

This is the first of its kind study from Pakistan that assessed the role of strontium ranelate in long bone fractures that have undergone non-union or delayed union. A previous study has assessed its role in tibial fractures but they had not included patients with non-union or delayed union.11 However, larger multi center studies are needed to further stress upon the beneficial role of systemic strontium ranelate in healing long bone fractures that have undergone non-union or delayed union. This study could not eliminate fracture healing delaying factors such as smoking, diabetes mellitus and steroid usage. More controlled studies are needed, which we presume to report even higher efficacy with strontium ranelate.

As mentioned earlier, among the anti-catabolic and anabolic drugs, strontium ranelate has shown the most exciting outcomes and has attracted many researchers and clinical practitioners. Although the first study12 on the use of strontium ranelate long bone fracture healing showed neither beneficial nor-harmful effects in rat tibia, later another study13 revealed improved healing of osteoporotic fractures with systemic use of strontium ranelate in ovari-ectomised rats with fractured tibiae.

Strontium ranelate has also been studied to improve bone implant osseo-integration as it enhances both bone micro-architecture and bone bio-material properties.14 Strontium ranelate-treated osteoporotic fractures have shown higher mechanical strength, mature woven bone and significant call us maturity in rats.15

Contrary to these findings, Ibrahim et al16 conducted a study on the healing of fractured ulna with bone gap in a rabbit model. Based on the x-ray findings, 80% of the fracture united and by CT scan, 60% of the fracture united in the control group at the end of the six-week study. However, none of the fractures united in the test group (strontium ranelate was given). However, histo-pathology report indicated callus at different stages being formed in both groups. Furthermore, they concluded that strontium ranelate may begin with its effect slowly, interfere in the mineralization and delay the acute stage of fracture healing. As per their recommendation, we conducted a long durational study with a larger and human sample to prove their results otherwise.

However, osteoporotic patients treated with strontium ranelate have shown an unfavourable cardiovascular risk profile and higher mortality as compared with users of other osteoporosis drugs according to the Danish National Prescription Database.17 However, as compared to its efficacy, the adverse outcomes aren't as significant.18 As far as the overall safety profile of strontium ranelate is concerned, studies

have reported nausea along with both diarrhea and constipation;19 hence, the use of laxatives becomes case sensitive; as per the judgement of the treating physician and need of the patients individually.

Hence, now that the role of strontium ranelate has been established in improvement of osteoporotic as well as healthy long bone fractures and also in non-union of fractures, more experimentation and concentration is needed upon identifying the potential adverse effects of strontium ranelate and to determine if the adverse effects are actually significant against its beneficial effects. There are certain limitations in our study. The study was conducted in a single centre, more good results will be produced if it is multicentric. Moreover, the union rate among different diaphyseal fractures should be compared like femur and tibia. So, further studies should be conducted to elaborate the results more accurately.

Conclusion:
Systemic strontium ranelate has an exciting and promising role in management of fractures that have undergone non-union or delayed union in non-osteoporotic long bones. This pharmacological method of stimulating fracture healing significantly reduces long-term morbidity and other complications with delayed fracture healing.

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Role and contribution of authors:
Dr Ijaz Ahmad, collected the data, referecnes and did the initial write up.

Dr Ashfaq Ahmed, collected the data and helped in introduction writing.

Dr Muhammad Imran Javed, collected the data, references and helpd ion the interpretation of data.

Dr Ahsan Atta, collected the references and hlepd in material and methodology writring

Dr Ammar Dogar, collected the references and helped in intrpretation of data and result writing.

Dr Rizwan Akram, collected the data, references , critically review the article advised useful changes

Dr Amer Aziz, critically review the article and made the final changes.

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