ROLE OF STRONTIUM RENELATEIN ENHANCEMENT OF REGENERATE DURING BONE TRANSPORT: DOES IT HOLD PROMISE?

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Abstract:

Introduction: Distraction osteogenesis (DO) for the management of bone defects in long bones is a longtime technique. **Objective:** To analyse the Issues with bone regeneration are a standard incidence and literature is filled with totally different modalities to reinforce regenerate formation and quality. Metal Ranelate (SR) incorporates a twin mode of action and enhances bone formation additionally to decreasing osteoclastic activity. Thanks to this twin mode of action yet as easy administration during a suspension type, it makes a perfect drug in eventualities wherever realignment of bone physiological condition towards positive bone balance is fascinating. We tend to study the connection of administration of SR with rate of regenerate progression, moorage web site union and complications related to bone transport in forty eight patients undergoing bone transport for management of bone defects. **Coclusion:** The findings of our retrospective observation study indicated that compliant use of SR was related to sensible regenerate progression, slashed issues with moorage web site union and slashed the requirement for extra interventions.

Key Words: Distraction Osteogenesis (DO) , Strontium Ranelate (SR), Regenerate Progression, Docking Site Union.

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Introduction

Loss of diaphyseal bone in femur and tibia can result from trauma, infection or after tumor resection[1,2]. The defects can be managed by a variety of methods including use of non-vascularized and vascularized autografts, allografts, masquelet technique and bone transport[3-5]. For management of defects complicated by infection, poor soft tissue condition, deformity and length inequality, distraction osteogenesis (DO) with the Ilizarov apparatus and is regarded as one of the most successful methods[6,7]. However, it is also fraught with its own problems and complications. In addition to the known complications associated with external fixation, length of treatment, quality of regenerate especially in infection and osteoporosis as well as docking site non-union are some of the established problems associated with this mode of treatment [8-10].

Strontium Ranelate(SR) is a drug used for the treatment of postmenopausal osteoporosis[11]. A divalent strontium salt, it increases bone formation and reduces bone resorption thereby rebalancing bone homeostasis in favor of bone formation[12-14]. The drug has shown to be effective in improving bone mineral density and increases markers for bone formation. Available as a suspension it eases administration and is generally well-tolerated with a more or less safe adverse event profile [11, 15, 16].

In our series, we sought to study the effect of strontium on enhancing quality of regenerate and rates of docking site union. We postulated that compliant use of SR decreases fixation time in patients undergoing bone transport for management of defects of long bones. To the best of our knowledge there is no clinical report published reporting efficacy of SR in this clinical scenario.

Materials and Methods

The study was conducted at Liaquat National Hospital and Medical College, Karachi. The duration of the study was from September 2014 to March 2017. Hospital Ilizarov registry was used to identify cases.Inclusion criteria was all adult patients undergoing mono-focal bone transport with the use of Ilizarov apparatus. Only patients who completed treatment and had frame removal by September 2017 were included. A single surgeon operated all patients. Patients were called for clinic followup and a

standardized questionnaire was administered regarding use of Strontium Ranelate (SR) during the course of their treatment. Serial radiographs were used to determine distraction rate, time for docking site union and other outcome variables.The study was approved by the hospital ethical review committee.

All patients were prescribed calcium and vitamin-D in supplemental dose and Strontium Ranelate2 grams once a day before bedtime. Compliance was monitored and patients were divided into 2 categories SR compliant and SR non-compliant. For ease of analysis those who had taken SR for > 50% of the duration of treatment were grouped under SR compliant group and those with < 50% usage, frequent breaks or gaps in treatment were grouped under SR non-compliant group. Outcome variables were regenerate progression rate calculated in millimeters per week, time taken for docking site to unite, docking site or regenerate complications and second OR procedure requirements. Cohorts were matched for age, gender, comorbids, types of and pathology leading to bone defect.

$$\text{Regenerate Progression Rate} = \frac{\text{Size of Defect in long bone (mm)} \times 100}{\text{Time taken from corticotomy to docking (weeks)}}$$

All patients had a standard distraction protocol with distraction starting at 5th day post operatively at 0.25 mm every 6hours to result in a maximum distraction rate of 1 mm / day. Range of motion exercises and full weight bearing ambulation was instituted on 1st postoperative day. For upper extremity loading exercises were started similarly. Patients were followed at 2 weeks after index surgery and thereafter at 4-6 weeks interval where radiographic evaluation of regenerate was done. Depending on quality of regenerate, the rate of distraction was slowed down if required or accordion maneuver was used[17].

Of the 56 patients who underwent bone transport treatment during the study period, 48completed follow up and were available for inclusion in the study. Of the other 8 patients, 3 had amputations due to infection and failure of treatment and 5 were lost to follow up.(Table 1).18 patients had femoral defects, 3 had humeral defects and 27 had tibial defects. The average size of the defects treated in the tibia was 7.5 cm (Range 2.5 – 18 cm). The average size of the defect treated in femurwas 6 cm (Range 3 – 12 cm).

Statistical analyses was conducted to determine whether the compliant use of bisphosphonates decreased fixation time and precluded the need to slow down rate of distraction. SPSS ver.21 statistical package was used for analyses. Chi-squared test was used for categorical variables and student T-test was used for continuous variables. P value of ≤ 0.05 was taken as statistically significant.

Results

Of the 48 patients followed, 29 patients were categorized in the SR compliant group, and 19 in the non-compliant group. The most common cause of non-compliance was non-availability of the drug followed by financial constraints. Comparing the two groups, it was observed that they matched well with regards to patient demographics, age (p=0832), gender distribution (p=0.456), and comorbids (p = 0.680). There was no statistical difference between the two groups on analysis for location, size and etiology of defect (p=0.578), (p=0.129) and (p=0.219) respectively. Comparing the status of soft tissue coverage, both groups were also found to bear no statistical difference (p= 0.458). Number of median surgeries performed prior to bone transport was two in each group (p = 0.92). Adjunct procedures at the time of surgery were also similar with 3 flap coverage performed in SR compliant group as opposed to 2 in SR non-compliant group, 1 vascular reconstruction in each group, 3 tumor resection, 2 for Giant cell tumor and 1 for Osteosarcoma all of which were SR compliant (p=0.098). (Table 2)

Hypoplastic regenerate formation is initially managed by slowing of distraction rate, sometimes needing complete cessation of distraction or even reversal as in the accordion maneuver(17, 18). This results in a much slower over regenerate progression rate. The usual distraction rate advised to patients is 1 mm per day resulting in a maximum of 7 mm per week(18-20). We observed that in our series, the overall rate of regenerate progression in the SR compliant group was 6.3 mm as opposed to 3.9 mm in the SR non-compliant group. This was statistically significant (p=0.039). Trends towards significance was also observed when we compared time taken for docking site union in the SR compliant group mean 9.5 weeks compared to 13.3 weeks in the SR non-compliant group (p=0.069). Similar number of patients required pin tract site debridement in both groups with 2 patients requiring broken pin exchange in the SR compliant group. It was observed that all 3 docking site failures that required bone grafting happened in the SR non-compliant group. 6 patients had to undergo the accordion maneuver to enhance bone regenerate formation in the SR non-compliant group whereas none required this treatment in the compliant group. The difference in the requirement of additional interventions was also statistically significant (p=0.046). (Table 3)

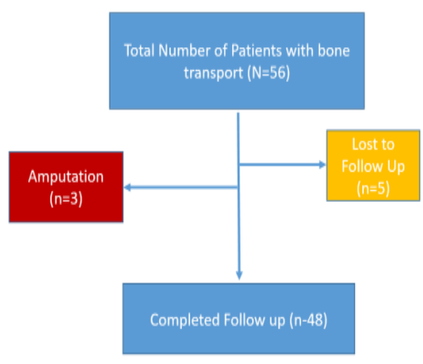

TABLE 1: Schematic Representation of Patient selection methodology			
	SR- Compliant (n= 29)	**SR – Non Compliant (n=19)**	**P=Value**
Age (yrs)	29 (16 – 48)	32 (18 – 65)	0.832
Gender			
Male	18	14	0.456
Female	11	5	
Comorbids			
HTN	15	10	0.680
DM	3	3	
IHD	1	2	
CRF	0	0	
Others	12	12	
Bone Involved			
Femur	11	7	0.578
Tibia	16	11	
Humerus	2	1	
Avg. Size of Defect (cms)			
Femur	5.9	6.1	0.129
Tibia	6.8	7.9	
Humerus	4.5	2.8	
Etiology of Bone Loss			
Trauma	8	4	0.219
Infection	18	15	
Tumor	3	0	
Soft Tissue Cover			
Intact	Healthy = 3 Scarred = 14	Healthy = 6 Scarred = 6	0.458
Damaged	Sinus Tract = 4 Open Fracture = 8	Sinus Tract = 2 Open Fracture = 4	
Median No. of Previous Surgeries	2 (Range 0-18)	2 (Range 0-5)	0.921
Adjunct Procedures Performed at index surgery			
Flap Coverage	3	2	0.098
Vascular Reconstruction	1	1	
Tumor Resection	3	0	

TABLE 2: Comparison of SR compliant and SR non-compliant groups for pre-treatment and intra-treatment variables.			
	SR- Compliant (n= 29)	**SR – Non Compliant (n=19)**	**P=Value**
Regenerate Progression Rate (mm/week)	6.3	3.9	0.039
Time for docking site union (weeks)	9.5	13.3	0.069
Additional Interventions			
Pin tract debridement	8	6	0.046
Broken wire exchange	2	4	
Docking site bone graft	0	3	
Accordion method	0	6	
Complications			
Pin tract infection	15	9	0.098
Docking site failure	0	3	
Deformity	1	2	

TABLE 3: Comparison of SR compliant and SR non-compliant groups for outcome variables

Discussion

Since GavrielIlizarov presented his work on law of tension stress, distraction osteogenesis (DO) has formed the basis of treating many orthopaedic problems and skeletal deformities [18-20]. It is also an established treatment method used to treat bone defects[21-23]. This can be successfully achieved using monolateral or biplanar fixators such as Orthofix™ fixator (Orthofix International, Verona, Italy)designed for DO as well as intramedullary devices such as

PRECICE system (Ellipse Technologies, Irvine, CA) and ISKD (Orthofix International, Verona, Italy)[24,25]. In a socio-economically poor country, the use of the cheap basic ilizarov frame components is much more viable. Problems with regenerate quality is a frequent occurrence and focus of intense research in the field of external fixation[8-10, 26].

Non-pharmacological treatments such as Low Intensity Pulsed Ultrasound (LIPUS) and pulsed electromagnetic fields (PEMF) have been investigated and shown promise, however availability and cost precludes their use in most clinical settings. Despite avid literature support, there is still no consensus guideline on the use of these treatment modalities[27-30].

Surgical strategies to decrease fixation time such as hemicorticotomy, transport over nail and external fixation followed by nailing have also been described as effective methods of decreasing fixation time. However, studies reporting these techniques do not show any of the above having a direct effect on regenerate progression. Stabilization of the regenerate and early frame removal is the concept for the latter two techniques[27, 30-33].

Injection of recombinant BMP-7 and growth factor concentrate such as Platelet Rich Plasma(PRP) and bone marrow aspirate into the regenerate has also been studied with varying degrees of success[27, 34, 35].

Pharmacological interventions have also been described. In 2007, Kiely et al reported successful healing in 6 of 7 children treated with bisphosphonates without needing any additional intervention. No side effects were reported in his series[36]. Other anticatabolic agents (e.g. calcitonin) may have a role to play in enhancement of bone formation during DO[37].

Several other agents, such as parathyroid hormone[38], vitamin D analogs[39], and hyperbaric oxygen[40,41], have been studied in animal models of distraction osteogenesis with encouraging results. However, no human study of such therapies is available.

Strontium ranealate has a dual mode of action. It is known to increase in vitro osteoblast differentiation from progenitors, as well as osteoblast activity and survival[12,13,42], and regulate osteoblast-induced osteoclastogenesis both in vitro[42,43] and in vivo[44]. Concerning bone anti-resorbing mechanisms, SR decreases osteoclast differentiation and activity, while increasing their apoptosis [13].

We intended to use SR because of its dual mode of action, ready availability and ease of administration (oral vs. parenteral) as compared to most other modalities with this pharmacological profile[12-14]. Observations of our study favored use of Strontium Ranealate (SR) in enhancing bone regenerate during bone transport and distraction osteogeneis (DO). In our experience, it successfully maintained patients close to maximum distraction rate and had lesser chances of adding intervention such as accordion maneuver to enhance regenerate. It also appeared to enhance docking site union rate. Our study was limited by the study design, as this was a retrospective observational study. The size of the patient cohorts is small for us to generalize and validate our results. A large randomized multi-centric trial would be required to confirm our findings.

Within the limitations of this study, we conclude that compliant use of Strontium Ranelate positively effects regenerate quality and docking site union thereby decreasing fixation time in patients with bone transport using distraction osteogenesis (DO).

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