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Histological evaluation of the effects of systemic administration of strontium ranelate on bone healing in rat tibia fractures

Evaluación histológica de los efectos de la administración sistémica de ranelato de estroncio sobre la curación ósea en fracturas de tibia de rata.

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ABSTRACT

This study aimed to investigate the effects of strontium renelate, a known bisphosphonate-like agent with effects on bone tissue, on bone fracture and defect healing using histological methods. For this purpose, a fracture study was conducted using 28 rats, each consisting of healthy controls (n = 7), fracture controls, and treatment groups, receiving strontium dose 1 (450 mg/kg three times per week), and strontium dose 2 (900 mg/kg three times per week). After a six-week fracture healing period, tibia bones were subjected to histological analysis for new bone formation. Data were analyzed using Kruskal Wallis and Mann Whitney U tests. New bone formation was significantly lower in the fracture groups compared to healthy controls ($P < 0.001$). An increase in new bone formation ratios was observed in the strontium ranelate-administered groups compared to the fractured controls ($P < 0,05$). New bone formation was significantly higher in the high-dose strontium ranelate group compared to the low-dose strontium ranelate group ($P < 0,05$). When histological evaluations and numerical analyses were evaluated together, it was concluded that systemic strontium ranelate administration significantly accelerated new bone formation and maturation processes during fracture healing, depending on the dose used (450 and 900 mg/kg).

Key words: Strontium renelate; tibia fracture; bone healing; new bone formation; rat.

RESUMEN

Este estudio tuvo como objetivo investigar los efectos del ranelato de estroncio, un agente conocido similar a los bisfosfonatos con efectos sobre el tejido óseo, en la cicatrización de fracturas y defectos óseos mediante métodos histológicos. Para ello, se realizó un estudio de fracturas con 28 ratas, cada una compuesta por controles sanos (n = 7), controles con fractura y grupos de tratamiento, que recibieron una dosis de estroncio de 450 mg/kg tres veces por semana y una dosis de 900 mg/kg tres veces por semana. Tras un periodo de cicatrización de seis semanas, se realizó un análisis histológico de las tibias para evaluar la formación de hueso nuevo. Los datos se analizaron mediante las pruebas de Kruskal-Wallis y U de Mann-Whitney. La formación de hueso nuevo fue significativamente menor en los grupos con fractura en comparación con los controles sanos ($P < 0,001$). Se observó un aumento en la proporción de formación de hueso nuevo en los grupos tratados con ranelato de estroncio en comparación con los controles con fractura ($P < 0,05$). La formación de hueso nuevo fue significativamente mayor en el grupo tratado con dosis altas de ranelato de estroncio en comparación con el grupo tratado con dosis bajas ($P < 0,05$). Al evaluar conjuntamente los análisis histológicos y numéricos, se concluyó que la administración sistémica de ranelato de estroncio aceleró significativamente los procesos de formación y maduración de hueso nuevo durante la consolidación de la fractura, dependiendo de la dosis utilizada (450 y 900 mg/kg).

Palabras clave: Ranelato de estroncio; fractura de tibia; consolidación ósea;, formación de hueso nuevo; rata.

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INTRODUCTION

Bone tissue has a high regenerative capacity under physiological conditions. However, this natural regenerative process can be disrupted in situations such as traumatic fractures, extensive tissue loss, systemic diseases, or medication use, resulting in the development of fracture healing failure (non-union) [1, 2]. The slowing of bone regeneration, particularly in metabolic disorders such as osteoporosis, diabetes, or advanced age, increases the need for regenerative therapies [3, 4].

Therefore, in recent years, studies have been conducted to find alternative methods and biological materials to treat impaired fracture healing [5, 6]. Numerous approaches have been investigated to accelerate the maturation of regenerated bone, including various growth factors, hormones such as calcitonin, calcium sulfate, bisphosphonates, and electronic and ultrasonic stimulation [7, 8, 9, 10].

Strontium (Sr), the element at the center of these studies, is an element that readily integrates into the bone matrix due to its chemical similarity to calcium. When used in the form of Strontium Ranelate (SrR), it increases osteoblast activity while simultaneously suppressing osteoclast-mediated resorption, shifting the balance between bone formation and resorption in favor of osteogenesis. This bidirectional property distinguishes it from bisphosphonates [11, 12, 13].

Strontium's effects on bone metabolism are mediated through the calcium-sensing receptor (CaSR), Wnt/β-catenin, and RANKL/OPG signaling pathways [12, 14]. Sr also increases the expression of markers such as bone morphogenetic protein-2, alkaline phosphatase, and osteocalcin , which stimulate osteoblast differentiation [15, 16].

Strontium ranelate has been used clinically in the treatment of osteoporosis for many years, and clinical studies have shown that it significantly reduces the risk of fractures. However, evidence that high-dose and long-term systemic administration may increase cardiovascular risks has limited its clinical use [17].

The limited side effects associated with systemic administration have encouraged researchers to investigate the targeted use of Sr via local or controlled-release systems. Sr-containing biomaterial systems (especially calcium phosphate-based scaffolds, gelatin or collagen membranes, and hydrogel coatings) have both increased new bone formation and enhanced tissue integration [15, 18, 19]. Topical SrR gels have been observed to significantly increase osteogenic activity without systemic side effects, particularly in diabetic or osteoporotic models [20, 21].

Bone regeneration is recognized as a complex biological process that is not limited to cell proliferation but rather is shaped by the coordination of multifaceted interactions within the neuroimmune microenvironment. In this context, the concept of the "neuro-osteo axis" points to the role of nerve growth factors (NGF) and neuropeptides in regulating cellular signaling networks within bone tissue. The interaction of these neurotrophic factors with Sr has been shown to enhance tissue integration and regenerative responses by increasing cell viability [22, 23, 24]. This synergistic effect is considered an innovative approach, particularly in the field of guided bone regeneration (GBR).

On the other hand, Sr-containing biomaterials have been reported to direct macrophage polarization from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype and, through this mechanism, suppress the inflammatory response, thereby supporting the regenerative process [18]. Furthermore, Sr ions have been shown to stimulate angiogenesis, facilitate the formation of new vascular networks, and consequently increase oxygen and nutrient transport to the tissue [16, 25].

These findings suggest that SrR can be considered an important biological agent in the regenerative process not only for its osteogenic effects but also for its immunomodulatory and angiogenic properties. The safe translation of Sr biological effects into clinical practice depends primarily on more comprehensive research on dose optimization, release rate, and long-term biocompatibility [5, 25].

Locally controlled-release systems developed in recent years are considered innovative approaches that could enable Sr to exert regenerative activity in the target area without exceeding its toxicity limits. However, in cases where bone metabolism is systemically affected, such as osteoporosis and common skeletal pathologies, local applications alone may be insufficient to provide adequate therapeutic responses. Therefore, systemic use of Sr remains clinically important due to its potential to regulate the overall metabolic balance of bone turnover and promote bone healing [26].

From this perspective, laboratory findings from experimental studies comparing systemic Sr administration at the histological level are of critical importance in translating them into clinical practice. In this context, the aim of the present study was to evaluate the effects of SrR administration on experimental fracture healing in rat (*Rattus norvegicus*) tibias.

MATERIAL AND METHODS

Animals and study design

This experimental study was conducted at the Fırat University Experimental Research Center laboratories. Prior to the study, approval was obtained from the Fırat University Animal Experiments Local Ethics Committee (Ethical Approval Date and Number: 22 January 2024-21568). In this study, the effects of systemic administration of SrR, which is known to have bisphosphonate-like effects on bone tissue metabolism, on bone healing in experimentally induced rat tibia fractures were evaluated histologically.

The study used female Sprague–Dawley rats (n = 28), 4–6 months old, weighing an average of 250–300 grams (WL, Shimadzu, Japan). All rats included in the study were in the same stage of the estrous cycle. The rats were housed and fed under standard laboratory conditions.

Experimental groups

A total of 28 rats were randomly assigned to four groups (TABLE I). Considering possible losses during surgery, a plan was

made to include at least 7 subjects in each group as a result of statistical power analysis.

TABLE I
The distribution of rats used in the experiment according to groups.

Groups	Applications	n
Group 1	Healthy Controls	7
Group 2	Fracture Control	7
Group 3	Fracture + Strontium ranelate (450 mg/kg)	7
Group 4	Fracture + Strontium ranelate (900 mg/kg)	7

Surgical procedures

All surgical procedures were performed under sterile conditions and deep anesthesia. A combination of 10 mg/kg Xylazine (Rompun, Bayer, Germany) and 40 mg/kg Ketamine (Ketasol, Richter Pharma, Austria) was administered for anesthesia.

The right tibia was shaved and antiseptically cleansed with 10 % Povidone-iodine. A longitudinal incision approximately 2 cm long was made, ensuring contact with the bone. The soft tissues and periosteum were removed using a periosteal elevator.

In the fracture groups, a transversal osteotomy was performed in the tibial diaphysis using a rotary instrument (NSK, Japan) at 600 rpm under physiological saline cooling. The fracture line was fixed with a Kirschner wire after achieving anatomical positioning. The muscle and skin layers were then returned to their original positions and closed primarily with 4-0 silk sutures. To prevent postoperative infection and pain, all rats received antibiotics (Cefazolin sodium, 40 mg/kg) and analgesics (Tramadol hydrochloride, 1 mg/kg) for three days. After surgery, rats were kept in individual cages and their feeding and movements were monitored daily.

Strontium ranelate application

Strontium ranelate was administered to the fracture treatment groups via oral gavage three times a week for six weeks, starting 24 hours (h) after surgery:

- Group 3 (SrR low dose): 450 mg/kg
- Group 4 (SrR high dose): 900 mg/kg

The healthy control group received no intervention, while the fracture control group received only surgery.

At the end of the six-week recovery period, all subjects were euthanazied under deep anesthesia. The right tibias were carefully dissected from the soft tissues, and tissue samples were fixed in appropriate solutions for histological evaluation.

Histological processing and evaluation

Tibia samples were fixed in 10 % neutral formalin for 48 h before being decalcified. The bone tissue was then transferred to 10 % formic acid to soften it. Following routine histological procedures, sections were stained with hematoxylin-eosin (H&E). Histological examination assessed new bone formation (ossification) at the fracture site. Histomorphometric measurements were performed using microscopic images (Olympus BX42, Japan) to calculate the new bone formation rate (NBF, %) for each sample.

Statistical analysis

Data obtained were analyzed using SPSS 25.0 (IBM Corp., Armonk, NY, USA) statistical software. After the normality tests (to analysing skewness and curtosis); Kolmogorov-Smirnov and Shapiro-Wilk, intergroup differences were assessed using the Kruskal–Wallis test, and in cases where significant differences were found, pairwise comparisons were made using the Mann–Whitney U test. The results are presented as mean/median values, and the statistical significance level was accepted as $P < 0.05$.

RESULTS AND DISCUSSION

The new bone formation rate values obtained from histomorphometric analyses are presented (TABLE II). The Kruskal–Wallis test revealed a statistically significant difference between the groups ($P < 0.05$) ($P = 0.000$).

TABLE II
Percentage assessment of new bone formation after fracture healing in experimental groups

Groups	NBF (%) (Mean/Median)	Min.	Max.	P*
Healthy Control	100/100	100	100	
Fracture Control[a]	44.71/42	39	55	0.000
Fracture Str. Dosage 1[a,b1]	54/51	46	63	
Fracture Str. Dosage 2[a,b2,c]	62.71/62	53	77	

*Krusskal Wallis. a Statistically significantly different compared with Healthy Control (a:0.001).b Statistically significantly different compared with Fracture Control (b1: 0.029 b2: 0.003). Statistically significantly different compared with Fracture Str. Dosage 1 (c: 0.040). a,b1,b2,c: Mann Whitney U test.

As a result of the examination of histological sections obtained at the end of the six-week healing period, it was observed that new bone tissue formation occurred at the fracture line in all groups. In the healthy control group, the tibia cortical structure was fully organized, lamellar bone tissue was homogeneously distributed, and the medullary cavity was regular. In the fracture control group, dense fibrous connective tissue and irregularly organized immature bone trabeculae were observed at the fracture site; new bone formation was limited. In the SrR-treated groups, especially in the high-dose group, the fracture site was significantly filled with osteoid tissue and new bone trabeculae, and the transition to mature bone structure began (FIGS. 1 and 2). Histologically, significant bone bridging was observed at the fracture site, especially in the 900 mg/kg SrR-treated group; were significantly increased compared to the fracture control group ($P < 0.05$).

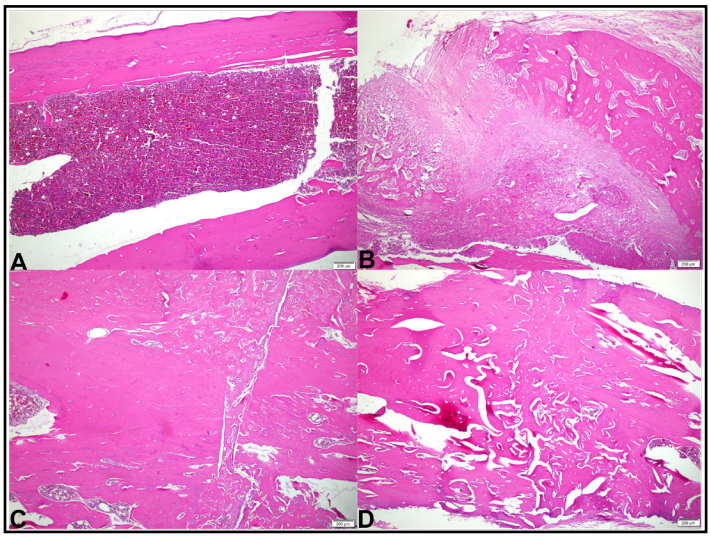

FIGURE 1. General view of the healing area at the fracture site in the Control (B) and treatment groups (C: dose1 and D: dose2), excluding the healthy control (A). 40X Magnification, H&E.

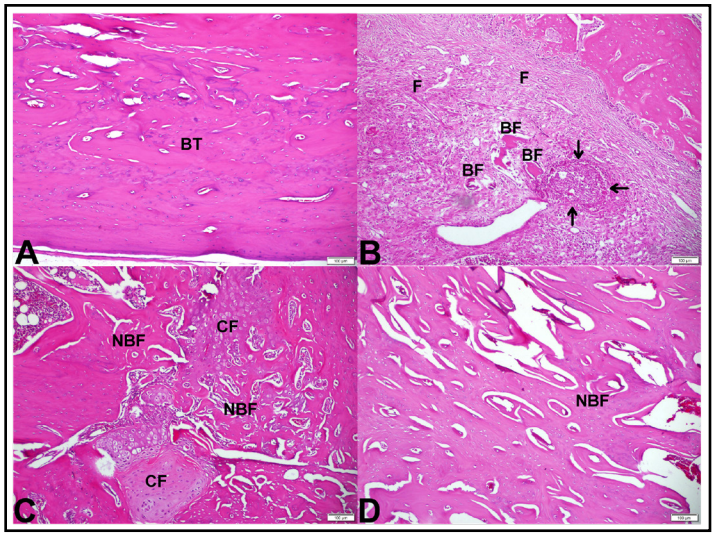

FIGURE 2. Normal bone tissue (BT) in the healthy control (A) group, and areas of new bone formation (NBF), fibrosis or fibrous callus (F), and cartilage formation (CF) in the experimental groups. In the control group, non-resorbed necrotic bone fragments (BF) and the pyogranulomatous inflammatory reaction (arrows) that formed against them. 100X Magnification, H&E.

Statistical analyses showed that SrR administration significantly enhanced fracture healing. NBF was significantly lower in the fracture control group compared to the healthy control group ($P < 0.001$). The increased NBF rates in the SrR-administered groups demonstrated the supportive effect of this agent on osteogenic activity. The significantly higher rate of NBF in the high-dose SrR group compared to the low-dose SrR group ($P = 0.040$) demonstrates that the effect is dose-dependent. When histological evaluations and numerical analyses were evaluated together, it was concluded that systemic Sr ranelate administration at a dose of 900 mg/kg significantly accelerated NBF and maturation processes during fracture healing.

In this study, the effects of systemically administered SrR on bone regeneration in an experimental tibia fracture model were histologically evaluated. The findings show that new bone formation was significantly increased in the SrR-treated groups, and this effect was more pronounced in the high-dose group. These results are consistent with the studies reported by Gusman *et al.* [13] and Matvieienko *et al.* [21] demonstrating the osteogenesis potential of systemic SrR. Both studies reported that SrR increases osteoblast activity by limiting inflammatory processes and accelerates the regenerative process.

The findings of this study suggest that these mechanisms may be active in the early stages.The development of non-union during fracture healing is associated with a lack of biological stimulation, inadequate vascularization, and cellular homeostasis [1, 2, 3, 4].

The enhancement of osteoblast differentiation by Sr ions via the CaSR and the regulation of the RANKL/OPG ratio have been identified as mechanisms that can address this biological deficiency [11, 12].

The dual effect of Sr on bone metabolism was explained by Marx [12] through increased osteoblastic activity and suppression of osteoclastic resorption. Supporting this effect, Kołodziejska [11] reported that Sr accelerates mineralization through CaSR activation and modulation of the Wnt/β-catenin pathway. The distinct trabecular organization and osteoid deposition observed in the high-dose SrR group in this study can be considered a histological reflection of this dual effect. Furthermore, You *et al.* [14] showed that Sr-containing biomaterials shortened the inflammatory phase by shifting macrophage polarization from the M1 to the M2 phenotype. The reduction of early inflammatory infiltration in this study suggests that systemic SrR may have a similar immunomodulatory effect..

The dose-efficacy relationship between SrR and bone mineral density (SrR) has been previously evaluated by Gusman *et al.* [13] using low-dose systemic administration and by Ozturan *et al.* [27] in osteoporotic models. Both studies reported that SrR increased the rate of osteogenesis in a dose-dependent manner. The significant increase in new bone formation in the high-dose group in this model parallels these findings. Falgayrac *et al.* [17] reported that SrR improved bone matrix quality in postmenopausal women treated with SrR and alendronate. The regular trabecular structure and increased mature osteoid areas observed in this study findings are consistent with these clinical findings.

Ther findings in this study also demonstrate that SrR can support regenerative processes not only in pathological or metabolic disorders but also under physiological conditions. Matvieienko *et al.* [21] reported that SrR increased the percentage of new bone in diabetic rats, and Gusman *et al.* [13] reported that systemic SrR stimulated osteoblastic activity in a periodontitis model. Similar to these studies, the increase in trabecular density and osteoid area in this study suggests that SrR may also be effective in basal healing processes..

The most important advantage of SrR over bisphosphonates is that it not only suppresses resorption but also increases osteoblastic activity. Falgayrac *et al.* [17] reported that SrR provides a more homogeneous mineral-matrix ratio than alendronate, while Gonçalves *et al.* [28] reported that the additional application of SrR during extraction socket healing after bisphosphonate treatment accelerated bone repair. These

results demonstrate that SrR is a physiological modulator that does not completely halt the remodeling process. Furthermore, compared to agents such as denosumab and teriparatide, SrR has been reported to maintain a balanced RANKL/OPG ratio without excessively suppressing osteoclastic activity [29].

Local Sr-containing biomaterials create an osteogenic microenvironment through controlled ion release. Byeon et al. [18] reported that Sr-containing CaP membranes improved GBR performance, and Markel *et al*. [30] reported that injectable Sr-containing systems increased new bone volume. However, the effectiveness of these systems is anatomically limited. In this study, systemic SrR administration via the circulation induced osteogenic activity in bilateral and multifocal areas. These results support the clinical applicability of the combined systemic-local approaches proposed by Mehta and Gentleman [31].

CONCLUSION

Systemic SrR administration promotes bone regeneration through multiple mechanisms. Findings indicate that SrR can accelerate fracture healing by both increasing osteoblastic activity and regulating osteoclastic resorption. This effect is consistent with the dual biological role of SrR reported in the literature. Short-term, controlled systemic use of SrR may be considered as adjuvant therapy, particularly in osteoporotic or diabetic patients.

Future approaches combining SrR with local regenerative systems, such as Sr-releasing biomaterials or promotes renegeration, offer promise for clinical translation, offering the advantages of controlled release and minimal toxicity.

Conflicts of interest

The authors of this study declare that there is no conflict of interest with the publication of this manuscript.

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