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Histopathologic evaluation of effects of systemic Strontium Ranelate application on bone healing after grafting tibial defect

Evaluación histopatológica de los efectos de la aplicación sistémica de Ranelate de Estroncio en la curación ósea tras injerto de defecto tibial

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ABSTRACT

This study evaluated the effects of different doses of strontium ranelate combined with a bovine-derived deproteinized xenogeneic bone graft on bone healing in a rat defect model. Thirty-five female Sprague Dawley rats were randomly assigned to five groups (n = 7). A healthy control group received no treatment. In all other groups, a standardized 4 mm × 4 mm defect was created in the metaphyseal region of the rat tibia. The defect control group received no additional treatment. In the defect–graft group, the defect was filled with a bovine-derived deproteinized xenogeneic bone graft. In the defect–graft + strontium groups, the defect was filled with the same graft and strontium ranelate was administered by oral gavage at doses of 450 mg/kg or 900 mg/kg, three times per week for eight weeks. All rats were euthanized at the end of the eight-week experimental period. Bone tissues were harvested and processed for histological analysis. Data normality was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. As normality assumptions were not met, group comparisons were performed using the Kruskal–Wallis test followed by Mann–Whitney U post hoc tests. Mean horizontal defect sizes were 0 in the healthy control group, 716.86 in the defect group, 658.57 in the defect–graft group, 604.57 in the defect–graft dose 1 group, and 598.86 in the dose 2 group. Mean vertical values were 0 in the healthy group, 575.14 in the defect group, 596.43 in the defect–graft group, 569 in the dose 1 group, and 503.29 in the dose 2 group. In conclusion, strontium ranelate had a positive effect on bone healing compared to the control group, particularly when combined with grafting. A significant difference was also observed between the defect group and the high-dose group, confirming its beneficial effect on bone healing.

Key words: Strontium ranelate; bone defect; bone grafting; guided bone regeneration; tibia bone; rat

RESUMEN

Este estudio evaluó los efectos de diferentes dosis de ranelato de estroncio combinadas con un injerto óseo xenogénico desproteinizado de origen bovino sobre la cicatrización ósea en un modelo de defecto en ratas. Treinta y cinco ratas Sprague Dawley hembra fueron asignadas aleatoriamente a cinco grupos (n = 7). El grupo control sano no recibió tratamiento. En los demás grupos se creó un defecto estandarizado de 4 mm × 4 mm en la región metafisaria de la tibia. El grupo con defecto no recibió tratamiento adicional. En el grupo defecto–injerto, el defecto se rellenó con el injerto óseo. En los grupos defecto–injerto + estroncio, además del injerto, se administró ranelato de estroncio por vía oral a dosis de 450 mg/kg o 900 mg/kg, tres veces por semana durante ocho semanas. Al final del período experimental, todas las ratas fueron eutanasiadas y los tejidos óseos se procesaron para análisis histológico. La normalidad de los datos se evaluó mediante las pruebas de Shapiro–Wilk y Kolmogorov–Smirnov. Dado que los datos no siguieron una distribución normal, las comparaciones entre grupos se realizaron con la prueba de Kruskal–Wallis y la prueba U de Mann–Whitney como análisis post hoc. Los valores medios del defecto horizontal fueron 0 en el grupo control sano, 716,86 en el grupo con defecto, 658,57 en el grupo defecto–injerto, 604,57 en el grupo defecto–injerto dosis 1 y 598,86 en el grupo dosis 2. Los valores medios verticales fueron 0 en el grupo sano, 575,14 en el grupo con defecto, 596,43 en el grupo defecto–injerto, 569 en el grupo dosis 1 y 503,29 en el grupo dosis 2. En conclusión, el ranelato de estroncio mostró un efecto positivo sobre la cicatrización ósea, especialmente cuando se combinó con injerto, observándose una diferencia significativa entre el grupo con defecto y el grupo de dosis alta.

Palabras clave: Ranelato de estroncio; defecto óseo; injerto óseo; regeneración ósea guiada; tibia; rata

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INTRODUCTION

Bone augmentation procedures have become increasingly common in individuals receiving implants. The goal of this procedure is to ensure good stability by completely anchoring the implants circumferentially to the bone after the bone healing process is complete. Surgeons have also used autogenous bone chips to enhance bone formation [1].

The frequency of implant treatment in older patients is increasing. Systemic metabolic disorders are more common in older individuals. Therefore, appropriate treatment protocols should be defined for this patient group during implant placement and bone regeneration [2].

Bone regeneration must allow cells with regenerative capacity to infiltrate the wound to facilitate regeneration in a specific tissue. This allows guided bone regeneration to be achieved by applying a biological concept [3 , 4 , 5]. Studies have proven the benefits of guided bone regeneration (GBR). These studies have reported similar survival rates for implants in alverolar ridges with defects and bone crests with normal structure [6]. Although both biological and synthetic grafts have been employed in the management of bone defects, autografts remain the preferred and most widely accepted option [7]. However, owing to the limited supply of autogenous grafts, the risks involved in their production, and the lower performance of synthetic grafts, the need to develop effective and safer alternatives has emerged [8 , 9].

To address these issues, the use of osteoinductive factors and osteoprogenitor cells is recommended to mitigate the negative effects of disruptions in the healing process and to improve osteogenesis [10 , 11 , 12]. Strontium (Sr) is an element that has a positive effect on bone formation and protects against bone resorption. Strontium ranelate (SR) can cause cardiovascular complications. Therefore, caution should be exercised in its indication [13 , 14 , 15]

Several preclinical studies performed in both normal and osteoporotic animal models have corroborated earlier *in vitro* findings, demonstrating the beneficial effects of SR in enhancing bone structure and strength [14 , 15 , 16]. Consequently, SR has recently been integrated into various bone substitute materials to promote bone regeneration and repair. This approach seeks to achieve high local concentrations of the agent, thereby enhancing bone formation while minimizing systemic side effects and enabling safer utilization of its osteoanabolic and anti-osteoclastic properties. However, there is a scarcity of in vivo studies, and many existing reports lack the inclusion of appropriate control groups. The efficacy and safety of SR-enriched materials remains a matter of debate, and more information and uniform criteria for topical SR use are needed. Studies using SR, particularly those requiring evaluation before clinical trials, have been conducted. As a result of these evaluations, increases in bone structure and strength were observed in both healthy and osteoporotic animal models [16 , 17 , 18].

Based on these studies, SR has been used as various bone substitutes to enhance bone repair. This application ensures that high doses reach the local area, reducing systemic effects and improving bone formation. It also aims to achieve osteoanabolic and anti-osteoclastic activity in a safer and more feasible manner. Discussions regarding the use of Sr-enriched materials continue. More definitive data requires further study [19].

The aim of this study was to evaluate the effects of administering different doses of Strontium Ranelate to bovine deproteinized xenogeneic bone graft after creating a bone defect on the bone healing process.

MATERIALS AND METHODS

Animals and study design

Since the study will be conducted on female rats (*Rattus norvegicus*), vaginal smears will be taken on all selected rats, and rats in the same estrus phase will be included in the study. Before starting this study, an application for study approval was made to the Fırat University Animal Experimentation Local Ethics Committee (Protocol No: 2024-02-09, Date: 17 January 2024), and the committee granted approval.

The rats were produced by the Fırat University Experimental Research Center (Elazığ, Türkiye) and were delivered to the academics conducting the study once the specified criteria were met. This study adhered to all recommendations of the European Declaration of Helsinki and was conducted in Elazığ (Türkiye) within the animal experimentation protocol of the Ministry of Agriculture of the Republic of Türkiye. No animals were subjected to pain during the experiments, and utmost attention was paid to all ethical committees. All recommendations in the Declaration of Helsinki for the protection of experimental animals were adhered to.

Thirty-five female Sprague Dawley rats, aged 6-12 months, were used in this study. The average weight of the rats used in our experimental study was between 270 and 300 g/m (WL, Shimadzu, Japan). To prevent harm to the animals during the experiment, temperature was constantly controlled, and a 12-hour (h) light/12-h dark cycle was applied. Groups of 35 rats were randomly selected. The rats were divided into 5 groups of 7 rats each.

1. Defect-Healthy Control Group: No treatment was administered to the healthy control group.

2. Defect-Control Group: In the defect study design, bone defects measuring 4 mm in diameter and 4 mm in depth were created in the corticocancellous region of the metaphyseal portion of the tibia in the experimental groups.

3. Defect-Graft Group: In the defect study setup, bone defects measuring 4 mm in diameter and 4 mm in height were created in the corticocancellous bone of the tibial metaphysis in the experimental groups. The defect area was filled with bovine-derived deproteinized xenogeneic bone graft.

4. Defect Graft Strontium Dose 1 Group: In the defect study setup, bone defects of 4 mm in diameter and 4 mm in height were created in the corticocancellous bone of the tibial metaphysis in the experimental groups. The defect area was filled with bovine deproteinized xenogeneic bone graft. 450 mg/kg strontium ranelate was administered by oral gavage three times per week for eight weeks.

5. Defect Graft Strontium Dose 2 Group: In the defect study setup, bone defects measuring 4 mm in diameter and 4 mm in height were surgically created in the corticocancellous bone of the tibial metaphysis in the experimental groups. The defect area was filled with bovine deproteinized xenogeneic bone graft. 900 mg/kg strontium ranelate was administered by oral gavage three times per week for eight weeks.

Surgical procedures

Surgical procedures were performed under deep anesthesia to prevent pain in the rats. The animals were anesthetized using 50 mg/kg Ketamine (Ketasol; Richter Pharma, Wels, Austria) and 10 mg/kg Xylazine (Rompun; Bayer, Germany). A 2-cm full-thickness incision was made to access the crestal bone of the tibia. The soft tissues and periosteum were prepared for the operation using a periosteum elevator. A rotary tool was used at 600 rpm under serum cooling to create the defect (NSK, Japan). After the surgical applications the soft tissues were attached original positions. And after suturing with 3-0 prolen sutures antibiotic (Cefazolin sodium 40 mg·kg^{-1}, iespor 250, I.E. Ulagay, Türkiye) and analgesic (Tramadol hydrochloride 0.1 mg·kg^{-1}, Contramal, Abdi Ibrahim, Türkiye) were injected intramusculary.

After the procedures were completed, the experiment was terminated, and an eight-week recovery period was awaited. The rats were then euthanized. Histological analysis was then performed.

Histopathological analysis procedure

Histopathological analyses of the study were completed in the Pathology Department laboratory of Fırat University, Faculty of Veterinary Medicine. After the animals were euthanized, bone samples (tibias) encompassing the defect sites were preserved in 10 % neutral formalin for three days (d).

All soft tissues (muscle, tendon, and fascia) were then removed. They were then decalcified in 10 % formic acid solution for 1 week. Following these procedures, they were processed through alcohol, xylene, and paraffin series using an automatic tissue processing device (Leica TP 1020, Germany). The tissues processed in these solutions were embedded longitudinally in paraffin (Leica EG1150 H-C, Germany). 3-micron-thick sections were cut from the paraffin blocks using a rotary microtome (Leica RM2125 RTS, Germany) and stained with hematoxylin-eosin (Leica Autostainer XL). Histopathological examination was performed using a standard light microscope (Olympus BX42, Japan). Analyses were performed by measuring the widest and deepest points of the defect areas longitudinally and the thickest part of the callus tissue transversely (cellSens Standard, Japan).

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 23. The normality of the data was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Since the data did not meet the assumptions of normality, group differences were evaluated using the Kruskal–Wallis test, followed by pairwise comparisons with the Mann–Whitney U test as a post hoc analysis. Results are expressed as mean/median, min-max, with statistical significance defined as $P < 0,05$. All analyses were conducted by a blinded investigator, who was unaware of the group assignments.

RESULTS AND DISCUSSION

Histological analyses were performed by measuring the remaining open defects. These measurements were performed in two different dimensions. They were evaluated separately for vertical and horizontal measurements (FIG. 1).

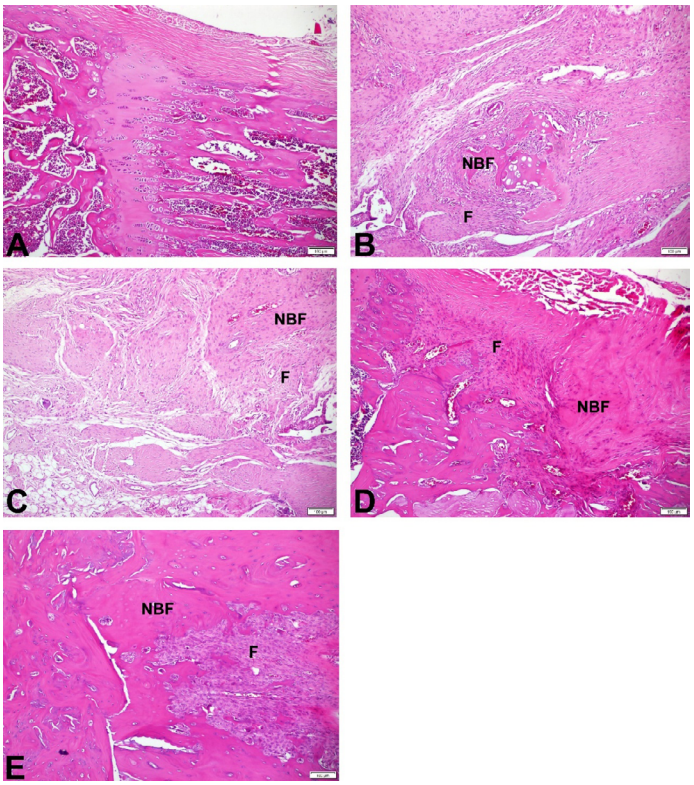

FIGURE 1. New bone formation and fibrosis areas in the defect area of systemic Strontium Ranelate application on bone healing after grafting tibial defect in the healthy control (A) and experimental groups, B: Defect control, C: Defect graft control, D: Defect graft dose 1, E: Defect graft dose 2, NBF: New bone formation, F: Fibrosis.

The mean horizontal defect sizes were 0 in the healthy control group, 716.86 in the defect group, 658.57 in the defect graft group, and 604.57 in the defect graft dose 1 group and 598.86 in the dose 2 group. In the vertical evaluation, the mean values were 0 in the healthy group, 575.14 in the defect group, 596.43 in the defect graft group, and 569 in the defect graft dose 1 group and 503.29 in the dose 2 group.

Significant differences were found between the healthy group and all groups ($P < 0.05$). Analyses between the defect group and the graft and strain ranelate groups revealed significant differences only in the horizontal defects and in the dose 2 group. $P = 0.015$ (TABLE I).

TABLE I
Horizontal and vertical defect healing of systemic Strontium Ranelate application on bone healing after grafting tibial defect

Parameters	Groups	N	Mean/Median	Minimum	Maximum	P*
Horizontal	Defect-Healthy Control	7	0/0	0	0	0.001
	Defect control[A]	7	716.86/677	612	821	
	Defect graft[A]	7	658.57/644	501	756	
	Defect graft dosage 1[A]	7	604.57/661	411	771	
	Defect graft dosage 2[A.C]	7	598.86/601	524	746	
Vertical	Defect-Healthy Control	7	0/0	0	0	
	Defect control[B]	7	575.14/544	511.00	736	
	Defect graft[B]	7	596.43/533	512.00	742	
	Defect graft dosage 1[B]	7	569/551	433.00	771	
	Defect graft dosage 2[B]	7	503.29/506	403.00	605	

The Krusskall-Wallis* test was used to determine whether there was a difference between the groups. Pairwise comparisons were made with the Mann-Whitney U test. A: Statistically different compared to Healthy (A, B: P = 0.000). C: Statistically different compared to the defect control (C: P = 0.015). Since no defect was created in the health control group, vertical and horizontal bone defects could not be detected

Among the studies conducted by Cardemil *et al*., [20] the study was evaluated 4 weeks after implantation and found no difference between the groups. However, studies by some authors reported significant improvement at 2 and 4 weeks [21]. This is thought to be related to the duration of SR exposure.

When the studies were evaluated, it was determined whether there was a significant difference between the experimental and control groups, and there was a large similarity between the number of studies reporting a positive effect and the number of studies reporting no difference. The studies evaluated new bone formation. In this case, superiority was found in the 6-week studies. This confirms the positive effect of SR use on bone differentiation and osteogenesis reported in previous studies [22 , 23 , 24 , 25 , 26]. In this study, similar to the studies conducted, was conducted over a longer period of 8 weeks. This is because the effects are more pronounced in longer-term studies.

Studies conducted with SR have not reported any adverse effects on bone formation and remodeling in healthy and patient models at any time. Positive effects on osteogenesis have been observed even in osteoporotic experimental models [27]. Studies have shown that even a 0.1 % dose of SR in the compound can be effective in both bone formation and remodeling [28 , 29].

Other studies have reported that the positive effect on bone formation increases with increasing SR dose. However, according to the studies, no definitive measurement for the optimal dose has been established [30 , 31].

One study on the subject observed minor changes in osteolytic activity and bone resorption. A decrease in the proinflammatory cytokine IL-6, which is involved in inflammation, was observed during healing, highlighting its positive effect on bone formation and remodeling. The positive effects of SR are evidenced by the observed increases in osteocalcin and bone morphogenetic protein during the bone formation process [32].

In this study, increases in bone healing were observed in the SR groups. This is thought to be due to increases in osteocalcin and bone morphogenetic protein. Studies have indicated that SR administration leads to increased bone formation and reduced bone resorption. Studies have observed an increase in bone mineral density, and this is attributed to an increase in bone mechanical properties. It has also been highlighted that SR promotes osteogenic bone formation while inhibiting osteoclastic resorption [33].

SR stimulates increased expression of cytokines, including alkaline phosphatase (ALP), osteocalcin (OC), and bone sialoprotein, all of which are key members of the osteoblastic gene family. This results in an increase in bone nodules and a decrease in mature osteoclasts in vitro [14 , 34].

Furthermore, studies have reported increased levels of type 1 collagen, ALP, ALP, bone sialoprotein, OC, and ultimately bone matrix mineralization in bone marrow stromal cell cultures and immature osteoblasts. Furthermore, it has been reported that it induces pre-osteoblast proliferation and increases osteoblast activity [9 , 35].

Takaoka *et al*. [36] reported that the use of SR inhibits osteoclast-mediated bone resorption and osteoclast activation, stimulating osteoblast bone-forming activity and differentiation. In a recent study, Almeida *et al*. [37] investigated the use of SR and observed significant increases in organic bone matrix. They also observed increased expression of type 1 collagen and osteopontin.

A study by Pilmane *et al*. [38] emphasized that the use of SR promotes the formation of bone-like nodules in osteogenic cultures and increases osteoblastic activity, suggesting that it may help reduce fractures due to bone hardening, particularly in postmenopausal women.

CONCLUSION

In this study, SR was administered in two doses (450 mg/kg and 900 mg/kg). Compared to the control group, it was found to have positive effects on bone healing, especially when

administered in conjunction with graft. Statistically significant differences were obtained between the defect group and the dose 2 group. This demonstrates the positive effect of SR on bone healing. When compared with similar studies, the results support these findings. This is thought to be primarily due to its effect on osteoblast activity.

However, dose adjustments should be made more carefully, and the optimal dose should be precisely determined; therefore, further studies are needed.

Conflict of interest

All authors have declared no conflicts of interest.

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