https://doi.org/10.52973/rcfcv-e362913
Revista Científica, FCV-LUZ / Vol. XXXVI

Histopathological investigation of the effect of levofloxacin and cephalexin derivative antibiotics on bone healing in experimentally induced fractures in rat tibias.

Investigación histopatológica del efecto de los antibióticos derivados de levofloxacino y cefalexina sobre la curación ósea en fracturas inducidas experimentalmente en tibias de ratas.

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ABSTRACT

This study compared the effects of systemic Levofloxacin and Cephalexin on bone healing in a rat tibial fracture model. The subjects were divided into six groups (n=7 each): healthy control, fracture control, healthy Levofloxacin, healthy Cephalexin, fractured Levofloxacin, and fractured Cephalexin. In total, 42 Sprague–Dawley rats were used. In the fractured groups, a transverse fracture was created in the right tibial diaphysis, and the bone fragments were stabilized with Kirschner wire. No surgical intervention was performed in the healthy control and healthy antibiotic groups. The antibiotic groups received systemic Levofloxacin (25 mg/kg) or Cephalexin (20 mg/kg) three times a week for 4 weeks, starting on the same day as the fractured subjects. At the end of the experimental process, all animals were euthanised. After the decalcification process, the obtained samples were evaluated histopathologically, and bone filling ratio percentages were analyzed using histomorphometric methods. In the statistical analysis, differences between groups were examined using one-way analysis of variance. In cases where the variances were not homogeneous, pairwise comparisons were performed using the Games–Howell post-hoc test. Bone formation ratios (%) showed significant differences between the groups ($P < 0.05$). In this study, bone formation rates were found to be 90.71 in the healthy control group, 67.86 in the fracture control group, 61 in the fracture cefelaxin group, 51.14 in the fracture levofloxacin group, 90.29 in the healthy cefelaxin group, and 90.43 in the healthy levofloxacin group. While there was no difference in bone formation among the healthy groups, it was determined that bone formation was reduced in the fractured groups. Among the fractured groups, bone formation in the group treated with Levofloxacin was found to be significantly lower compared to the groups treated with only fracture and Cephalexin ($P < 0.05$). Considering the results of this study, it is thought that levofloxacin, in particular, has a bone formation-suppressing effect.

Key words: Levofloxacin; cephalexin; antibiotics; bone fracture; bone healing.

RESUMEN

Este estudio comparó los efectos de Levofloxacina y Cefalexina sistémicas en la consolidación ósea en un modelo de fractura de tibia de ratas. Los sujetos se dividieron en seis grupos (n = 7 cada uno): control sano, control confractura, Levofloxacina o Cefalexina sano, Levofloxacina fracturado y Cefalexina fracturado En total, se utilizaron 42 ratas Sprague-Dawley. En los grupos fracturados, se creó una fractura transversal en la diáfisis tibial derecha y los fragmentos óseos se estabilizaron con una aguja de Kirschner. No se realizó ninguna intervención quirúrgica en los grupos control sano y antibiótico sano. Los grupos antibióticos recibieron Levofloxacina sistémica (25 mg/kg) o Cefalexina (20 mg/kg) tres veces por semana durante 4 semanas, comenzando el mismo día que los sujetos fueron fracturados. Al final del proceso experimental, todos los animales fueron eutanaziados. Después del proceso de descalcificación, las muestras obtenidas se evaluaron histopatológicamente y los porcentajes de índice de llenado óseo se analizaron mediante métodos histomorfométricos. En el análisis estadístico, las diferencias entre los grupos se examinaron mediante un análisis de varianza unidireccional. En los casos en que las varianzas no fueron homogéneas, se realizaron comparaciones por pares mediante la prueba post-hoc de Games-Howell. Los índices de formación ósea (%) mostraron diferencias significativas entre los grupos ($P < 0,05$). En este estudio, se encontró que las tasas de formación ósea fueron de 90,71 en el grupo de control sano, 67,86 en el grupo de control de fracturas, 61 en el grupo de fracturas con cefelaxina, 51,14 en el grupo de fracturas con levofloxacino, 90,29 en el grupo sano con cefelaxina y 90,43 en el grupo sano con levofloxacino.Si bien no hubo diferencias en la formación ósea entre los grupos sanos, se determinó que la formación ósea se redujo en los grupos fracturados. Entre los grupos fracturados, la formación ósea en el grupo tratado con Levofloxacino fue significativamente menor en comparación con los grupos tratados solo con fractura y Cefalexina ($P < 0,05$). Según los resultados de este estudio, el levofloxacino parece suprimir la formación ósea.

Palabras clave: Levofloxacino; cefalexina; antibióticos; fractura ósea; consolidación ósea.

Recibido: 05/02/2026 Aceptado: 13/04/2026 Publicado: 06/05/2026

INTRODUCTION

Bone tissue is a connective tissue with high mechanical strength formed by the mineralisation of an organic skeleton composed primarily of collagen. [1]. Bone remodeling is a continuous and tightly regulated process that depends on the coordinated activity of osteoblasts responsible for bone formation and osteoclasts that mediate bone resorption [2, 3].

The healing process following a bone fracture is a multi-stage, coordinated regenerative mechanism aimed at restoring tissue integrity. [4]. This process occurs in two different ways: primary (direct) and secondary (indirect) healing. Primary healing occurs when fracture fragments are fixed under compression conditions where they are anatomically stable and there is no micromobility at the fracture line [5].

In this repair mechanism bone repair is achieved through the direct remodeling of lamellar bone and the Haversian canal system [5]. Although primary bone healing can be achieved through open reduction and compression internal fixation, secondary bone healing is the most common healing pattern in clinical practice. This repair method involves intramembranous and endochondrial ossification and follows three stages: inflammation, tissue repair, and eventual remodeling [6, 7].

The repair process in secondary fracture healing begins with the early inflammatory response that develops following the fracture. During this period, a hematoma develops along the fracture line, and this structure plays a fundamental role in initiating the local inflammatory process. Cytokines released by migrating immune cells play a crucial role in recruiting mesenchymal stem cells to the fracture area, thereby creating a biological environment that supports the subsequent bone healing phase [8].

After the inflammatory response subsides, fracture healing enters the callus stage, which forms within the first few days after injury. During this stage, mesenchymal stem cells differentiate into chondrocytes and osteoblasts, eventually forming a callus rich in fibrocartilage. This newly formed tissue temporarily stabilizes the fracture space and provides a temporary scaffold, promoting further bone regeneration [9].

As fracture healing progresses, the temporary cartilaginous callus is gradually replaced by a mineralized calcified callus. This stage, which is usually completed within weeks, marks the beginning of the bone's reorganisation process. During this process, mineral deposition in the extracellular matrix synthesized by osteoblasts enhances the mechanical strength of the fracture site and creates favorable conditions for the final stage of bone healing [10].

The final stage of fracture healing is the remodeling period, which can last for months or even years. During this stage, the mineralized callus gradually transforms into mature lamellar bone, restoring the tissue to its original structural and mechanical integrity. During this period, osteoblasts, osteoclasts and mesenchymal progenitor cells work in a coordinated manner to ensure bone formation and functional recovery [11].

Bone healing is a highly dynamic biological process regulated by a variety of systemic and local factors. Malnutrition, smoking, metabolic disorders including diabetes, and advanced age can impair angiogenesis and cell activity, thus prolonging the healing process. Parathyroid hormone is an important regulator of bone metabolism maintaining skeletal homeostasis by controlling the dynamic balance between osteoblast-induced bone formation and osteoclast-mediated bone resorption. Furthermore local factors such as infection, fracture morphology, and poor callus formation can also interfere with the normal healing process. Moreover, certain pharmacological agents and systemic pathologies may inhibit bone regeneration, ultimately compromising the effectiveness of the repair process [12, 13].

Traumatic injuries often occur through high-energy mechanisms, and are therefore prone to infection due to open injuries accompanied by soft tissue damage and the need for surgical intervention. Although rarer, it has been shown that closed injuries may also be associated with the development of infection [14].

In this sense, antibiotics have formed the basis of modern medicine in the treatment of infection, and the use of antibiotics, especially in reducing the risk of infection after traumatic injuries and surgical procedures, has made a significant contribution to reducing patient morbidity and mortality [15].

In the management of many fractures, such as traumatic jaw fractures, the use of antibiotics is accepted as an approach to prevent the development of infection. However, it is also reported that there are significant differences in antibiotic protocols, application times, and classes of antibiotics used in various literatures [16].

Previous studies indicate that prolonged intravenous antibiotic therapy offers no clear benefit compared with oral administration in the management of complex orthopedic infections. In contrast the efficacy of systemic antibiotic use in wound infections developing after trauma is supported by randomised controlled trials [17].

Cephalosporins are commonly utilized in fracture management owing to their effective bone penetration and favorable cost profile. Cephalexin, an orally administered first-generation cephalosporin, is widely employed for both prophylactic purposes and the treatment of bone-related infections due to its efficient distribution within osseous and surrounding soft tissues [18, 19].

Fluoroquinolone antibiotics are broad-spectrum antimicrobial agents used in the treatment of bone, joint, and soft tissue infections. Fluoroquinolones are particularly preferred in cases of chronic osteomyelitis caused by Staphylococcus aureus and gram-negative bacilli due to the need for long-term treatment. Levofloxacin, a third-generation fluoroquinolone, is among the agents widely used in bone and joint infections, especially due to its good penetration into bone tissue and broad antibacterial activity [20, 21].

In clinical practice, antibiotics are widely used in various applications to prevent the development of infection in the postoperative period. However it has been reported that the biological effects of some classes of antibiotics on bone tissue are not always neutral. In particular it has been suggested that fluoroquinolones may slow down tissue regeneration by modulating osteogenic cell activity and may adversely affect the osseointegration process. In contrast cephalosporins are

thought to have a more limited effect on bone healing. Therefore a comparative assessment of the effects of these two antibiotic groups, which are commonly used in the postoperative period, on bone repair is clinically significant for the decision making process [22].

Bone fracture healing is a multi-stage biological process beginning with hematoma formation, followed by granulation tissue development and hard callus formation, and ending with a long-term remodeling phase. In this process, with the early activation of the inflammatory response, mesenchymal stem cells migrate to the fracture site. In the subsequent stages, granulation tissue matures, osteogenic activity increases, and new bone tissue is formed. In the final stage of healing, under the influence of mechanical loads, the bone tissue reorganizes and achieves its structural and functional integrity. Bone formation and mechanical stability are maintained through the coordinated actions of osteoblasts, osteocytes, osteoclasts, and osteogenic precursor cells, together with type I collagen fibers and a range of non-collagenous matrix constituents [23, 24, 25].

Antibiotics are routinely preferred for the prevention and treatment of infection in fracture management; however, the biological effects of these agents on the bone repair process remain unclear. Experimental findings regarding the potential effects of different antibiotic groups on bone cell functions and regenerative mechanisms are still limited. Within the scope of this study, the effects of levofloxacin and cefalexin treatments on bone repair were histopathologically analysed using an experimental tibial fracture model developed on Rattus norvegicus.

MATERIALS AND METHODS

The study protocol was approved by the Fırat University Local Ethics Committee for Animal Experiments (Protocol No: 21839; 31 January 2024). All procedures were conducted in accordance with the relevant guidelines on the Use of Laboratory Animals and the Declaration of Helsinki. The experimental procedures were carried out at the Fırat University Experimental Research Centre.

Experimental animals and study design

In this study, a total of 42 Sprague-Dawley female rats, aged 3.5–4 months and weighing 250–300 g, (WL, Shimadzu, Japan) were used. To eliminate variability due to hormonal cycles, vaginal smears were taken from all rats, and rats in the same estrus cycle were included in the study.

The experimental animals were obtained from the Firat University Experimental Research Center, Elazig, Türkiye. All animals were housed in rooms with a special ventilation system, a 12-hour light/12-hour dark light cycle, and a constant temperature of 25 ± 2 °C throughout the experiment. Laboratory animals had free access to water and standard laboratory feed. This study aimed to investigate the effects of levofloxacin and cephalexin on fracture healing.

Subjects were divided into six groups: a healthy control group (n = 7), a fracture control group (n = 7), a healthy levofloxacin group (n = 7), a healthy cephalexin group (n = 7), a fracture levofloxacin group (n = 7), and a fracture cephalexin group (n = 7). In the fracture group a transverse fracture of the right tibial shaft was induced, and the bone fragments were fixed with Kirschner wires.

Surgical procedures

All surgical interventions were carried out under sterile conditions. General anesthesia was induced via intraperitoneal injection of 10 mg/kg xylazine (Rompun, Bayer, Germany) combined with 40 mg/kg ketamine (Ketasol, Richter Pharma, Austria). Before surgery, the operative area was shaved and disinfected using a povidone-iodine solution, and the procedures were conducted in accordance with aseptic techniques.

In the experimental fracture groups, an incision was made through the skin and underlying soft tissues over the diaphyseal region of the right tibia using a No. 15 scalpel blade. After elevation of the periosteum, a transverse osteotomy was created by performing controlled cuts with a rotating steel disc (NSK, Japan). The resulting fracture was stabilized internally with a 1.0-mm Kirschner wire. To minimize the risk of thermal injury during bone cutting, continuous saline irrigation was applied to the surgical area.

After completion of the operation, the incised soft tissues were closed primarily with 4/0 absorbable polyglactin sutures.All subjects received standard postoperative care, and intramuscular analgesics (Tramadol hydrochloride, 1 mg/kg) was administered for three days (d) for pain control. No surgical intervention was performed in the healthy control and healthy antibiotic groups. The antibiotic groups received systemic Levofloxacin (25 mg/kg) or Cephalexin (20 mg/kg) three times a week for 4 weeks, starting on the same d as the fractured subjects. At the termination of the experiment all animals were euthanized in compliance with ethical standards.

Histopathological analysisHistopathological analysis

Histopathological examinations were performed in the laboratory of the Department of Pathology, Faculty of Veterinary Medicine, Fırat University. Tibia samples obtained from animals after euthanasia were fixed in a 10 % neutral formalin solution three days for fixation. Subsequently, the bone samples were cleaned of soft tissues such as muscle, tendon, and fascia and decalcified in a 10 % formic acid solution for approximately one week.

After decalcification, the specimens were passed through graded alcohol solutions, cleared in xylene, and infiltrated with paraffin using an automatic tissue processor (Leica TP 1020, Germany), then embedded longitudinally in paraffin blocks (Leica EG1150 H–C, Germany). Sections measuring 3 µm in thickness were obtained from the paraffin blocks with a rotary microtome (Leica RM2125 RTS, Germany) and subsequently stained with hematoxylin–eosin (HxE) using an automated stainer (Leica Autostainer XL, Germany).

The sections were evaluated under a light microscope (Olympus BX42, Japan). Measurements were performed by taking the widest and deepest points of the defect areas in the

longitudinal and vertical planes and the thickest part of the callus tissue in the transverse plane as references (cellSens Standard, Japan).

RESULTS AND DISCUSSION

In this study, bone formation rates were found to be 90.71 in the healthy control group, 67.86 in the fracture control group, 61 in the fracture cefelaxin group, 51.14 in the fracture levofloxacin group, 90.29 in the healthy cefelaxin group, and 90.43 in the healthy levofloxacin group. Histopathological analyses revealed statistically significant differences in bone formation ratios (BFR) between the groups ($P < 0.05$). BFR values were higher in the healthy control group, while bone formation rates were significantly reduced only in the fractured group (FIG. 1 and FIG. 2). Comparisons between fracture groups showed that BFR values were statistically significantly lower in the fracture + levofloxacin group compared to both the fracture control and fracture + cephalexin groups. Bone formation rates were higher in the fracture + cephalexin group compared to the levofloxacin group. No statistically significant difference was found between the BFR values of the healthy levofloxacin and healthy cephalexin groups and the healthy control group (TABLE I, and FIG. 3).

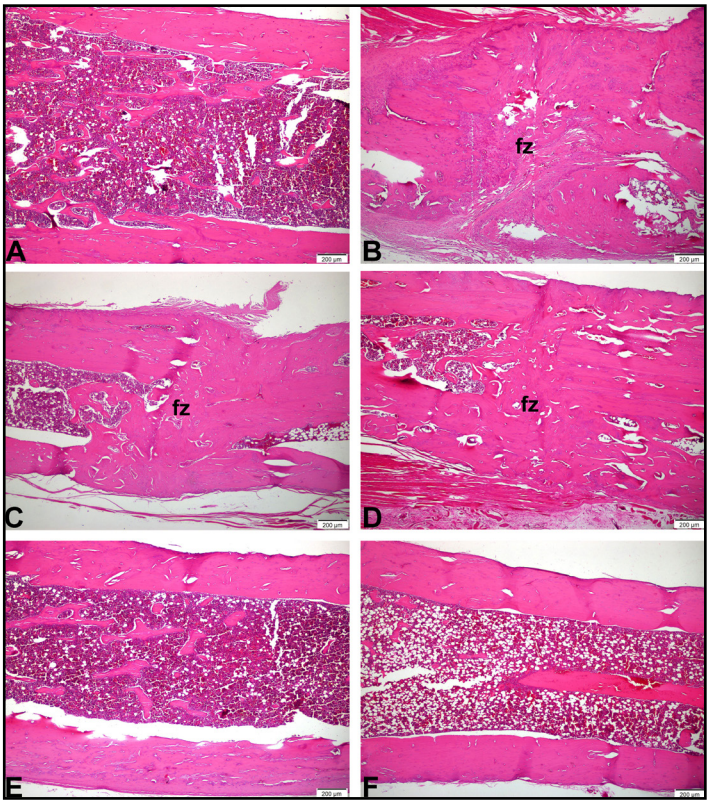

FIGURE 1. A general histological view of normal bone tissue is shown in A, E, and F, whereas B, C, and D demonstrate the healing area (fracture zone: fz) at the fracture site. A represents the Healthy Control group. B, C, and D correspond to the experimental fracture groups: Fracture Control (B), Fracture Cefalexin (C), and Fracture Levofloxacin (D), respectively. E and F represent the non-fractured antibiotic control groups: Cefalexin Control (E) and Levofloxacin Control (F), respectively. 4X objective, 40X total magnification, scale bar=200 µm, HxE.

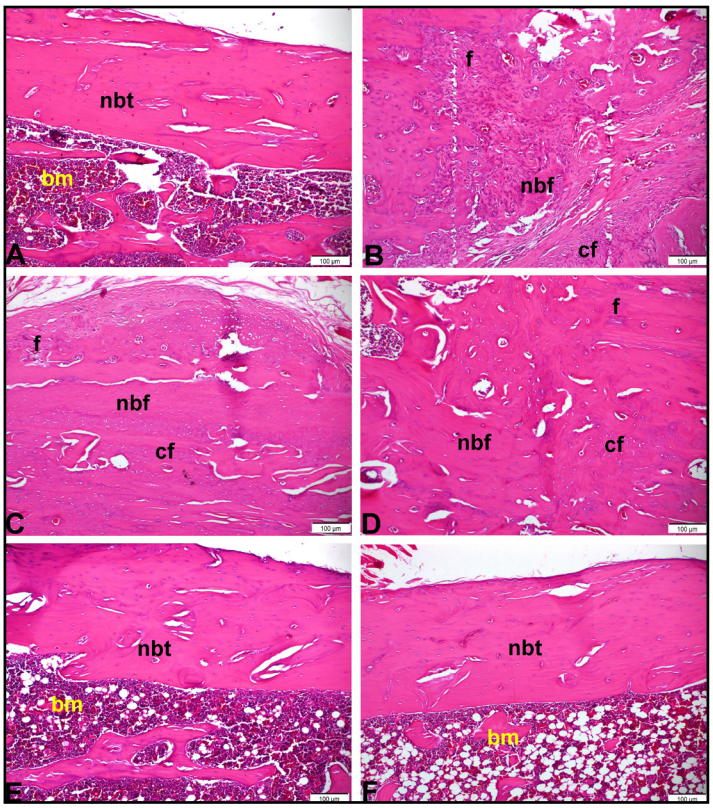

FIGURE 2. The appearance of normal bone tissue (nbt) and bone marrow (bm) is observed in the Healthy Control group (A) as well as in the Cefalexin Control (E) and Levofloxacin Control (F) groups. In contrast, the fracture healing area in the experimental groups demonstrates regions of new bone formation (nbf), cartilage formation (cf), and fibrosis (f). These findings are shown in the Fracture Control group (B), Fracture Cefalexin group (C), and Fracture Levofloxacin group (D).
10X objective, 100X total magnification, scale bar=100 µm, HxE.

TABLE I

Bone formation ratios of the groups after the pathologic analysis

Groups	N	Mean (BFR ratio)	Std. Deviation	P*
Healthy controls	7	90.71[b,c,d]	1.38	
Fracture control	7	67.86[a,e,f]	1.87	
Fracture Cephalexin	7	61[a,e,f]	8.74	<0.05
Fracture Levofloxacin	7	51.14[a,b,e,f]	6.36	P=0.000
Healthy Cephalexin	7	90.29[b,c,d]	0.95	
Healthy Levofloxacin	7	90.43[b,c,d]	1.72	

*One Way Anova Test. aDifferent when compared with Healthy controls. [b]Different when compared with fracture only. [c]Different when compared with Fracture[c]ephalexin. [d] Different when compared with Fracture Levofloxacin. [e] Different when compared with Cephalexin. [f]Different when compared with Levofloxacin. BFR: Bone formation ratio.

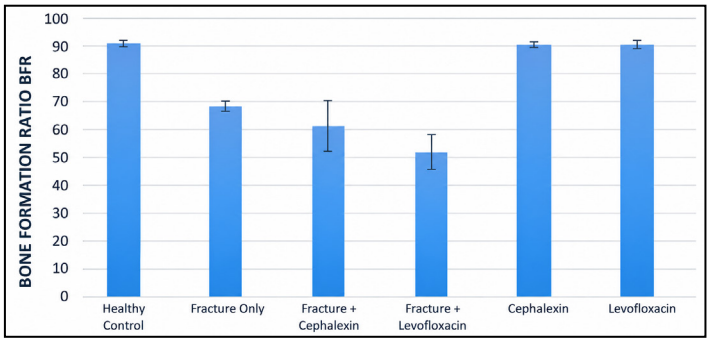

FIGURE 3. Comparison of bone formation ratio values among the study groups. Data are presented as mean ± standard deviation.

In the present experimental design, a tibial fracture model was preferred because of its embryological similarity to the mandible. The creation of a defect by surgical drilling was performed in accordance with the methodology described by Krischak *et al*. [26]. Cefalexin was included in the study as it is a commonly prescribed antibiotic in clinical practice for the prevention of hospital-acquired infections. Levofloxacin was also evaluated due to its high penetration into bone tissue and its classification as a new-generation antibiotic.

There are experimental studies in the literature that have been planned with follow-up periods of four and six weeks to evaluate the phases of fracture healing. Özbay *et al*. [27] reported that sufficient hard callus formation could be observed histopathologically in their study on a rat fracture model in the fourth week. Based on this finding, it can be stated that a four-week period is suitable for evaluating bone formation in the early healing period. In addition, as stated in previous studies, a four-week evaluation period is considered sufficient to reveal the biological changes of the early phases of fracture healing. For this purpose, the follow-up period in the present study was determined as four weeks [28].

Fracture healing begins with the activation of cellular responses in the early stages and is a multi-stage process followed by osteogenesis and new bone formation. Some studies have shown that the use of fluoroquinolones may weaken the functions of cells involved in the bone formation process and reduce tissue synthesis. [29, 30]. It is reported that these effects may negatively affect new bone formation during fracture healing.

The histological data obtained indicate that bone formation in animals administered levofloxacin occurred at a lower level compared to the control group. However, the observation of higher levels of bone formation in the cefalexin group compared to the levofloxacin group suggests that the biological effects of cephalosporins on bone healing may be more limited than those of fluoroquinolones. These findings indicate that the antibiotic class may affect the bone healing process through different mechanisms.

According to the findings of the present study the bone formation rates in the fracture group treated with levofloxacin were statistically significantly lower than those in the control group. This finding is consistent with the findings of Perry *et al*. [31] who reported that the use of levofloxacin may adversely affect fracture healing. Levofloxacin is a fluoroquinolone antibiotic that is effective against a broad spectrum of microorganisms and exhibits high penetration into bone tissue and intracellular fluid. Despite these properties it should be noted that it may have adverse biological effects on the bone healing process.

In the experimental study conducted by Golestani *et al*. [32] the healing process of fractures created in rat tibias was evaluated based on histological scores among groups administered levofloxacin, cefalexin, and saline. In the analyses performed at the fourth week, it was reported that the fracture healing score of the saline group was significantly higher than that of the levofloxacin group ($P = 0.015$). In contrast no statistically significant difference was found between the cephalexin group and the control group ($P > 0.05$). In light of these findings the researchers stated that levofloxacin may adversely affect fracture healing, but cephalexin did not show any effect different from that of the control group.

This current study noted that the rates of bone formation were significantly lower in the levofloxacin-treated group than in the control group. This aligns with the reports of Golestani *et al*. [32]. The similarity reinforces the theory that fluoroquinolone antibiotics are likely to have an adverse effect on the process of fracture healing.

On the other hand, in Golestani *et al*. [32] reported that; there was no significant difference between the cephalexin and control groups; similarly, in this study, no statistically significant difference was found between the cephalexin group and the control group in terms of bone formation rate. This agreement suggests that the effect of cephalexin on bone healing may be more limited compared to other antibiotic classes.

The experimental tibial fracture model creates a biological microenvironment that closely resembles natural bone repair, enabling assessment of healing responses under physiologically relevant conditions. Experimental bone defects should be consistent, reproducible, and standardized, while also allowing repair within a defined observation period. Tibial fractures largely fulfill these experimental requirements and are therefore widely used in bone healing studies [33]. The effects of two different antibiotic applications were analysed using an experimental fracture model created on the tibia, which possesses endochondral ossification properties, thereby revealing the potential biological contributions of antibiotics in fracture healing.

CONCLUSION

According to the findings, bone formation rates were statistically significantly lower in the levofloxacin-treated group compared to the control group. In contrast, no significant difference was observed between bone formation rates in the cephalexin-treated group and the control group.

In this study, it was observed that the healing process continued in all groups, and bone regeneration was affected to varying degrees depending on the antibiotic class. In particular, findings indicated that fluoroquinolone antibiotics may negatively affect the bone healing process, while cephalexin exhibited a more neutral profile in terms of bone healing compared to fluoroquinolones.

These results indicate that the antibiotics used in fracture treatment should be considered not only for their antimicrobial efficacy but also for their biological effects on bone healing. Further experimental and clinical studies are needed to more comprehensively demonstrate the effects of antibiotics on bone healing.

Conflict of interests

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Funding

The authors received no specific funding for this work.

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