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Original Article

The effects of rifampicin on wound healing

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Abstract

Aim: The effects of topical antibiotics on the wound healing are one of the interesting aspects of medicine. The aim of this study is to investigate the effects of topically applied rifampicin on wound healing in skin defects.

Material and Methods: Forty-two male adult Sprague Dawley rats were divided into two groups: Group A (n = 21) and Group B (n = 21). Circular full-thickness skin defects were formed in the right thoracoabdominal regions. Group A received once daily local saline and Group B received once daily rifampicin 1 cc topically applied on the wounds. The defect sizes were photographed at the baseline, and days 3, 7 and 10 and the reductions in wound sizes were measured. In each group, 7 rats were sacrificed on each of days 3, 7 and 10 and their defected region was resected. Specimens were histopathologically evaluated, and scored for inflammatory cells, collagen accumulation, granulation tissue, re-epithelialization, and features of skin defect such as what layers of the skin are affected by it, its size and whether it involves any abscess-necrosis. The results were statistically analyzed.

Results: There was no statistically significant difference between groups in terms of healing rate. Comparison of scores for inflammatory cells and features of skin defect revealed statistically significant differences. Statistically significant results were obtained for collagen accumulation and granulation tissue formation in both groups. No statistically significant difference was found in re-epithelialization between the groups.

Conclusion: Topically applied rifampicin in experimentally induced skin defects does not have a positive effect on wound healing.

Keywords: Wound healing; therapy; anti-infective agents; local; rifampicin

INTRODUCTION

Wound infection is a common problem that occurs after traumatic injuries and surgical incisions. Many factors are involved in the formation of infection in the wound area, such as the mechanism by which the injury occurs, the type and degree of contamination, the time to medical treatment after injury, patient's susceptibility, and presence of chronic illnesses (1). It is a common knowledge that, when an infection forms in a wound anywhere in the body, serious delay in wound healing process occurs and morbidity-mortality increases. This disrupts the patients' quality of life, shakes the confidence in the physician and the hospital and leads to labour loss, prolonged hospital stay, and increased healthcare costs.

The use of topical antibiotics in the wound healing process is a common practice in many surgical centers, including general surgery clinics. Topical antibiotics reduce bacterial load, eliminating the negative effect of bacterial colonization on wound healing and reducing the need for systemic antibiotics. In addition, these drugs are easy to administer, have no systemic toxicity due to their low systemic absorption, create high concentration at the wound site and prevent the development of antibiotic resistance. The topical antibiotic used should be safe and nontoxic, and should exhibit an appropriate antibacterial activity. Also, the mechanism by which it affects the wound healing phases and the effect on healing rate and epithelization must be acknowledged (2,3).

Rifampicin is a semisynthetic antibiotic derived from Streptomyces mediterranei for the first time in 1957 and is commonly used in the treatment of wounds and burns in Turkey. Although rifampicin is used topically in infected wounds both for infection treatment and maintenance purposes, there are limited numbers of studies in the literature reporting positive opinions about this practice (2,4).

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In this experimental study, the effects of topical application of rifampicin on acute surgical wound healing in full-thickness skin defects formed in thoracoabdominal region in rats were investigated and the obtained data were discussed in the light of the literature.

MATERIAL and METHODS

Population

This experimental study was conducted in 42 male adult Sprague Dawley rats from the same colony weighting 250–350 g. The rats were obtained from the Experimental Animals Laboratory of Karadeniz Technical University University. The purpose of using rats was easy availability, safety, their resistance to infections and surgical procedures and the high ratio of experiment repeatability (5).

The study was approved by the local ethics committee at Karadeniz Technical University University Faculty of Medicine, Animal Care and Use Committee. The rats were handled in accordance with the Guide for the Care and Use of Laboratory Animals.

Design

The rats were randomly assigned into two groups: Group A: control (n = 21) and Group B: Rifampicin (n = 21).

Group A: The control group. In this group, circular full-thickness skin defects approximately 1 x 1 cm in size were formed in the right thoracoabdominal region of the rats. No treatment was given to the rats except local saline solution applied on the wounds once daily to prevent the wound from drying. Seven rats were sacrificed on days 3, 7, and 10, and their defected regions were resected (Figure 1).

Group B: The rifampicin group. Circular full-thickness skin defects approximately 1 x 1 cm in size were formed in the right thoracoabdominal regions of the rats also in this group. Rifampicin (Rifocin 250 mg/3 ml, Aventis Pharma Sanayi ve Ticaret A.Ş., Istanbul, Turkey) was applied on the wounds of the rats topically at a dose of 1 cc / once a day. Seven rats were sacrificed on days 3, 7, and 10, and their defected regions were resected (Figure 1).

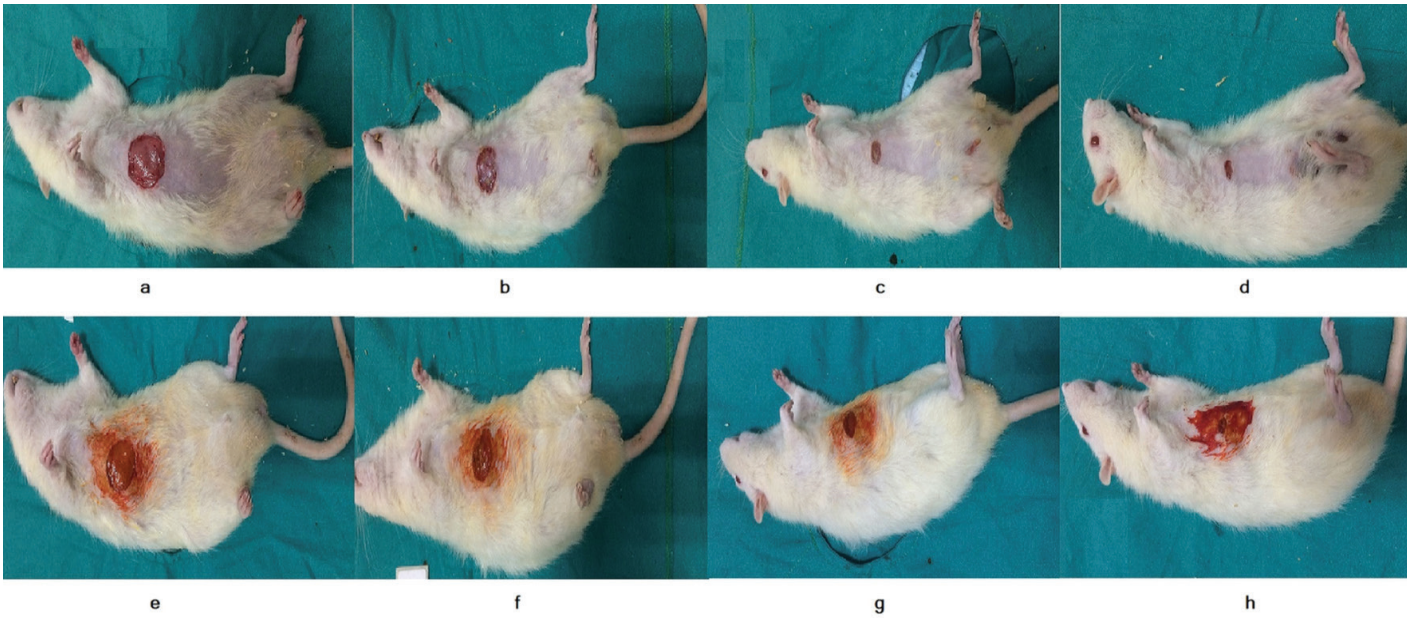

Figure 1. Macroscopic images of the skin defects created in the rats in Group A are seen in the upper figure A) at baseline, B) at day 3, C) at day 7 and D) at day 10 and those in Group B in the lower figure E) at baseline, F) at day 3, G) at day 7 and H) at day 10

The rats were kept under special pathogen-free conditions to prevent infections and placed separately in a light-controlled room with a 12:12 hour light-dark cycle. The temperature was kept fixed at 22 ± 0.5°C and the relative humidity at 65–70%. Caution was used to avoid undesired stress during the study. The rats were given standard laboratory rodent chow and water. The animals had not been used in another study or been given any medications previously. Their feeding was discontinued 12 hours before the experiment but the rats were allowed to take in water (6).

Technical and surgical procedures

All of the rats were anesthetized by intraperitoneal administration of ketamine hydrochloride (Ketalar®, Eczacıbaşı, Istanbul, Turkey) 50 mg/kg and xylazine hydrochloride (Rompun®, Bayer, Turkey) 3 mg/kg. Extremity pulling response was used to assess anesthetic depth and additional doses were administered when required. The procedures were performed in a position that allowed spontaneous breathing under sterile conditions. The rats were placed in a supine position. Right thoracoabdominal regions of the rats were shaved

and cleaned with 10% povidone iodine (Baticon® solution, Adeka, Turkey) and a circular full-thickness wound tissue 1x1 cm in size was formed by removing the skin and subcutaneous tissue without damaging the underlying aponeurosis.

No complications occurred in the rats and none of the rats were lost during the experiment.

Macroscopic assessment

The defect sizes of all rats were photographed at the baseline, and days 3, 7 and 10 of the experiment and the reductions in wound sizes were measured macroscopically on the computer using the metric system and the formula below to calculate the healing rates based on these data (7).

$$\frac{SA-SAC}{SA} \times 100 = \%\ \text{reduction in wound size}$$

(SA= surface area (length x width) at baseline, SAC= surface area (length x width) currently)

Histopathological examination

When the times indicated in the study protocol expired, the rats were sacrificed by high doses of intraperitoneal anesthetic administration and their defected areas were resected in full-thickness retaining at least 1 cm of unharmed tissue around the defect. The specimens were promptly fixed in 10% formalin and embedded in paraffin wax. Subsequently, tissue sections 5 µm in thickness were obtained with a microtome. Light microscopy (Olympus CX 41) was used for histopathological analysis of the Hematoxylin-Eosin and Masson's Trichrome stained sections. The histopathological assessment was carried out by the same pathologist blinded to the group to which tissue specimens belonged by randomly selecting from the tissue specimens. The histopathological examination was performed according to the scoring of wound healing assessment as shown in Table 1 and inflammatory cells, collagen accumulation, granulation tissue formation, re-epithelialization, and features of skin defect such as what layers of the skin are affected by it, its size and whether it involves any abscess-necrosis were assessed in the specimens (Table 1). In this scale, the parameters were scored from 0 to 3 and were recorded separately for the rats in each group.

Statistical analyses

All statistical analyses were performed using the SPSS statistics software version 15.0 for Windows (SPSS Inc., Chicago, IL). The results obtained for the groups on days 3, 7 and 10 were compared using the nonparametric Friedman test. The results of healing rate obtained for Group A and Group B were compared using the independent samples t test. The statistical significance level was accepted as $p<0.05$.

Table 1. Scale for histopathological assessment of wound healing

	Inflammatory Cells	Collagen Accumulation	Granulation Tissue	Re-Epithelialization	Features Of Skin Defect
0	None	None	None	None	None
1	Little (Scattered, small amount of mixed inflammation)	Little (Patch-like collagenization in the form of short strips)	Little (involving less than 10 new vessel formation in 1 HPF)	In less than 1/3 of the tissue	Very small (Limited to epidermis, smaller than 0-0.4 cm. in diameter microscopically)
2	Moderate (Moderate mixed inflammation concentrating around vessels)	Moderate (Strip-like thin collagenization)	Moderate (involving between 11-20 new vessel formation in 1 HPF)	In 1/3-2/3 of the tissue and thin shaped	Wide ulcer but not deep (Limited to epidermis and papillary dermis, 0.4-0.6 cm. in diameter microscopically)
3	Much (Intensive mixed inflammation concentrating around vessels and forming clusters)	Much (Strip-like coarse thick collagenization)	Much and mature (involving more than 20 new vessel formation in 1 HPF)	In the entire tissue and mature	Deep and wide ulcer or abscess formation (in epidermis and extending to reticular dermis, wider than 0.7 cm. microscopically or involving necrosis-abscess formation)

1 high power field (HPF): The part seen in 1 piece of x40 large magnification area (in high power field)

RESULTS

The healing rate values at day 3 were 22.1±9.8% for Group A and 5.3±7.7% for Group B (p=0.004). The healing rate values at day 7 were 56.8±4.6% in Group A and 49.4±5.1% in Group B (p=0.016). The healing rate values at day 10 were 67.4±4.7% in Group A and 68.8±3.7% in Group B (p=0.560). Although there were statistically significant differences between two groups on the day 3 and day 7, at the end of the experiment, there was no statistically significant difference between Group A and Group B in terms of healing rate (Figure 2).

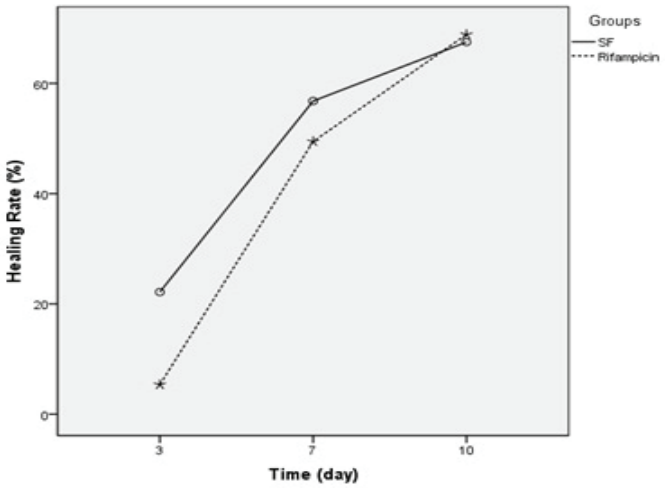

Figure 2. Healing rates of Group A and Group B during the study

The specimens were histologically evaluated and scored for inflammatory cells, collagen accumulation, granulation tissue formation, re-epithelialization, and features of skin defect in line with the scoring system shown in Table 1. Overall, inflammatory cell counts were found to have remained constant at high values throughout the experiment in Group A, whereas in Group B, they were relatively high on day 3, decreased on day 7 and remained constant at these values until day 10. When the scores were examined for collagen accumulation, it was observed that in Group A, the score tended to remain low and stable for the first 7 days, but showed a slight increase on day 10 whereas in Group B, the score that was low on day 3, increased on day 7, and remained at this level until day 10. The scores those were initially low for granulation tissue formation in Group A increased from day 7 and remained constant on average until day 10 whereas in Group B, the scores that increased on day 3 continued to increase until day 7 and remained constant at this level until day 10. Re-epithelialization remained constant at low scores in Group A and Group B throughout the experiment. High scores were obtained for features of skin defect from the beginning to the end of the experiment in Group A, whereas in Group B, the baseline high scores decreased slightly on day 7 and remained constant until day 10 (Figures 3 and 4).

All of the histopathological results were statistically analyzed for significance. Comparison of scores for inflammatory cells and features of skin defect showed statistically significant differences between the groups in favor of Group B. Statistically significant results were obtained for collagen accumulation and granulation tissue formation in both groups, with these results being more significant in Group A. No statistically significant difference was found in re-epithelialization between the two groups. All the results obtained are presented in Table 2.

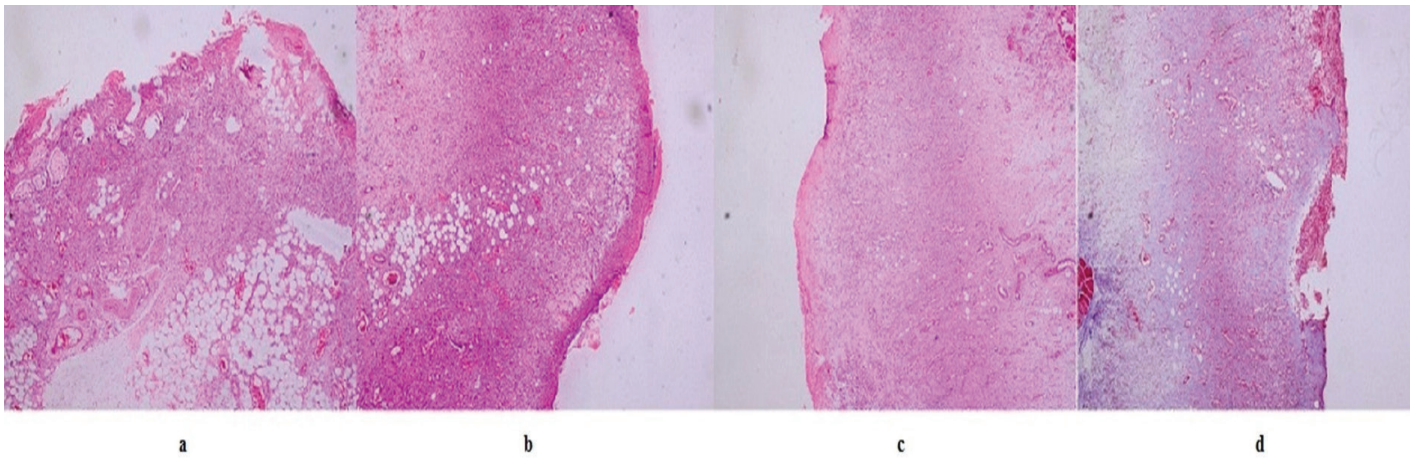

Figure 3.

A) Group A, Day 3: Deep and wide ulcer formation in middle parts, extensive inflammation and granulation tissue (Hematoxylin-Eosin, original magnification x 4)

B) Group A, Day 7: Deep and wide ulcer formation in middle parts, extensive inflammation and increased granulation tissue (Hematoxylin-Eosin, original magnification x 4)

C) Group A, Day 10: Deep and wide ulcer formation in middle parts, extensive inflammation and marked granulation tissue as well as slightly increased collagen tissue formation (Hematoxylin-Eosin, original magnification x 4)

D) Group A, Day 7: Moderate collagen increase and marked granulation tissue (Masson's Trichrome, original magnification x 4)

Table 2. Median inflammatory cells, collagen accumulation, granulation tissue, re-epithelialization and features of skin defect scores and p values in all groups

	Median [IQR: 25%-75%]	p
Inflammatory cells		
	Day 3: 3.0 [3–3]	
Group A	Day 7: 3.0 [3–3]	p=1.000
	Day 10: 3.0 [3–3]	
	Day 3: 2.0 [2-2]	
Group B	Day 7: 1.0 [0-2]	p=0.022
	Day 10: 1.0 [1-1]	
Collagen accumulation		
	Day 3 1.0 [1–1]	
Group A	Day 7: 1.0 [1-1]	p=0.007
	Day 10: 2.0 [1–3]	
	Day 3: 1.0 [1-1]	
Group B	Day 7: 2.0 [1–3]	p=0.016
	Day 10: 2.0 [2-2]	
Granulation tissue		
	Day 3: 1.0 [1-1]	
Group A	Day 7: 3.0 [3–3]	p= 0.001
	Day 10: 3.0 [3–3]	
	Day 3: 2.0 [2-2]	
Group B	Day 7: 3.0 [3–3]	p= 0.002
	Day 10: 3.0 [3–3]	
Re-epithelialization		
	Day 3: 1.0 [1-1]	
Group A	Day 7: 1.0 [1-1]	p=1.000
	Day 10: 1.0 [1-1]	
	Day 3: 1.0 [1-1]	
Group B	Day 7: 1.0 [1-1]	p=1.000
	Day 10: 1.0 [1-1]	
Features of skin defect		
	Day 3: 3.0 [3–3]	
Group A	Day 7: 3.0 [3–3]	p=1.000
	Day 10: 3.0 [3–3]	
	Day 3: 3.0 [3–3]	
Group B	Day 7: 2.0 [1–3]	p=0.019
	Day 10: 2.0 [2-2]	

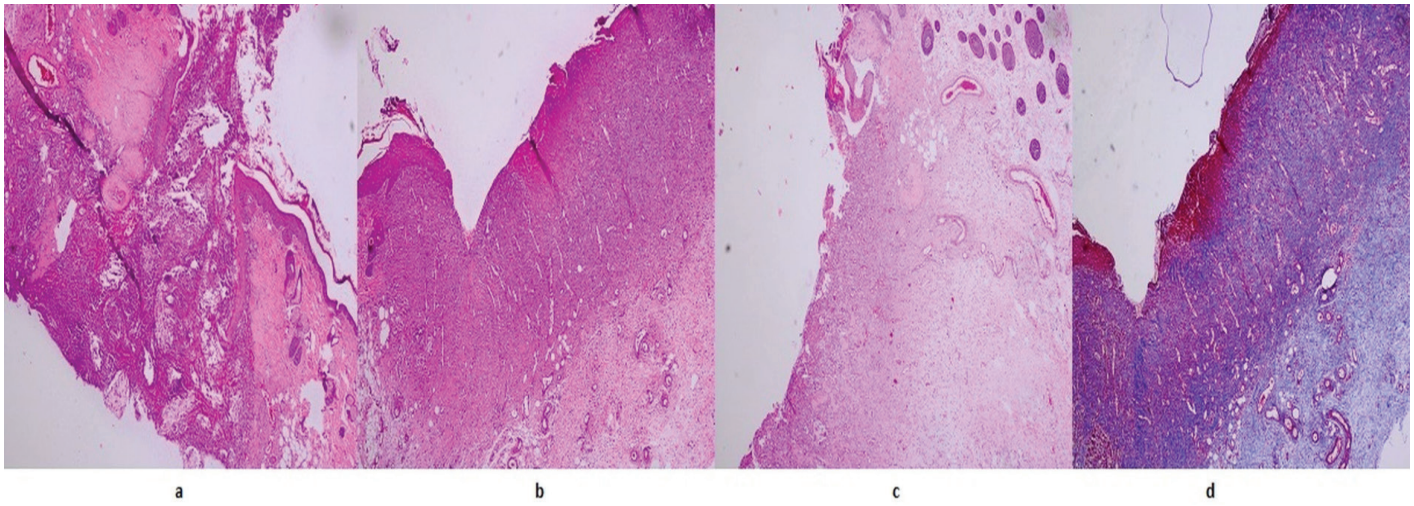

Figure 4.
A) Group B, Day 3. Excessive accumulation of inflammatory cells, deep and wide ulcer formation, and slightly increased granulation tissue are present (Hematoxylin-Eosin, original magnification x 4).
B) Group B, Day 7. Partial reduction in inflammatory cells, relatively superficial ulceration, partial re-epithelialization and marked granulation tissue are present (Hematoxylin-Eosin, original magnification x 4).
C) Group B, Day 10. Moderate inflammatory cells, superficial ulceration, and marked granulation tissue are present (Hematoxylin-Eosin, original magnification x 4)
D) Group B, Day 10. Moderately increased collagen content and marked granulation tissue are present (Masson's Trichrome, original magnification x 4).

DISCUSSION

This experimental study on the use of rifampicin in full-thickness skin defects highlights 6 issues: a) Rifampicin caused a slight decrease in the intensity of inflammatory cells in the defected region. b) In the rifampicin-treated group, collagen accumulation slightly increased in the defected region. c) Rifampicin caused an intense granulation tissue formation in the defected region. d) Rifampicin has not been effective in tissue re-epithelialization in the defected region. e) The use of rifampicin slightly reduced skin defect formation initially detected in the defected region. f) At the end of the experiment, the healing rates were similar between Group A and Group B.

Traumatic defects that disrupt skin integrity are not only commonly seen in surgical branches after an operation or biopsy, but also in emergency clinics. Skin is our most important organ that protects our body by forming a barrier against external factors such as pathogens and toxins that we encounter throughout our lives (8). A dynamic and complex wound healing process begins immediately after the wound occurs, which involves hemostasis and inflammation followed by proliferation and remodeling/scar formation (9, 10). Efficient wound repair, which is the primary target for wound healing, is achieved through coordinated effects of several different cell types (11). Inflammation is such an important phase in wound healing that the inflammation and tissue repair that occur during the process are body's interlocking defense mechanisms. The main purpose of inflammation is to clear out necrotic cells and tissues, which are the causes and consequences of cell injury. In the first days of wound healing process, the number of inflammatory cells, especially neutrophils, the first circulating inflammatory cells to move the wound, increases. However, the number of these cells needs to be reduced afterwards due to the fact that a successful repair requires resolution of the inflammatory response. However, strong inflammatory response such as overactive or prolonged neutrophil response interferes with wound healing by slowing down wound healing process, and even causes chronic wounds, impairs quality of repair and when considered as a complication, causes impairment and failure in organ functions (12). This additional tissue destruction causes persistent inflammation, which leads to further tissue damage, preventing proceeding to proper stages of the wound healing process. Thus, a vicious cycle is formed and smooth wound healing is particularly prevented. In this study, high inflammatory cells count at the baseline in the rifampicin-treated group began to decrease on day 7, but this decrease did not occur at desired levels. We think that this partial effect is due to the anti-inflammatory properties of rifampicin. In a study by Kim et al., it has been observed that rifampicin in human cell cultures reduces the secretion of cytokines and inflammatory mediators such as prostaglandin D2 (PGD2) and tumor necrosis factor alpha (TNF-alpha). Furthermore, rifampicin was found to have inhibited cyclooxygenase-2 (COX-2), which is associated with the inflammatory reaction, in

human cell cultures (13). Following injury, arachidonic acid is released from phospholipids in the cell membrane by the action of phospholipase A2 enzyme. Stimulants that cause inflammation increase the synthesis of prostacyclin and prostaglandin from this arachidonic acid via COX enzyme, during which the formation of cyclic endoperoxides, thromboxane A2 and platelet activating factor is also increased. These substances or the stable metabolites thereof are intensely present in the area of inflammation. Similarly, the amounts of leukotrienes, products of lipoxygenase pathway are also increased in the inflamed tissue. The effects of the above-mentioned and other similar chemical mediators, which are released during the inflammatory process, on cells are complex and variable (14). At this point, especially prostaglandin E2 (PGE2) production is essential for cutaneous wound healing. COX-2 enzyme, which is actively involved in these stages, is abundant in the area of inflammation in the traumatic defected region. COX–2 and PGD2 play an important role in mast cell-mediated inflammation. Many anti-inflammatory drugs work by inhibiting COX-2, inhibiting prostaglandin and thromboxane synthesis and suppress inflammation (15). Rifampicin also inhibits COX-2, but this is a partial effect. This explains the slight decrease in the number of inflammatory cells observed in the present study in the rifampicin group compared to the control group.

In the proliferation phase of wound healing, collagen synthesis starts at 48 hours and continues gradually increasing until days 5–7. (16). This organized new collagen formation in the defected region will make the new cells bind to each other by stronger bonds, making the new tissue stronger. In our study, collagen accumulation in the defected region slightly increased in Group B, which was not statistically significant. This can be interpreted as the absence of a significant effect of rifampicin on the collagen production in the wound area, which would adversely affect the wound healing process.

Natural wound healing process involves the increase of the amount of granulation tissue after the first few days of defect formation; the granulation tissue disappears after the healing of the wound. In this study, the defected region showed intense granulation tissue formation in the rifampicin group. A similar result was obtained in the control group in which wound is left to heal by itself with no medication being administered. Intense granulation tissue formation on the surface of a wound inhibits epithelialization, prevents the edges of the wound from joining together, and blocks collagen accumulation that would be effective in wound contraction. All these negative effects prevent wound healing. Regarding re-epithelialization during natural wound healing, mature reepithelial tissue, which gradually increases in amount during the course of the healing process and reaches its peak toward the final stages of healing, must be present at the defected region. In this study, the amount of re-epithelialization in both groups remained well below the desired levels. In one study, abundant amounts of COX-2 were detected in endothelial cells within small vessels and in fibroblast-like cells within the granulation tissue. Marked induction beginning within 12 hours and peaking 3 days after injury was observed in COX-2 concentration by Western analysis. This increased COX–2 level after injury, particularly in the early acute phase, promotes cell migration and proliferation that underlie re-epithelialization and angiogenesis. COX–2 appears to be important in epidermal and dermal recovery from injury (17). We think that re-epithelialization in the defected region is well below the desired levels due to the inhibition of COX-2 by rifampicin. In conclusion, rifampicin did not have a positive effect on wound healing in terms of these two histopathologic parameters.

Skin defects occur frequently in the wound area due to malnutrition, vascular pathologies, or infection (18, 19). Elimination of these negative factors will ensure disappearance of these skin defect areas during the wound healing process. In this study, we were observed to have reduced the amount of skin defect formation detected at the baseline in the defected region in rifampicin group. However, even on day 10 which is the day the experiment was terminated, intense ulcerations were detected in the defected region. For an effective healing, there should be no ulcer in the tissue, especially towards the end of the wound healing process. We believe that rifampicin fails to adequately prevent the vicious cycle of ulcer-infection and that this negatively affects the healing of the ulcers in the defected region.

At the end of the experiment the healing rates were similar between Group A and Group B. This may be considered as macroscopic evidence that rifampicin is not effective on wound healing.

Rifampicin is a well-tolerated semi-synthetic broad spectrum antibiotic with potent bactericidal effects, even in very low doses, against most aerobic gram-positive and many aerobic gram-negative bacteria, especially S. aureus, S. epidermidis and S. viridans except tuberculosis treatment. Rifampicin inhibits bacterial RNA synthesis by impeding bacterial DNA-dependent RNA polymerase (13). In the literature, there are limited information about the use of rifampicin for topical wound care (20,21). Experimental studies by Saydam et al. found that the combination of rifampicin and nitrofurazone had a broader spectrum of action in full thickness wounds formed in rats and did not adversely affect the wound healing process (22). Iselin et al. reported that, compared to iodinated polyvidone dermal solution, topical rifampicin was more successful in infection control in hand injury requiring a surgical operation and expedited wound healing (23). In an experimental study by Gurel et al., wound healing occurred more rapidly and in agreement with natural physiological processes in the areas on which rifampicin was applied, compared to the control areas. In this study, no negative effects from rifampicin were observed on wound healing (4). In the present study, no adequate and effective wound healing was observed in either group, where the wound tissue was either left to heal by itself or by topical application of rifampicin.

Limitations of this study include short study duration, limited number of rats, and the fact that mainly histopathological data are evaluated. We believe that more objective and comprehensive information can be obtained in this regard through future studies with longer duration and higher sample size investigating the effects of rifampicin on mediators or hormones involved in the wound healing process.

CONCLUSION

In conclusion, topically applied rifampicin in full-thickness skin defects does not have a positive effect on wound healing process.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study was approved by the local ethics committee at Karadeniz Technical University Faculty of Medicine, Animal Care and Use Committee. The rats were handled in accordance with the Guide for the Care and Use of Laboratory Animals.

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