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Research Article

COMPARISION OF THE EFFICIENCY OF EPIDERMAL GROWTH FACTOR, SILVER AND NAFTALAN IN THE WOUND HEALING OF RATS

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ABSTRACT. The aim of this study is to compare the effects of epidermal growth factor, silver and naftalan on wound healing in rats through clinical and histopathological studies. Four groups each containing 18 rats were formed. Group 1; control group, group 2; epidermal growth factor (EGF) group, group 3; epidermal growth factor (EGF) + silver group, group 4; epidermal growth factor (EGF) + naftalan group. Under anesthesia, a 20 mm long full layer skin resection was performed from dorsal interscapular region. On the 7th, 14th and 21st day postoperatively, wound sizes were measured with millimetric paper for all animals and 6 animals sacrified from each group under deep anesthesia and extensive skin resection of the wound area was performed to sent for histopathological examination. When the wound healing was examined macroscopically between groups, there was no statistical difference in wound diameter measurements on the 7th and 21st postoperative days, while a statistical difference was observed in the EGF + Ag and EGF + Naf groups compared to the sham group in the postoperative 14th day controls ($P<0.05$). In histopathological examinations, it was determined that neovascularization and epithelialization in the Silver and Naftalan containing group were significantly higher than the sham group in the 7th day samples ($p<0.05$). In the 14th day samples, inflammation was observed to be statistically higher in the silver and naftalan groups ($p<0.05$). In the 21st day samples, inflammation was found to be statistically less in the group containing silver and naftalan and bleeding was found to be statistically higher in the group containing silver ($P<0.05$). Consequently, it was observed that macroscopically and histopathologically, the wound healing was faster in animals treated with EGF + napthalan group compared to other groups.

Keywords: *Histopathology, naftalan, rat, silver, wound healing.*

INTRODUCTION

A wound is damage to the skin or mucosal tissues as a result of blunt or sharp trauma such as a cut, tear, or puncture. The main purpose of wound healing is to provide the ideal environment and stimulate or accelerate healing. In wounds with tissue loss in large areas, that heal slowly, or fail to heal, it is necessary to cover the wound with a dressing. Because it is necessary to isolate the lesion area from the physical environment. In addition, the wound dressing in question should have additional qualities such as preventing infection and preventing fluid and protein loss from the lesion area, thus it should be able to imitate the skin in a sense. Studies generally aim to ensure that one or more chemical agents that stimulate tissue repair are carried by a suitable material and come into contact with the

wound. One of the main features of wound dressings used for the treatment of wounds is creating a suitable environment for cellular activities, but this environment is also a fitting environment for bacteria and as a result, the applied dressing is likely to increase bacterial activity. At this point, limiting bacterial proliferation by adding antiseptic substances into the products is considered a suitable option [1, 2, 3].

Growth factors are a group of polypeptide molecules that affect proliferation in cells. Epidermal growth factor (EGF) has a very important role in the regeneration of epidermal cells and the proliferation and migration of keratinocytes, additionally; EGF not only stimulates the formation of granulation tissue but also contributes to quicken wound closure by stimulating fibroblast motility. In order for EGF to be effective in wound healing, it is essential to be in continuous contact (be present) with the wound in the environment because EGF is rapidly broken down by tissue proteases. Gelatin is a suitable material to be used with EGF as a carrier medium because this biodegradable material releases the EGF it carries into the environment as it breaks down and does not have a negative effect on wound healing [4, 5, 6, 7].

Silver has been widely used for wound care and local infection in metallic, solution, or cream forms for many years. Ionic silver (Ag+) is used as a prophylactic antimicrobial agent in wound dressings due to its effect on gram-positive and negative bacteria, as well as yeast and fungi. Silver interferes with the respiratory chain in the cytochromes of microorganisms, and also shows its antimicrobial effect by binding DNA and inhibiting replication [8, 9, 10, 11, 12].

The difference between naftalan oil and all other oil types is that it is very rich in cycloalkanes and these hydrocarbons, which are also called naphthene, are found in 55% of Naftalan oil, while the same compounds are detected at 3-5% in oil obtained from other petroleum sources. In addition to naphthene, naftalan contains 35% aromatic hydrocarbons and 14-16% resin-like compounds, sulfur nitrogen, and microelements [13]. Soviet and Azerbaijani researchers have demonstrated the anti-inflammatory, topical anesthetic, and antiseptic properties of this substance. Naftalan is still used in the treatment of eczema, burns, and dermatitis, however studies on how Naftalan's effectiveness occurs at the cellular and molecular level have not been uncovered in the literature research, but there are studies stating that it should be investigated [13,14,15,16,17].

Aim of the present study; it was aimed to compare the healing activities of EGF, silver, and naftalan, all of which are thought to be effective in wound healing, on full-layer skin wounds formed in rats.

MATERIALS AND METHODS

In vitro Phase

Preparation of wound dressings containing EGF: The liquid gelatin (Difco, USA) solution was stirred at 2000 rpm for 30 minutes at room temperature. Glutaraldehyde solution (Sigma, USA) was added to this mixture as a cross-linker. EGF (Sigma, USA) dissolved in 2 ml of phosphate buffer solution (pH 7.4) and 50 µl of heparin (Nevparin, Mustafa Nevzat İlaç Sanayi AŞ, Türkiye) were added to the gelatin solution. The resulting foam was poured into molds, frozen in liquid nitrogen, and dried in a lyophilizer machine for 24 hours. Ten-millimeter thick wound dressings were sterilized by being kept under UV for 1 hour.

Preparation of wound dressings containing EGF + Silver and EGF + Naftalan: The liquid gelatin (Difco, USA) solution was stirred at 2000 rpm for 30 minutes at room temperature. Glutaraldehyde solution (Sigma, USA) was added to this mixture as a cross-linker. EGF (Sigma, USA) dissolved in 2 ml of phosphate buffer solution (pH 7.4) and 50 µl of heparin (Nevparin, Mustafa Nevzat İlaç Sanayi AŞ, Türkiye) were added to the gelatin solution. After this, 1% silver sulfadiazine (Aldrich USA) or 1% Naftalan (Russian Federation) solution was added to this mixture. The resulting foam was poured into molds, frozen in liquid nitrogen, and dried in a lyophilizer machine for 24 hours. Ten-millimeter thick wound dressings were sterilized by being kept under UV for 1 hour. All chemical products used in the study were used as purchased, at analytical grade, and without any purification.

In vivo Phase

A total of 72 Wistar breed, adult, male, and albino rats were used in this study. Subjects were randomly divided into four groups. In the first group, the wound was allowed to heal naturally without using any material (sham group). EGF was used in the second group, EGF and silver were used in the third group, and EGF and naftalan were used in the fourth group. 2.5 ml xylazine hydrochloride (23.32 mg/ml) and 4.5 ml ketamine hydrochloride (100mg/ml) were drawn into a syringe and made up to 10 ml volume with 3 ml physiological saline solution (PSS). General anesthesia was performed by injecting the prepared anesthetic combination into the subjects intraperitoneally with the calculation of 0.1 ml/100 g live weight. An area of 4X4 cm was shaved in the interscapular region of the subjects, who were determined to be under deep anesthesia by checking their pedal reflexes. After the necessary antisepsis was provided, a sterile, 20 mm diameter full layer (dermis + epidermis) defect (wound) was crafted. Wound dressings were covered over the defect and the wound dressings were covered with tape that allowed air passage to protect against the reactions of the animals. For postoperative analgesia, flunixin meglumine at a dose of 2.5 mg/kg was administered subcutaneously (BID) to the subjects for 24 hours. Three sacrifice times (days 7, 14, and 21) were determined for each group, and at these time points, 6 subjects from each group were sacrificed with high dose anesthetic injection. For the histopathological evaluation of wound healing, the surrounding tissue was also removed and included in the assessment.

Histopathological Examinations

Biopsy samples taken from the wound area were fixed in 10% buffered paraformaldehyde for 48 hours and then trimmed to pass through the intact epidermis at the wound borders. After routine tissue follow-up procedures, 5 micrometer thick sections were taken from the tissue samples embedded in paraffin using a rotary microtome. Sections were routinely stained with hematoxylin and eosin and Masson Trichrome (Bio Optica, Italy) stains. Histopathological evaluations were performed and microphotographs were taken using a binocular microscope and DP25 digital camera. Histopathological findings observed were evaluated in terms of the presence of inflammation, re-epithelialization, neovascularization, fibrosis, and bleeding criteria and scored semi-quantitatively as described in the literature [18]. According to this; Number of inflammatory cells in the 20x objective field; 0=none, 1=between 1-5, 2=between 6-10, 3=between 10-15, 4=15 and more; re-epithelialization: 0=absent, 1=basement membrane formation, 2=spongious epidermal differentiation, 3=granular epidermal

differentiation, 4=epidermal migration; presence of neovascularization, fibroblasts, and collagen; 0=none, 1=Mild, 2=Moderate, 3=Intense, 4=Very intense.

Statistical Analyses

Statistical package for the social sciences (SPSS) v15 (SPSS Inc. Chicago, Illinois, USA) was used in the statistical analysis. Abnormal distribution of data was determined by the Shapiro-Wilk test. Therefore, a non-parametric test was used. Evaluation of histopathological data was performed with the nonparametric Kruskall-Wallis test. In cases where significance was observed, pairwise comparisons of groups were determined by the Mann-Whitney U test and $p<0.05$ was considered significant.

RESULTS AND DISCUSSION

Each time point was statistically different from the next time point at the baseline and 7th, 14th, and 21st days in terms of wound diameter measurements within the groups ($P<0.05$) (Table 1).

Table 1. *Comparison of wound sizes (mm^2) in the postoperative healing period within the groups*

Time	Sham	EGF	EGF+Ag	EGF+Naf
Baseline	320,00^{a}	320,00^{a}	320,00^{a}	320,00^{a}
7	173.0±103^{ab}	167.0±197^{ab}	170.0±107^{b}	126.5±85^{b}
14	47±52^{c}	37.0±33^{c}	27.5±33^{c}	10.0±26^{c}
21	4.5±9^{d}	3.0±12^{d}	1.5±14^{d}	0.0±2^{d}
P-Value*	p≤0.02	P<0.05	p≤0.03	p ≤0.01

a,b,c,d: Differences between the groups denominated by different letters in the same coulum are significant. Data are presented as median±IQR. EGF (Epidermal growth factor), EGF+Ag (Epidermal growth factor+Silver), EGF+Naf (Epidermal growth factor + Naftalan), 7(postoperative 7th day), 14 (postoperative 14th day), 21 (postoperative 21st day).

When the wound healing between the groups was evaluated, there was no statistical difference in wound diameter measurements on the 7th and 21st postoperative days, while a statistical difference was observed in the EGF + Ag and EGF + Naftalan groups compared to the sham group in the postoperative 14th day controls ($P>0.05$) (Table 2).

Signs of infection, which is the most important complication in the wound healing process, were not seen in any of the animals in the present study. On the 7th day, a hemorrhagic crust was detected at the wounds. At the 14th day controls, it was noted that the most crust formation was in the sham group, and that the crust formation in the EGF + Naftalan group was very thin and almost disappeared when compared to other groups. In the controls performed on the 21st day, it was observed that the wounds were closed with epidermis in all groups. Although there was no statistical difference in the EGF + Naftalan group at the end of the 21st day, it was observed that the wounds in most of the animals were completely closed, leaving only a thin scar line.

***Table 2**. Comparison of wound sizes (mm^2) between groups in the postoperative healing period*

Groups	7	14	21
Sham	173.0±103	47±52[a]	4.5±9
EGF	167.0±197	37.0±33[ab]	3.0±12
EGF+Ag	170.0±107	27.5±33[b]	1.5±14
EGF+Naf	126.5±85	10.0±26[b]	0.0±2
P-Value*	p=0.36	P=0.01	P=0.23

a,b: Differences between the groups denominated by different letters in the same coulum are significant. Data are presented as median±IQR. EGF (Epidermal growth factor), EGF+Ag (Epidermal growth factor+Silver), EGF+Naf (Epidermal growth factor + Naftalan), 7(postoperative 7th day), 14 (postoperative 14th day), 21 (postoperative 21st day).

In the examination of the 7th day samples, it was determined that neovascularization and epithelialization were significantly higher in the group containing silver and naftalan than in the sham group ($p<0.05$). In the 14th day samples, inflammation in the silver and naftalan group was statistically higher ($p<0.05$). In the 21st day tissue samples, inflammation was statistically lower in the group with silver and naftalan. In the bleeding controls during the same period, it was observed that bleeding was statistically higher in the group containing silver ($p<0.05$) (Table 3).

***Table 3.** Comparison of histopathological examination results between groups.*

		Time		
	Groups	**7**	**14**	**21**
Inflammation	**Sham**	2.55±1.18	2.30±0.92[a]	2.00±0.45[a]
	EGF	2.00±0.70	2.05±0.42[ac]	1.20±1.21[ac]
	EGF+Ag	2.05±0.74	1.46±0.50[b]	0.80±0.44[b]
	EGF+Naf.	2.40±0.67	2.00±0.69[bc]	1.01±0.70[bc]
Neovascularization	**Sham**	0.97±0.30[a]	1.60±1.05	2.25±0.70
	EGF	1.02±0.73[ab]	2.00±0.98	2.45±1.00
	EGF+Ag	1.32±0.87[bc]	1.92±0.63	2.70±1.09
	EGF+Naf.	1.50±0.63[c]	2.00±0.60	3.00±0.65
Fibrosis	**Sham**	1.10±0.80	1.25±0.45	2.05±0.56
	EGF	1.20±0.62	1.50±0.69	2.55±0.40
	EGF+Ag	1.40±0.56	1.62±1.08	2.60±0.78
	EGF+Naf.	1.30±0.50	1.45±0.65	2.42±1.10
Epithelization	**Sham**	0.00±0.00[a]	0.76±0.50	2.13±0.78
	EGF	0.19±0.02[b]	0.95±0.58	2.45±1.21
	EGF+Ag	0.20±0.01[b]	0.85±0.65	2.45±0.84
	EGF+Naf.	0.20±0.00[b]	0.76±0.49	2.55±0.55
Bleeding	**Sham**	3.65±0.85	1.03±0.43	0.00±0.00[a]
	EGF	2.85±1.10	1.00±0.60	0.00±0.00[a]
	EGF+Ag	3.08±0.84	1.05±0.66	0.20±0.00[b]
	EGF+Naf.	3.05±0.42	1.05±0.60	0.00±0.00[a]

a, b, c: Differences between the groups denominated by different letters in the same column are significant ($p<0.05$). Data are presented as median±IR. EGF (Epidermal growth factor), EGF+Ag (Epidermal growth factor+Silver), EGF+Naf (Epidermal growth factor+Naftalan), 7(postoperative 7th day), 14 (postoperative 14th day), 21 (postoperative 21st day).

Sham

7th day: In the wound area, necrotic cell residues and inflammatory cells consisting mostly of neutrophil leukocytes were observed in the surface epithelium. There was a widespread inflammatory cell infiltration and large capillaries in the dermis (Fig. 1A).

14th day: In addition to thin layer re-epithelialization, moderate neovascularization, inflammatory, and fibroblastic activity were detected in the dermis (Fig. 1B).

21st day: In the wound defect area, it was noteworthy that the epithelial layer was not formed and there was necrotic debris. There were dense connective tissue cells in the dermis, varying degrees of fibrosis, and newly formed capillaries (Fig. 1C).

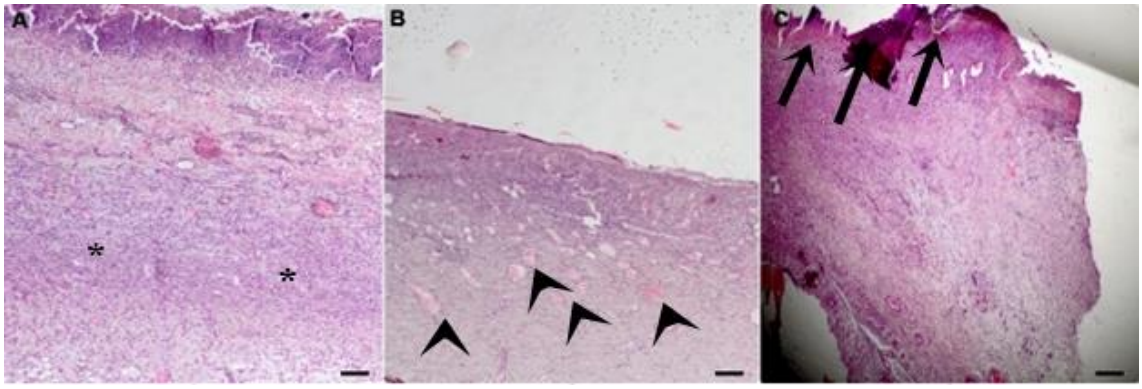

Fig. 1. *Histopathological images of the sham group on the 7th day(A), 14th day (B) and 21st day (C). Inflammatory cells (asterix) associated with necrotic cells (A). Neovascularization (arrowhead) and fibroblasticactivity (B). Incomplete healing and necrotic debris (arrow) (C). Hematoxylin and Eosin (HE) staining, Bar=100μm.*

Egf

7th day: In the samples examined; the epidermis was not visible at the upper layer of the healing area, instead there was a layer consisting of mostly amorphous and homogeneous pink exudation, numerous neutrophil leukocytes, and necrotic cell residues. Pyogranulomatous inflammation, consisting mostly of neutrophils, leukocytes and histiocytes, including fibroblasts, albeit weakly, was observed in the dermis and deeper subcutis. In Masson Trichrome staining, no regular or organized connective tissue repair areas were determined in these regions. Focal necrotic foci contained dense chromatin debris and bacterial colonies. In some severe cases, steatitis and fatty tissue necrosis in the subcutis and phlegmon progressing to the muscle tissue were observed (Fig. 2A).

14th day: While no epidermis was observed in the wound area, widespread suppurative inflammation was noted on the surface. Necrosis and pyogranulomatous inflammation were observed at the epidermis-dermis border. Although there were newly formed capillaries due to connective tissue proliferation starting from the dermis, it was determined that these areas contained dense neutrophils, leukocytes, and macrophages in all cases. At the bottom, deep down, in places where there was no inflammation, young connective tissue and healing efforts were noticeable (Fig. 2B).

21st day: In the wound area, the dermis was thinned enough to form a border with the subcutis, and many neutrophil leukocyte infiltration and exudate effusion were observed on the surface. Although it was observed that epithelialization started at the defect border, in the border areas where necrotic and degenerative epithelial cells were located, there was a superficial hydropic degeneration of the epidermis, initializing especially from the spinous layer, without inflammation. In addition to connective tissue repair in the dermis, neovascularization and dilated venous vessels were notable. Bleeding areas were detected in the dermis with mild mononuclear cell infiltration at the dermis subcutis border (Fig. 2C).

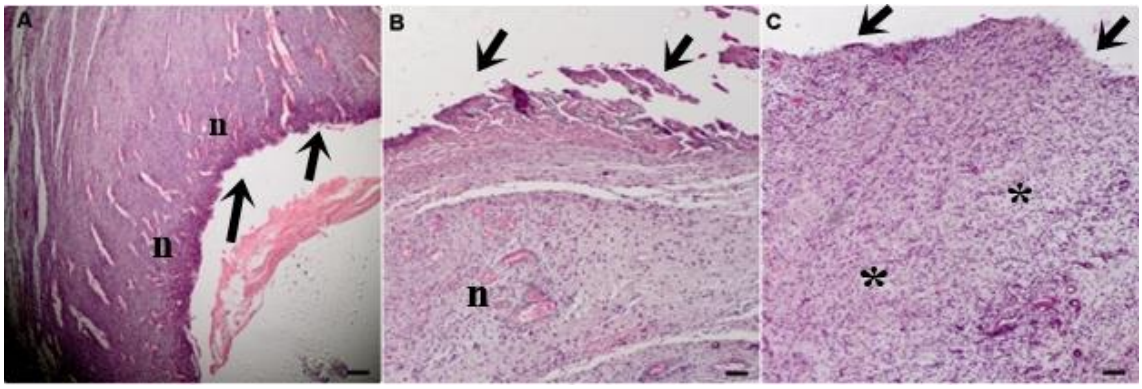

Fig. 2. *Histopathological images of the Epidermal Growth Factor group on the 7th day(A), 14th day (B) and 21st day (C). Absence of epidermal layer (arrow), neovascularization (n), inflammatory cells (asterix). Hematoxylin and Eosin (HE) staining, Bar = 100µm.*

Silver

7th day: In the wound area, intense necrotic and purulent inflammation, most severe at the level where the epidermis layer should be on the surface, progressing downwards was also continuing among the young connective tissue cells in the dermis. In Masson Trichrome staining, intense fibroblastic activity and connective tissue -collagen- fibrils oriented in different directions and stained in light blue were observed. It was noted that in areas where inflammation was severe, focal neutrophil and macrophage foci caused necrosis in young connective tissue proliferation areas. Young connective tissue, progressing below the epidermis at the wound border was more successful in collagen production (Fig. 3A).

14th day: Very intense suppurative and necrotic inflammation was observed at the epithelial border and dense bacteria were observed within. In some cases, the necrotic and pyogenic area at the surface was limited by the proliferation of connective tissue in the dermis - the crust - and degenerative and necrotic changes were observed in the connective tissue cells at the border between these two layers. Newly shaped and well-organized connective tissue proliferation was observed deeper in the dermis and subcutis. In some areas, the connective tissue had a scar appearance. However, there were focal areas of necrosis and calcification in some areas due to inflammation within the connective tissue (Fig. 3B).

21st day: Although in one case, there was epithelial regeneration developing from the border areas to cover the reparation area, there generally was a very intense purulent inflammation at the surface, along with pyogranulomatous inflammation, including mononuclear cells in some cases. Neat and organized connective tissue development was observed in the dermis and subcutis (Fig. 3C).

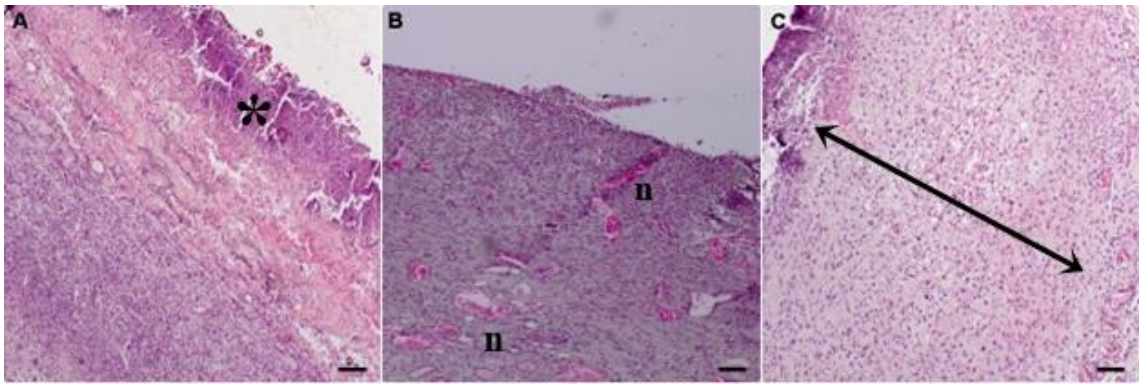

Fig. 3*. Histopathological images of the Silver group on the 7th day(A), 14th day (B) and 21st day (C). Intense necrotic and purulent inflammation (asterix), neovascularization (n), organized connective tissue development was observed in the dermis and subcutis (arrow area. Hematoxylin and Eosin (HE) staining, Bar = 100µm.*

Naftalan

7th day: In the samples examined, a pyogenic focus was observed at the surface, mostly consisting of macrophages with large cytoplasm, including neutrophil leukocytes. Masson Trichrome staining contained regular and parallel connective tissue threads and new capillaries in the dermis and subcutis, along with a cellular but organized connective tissue reparation deeper down (Fig. 4A).

14th day: In addition to a layer consisting of necrotic, intact, and degenerated leukocytes at the surface of the wound area, there was a young connective tissue consisting of regularly arranged fibroblasts in the inner parts where the cell type changes to mononuclear cells towards deeper areas. In some cases, despite a very thick organized scar tissue being formed, suppuration at the surface continued in a thin and limited form. It was noted that this young connective tissue had advanced below the epidermis layer at the wound border and findings indicating complete healing - wound fusion - were noted. Masson Trichrome staining showed that the connective tissue consisted of young inflammatory cells and fibroblasts and collagen production was limited. In one case, a limited pyogenic focus at the surface was observed to cause degenerative changes in the epidermis at the wound border (Fig. 4B).

21st day: While no inflammatory cells were found at the healing area, except for a limited number of macrophages, the connective tissue formation was shaped with fewer cells and threads running in the same direction. In histological sections, it was noted that the connective tissue reparation area was sunken from the surface and the dermis-subcutis area was reduced by 2/3 when compared to normal. No structures belonging to hair follicles and their appendages were found in these areas (Fig. 4C).

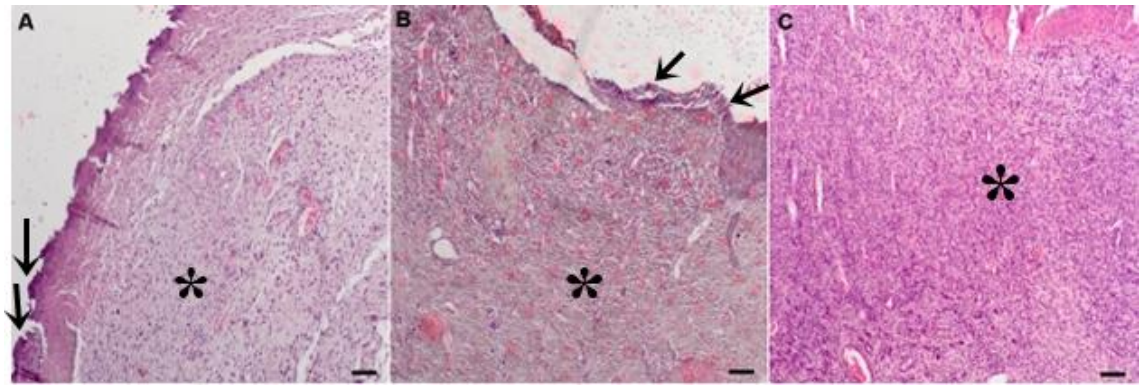

***Fig. 4**. Histopathological images of the Naftalan group on the 7th day(A), 14th day (B) and 21st day (C). Pyogenic focus on surface (arrow), young connective tissue consisting of regularly arranged fibroblasts (asterix). Hematoxylin and Eosin (HE) staining, Bar = 100µm.*

In recent years, efforts have been made to develop and commercialize more specific products that are effective and sufficient for every wound type, considering the cost/benefit ratio on wound healing. Wound healing is a complex series of reactions and relations of inflammatory mediators and cell growth interactions. Many intrinsic and extrinsic factors affect wound healing, thus a wide variety of commercial options are being developed that aim to eliminate the negative impact on wound healing or stimulate the healing process [19]. For successful wound healing, activation of three interrelated phases (inflammation, proliferation, and remodeling) carried out by platelets, leukocytes, fibroblasts, and keratinocytes is required. Keratinocytes being the main cellular component of the epidermis are very important not only for creating barriers but also for wound restoration by taking part in epithelialization. Platelets facilitate homeostasis and the release of growth factors, and then leukocytes participate in the inflammatory process. Fibroblasts and keratinocytes have a critical role in wound healing by enhancing re-epithelialization and extracellular matrix (ECM) remodeling [20]. One of the largest advantages of using animal models in wound healing is that they provide the opportunity to follow the wound healing process histologically as well as macroscopic, biochemical, and biomechanical measurements [21]. In many studies, many parameters such as wound crusting, edema, fibrin coagulation, neutrophil infiltration density, inflammatory cells such as white blood cells and macrophages, fibroblast density, angiogenesis, granulation tissue, re-epithelialization, and collagen density have been examined for histological evaluation [22]. It is reported that a clean wound should heal or show signs of healing within two to four weeks [23]. In the present study, histopathological examinations were performed to evaluate similar parameters. A full-layer skin wound was crafted and it was observed that the wounds healed within 2-4 weeks postoperatively, similar to the literature. When wound healing was examined macroscopically, there was a significant improvement when compared with the initial value in all groups, however it was determined that the healing in the sham group was not as good as the other groups. This is thought to be related with the fact that inflammation did not decrease in the sham group during the recovery period as in the other groups and neovascularization was less than the other groups.

It is narrated that collagen production in wound healing begins on the 7th day and continues until the end of the proliferation phase. During this period, the amount of collagen in the wound continuously increases. It is stated that there is a decrease in the amount of collagen with the end of the proliferation phase and if the amount of collagen in the wound is dense at the end of this period, this may be related to the prolongation of the proliferative phase [24]. It is reported that the use of silver nanoparticles in wound healing accelerates wound healing and makes a positive difference in the cosmetic appearance of the wound, depending on the dose used. It is also stated that silver reduces and stops inflammation in the wound thanks to its antimicrobial effect [25]. In the present study, microscopic examinations showed that the inflammation in the silver group was significantly lower than other groups and this was thought to be related to the fact that silver reduces inflammation in wound healing. While the presence of collagen was noted in the 7th day controls in the EGF + silver group, it was not observed in other groups. It is thought that this may be related to silver ending the inflammation phase on the wound earlier [25] and transitioning to the proliferation phase happens earlier.

The number of literature on the use of naftalan in wounds is quite limited. Naftalan, named after the region where it is located in the Caucasus, is an oil that has been used especially in skin diseases and rheumatic diseases since ancient times and is generally applied in the form of a bath. Creams obtained from naftalan are prepared without adding any vegetable or animal oil and are advantageous because of rapid absorption [26]. It is stated that naftalan is such a strong antiseptic that bacteria cannot survive in it. At St. Michael Hospital in Tbilisi; naftalan was reported to be frequently used as an excellent sedative for first and second degree burns, significantly reduced inflammation, and therefore had an excellent effect on skin diseases. For that matter, it was reported as very effective in conditions such as chronic eczema, psoriasis and pityriasis. It was reported that it accelerated wound healing thanks to its anti-inflammatory effect [27]. The findings of the present study are similar to the findings reported in the literature. The fact that neovascularization increased significantly in the treatment group with naftalan within the first week shows that naftalan accelerates wound healing.

CONCLUSION

In conclusion, it was observed that wound healing was performed faster in animals treated with Naftalan and Silver compared to EGF and control group. There was no negative effect of Naftalan on wound healing and results show that neovascularization is strong in Naftalan group compared to others. It mean that wound healing faster in this group.

Acknowledgement. This study was conducted with the permission of the Kırıkkale University Local Ethics Committee for Animal Experiments with the decision No. 12/29 dated 16.02.2012.

Conflict of Interest. The authors declared that there is no conflict of interest.

Authorship Contributions. Concept: B.K., Design: B.K., Data Collection or Processing: B.K., B.K., Analysis or Interpretation: B.K., B.K., Literature Search: B.K., B.K., Writing: B.K., B.K.

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