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The effect of Ranolazine on random pattern skin flap survival in rats

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ABSTRACT

Objective: Flap surgery is widely used in the field of plastic surgery for defect reconstruction. The most important problem of this surgery is ischemic necrosis which may occur in the distal of the flap. For this reason, studies have been conducted to develop many treatment methods to solve this problem. Our study aimed to investigate the effects of different doses of ranolazine, a selective late sodium current blocker, on the viability of skin flaps prepared from the back of the rat.

Material and Methods: A total of 32 rats, including 8 rats in each group, were included in the study. A random patterned caudal base 3x9 cm width : length modified McFarlane skin flap was elevated from the backs of all rats and adapted back to its place For 7 days postoperatively, 1 cc of saline was added to the control group (Group A), and 45 mg/kg, 90 mg/kg, and 180 mg/kg of ranolazine were added to the study groups (Group B, C, D), respectively, and administered daily with gastric lavage On the 7th postoperative day, photographs were taken to evaluate the viability of the flaps and scintigraphic evaluations were made. After the rats were sacrificed, the flaps were separated from their bases and evaluated histopathologically.

Results: As a result of the evaluations, the viable flap area was calculated as 12.7548 cm2 for Group A, 14.9533 cm2, 16.494 cm2 and 16.7599 cm2 for Groups B, C and D, respectively, and a statistically significant difference was found between the groups (P = 0.00 <0.05). The viable flap area percentages were calculated as 57.486% for Group A, 68.908% for Group B, 70.174% for Group C and 74.603% for Group D, and a statistically significant difference was found between the groups (P = 0.00 <0.05). As a result of scintigraphic evaluation, the viable flap area was found to be 61.57% for Group A, 71.04% for Group B, 70.21% for Group C and 73.85% for Group D, and a statistically significant difference was found between the groups (P = 0.03 <0.05). Histopathological evaluation revealed a decrease in the flaps' inflammation, edema and necrosis scores with the increasing drug dose.

Conclusion: As a result, although flap viability increased with increasing doses in the group given ranolazine, more detailed studies are needed before it can be used clinically.

Keywords: Skin flap, Ranolazine, Selective late sodium current blocker

INTRODUCTION

Repairing defects in appropriate form and function, resulting from congenital or acquired causes, is central to the aims of plastic surgery. For this purpose, a treatment plan has been defined, from the simplest to the most complex, which is defined as the "reconstructive ladder" for defect repair (1). According to the reconstructive ladder, applying the simplest repair method that meets the need means that other alternatives are still available if the applied repair method fails. However, in many cases, especially with the increase in knowledge and the development of microsurgical experience, complicated repair methods in the upper stages may be the primary treatment option (2).

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Random pattern skin flaps are commonly used in plastic and reconstructive surgery for defect repair. The most important problem limiting the use of these flaps is partial or full-thickness ischemic necrosis in the distal portion of the flap (3). Many techniques have been described to overcome necrosis, often requiring secondary surgical intervention. Various surgical procedures, including surgical delay, ischemic preconditioning, and flap prefabrication, as well as pharmacological agents like sympatholytic, vasodilators, calcium channel blockers, anticoagulants, free radical scavenging antioxidants, and growth factors (such as bFGF, PDGF, TGF, and VEGF), can be used for this purpose (4-8).

The antianginal agent ranolazine was approved for use by the FDA in 2006. The late sodium channel, activated during the action potential's plateau phase, increases its activity approximately 2-4-fold during hypoxia and ischemia, and is thus mainly responsible for the increase in intracellular sodium and, consequently, for the increase in intracellular calcium. Ranolazine, a derivative of piperazine, selectively blocks late sodium channels. During the action potential, the late sodium channels blocked by ranolazine act only on a very small portion of the sodium current. Therefore, ranolazine can be considered to have an ischemia-specific mechanism (9,10).

While there are studies in the literature on the effect of ranolazine on blood glucose, its anti-inflammatory effect and its antioxidant effect, apart from its cardiac effects, there is no study on its effect on flap viability (11-14). This study aimed to investigate the effects of ranolazine on the viability of modified Mcfarlane skin flaps with random circulation pattern prepared on rats.

MATERIAL and METHODs

Thirty-two male Sprague Dawley rats, aged between 2 and 4 months, weighing 200-250 g, were included in the study. The housing conditions of all animals were standardized in appropriate cages at 22-24 degrees ambient temperature and 12 hours light-dark cycle. All rats were fed with standard rat chow and tap water. Randomly 4 groups were formed with 8 rats (n:8) in each group. Drug doses were set as 45 mg/kg/day ranolazine for group B, 90 mg/kg/day ranolazine for group C and 180 mg/kg/day ranolazine for group D. The drug doses were administered to all groups by gastric lavage with 1 cc saline. Group A received 1 cc of saline daily.

Before the surgical procedure, rats were administered 87.5 mg/kg ketamine hydrochloride (Ketalar; Pfizer) intramuscularly and 12 mg/kg 2% xylazine hydrochloride (Rompun; Bayer) intramuscularly, and general anesthesia was induced. Rats in all groups were restrained with their fore and hind legs in the prone position on the experimental table, their backs were shaved, and then the antiseptic solution that is povidone-iodine was applied. The same surgeon performed all surgical procedures. First, both scapulae and the posterior iliac prominences of the rats were marked, then the skin, subcutaneous tissue, and panniculus carnosus muscle were elevated in the area between the marked points, according to the definition of the modified McFarlane flaps with an aspect ratio of 3x9 cm. The flaps were elevated on a caudal basis. After flap elevation, meticulous hemostasis was achieved and the flaps were adapted to their own locations with 4-0 polypropylene sutures (Propylene; Dogsan). After surgery, all rats were kept in separate cages and the drugs were administered via gastric lavage for seven days at the established doses.

On the seventh day after the surgery, the rats were once again anesthetized with the same combination of ketamine hydrochloride and xylazine hydrochloride. Photographs were taken and scintigraphic evaluations were performed to assess flap viability, as shown in Figure 1. After these procedures, the rats were euthanized with a high-dose injection of ketamine, and the flaps were separated from their bases and placed in formaldehyde solution for histopathological examination.

Measurement of Flap Survival

Standard optical zoom photographs of all flaps were taken from a distance of 1 meter with a ruler next to them. Flap photographs from all groups were analyzed using Digimizer, an analysis program based in Ostend, Belgium, by one of the blinded researchers. Survival flap rates were calculated by proportioning the living flap surface area to the total flap surface area, and the results were calculated as a percentage.

Radionuclide Scintigraphic Measurement

For the scintigraphic procedure, seven days after flap elevation, before the experiment was terminated and the rats were sacrificed, the skin sutures were taken, and the flap was suspended from the donor site. Lead plates covered with waterproof covers were placed around and under the flap. To prevent radioactive contamination, the waterproof covers of lead plates were changed after each scan. One mCi (37 MBq) technetium pertechnetate (Tc99m-PO4) was injected in 0.1 ml of saline solution via 24 G intracath placed in the tail vein of rats. Five minutes after injection, images were obtained using a pinhole collimator with a gamma camera (Siemens eCAM, Hoffman Estates, IL, USA) for a total of 5 minutes with 256 x 256 matrices in the blood pool phase. The viable areas of the flaps were calculated using these images. Then the flaps were cut from the distal tip and separated from the rats. Possible background activity resulting from scintigraphic counts was eliminated by using flap-only images obtained from the separated flaps. Imaging was performed using a point source to determine the aspect ratio while obtaining images. Afterwards, the region of interest (ROI) was drawn on the scintigraphic images and viable flap areas were calculated according to the percentage of the total flap area.

Histological Examination

After the rats were sacrificed, the flaps were excised and sent for histopathological examination in formaldehyde solutions. The tissue samples were washed overnight in a stream of water flow to remove the formalin. After routine pathological tissue inspection, samples were passed through graded alcohol (50%, 75%, 96%, 100%) and xylol series and blocked in paraffin. Paraffin sections at 5µm thickness were prepared using the Leica RM 2125 RT and the first three sections and the tenth section were mounted in slides. The slides were processed through alcohol and xylene series and stained with hematoxylin-eosin (HE) and trichrome. All specimens were examined under high-resolution light microscopy (Olympus DP-73 camera, Olympus BX53-DIC microscope; Tokyo, Japan) at 40x and 100x magnification. The parameters evaluated in these examinations included the number of vascularizations, inflammation, edema, and necrosis scores.

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For the assessment of vascularization, the vessels of the papillary dermis in the transitional healthy transition zone (near the necrotic area) were counted per 10 high-power fields (x40) and the average numbers were calculated. Scoring system for inflammation, edema, and necrosis; 0: None, 1: Mild, 2: Moderate, 3: Severe, and 4: Very severe. All analyzes were performed blindly by the same pathologist (N.Y.).

Statistical Analyses

The SPSS Statistics 23.0 program for Windows program was used for statistical analysis. Each measurement was obtained as mean SD and median (first quartile-third quartile). Pie charts and percentages are given to show the distributions for categorical variables. Kruskal-Wallis H and Dunn-Bonferroni pairwise comparison tests were used to compare groups. P<0.05 was considered statistically significant.

RESULTs

The parameters total flap area (cm²), viable flap area (cm²) and percentage of viable flap area (%, (viable flap area / total flap area) x 100) were calculated by digital measurements. The mean viable flap area in group A was 12.7548 cm², in group B the mean viable flap area was 14.9533 cm², in group C the mean viable flap area was 16.494 cm², in group D the mean viable flap area was 16.7599 cm². Calculated (P=0.000< 0.05).

There is a statistically significant difference in the survivable area of the subjects in groups A, B, C and D.

The average percentage of surviving flap area in group A was 57.486%, in group B the average percentage of surviving flap area was 68.908%, in group C the average percentage of surviving flap area was 70.174%, and in group D the average percentage of surviving flap area was 74.603% (P=0.000< 0.05). A statistically significant difference was found between the average percentages of living area of the subjects in groups A, B, C, and D.

As a result of the scintigraphic area evaluations, it was found that the mean area of living flaps in group A was 61.57%, in group B was 71.04%, in group C was 70.21%, and in group D was 73.85%. The statistical analysis showed that there was a significant difference between the groups (P=0.003< 0.05) in terms of the mean living flap area. A statistically significant difference was found between the scintigraphy percentages of subjects in groups A, B, C, and D (**Table 1**).

The histopathological evaluation revealed that the mean number of neovascularizations in the healthy transition zone was 7,625 in group A, 14,625 in group B, 19,875 in group C, and 19 in group D. Statistical analysis showed a significant difference (P=0.000< 0.05) between the groups in terms of the mean number of neovascularizations. A statistically significant difference was found between the neovascularization numbers of the subjects in groups A, B, C and D. In addition, the parameters of inflammation, edema and necrosis in the healthy transition zone were also evaluated. It was found that the severity of all three parameters was lower in the study groups compared to the control group. With the increase of ranolazine dose, the severity of inflammation, edema and necrosis decreased (Fig. 2, 3 and 4).

Table 1: Comparison of the Total Flap Area, Viable Flap Area, Scintigraphic Measurement and Vascular Density Between the 4 Groups

		Group A	Group B	Group C	Group D	p-value
Total flap area (cm²)	Mean ± SD	22.188 ± 2.070	21.701 ± 1.042	23.505 ± 2.121	22.463 ± 1.421	0.137
	Md (Q1–Q3)	21.762 (20.428 - 24.186)	21.870 (20.968 - 22.583)	23.477 (22.854 - 25.333)	22.711 (21.603 - 23.626)	
Viable flap area (cm²)	Mean ± SD	12.737 ± 1.113	14.924 ± 1.160	16.490 ± 1.721	16.963 ± 1.386	0.000
	Md (Q1–Q3)	12.821 (11.757 - 13.698)	14.967 (14.228 - 15.791)	17.050 (15.196 - 17.934)	17.097 (16.009 - 17.917)	
Viable flap area (%)	Mean ± SD	57.486 ± 2.891	68.908 ± 2.364	70.174 ± 4.146	74.603 ± 3.843	0.000
	Md (Q1–Q3)	58.270 (54.798 - 71.108)	68.535 (67.915 - 71.108)	69.035 (67.923 - 74.673)	73.970 (71.473 - 78.728)	
Scintigraphic measurement (%)	Mean ± SD	61.576 ± 5.701	71.040 ± 5.182	70.205 ± 3.377	73.854 ± 3.903	0.003
	Md (Q1–Q3)	62.240 (56.390 - 64.465)	69.835 (67.035 - 75.760)	70.095 (67.770 - 73.115)	71.930 (71.100 - 77.50)	
Vascular density	Mean ± SD	7.625 ± 3.204	14.625 ± 4.749	19.875 ± 3.091	19 ± 3.464	0.000
	Md (Q1–Q3)	7 (5 - 10.5)	14.5 (13.25 - 18.25)	20 (19.25 - 22)	20.5 (15.5 - 21)	

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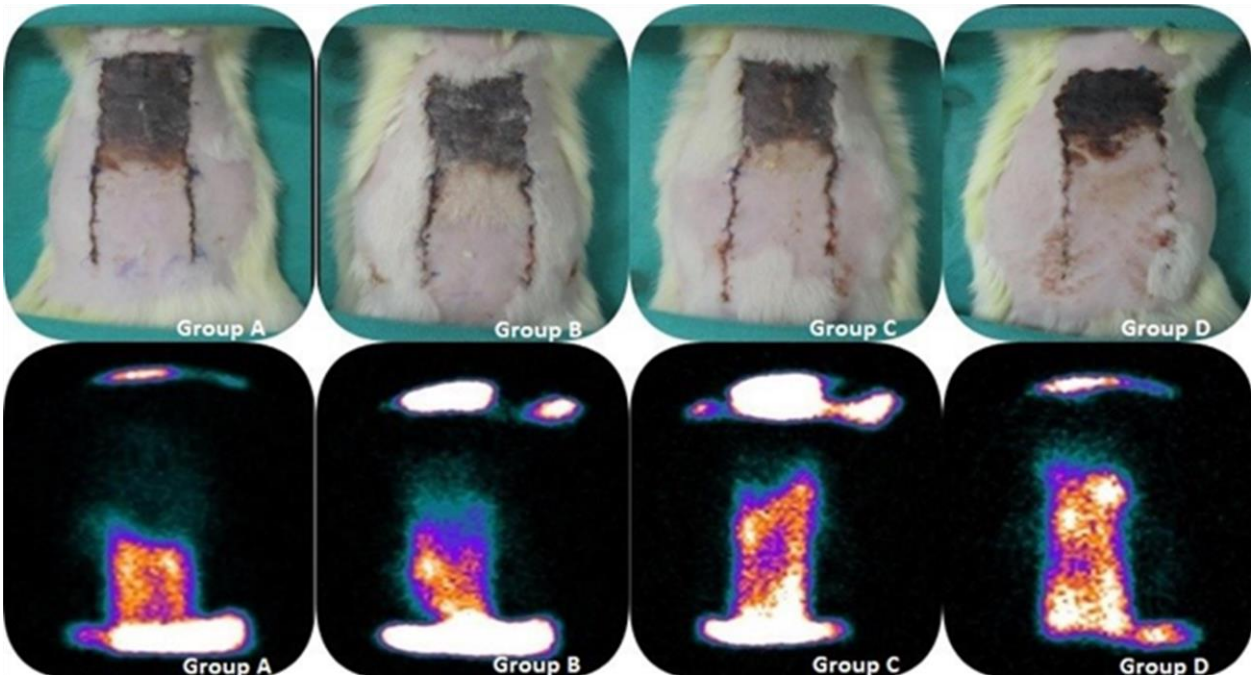

Figure 1: Photographs (upper row) and scintigraphic images (lower row) of the flaps on day 7.

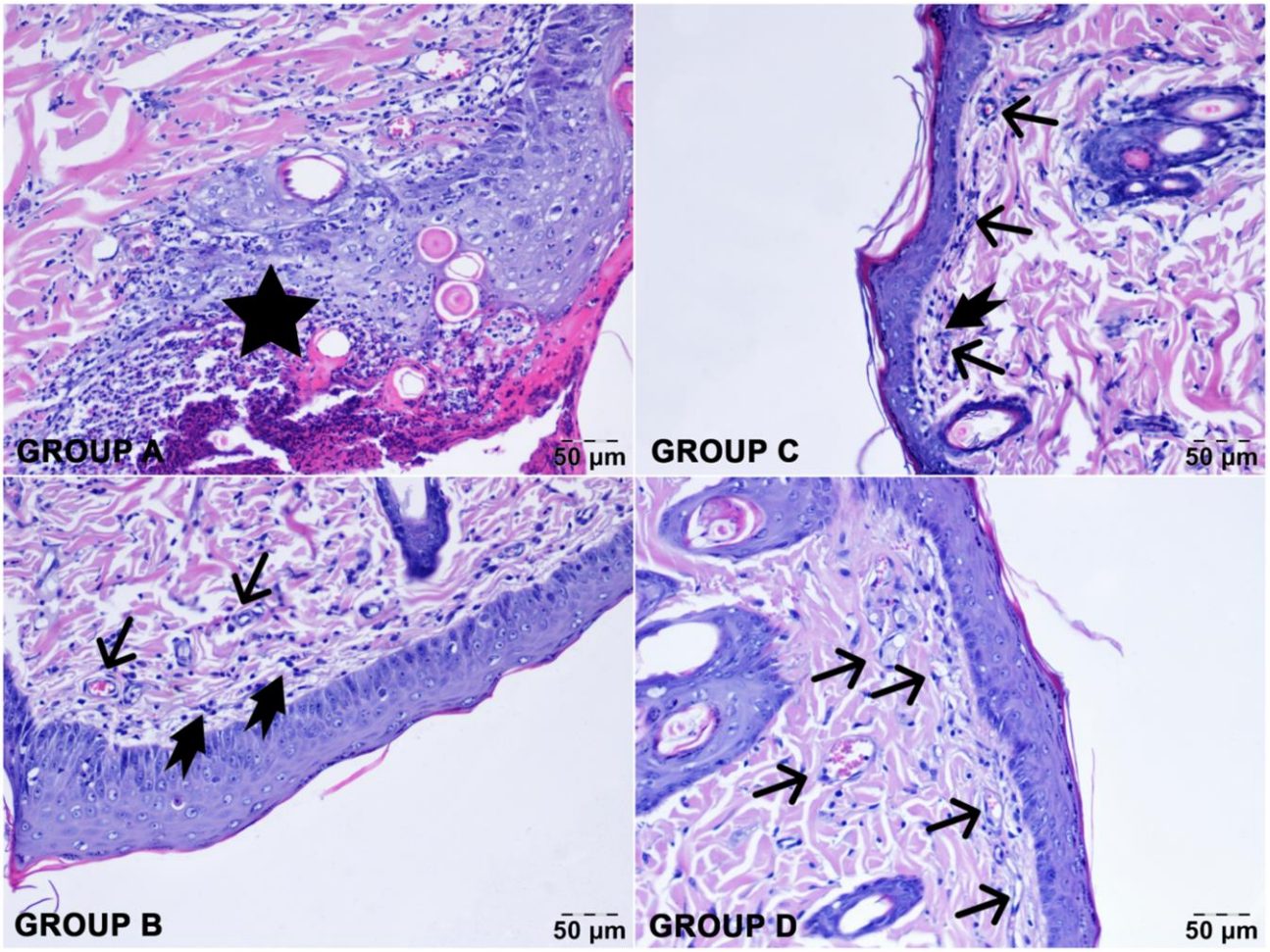

Figure 2: Hematoxylin-eosin stained histopathologic sections of the flaps. The area marked with an asterisk indicates the area of severe necrosis, inflammation and edema. The thin arrow indicates areas with neovascularization, and the thick arrow indicates areas of inflammation (original magnification 40).

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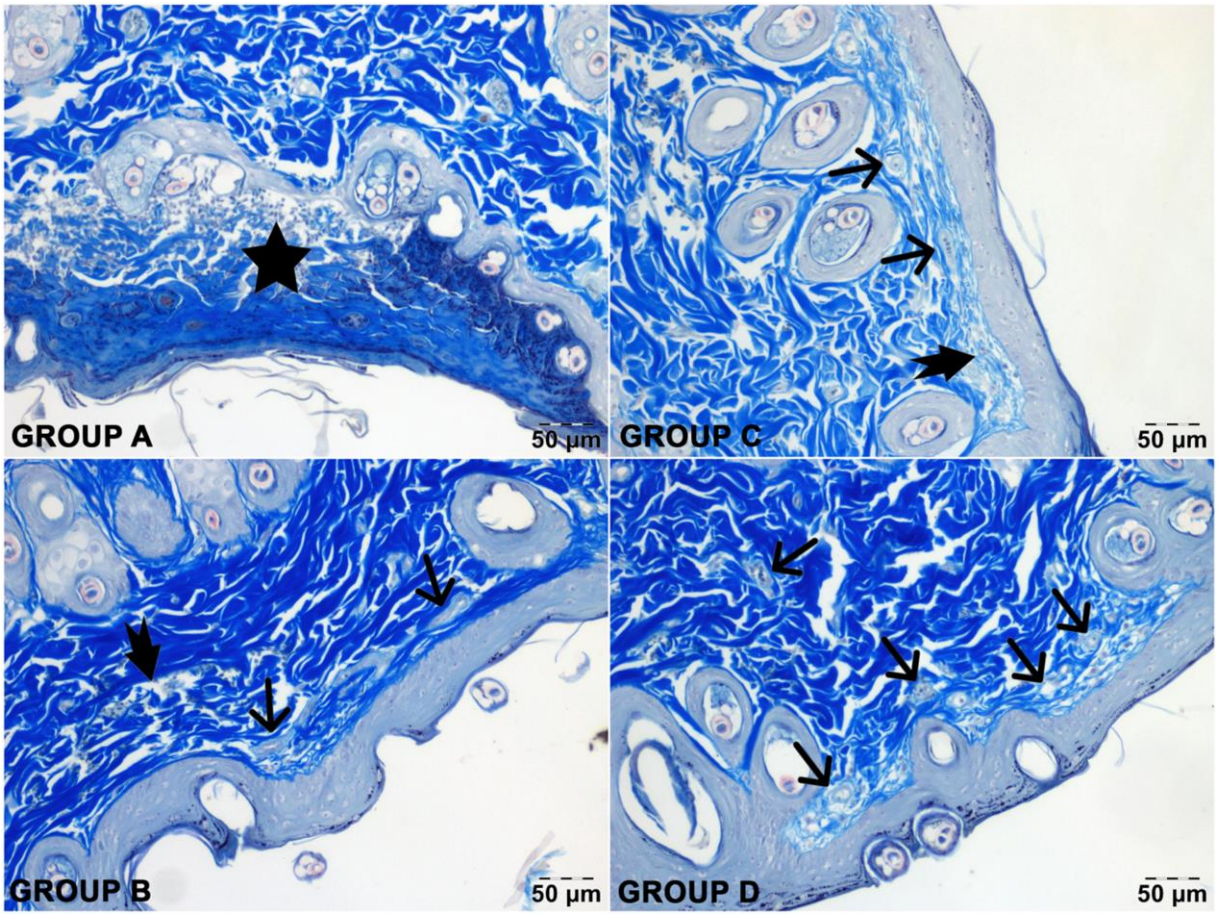

Figure 3: Masson trichrome stained histopathologic sections of the flaps. The area marked with an asterisk indicates the area of severe necrosis, inflammation and edema. The thin arrow indicates areas with neovascularization, and the thick arrow indicates areas of inflammation (original magnification 40).

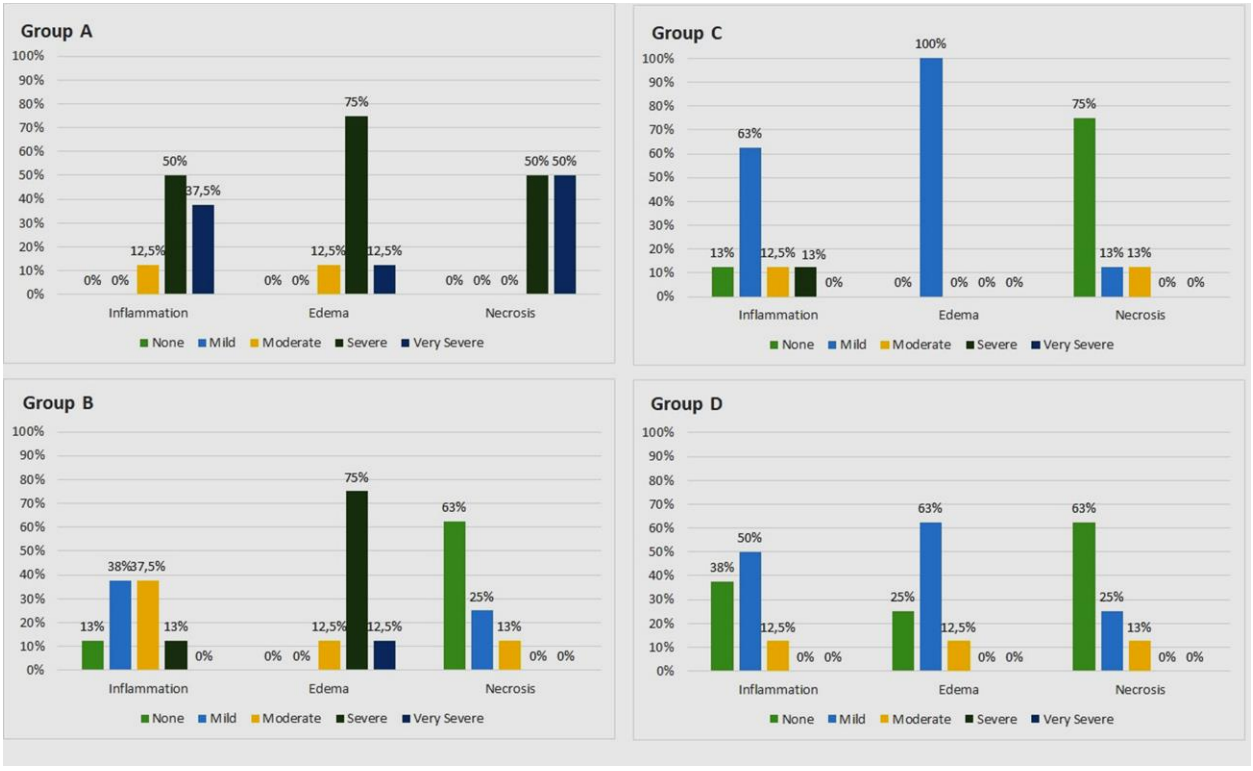

Figure 4: Percentages of inflammation, edema and necrosis according to histological examination from the healthy transition zone in all groups

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DISCUSSION

Flap surgery, by definition, is the transfer of various tissues individually or as a composite from one point to another with their own vascular support. Flap surgery has been used for the repair of many defects since prehistoric times and its first known use is for nasal reconstruction. Many different criterias are used in the classification of flaps. Flaps are divided into two subgroups according to their nutrition. If the flap is supplied by the subdermal plexus and not by a defined vascular source, it is called a random pattern flap, and if a known artery supplies it, it is called an axial pattern flap.

In the field of plastic surgery, random pattern skin flaps are widely used in the repair of defects due to primarily trauma, congenital malformations, after cancer surgery and various causes.The most important problem limiting the use of flaps is necrosis which is almost always at the distal region (3). In order to overcome the problem of necrosis occuring in the distal flap, many surgical techniques and pharmacological agents have been tried to date. At the center of this effort is to increase flap blood supply and prevent ischemia-reperfusion injury. Surgical procedures such as surgical delay, ischemic preconditioning, and flap prefabrication, as well as pharmacological agents such as sympatholytics, vasodilators, calcium channel blockers, anticoagulants, free radical scavenging antioxidants, and growth factors (bFGF, PDGF, TGF, VEGF), can be used for this purpose. (4-8).

Coronary artery disease is one of the leading causes of mortality and morbidity in the world, with an increasing prevelance. There are approximately 16 million coronary artery disease patients in the United States, mostly asymptomatic (15). According to statistics from the World Health Organization in 2007, approximately 33.7% of deaths are due to cardiovascular disease (16). The costs of death and morbidity due to cardiovascular diseases are also extremely high, thus increasing the importance of these diseases even. Due to the significance of coronary artery diseases, various revascularization strategies have been developed for the myocardium. However, despite these efforts, complete revascularization cannot be achieved in some patients, and they continue to experience symptoms known as 'angina pectoris,' which is characterized by discomfort or pain in the chest, jaw, shoulder, back, and arm, caused by myocardial ischemia. Angina pectoris is very important because it affects both quality of life and life expectancy. Three main groups of drugs are used to relieve the symptoms of angina pectoris; nitrates, beta-blockers, calcium channel blockers (17). Antianginal effects of nitrate group drugs are venodilation, afterload reduction and coronary dilatation. By blocking primarily beta-1 receptors, beta-blockers reduce myocardial oxygen consumption by lowering heart rate and contractility. On the other hand, calcium channel blockers inhibit the influx of calcium into myocardial and smooth muscle cells, leading to vasodilation and decreased myocardial contractility. The activity of ranolazine is on the late sodium channel, which is responsible for much less of the total sodium current.

Ranolazine, a piperazine derivative, has been evaluated as a “selective late sodium channel blocker” with its mechanism of action, unlike antianginal drugs. There are two sodium channels in the myocardium, which are active in different phases of the action potential, a fast sodium channel responsible for the large amount of total sodium current, and a late sodium channel responsible for much less sodium current18. In the case of ischemia, late sodium channel activity increases significantly, and accordingly, the amount of intracellular sodium increases. In order to balance the increased intracellular sodium amount, the sodium-calcium exchanger is activated and eventually, intracellular sodium is taken out of the cell and extracellular calcium is taken into the cell. Elevated intracellular calcium levels can cause mechanical dysfunction in the myocardium, increased ATP consumption, and a disruption in the balance between oxygen supply and demand due to decreased ATP production (19).

Calderon-Sanchez et al. investigated the effects of ranolazine on calcium homeostasis in cardiomyocytes of rats in their study in 2016. It was found that during ischemia-reperfusion injury, calcium concentration in cardiomyocytes increased, with the effect of ranolazine, calcium concentration in cardiomyocytes decreased and calcium concentration in sarcoplasmic reticulum increased (20).

The effects of ranolazine treatment on mitochondria before ischemia and reperfusion at different time points were investigated in the study by Aldakrak et al. in 2011. Ranolazine was thought to decrease intracellular calcium levels and oxidative stress, and enhance mitochondrial integrity against ischemia-reperfusion injury (21). In a study conducted by Dehina et al., ranolazine was found to significantly reduce all the potential harmful consequences of ischemia-reperfusion injury in porcine cardiomyocyte mitochondria (22).

In their 2015 study, Virsolvy et al. aimed to investigate the vasodilatory mechanism of ranolazine. The study was based on the hypothesis that voltage-gated sodium channels are present in arteries and contribute to vasoconstriction, and that ranolazine can inhibit these channels and induce vasodilation. The study found that ranolazine's vasodilator effect may be due to its ability to block alpha-1 adrenergic receptors and inhibit voltage-gated sodium channels in smooth muscle cells (23).

To investigate the effect of ranolazine on the viability of the flap, in our study, a 3x9 cm (width:length) modified McFarlane flap with random pattern caudally based was elevated from the rats' back and adapted to its place. After the operation, saline was administered to the control group and ranolazine was administered to the study groups at specific doses via gastric lavage for seven days. On the seventh postoperative day, photographs were taken at a standard distance of 1 meter to determine the viability of the flaps, they were evaluated by scintigraphy, and after sacrification of the rats, the flaps were excised from their bases and histopathological examinations were performed. In all evaluations, ranolazine was found to increase the viability of the flaps with increasing dose. Furthermore, ranolazine was found to increase neovascularisation and reduce edema, inflammation, and necrosis in histopathological examination.

More detailed and advanced studies are needed to examine in detail the side effect profile of ranolazine with increasing doses, to determine the minimum and maximum doses of efficacy, to determine the degree of efficacy depending on the application in different time periods, and to reveal the mechanism of action on flap viability unambiguously.

CONCLUSION

Our study found that ranolazine increased flap viability and neovascularization while reducing edema, inflammation, and necrosis. However, the mechanism of action on flap viability is not clearly known and more detailed and advanced studies are required.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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