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Investigation of ideal ointment combination to use in septorhinoplasty or nasal flap surgeries

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Abstract. – OBJECTIVE: We aimed to create an ideal ointment combination to provide fast wound healing with the highest patient comfort after nasal surgery and nasal flap surgery.

MATERIALS AND METHODS: Twenty-one male Wistar rats were included. The flap survival method was used. The rats' healing process was evaluated in all groups. After having the same surgical procedure, the following ointments were applied to flap borders twice a day for seven days in each of the groups. In group 1 (Control, n=7), Dexpanthenol 5% (Dex); in group 2, Dex, Ciprofloxacin 0.5 % (Cip) and Ephedrine hydrochloride 1% (Eph); in group 3, Dex+Cip+Eph and Ketoprofen 2.5% (Ket) was applied. On the seventh postoperative day, the size of the necrosis on the flap was evaluated.

RESULTS: Median necrotic areas on skin flaps were 36.00% sq mm in group 1, 23.00% sq mm in group 2, and 5.00% sq mm in group 3. Flap necrosis areas on skin flaps were group 3 <group 2 <group 1 ($p_{adjusted}$ <0.0175). The necrosis areas of groups 2 and 3 were significantly lower than the control group, and the necrosis areas of group 3 were significantly lower than group 2 ($p_{adjusted}$ <0.0175).

CONCLUSIONS: For the postoperative healing process and to prevent flap necrosis, the Dex+Cip+Eph+Ket combination was recommended in the first order. Dex+Cip+Eph combination also reduced skin necrosis in the flaps as the second order. Only Dex treatment is not enough for the completion of the healing process. The best results were provided by the Dex+Cip+Eph+Ket combination and recommended its usage after septorhinoplasty surgeries or nasal flap surgeries to prevent flap necrosis.

Key Words:
Flap necrosis, rat, Dexpantenol, Ciprofloxacin, Ephedrine hydrochloride, Ketoprofen.

Introduction

Septoplasty, rhinoplasty, septorhinoplasty, and various turbinoplasty procedures, are very frequently done at all ENT clinics. Although the history of rhinoplasty goes back to Ebers papyri in Egypt, today it continues to be a research subject in terms of approaches that emphasize patient comfort with the development of modern techniques, devices, and postoperative patient care products[1].

Although there are different approaches in terms of surgical technique, in the most basic form of septoplasty, the septal mucosa that may be named the septal flap is elevated to perform the necessary procedures to straighten the septum. The applied methods may vary, such as taking out or trimming the cartilage and straightening the cartilage's curved section by scoring or burring the bony irregularities. After the cartilage and bone structures are intervened, the flap is returned to its original place and sutured. The surgical area is expected to recover[2].

The most frequent postoperative disturbances and complications of intranasal surgery are infection, pain, inflammation, and edema, which are essential in disrupting patient comfort and reducing surgical success[3].

This study aimed to create an ideal combination to determine the appropriate ointment to provide fast wound healing after nasal surgeries and septorhinoplasty surgeries. So, we planned to add an antibiotic, analgesic, and anti-inflammatory drug, a decongestant within a moisturizing base cream. Following this animal study, toxicity studies in cell cultures will be planned, and the last step will be clinical studies.

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Materials and Methods

The study was conducted at Eskisehir Osmangazi University, Turkey. Adaptation and care of the animals and experimental studies were performed at Experimental Studies Center of Eskisehir Osmangazi University (TICAM). The animals were treated in compliance with AAALAC International in both adaptation and experiment periods. The experimental protocol was reviewed and approved by the Eskisehir Osmangazi University Rectorship, Animal Experiments Local Ethics Committee (HADYEK) (Date: 19.06.2020, Number: 796-1).

Animal Subjects

Twenty-one male Wistar rats were used in this study. All the animal procedures were performed following the approved protocol.

The male rats were housed under the same experimental environmental conditions in a temperature and humidity-controlled room (20-22°C, 55% relative humidity) and 12 h light/dark cycle conditions one week in advance. Tap water and standard pelletized food are provided *ad libitum*. External appearance and weight tracking of animals was carried out. Significant changes were saved. There were no restrictions on diet and water in all groups.

All animals were kept in the experiment conditions for more than 24 hours before the experiment.

Experimental Design

We planned to use the "flap survival method", which has been used in many previous studies, to determine the effectiveness of the healing process[4,5]. The dorsal skin flap described by McFarlane et al[6], 3 x 10 cm in size, was removed from rats' dorsal skin under general anesthesia (Figure 1), and then the removed flap was primarily sutured in its place[4,5].

After having the same surgical procedure, all experimental animals were randomly divided into three groups of 7 animals.

Group 1 (Control): The first group was kept as the control group, and the animals of that group were named as 1.1, 1.2, 1.3, and so on. Only Dexpanthenol 5% (Dex) was applied to flap borders twice a day in this group (n=7).

Group 2: The second group was named group 2, and the animals of that group were named 2.1, 2.2, 2.3, and so on. Dexpanthenol 5% (Dex), Ciprofloxacin 0.5 % (Cip), and Ephedrine hydrochloride 1% (Eph) was applied to flap borders twice a day in this group (n=7).

Group3: The third group was named group 3, and the animals of that group were named 3.1, 3.2, 3.3, and so. Dexpanthenol 5% (Dex), Ciprofloxacin 0,5 % (C) and Ephedrine hydrochloride 1% (Eph) and Ketoprofen 2.5% (Ket) was applied to flap borders twice a day in this group (n=7).

All experimental animals survived till the end of the experiment. On the seventh postoperative day, rats were given general anesthesia again, and the size of the necrosis on the flap (Figure 2, 3) or in other words, the flap viability ratio was calculated using the Photoshop program (Figure 4). The necrosis patterns of flaps were transferred to computer-drawn diagrams, and areas were calculated in sq mm.

Figure 1. The flap measuring 3cm by 10 cm was harvested from the skin of the back.

Figure 2. Necrosis areas of flaps.

Figure 3. Necrosis areas of flaps.

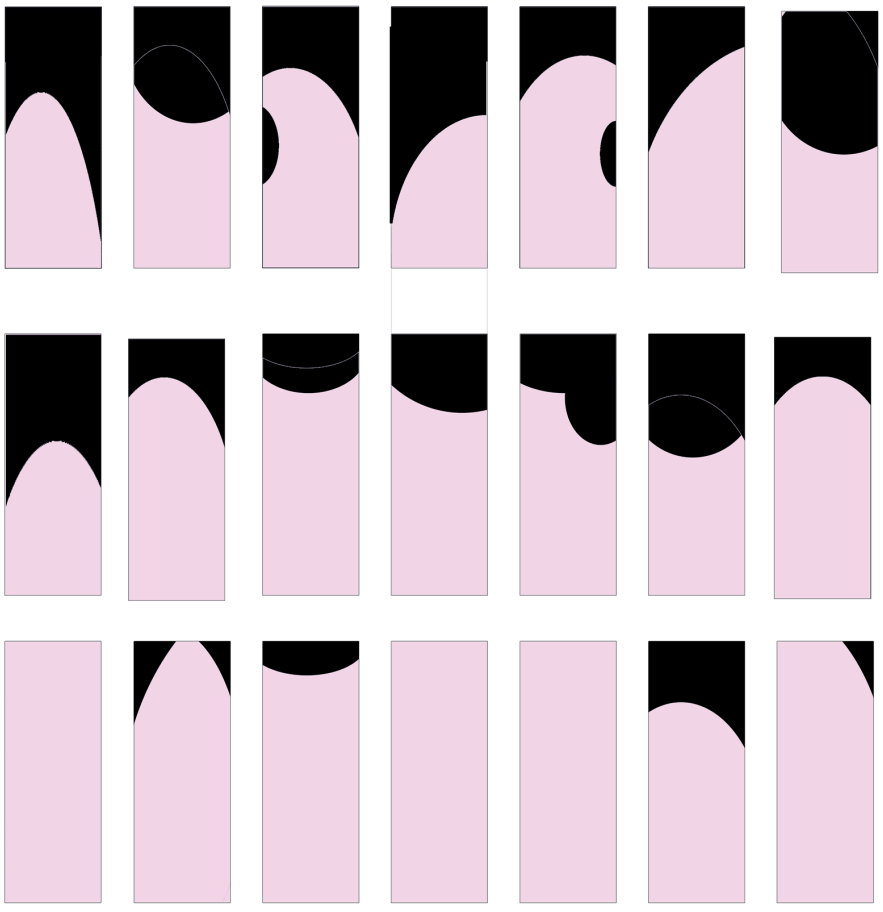

Figure 4. The flap viability ratio was calculated using the Photoshop program. The necrosis patterns of flaps were transferred to computer-drawn diagrams, and areas were calculated in sq mm. In all diagrams, flap necrosis areas were shown as black color.In the upper line, seven diagrams show the flap necrosis areas of group 1 (control group, only Dexpanthenol 5% was applied (n=7); in the middle line, seven diagrams show the flap necrosis areas of group 2 (Dexpanthenol 5%, Ciprofloxacin 0.5%, and Ephedrine hydrochloride 1% was applied); and in the lower-line seven diagrams show the flap necrosis areas of group 3. Dexpanthenol 5%, Ciprofloxacin 0.5%, Ephedrine hydrochloride 1%, and ketoprofen 2.5% were applied.

Statistical Analysis

The data obtained in the study were analyzed using SPSS for Windows 16.0 software (IBM Corp., Chicago, IL, USA). Kruskal-Wallis' variance analysis and for pairwise comparisons, Mann-Whitney U test with Bonferroni adjustment were used.

A value of $p< 0.05$ was considered statistically significant.

A $p_{adjusted}<0.0175$ was considered statistically significant.

Results

The necrotic areas on skin flaps of each animal in groups 1-3 were shown in Table I. The necrosis values were presented as % sq mm.

Median necrotic areas on skin flaps were 36.00% sq mm in group 1, 23.00% sq mm in group 2, and 5.00% sq mm in group 3. The difference between the flap necrosis values of the groups was statistically significant (p=0.001) (Table II).

Mann Whitney U test with Bonferroni adjustment was performed for pairwise comparisons to find the values which caused the difference.

Flap necrosis areas on skin flaps were group 3 < group 2 < group 1 ($p_{adjusted}<0.0175$) (Table II). The necrosis areas of groups 2 and 3 were significantly lower than the control group, and the necrosis areas of group 3 were significantly lower than group 2 ($p_{adjusted}<0.0175$) (Table II).

Discussion

This study aimed to create an ideal combination to determine the appropriate ointment to provide fast wound healing after nasal surgeries. Our results showed that median necrotic areas on skin flaps were 36.00% sq mm in group 1, 23.00% sq mm in group 2, and 5.00% sq mm in group 3. Flap necrosis areas on skin flaps were group 3<group 2<group 1. The necrosis areas of groups 2 and 3 were significantly lower than the control group, and the necrosis areas of group 3 were significantly lower than group 2.

Dexpanthenol is a real "provitamin" that supports the normal epithelial function. It accelerates wound healing, reduces dryness of the nasal mucosa, and diminishes the emergence of annoying scabs. It will be used as the base of the combination to include other active ingredients. Dexpanthenol was used as the base ointment because of its softening and moisturizing effect. It is the alcoholic analog of pantothenic acid, and it is oxidized to this substance within the tissues[7]. Several previous studies[4,8] proved its antioxidants such as ischemia-reperfusion-induced renal injury model, a testicular ischemia-reperfusion model, and reduced oxidative stress. Dexpanthenol spray protects the epithelium and promotes cell proliferation. Wound healing on paranasal sinuses was investigated in an experimental study by Hosemann et al[5]. The combi-

Table I. Necrotic areas on skin flaps in each of the animals in groups 1-3.

Groups	Necrosis areas in rats (% sq mm)						
	1	2	3	4	5	6	7
Group 1 (Control)	37	39	30	48	24	30	36
Group 2	35	23	16	22	25	29	16
Group 3	0	5	10	0	0	26	5

Table II. Analyses of necrosis areas between groups 1-3.

Groups	Flap necrosis (% sq mm)				Pairwise comparisons
	Mean	Median	Std. Dev	p*	$p_{adjusted}$**
Group 1 (Control)	34.85	36.00	7.75	0.001	Group1-2 = 0.011 (<0.0175)
Group 2	23.71	23.00	6.82		Group1-3= 0.001 (<0.0175)
Group 3	6.57	5.00	9.34		Group2-3 = 0.011 (<0.0175)

*p-value shows the results of Kruskal Wallis Variance analysis.
**adjusted value shows the results of Mann Whitney U test with Bonferroni adjustment. $p_{adjusted}$ <0.0175 was considered as statistically significant.

nation of dexpanthenol with nasal decongestants decreased the toxic effects by improving the cilia function and cell growth[9]. This cream was used in all groups (1, 2, 3).

Wound infection after all surgical procedures is one of the significant surgical problems in all fields. Although routine systemic antibiotic use after nasal surgery is not recommended in most studies, it is left to the clinician to plan appropriate antibiotic treatment on a case-by-case basis. In this study, it was planned to add ciprofloxacin for the ointment component as an appropriate antibiotic[10]. Antibiotic was used in groups 2 and 3.

Nasal blockage is the most uncomfortable situation in patients who have undergone nasal surgery, especially in the postoperative period. Ephedrine hydrochloride may be added to the ointment component to prevent or decrease edema[11,12], increasing the patient healing process. Decongestant was used in groups 2 and 3.

Possible pain and inflammation are common problems, especially after rhinoplasty[2,11]. Ketoprofen, a nonsteroidal anti-inflammatory drug, has been included in the ointment as both an analgesic and anti-inflammatory agent[11,12]. This ointment was used only in group 3.

According to our results, the Dex+Cip+Eph+Ket combination of ointment presented the best result as the least flap necrosis (median 5.00% sq MMS) in group 3. Group 3 combination achieved results superior to groups 2 and 3.

Dex+Cip+Eph combination in group 2 achieved better results than in group 1. However, this combination achieved worse results than the Dex+Cip+Eph+Ket combination of group 3.

Applying only Dex treatment in the control group achieved worse results than the Dex-+Cip+Eph+Ket combination of group 3 and the Dex+Cip+Eph combination of group 2.

Conclusions

We concluded that for the postoperative healing process and to prevent necrosis in the flaps, the Dex+Cip+Eph+Ket combination provided the best results. This work used an animal model, and it is uncertain whether the results can be extrapolated to humans. We recommend a study using the Dex+Cip+Eph+Ket combination after septorhinoplasty surgeries or nasal flap surgeries to see if flap necrosis can be reduced or prevented. A further clinical trial should be suggested to see if the results will be applied to humans.

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Conflict of Interest
The authors declare that they have no conflict of interest.

Ethics Approval
Ethics committee approval was obtained from Eskisehir Osmangazi University Rectorship, Animal Experiments Local Ethics Committee (HADYEK) (Date: 19.06.2020, Number: 796-1).

Authors' Contributions
Cafer Yildirim: Planning, designing, data collection, performing the experiment, literature survey, interpretation of the results, active intellectual support.
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Murat Kar: Planning, designing, data collection, literature survey, interpretation of the results, active intellectual support.
Furkan Kaya: Planning, designing, literature survey, data collection, performing the experiment.
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