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The effect of hypertonic alkaline nasal irrigation on nasal wound healing in an experimental animal model

Deneysel bir hayvan modelinde hipertonik alkali nazal irrigasyonun nazal yara iyileşmesine etkisi

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ABSTRACT

Objectives: This study aimed to examine the effect of a hypertonic alkaline nasal irrigation (HANI) solution on nasal healing in an animal model of nasal septal perforation (NSP).

Materials and Methods: In the experimental animal study, 22 healthy male Sprague-Dawley rats were divided in to two groups: the HANI (study) group and the saline (control) group. An NSP about 2 mm in size was formed in each rat. In the study group, 0.1 mL of HANI was intranasally administered each day for 14 days, whereas the control group daily received 0.1 mL of saline for the same period. The animals were sacrificed on Day 14, and the subjects' nasal septums were excised for histopathology. The amount of regeneration and degeneration of epithelial tissue, inflammatory cell count, fibroblast count, amount of collagen, new vessel formation, amount of granulation, giant cell count, eosinophil count, and the degeneration and regeneration of cartilage tissue were examined. The macroscopic recovery rates of NPSs and microscopic parameters were statistically analyzed.

Results: The acute inflammatory cell density was significantly lower in the study group (p=0.033). The epithelial and cartilage regenerations, fibroblast number, vascularization, amount of granulation, and collagen density were higher in the study group. In addition, the epithelial and cartilage degenerations were lower in the study group. However, no significant difference was detected in the evaluation of the remaining parameters (p>0.05).

Conclusion: Hypertonic alkaline nasal irrigation may not adversely affect nasal wound healing and may reduce acute inflammation in nasal septal wound healing in an NSP animal model.

Keywords: Animal, nasal irrigation, nasal septal perforation, nose, wound healing.

ÖZ

Amaç: Bu çalışmada deneysel bir hayvan nazal septal perforasyon (NSP) modelinde hipertonik alkali nazal irrigasyon (HANI) solüsyonunun nazal yara iyileşmesi üzerindeki etkisi araştırıldı.

Gereç ve Yöntemler: Deneysel hayvan çalışmasında 22 sağlıklı erkek Sprague-Dawley sıçan iki gruba ayrıldı: HANI (çalışma) grubu ve salin (kontrol) grubu. Her sıçanda yaklaşık 2 mm çapında NSP oluşturuldu. Çalışma grubuna 14 gün boyunca her gün 0.1 mL HANI intranazal olarak uygulanırken, kontrol grubuna aynı süre boyunca günlük 0.1 mL salin uygulandı. Hayvanlar 14. günde feda edildi ve deneklerin nazal septumları histopatolojik inceleme için eksize edildi. Mukozal epitel rejenerasyonu ve dejenerasyonu, akut enflamatuar hücre sayısı, fibroblast sayısı, kollajen yoğunluğu, vaskülarizasyon, eozinofil sayısı, granülasyon dokusu oluşumu, dev hücre sayısı ve nazal kıkırdak dejenerasyonu ve rejenerasyonu incelendi. Perforasyonların makroskopik kapanma oranları ve mikroskopik parametreleri istatistiksel olarak analiz edildi.

Bulgular: Akut enflamatuar hücre yoğunluğu çalışma grubunda anlamlı olarak daha düşüktü (p=0.033). Çalışma grubunda epitel ve kıkırdak rejenerasyonları, fibroblast sayısı, vaskülarizasyon, granülasyon miktarı ve kollajen yoğunluğu daha yüksekti. Ayrıca çalışma grubunda epitel ve kıkırdak dejenerasyonları daha düşüktü. Ancak diğer parametrelerin karşılaştırılmasında istatistiksel olarak anlamlı bir fark bulunmadı (p>0.05).

Sonuç: Hipertonik alkali nazal irrigasyon, NSP hayvan modelinde nazal yara iyileşmesini olumsuz etkilemeyebilir ve nazal septal yara iyileşmesinde akut enflamasyonu azaltabilir.

Anahtar sözcükler: Hayvan, nazal irrigasyon, nazal septal perforasyon, burun, yara iyileşmesi.

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A hypertonic solution is defined as a solution containing >9 g/L of sodium chloride (NaCl) with a potential hydrogen (pH) of >7. Van Lake-based hypertonic alkaline nasal irrigation (HANI) solution is a hypertonic alkaline solution that contains 12 g/L of NaCl, 1.1 g/L of magnesium sulfate heptahydrate ($MgSO_4.7H_2O$), 0.1 g/L of calcium chloride dihydrate ($CaCl_2.2H_2O$), 0.8 g/L of potassium chloride (KCl), 4 g/L of sodium bicarbonate ($NaHCO_3$), and 2 g/L of sodium sulfate (Na_2SO_4), and its pH is 9. In a clinical study, it has been shown that HANI reduces the nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) load and alleviates the clinic associated with coronavirus disease 2019 (COVID-19).[1,2]

The wound is the disruption of the normal functional anatomy of the tissues due to internal or external causes.[3] Nasal mucosal wounds are usually caused by trauma. It most commonly occurs due to iatrogenic trauma during surgery, such as septoplasty, septorhinoplasty, endoscopic nasal surgeries, and turbinate surgeries, or after surgery, such as nasal packing. Nasal mucosal wounds cause nasal crusts and mucosal synechiae, which negatively affect surgical success.[4]

Many different cells and molecules are involved in wound healing consisting of hemostasis, inflammation, proliferation, and remodeling phases.[5] Wound healing is affected positively or negatively by many factors. In previous studies, several medical wound healing agents have been used during or after nasal surgeries with different application methods to prevent postsurgical complications, such as nasal crusting, nasal septal perforation formation, mucosal adhesion formation, and mucosal scar formation.[4,6-9] Nasal irrigation is frequently used in the management of allergic rhinitis, treatment of sinonasal infections, and after sinonasal surgeries due to its positive properties, including anti-inflammatory effects, increasing mucociliary clearance, cleaning mucus, crust, mucosal debris, and harmful substances in the air, and moisturizing.[10-12] Several solutions, such as saline, hypertonic solutions, and Ringer's lactate, can be used for nasal irrigation using different tools. There are previous studies examining the use of these solutions in the postoperative period and their effects on wound healing.[10,13-15] However, there is no study examining the effects of HANI on wound healing. The current study aimed to investigate the effect of HANI on wound healing of the nose. For this purpose, an nasal septal perforation (NSP) model was developed in rats, and wound healing results are presented histopathologically.

MATERIALS AND METHODS

Subjects

Twenty-two healthy male Sprague-Dawley rats, weighing between 220-400 g and aged nine to 10 weeks, were included in the experimental animal study. The rats were housed in a normalized husbandry condition with a 12-h day and 12-h night cycle at 22±2°C. The rats were kept in cages, with each cage containing four subjects. Standard pelletized food and tap water were provided ad libitum.

Chemicals and drugs

Hypertonic alkaline nasal irrigation solution (Nasovan; Orzaks Ilaç, Istanbul, Türkiye) and 0.9% saline (Adeka Ilaç Sanayi ve Ticaret A.Ş, Istanbul, Türkiye) were used in this study. The saline and HANI were stored at room temperature. 0.1 mL saline and 0.1 mL HANI were administered to each subject once a day.

All animals were intramuscularly anesthetized with 45 mg/kg ketamine hydrochloride (Ketalar, Pfizer Ilaçları Ltd. Şti., Istanbul, Türkiye) and 5 mg/kg xylazine hydrochloride (Basilazin; Baver, Germany). The subjects were positioned 10 min after anesthesia induction. An NSP, about 3 mm posterior to the nasal septal columella and about 2 mm in size, was created through the right side of the nose using a cannula (Vasofix IV Cannula 14G, 2.2×50 mm; Braun, Melsungen, Germany) (Figure 1a). The rats were placed with the left nasal cavity facing down to avoid aspiration.

Animals were randomized into two groups: the HANI (study) group, in which 0.1 mL of HANI was administered to the right cavity once a day after the NSP procedure (Figure 1b), and the saline (control) group, in which 0.1 mL of saline was administered to the right nasal cavity once a day after the NSP surgery. The same person applied the solutions to the right nasal cavity at the same time for 14 days. On the last day (14th day after the NSP procedure), the animals were sacrificed with 100 mg/kg intraperitoneal pentobarbital (Penbital; Bioveta Inc., Ivanovice na Hané, Czech Republic).

Histopathological examination

On the 14th day, the nasal septal cartilage of the subjects was dissected (Figure 2a). Each excision material was put in different containers and numbered. The surgical specimens were fixed with a 10% formaldehyde solution, and paraffin-embedded blocks were prepared. Three µm-thick sections were prepared from the paraffin-embedded blocks. The sections were stained with hematoxylin and eosin and trichrome

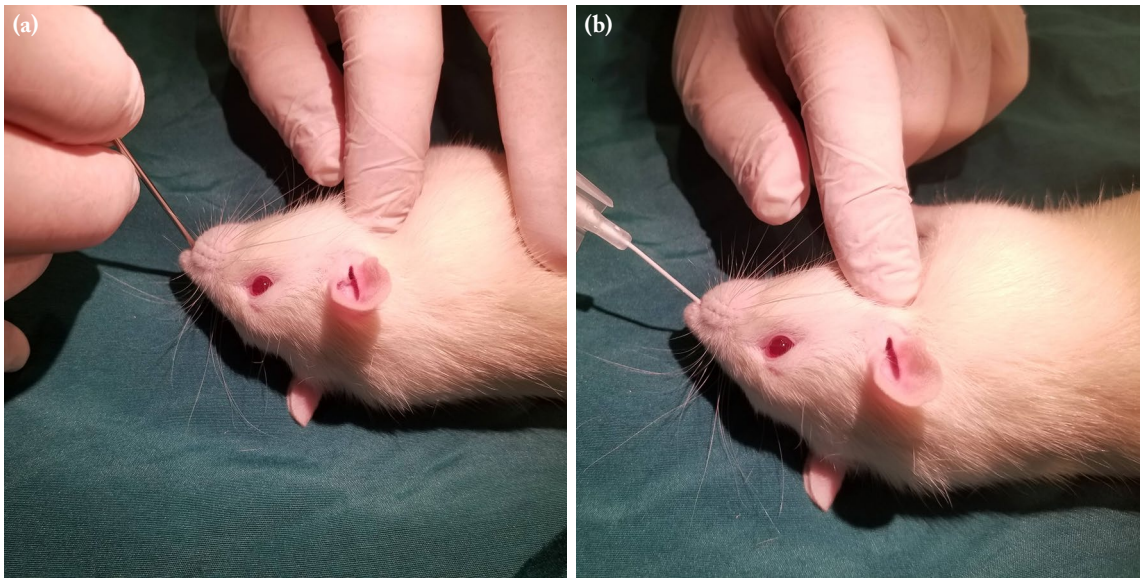

Figure 1. **(a)** The creation of the perforation. **(b)** The application of the solution to the right nasal cavity.

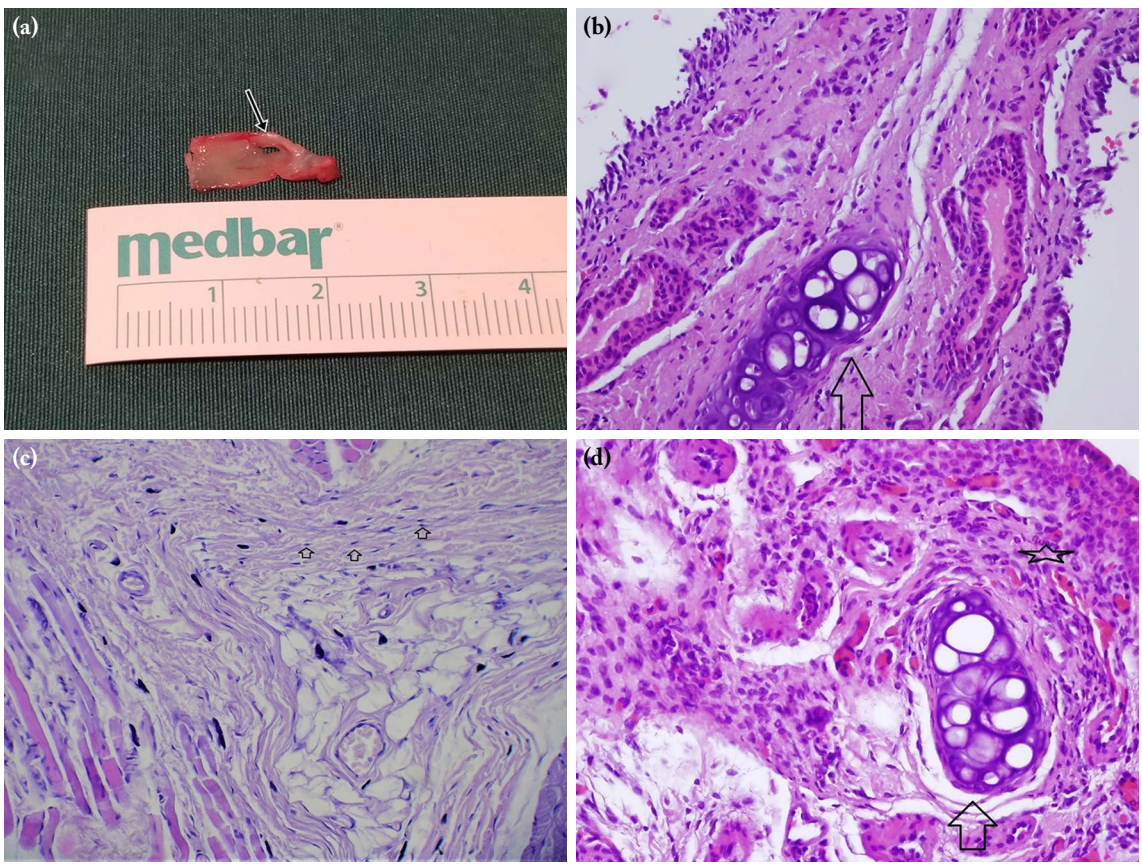

Figure 2. **(a)** The excision material. Nasal septum was excised subtotally (the arrow shows the perforation). **(b)** Cartilage regeneration (arrow) and lower acute inflammatory reaction (H&E, ×400). **(c)** Intense fibroblast activation; the arrows show fibroblasts (H&E, ×100). **(d)** Cartilage regeneration (arrow) and acute inflammatory reaction (asterisk) (H&E, ×400).

Table 1
Investigation of histopathological and macroscopic parameters in the HANI group and the saline group

	HANI[a] group (n=11)									Control group (n=11)									
	None		Mild		Moderate		Intensive			None		Mild		Moderate		Intensive			
	n	%	n	%	n	%	n	%	Median (Q1-Q3) Mean Ranks	n	%	n	%	n	%	n	%	Median (Q1-Q3) Mean Ranks	*p*
Epithelial regeneration	0	0	6	54.5	5	45.5	0	0	1 (1-2) 12.82	3	27.3	4	36.4	4	36.4	0	0	1 (0-2) 10.18	0.298
Epithelial degeneration	5	45.5	6	54.5	0	0	0	0	1 (0-1) 11.23	5	45.5	5	45.5	1	9.1	0	0	1 (0-1) 11.77	0.824
Cartilage regeneration	4	36.4	4	36.4	3	27.3	0	0	1 (0-2) 13.59	8	72.7	2	18.2	1	9.1	0	0	0 (0-1) 9.41	0.094
Cartilage degeneration	9	81.8	2	18.2	0	0	0	0	0 (0-0) 10.32	7	63.6	2	18.2	2	18.2	0	0	0 (0-1) 12.68	0.274
Acute inflamatory cells density	3	27.3	8	72.7	0	0	0	0	0 (0-1) 8.82	2	18.2	6	54.5	2	27.3	0	0	1 (1-2) 14.18	0.033*
Fibroblast count	3	27.3	6	54.5	2	18.2	0	0	1 (0-1) 11.91	4	36.4	5	45.5	2	18.2	0	0	1 (0-1) 11.09	0.747
Collagen density	1	9.1	3	27.3	6	54.5	1	9.1	2 (1-2) 11.91	1	9.1	4	36.4	5	45.5	1	9.1	2 (1-2) 11.09	0.748
Vascularization	4	36.4	4	36.4	3	27.3	0	0	1 (0-2) 12.09	3	27.3	8	72.7	0	0	0	0	1 (0-1) 10.91	0.634
Granulation tissue	3	27.3	4	36.4	2	18.2	2	18.2	1 (0-2) 11.82	2	18.2	6	54.5	3	27.3	1	9.1	1 (1-2) 11.18	0.807
Eosinophil count	4	36.4	5	45.5	2	18.2	0	0	1 (0-1) 11.91	5	45.5	4	36.4	2	18.2	0	0	1 (0-1) 11.09	0.750
	Partial				Complete					Partial				Complete					
Macroscopically closed perforation	4		36.4		7		63.6		4 (2-4) 12.45	7		63.6		4		36.4		3 (3-4) 10.55	0.455

HANI: Hypertonic alkaline nasal irrigation; * The Mann-Whitney U test; p<0.05. Q: Quartile.

stains and evaluated with microscopy (Primo Star ILED; Carl Zeiss Meditec AG, Jena, Germany). An expert blinded pathologist performed the pathological evaluations. The epithelial and cartilage regenerations, the epithelial and cartilage degenerations, fibroblast number, collagen density, vascularization, amount of acute inflammatory cell, eosinophil number, amount of granulation, and presence of giant cell were examined in four categories (0, none; 1, mild; 2, moderate; 3, intensive). The macroscopic healing rates of the NSPs were scored by dividing into five categories (0, excessively increased, 1, slightly increased; 2, unchanged; 3, partially closed; 4, completely closed) (Figures 2b-d).[13]

Statistical analysis

The minimal subject number was determined as 22 by the G*Power version 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany)[16] based on the study of Ceylan et al.[4] with a 95% confidence interval and 5% tolerable error assumptions. The statistical analysis was performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was used for paired comparisons. The significance level was set at $p<0.05$.

RESULTS

No significant difference was present in terms of the subject age and weight (245±32 g in the study group *vs.* 241±23 g in the control group) between the groups at the beginning of the study ($p>0.05$). All subjects lived till the end of the study. There were no complications in any of the rats, such as infections, bleeding, and synechiae. There was no significant difference in terms of weight (280±36 g in the study group *vs.* 282±20 g in the control group) between the groups at the end of the study ($p>0.05$).

The acute inflammatory cell density was significantly lower in the study group ($p=0.033$). The epithelial and cartilage regenerations, fibroblast number, vascularization, amount of granulation, and collagen density were higher in the study group. In addition, the epithelial and cartilage degenerations were lower in the study group. However, no significant difference was detected in the evaluation of the other parameters ($p>0.05$, Figures 2b-d, Table 1).

Septal perforations were completely closed in seven (63.6%) subjects, partially closed in one (9.1%) subject, unchanged in two (18.2%), and slightly increased in one subject in the study group. However, in the control group, the NSPs were completely closed in four (36.4%) subjects, partially closed in five (45.5%) subjects, unchanged in two subjects, and slightly increased in one subject. No significant difference was found in the macroscopic closure rates of NSPs ($p=0.455$, Table 1).

DISCUSSION

Nasal irrigation is a treatment method that is frequently used after sinonasal surgeries, can be applied with various solutions and medical instruments, and has been shown to positively affect postoperative recovery in previous studies.[10,15,17,18] Treatment methods for many diseases have changed in the COVID-19 era. In this study, we aimed to determine whether it is appropriate to use HANI, which has been shown to reduce the nasopharyngeal load of SARS-CoV-2, in the postoperative period by evaluating its effects on wound healing. The study revealed that acute inflammation, which negatively affects wound healing, was significantly less in the HANI group ($p=0.033$. No significant difference was detected in the groups according to other histopathological parameters of wound healing ($p>0.05$). However, the epithelial and cartilage regenerations, fibroblast number, vascularization, amount of granulation, and collagen density were higher in the study group, and the epithelial and cartilage degenerations were lower in the study group.

The use of nasal irrigation is recommended after sinonasal surgeries as it increases mucociliary clearance, provides mechanical cleaning by removing blood clots and crusts formed after surgery, and reduces mucosal edema and inflammation.[15,17] Solutions with different contents and concentrations, such as saline, Ringer's lactate, and hypertonic solutions, can be used for nasal irrigation. The use of hypertonic solutions is preferred to isotonic saline due to its properties, including reducing mucosal edema faster, increasing mucociliary clearance more, and being more effective against infective agents.[15,17,18]

There are differences between the sexes, mainly due to hormonal effects, particularly estrogen, on wound healing.[19] Therefore, only male rats participated in the present study. In our study, we planned to examine the healing parameters of a wound belonging to the nasal septum as it is the formation containing the most different types of tissue in the nasal cavity. The septal perforations were performed with a cannula to standardize the NSPs. Similar to the previous studies, we concluded our experiment at the end of the 14th day.[20,21]

In most of the previous studies, it was reported that an alkaline environment impairs wound healing

with its properties, such as affecting the functioning of enzyme systems, increasing the number of toxic end products by stimulating protein degradation, and leading higher risk of infection by causing the proliferation of harmful microorganisms.[22,23] However, Kruse et al.[23] reported that an alkaline environment increased fibroblast proliferation, accelerated reepithelialization, and had no negative effect on wound closure. In addition, several elements have different effects on wound healing. Magnesium and zinc have positive effects on wound healing with their antiapoptotic and anti-inflammatory properties.[24,25] Potassium accelerates reepithelialization by increasing respiratory epithelial repair via the EGF (epidermal growth factor)/EGF receptor pathway.[26] In our study, the significantly decreased acute inflammatory response seen in the HANI group may be due to the hypertonic properties of the solution and the amount of magnesium it contains. In the HANI group, decreased epithelial and cartilage degeneration may be due to the antiapoptotic properties of the ions it contains. The increased epithelial and cartilage regenerations, fibroblast number, vascularization, granulation amount, and collagen density in the study group may be attributed to the induced fibroblast activity due to an alkaline environment. Although the most of positive changes in the parameters of wound healing were not statistically significant, it is more valuable for our hypothesis that there was no negative change in the wound healing parameters due to the use of HANI.

The present study, which is the first in the English literature investigating the beneficial effects of HANI on nasal wound healing, has some limitations. The subjective scoring system for histopathological investigations limits our study. Evaluations were performed by an expert pathologist to minimize this effect. However, we could have acquired more objective outcomes with image analysis software. Another limitation is that we used HANI with the nasal irrigation method. The nasal irrigation method also has positive effects on wound healing. Therefore, one cannot exclude a synergistic relationship between nasal irrigation and HANI. Hence, there is a need for a more comprehensive study with a third group in which no procedure other than surgery was performed. The small sample size due to the ethical principle of reduction also limits our study.

In conclusion, HANI may reduce acute inflammation and has no negative effect on nasal septal wound healing in an NSP model in rats. Hypertonic alkaline nasal irrigation may be used in the postsurgical period. Future comprehensive studies with more animals and objective investigation methods are needed to support our results.

Ethics Committee Approval: This experimental study was approved by Bezmi Alem University Animal Experiments Ethics Committee (decision date: 21.09.2021, no: 2021-242) and conducted in Bezmi Alem University Experimental Animal Application and Research Center.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Material preparation, data collection and analysis was performed: D.Ç.; Statistical analysis was performed: Y.Z.Y.; The first draft of the manuscript was written: D.Ç., and Y.Z.Y., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Tomonaga Y, Brennwald MS, Livingstone DM, Kwiecien O, Randlett MÈ, Stockhecke M, et al. Porewater salinity reveals past lake-level changes in Lake Van, the Earth's largest soda lake. Sci Rep 2017;7:313.
2. Yilmaz YZ, Yilmaz BB, Ozdemir YE, Kocazeybek BS, Karaali R, Çakan D, et al. Effects of hypertonic alkaline nasal irrigation on COVID-19. Laryngoscope Investig Otolaryngol 2021;6:1240-7.
3. Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Pecoraro RE, Rodeheaver G, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol 1994;130:489-93.
4. Ceylan SM, Uysal E, Sokucu M, Sezgin E, Kanmaz MA, Yurtseven DG, et al. The effects of halofuginone on wound healing in the rat nasal mucosa. Am J Rhinol Allergy 2020;34:9-15.
5. Lindley LE, Stojadinovic O, Pastar I, Tomic-Canic M. Biology and biomarkers for wound healing. Plast Reconstr Surg 2016;138(3 Suppl):18S-28S.
6. Beule AG, Scharf C, Biebler KE, Göpferich A, Steinmeier E, Wolf E, et al. Effects of topically applied dexamethasone on mucosal wound healing using a drug-releasing stent. Laryngoscope 2008;118:2073-7.
7. El-Anwar MW, Abdelmonem S, Abdelsameea AA, AlShawadfy M, El-Kashishy K. The effect of propolis in healing injured nasal mucosa: An experimental study. Int Arch Otorhinolaryngol 2016;20:222-5.
8. Valentine R, Athanasiadis T, Moratti S, Hanton L, Robinson S, Wormald PJ. The efficacy of a novel chitosan gel on hemostasis and wound healing after endoscopic sinus surgery. Am J Rhinol Allergy 2010;24:70-5.

9. Çakan D, Aydın S, Demir G, Başak K. The effect of curcumin on healing in an animal nasal septal perforation model. Laryngoscope 2019;129:E349-E354.
10. Bastier PL, Lechot A, Bordenave L, Durand M, de Gabory L. Nasal irrigation: From empiricism to evidence-based medicine. A review. Eur Ann Otorhinolaryngol Head Neck Dis 2015;132:281-5.
11. Tabary O, Muselet C, Miesch MC, Yvin JC, Clément A, Jacquot J. Reduction of chemokine IL-8 and RANTES expression in human bronchial epithelial cells by a seawater derived saline through inhibited nuclear factor-kappaB activation. Biochem Biophys Res Commun 2003;309:310-6.
12. Hermelingmeier KE, Weber RK, Hellmich M, Heubach CP, Mösges R. Nasal irrigation as an adjunctive treatment in allergic rhinitis: A systematic review and meta-analysis. Am J Rhinol Allergy 2012;26:e119-25.
13. Liu DQ, Liu JW, Liu JM. Effect of nasal endoscopic rinse fluid temperature on the healing time of nasal mucosa. Chin J NurTra 2008;23:1782-3.
14. Bonnomet A, Luczka E, Coraux C, de Gabory L. Non-diluted seawater enhances nasal ciliary beat frequency and wound repair speed compared to diluted seawater and normal saline. Int Forum Allergy Rhinol 2016;6:1062-8.
15. Low TH, Woods CM, Ullah S, Carney AS. A double-blind randomized controlled trial of normal saline, lactated Ringer's, and hypertonic saline nasal irrigation solution after endoscopic sinus surgery. Am J Rhinol Allergy 2014;28:225-31.
16. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-91.
17. Liu L, Pan M, Li Y, Tan G, Yang Y. Efficacy of nasal irrigation with hypertonic saline on chronic rhinosinusitis: Systematic review and meta-analysis. Braz J Otorhinolaryngol 2020;86:639-46.
18. Kanjanawasee D, Seresirikachorn K, Chitsuthipakorn W, Snidvongs K. Hypertonic saline versus isotonic saline nasal irrigation: Systematic review and meta-analysis. Am J Rhinol Allergy 2018;32:269-79.
19. Ozawa S, Mukudai S, Sugiyama Y, Branski RC, Hirano S. Mechanisms underlying the antifibrotic potential of estradiol for vocal fold fibrosis. Laryngoscope 2021;131:2285-91.
20. Khalmuratova R, Kim DW, Jeon SY. Effect of dexamethasone on wound healing of the septal mucosa in the rat. Am J Rhinol Allergy 2011;25:112-6.
21. Khalmuratova R, Jeon SY, Kim DW, Kim JP, Ahn SK, Park JJ, et al. Wound healing of nasal mucosa in a rat. Am J Rhinol Allergy 2009;23:e33-7.
22. Power G, Moore Z, O'Connor T. Measurement of pH, exudate composition and temperature in wound healing: A systematic review. J Wound Care 2017;26:381-97.
23. Kruse CR, Singh M, Targosinski S, Sinha I, Sørensen JA, Eriksson E, et al. The effect of pH on cell viability, cell migration, cell proliferation, wound closure, and wound reepithelialization: In vitro and in vivo study. Wound Repair Regen 2017;25:260-9.
24. Ludwig P, Petrich K, Schewe T, Diezel W. Inhibition of eicosanoid formation in human polymorphonuclear leukocytes by high concentrations of magnesium ions. Biol Chem Hoppe Seyler 1995;376:739-44.
25. Tesfaigzi Y. Roles of apoptosis in airway epithelia. Am J Respir Cell Mol Biol 2006;34:537-47.
26. Trinh NT, Privé A, Maillé E, Noël J, Brochiero E. EGF and K+ channel activity control normal and cystic fibrosis bronchial epithelia repair. Am J Physiol Lung Cell Mol Physiol 2008;295:L866-80.