

The superiority of Dexpanthenol or Vaseline as excipient in nasal formulations

O.N. DEVELIOGLU¹, M. DILBER², N. BAYAR MULUK³, C. VEJSELOVA SEZER⁴,
H. MEHTAP KUTLU⁴, V. TOPSAKAL⁵, C.C. CINGI⁶

¹Department of Otorhinolaryngology, University of Health Sciences, Istanbul Gaziosmanpasa Training and Research Hospital, Istanbul, Turkey

²Otorhinolaryngology Section, Dilber Private Clinic, Istanbul, Turkey

³Department of Otorhinolaryngology, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey

⁴Department of Biology, Faculty of Science, Eskisehir Technical University, Eskisehir, Turkey

⁵Department of Otorhinolaryngology, Head and Neck Surgery, Brussels Health Campus, Vrije Universiteit Brussel, University Hospital Brussels, Brussels, Belgium

⁶Department of Otorhinolaryngology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

Abstract. – OBJECTIVE: Dexpanthenol is an ingredient in multiple topical pharmaceutical preparations thanks to its high penetration and localized concentration. It is included in many ointments or lotions for dermatological use, assisting in healing and reducing pruritus. Vaseline is a synthetic product obtained by distilling crude oil. It is commercially available in several grades. The study presented here examined how topically applied agents (dexpanthenol or vaseline) affect nasal epithelial cells in culture. In particular, the study aimed to identify any alterations to epithelial cells which might indicate toxicity.

MATERIALS AND METHODS: The nasal epithelial cells used were sourced from mucosal tissue fragments left over the following septorhinoplasty on five patients not suffering from rhinosinusitis. The first step was to dissect the mucosal fragments into smaller pieces on a sterilized Petri dish. These fragments were then placed into the DMEM-F12 cell culture medium, which had been freshly prepared. The dexpanthenol and vaseline were diluted in dimethylsulfoxide (DMSO) to a concentration of 5 mg/mL. The cells in the wells were exposed to varying concentrations of dexpanthenol or vaseline. The actual concentration of the test reagent to which the epithelial cells were exposed ranged from 0.15 mg/mL to 5 mg/mL. The exposure period was 24 hours. The cells were finally examined using a Leica SP5II confocal microscope. The features sought were DNA fragmentation, condensation of the nuclei, changes in the outer membrane, or cytoskeletal abnormality. These features, if present, indicate cytotoxicity.

RESULTS: The viability of the cultured nasal epithelial cells was unaltered by a 24-hour exposure to dexpanthenol, nor was the cellular proliferation rate affected at the level of statistical sig-

nificance. There was evidence of a cytotoxic effect from exposing nasal epithelial cells to vaseline in liquid form for 24 hours. There was a reduction in cellular viability in the plates where the highest dose of vaseline (5 mg/mL) was used. Cellular viability was not affected significantly at any of the doses below 5 mg/mL.

CONCLUSIONS: The absence of cytotoxic effects from the application of dexpanthenol to the nasal mucosa indicates that this agent may be safely used within the nose. The cytotoxic effects of liquid vaseline observed in this trial (condensed nuclear chromatin, loss of cellular volume) indicate that this agent may be harmful when used intranasally. For patients who require nasal packing due to nose bleeds or following endoscopic sinus surgical procedures, dexpanthenol should be preferred to vaseline from the point of view of maximizing healing of a nasal injury.

Key Words:

Dexpanthenol, Vaseline, Nasal formulation, Intra-nasal application.

Introduction

An intact mucosal barrier is vital in the body's natural defenses against invading pathogens. There is a dense network of capillaries just underneath the epithelium, providing heat and water to the nasal cavity so that the air inhaled into the lungs is warm and moist^{1,2}. The secretions in the nose consist of various fluids, namely serous and seromucous glandular secretions, mucus from goblet cells, tears, sinus secretions, and

water which condenses in the nasal cavity as air is exhaled³. There are several ways in which the standard humidity of the nasal interior may be disrupted, resulting in symptoms of a dry nose. The loss of humidity may cause desiccation of the nasal epithelium, impairment of mucociliary clearance, and, eventually, damage to the integrity of the nasal epithelium⁴.

Nasal dryness may be termed “dry nose”, “rhinitis sicca”, or “atrophic rhinitis”. There is a degree of imprecision in how the terms are applied, since diagnosing and defining the condition depends on the features noted in the patient history. Patients frequently complain of excessively dry noses, mildly painful burning, nasal pruritus, or blockage. These symptoms may be accompanied by visible manifestations of the problem, such as nasal crusting, nose bleeds, hyposmia, or a foul-smelling discharge from the nose. The nasal mucosal lining is frequently hypertrophic. Rhinitis sicca is one condition amongst several that can cause nonallergic, non-infectious nasal inflammation⁵⁻¹⁰. Nasal dryness may occur in isolation or be seen in conjunction with ocular and oral dryness in certain conditions¹¹⁻¹³.

Dexpanthenol is structurally related to pantothenic acid. Pantothenic acid is a B-vitamin vital for the healthy physiology of epithelial surfaces. Dexpanthenol is converted to pantothenic acid by an enzymatically catalyzed reaction. The acid is then used to form Coenzyme A, a vital co-factor in multiple steps in synthesizing proteins by the epithelium^{14,15}.

Dexpanthenol is an ingredient in multiple topical pharmaceutical preparations thanks to its high penetration and localized concentration. It is included in many ointments or lotions for dermatological use, assisting in healing and reducing pruritus. When used on the skin, it promotes fibroblast proliferation and increases the rate at which epithelial regrowth occurs to cover damage to the skin. Moreover, it is topically protective, adds moisture, and has been shown to decrease the inflammatory response^{14,16}.

Vaseline is a synthetic product obtained by distilling crude oil. It is commercially available in several grades. Vaseline comprises mainly unbranched hydrocarbons with a chain length of between 10 and 18 carbon atoms. It may contain dotriacontane and olefinic acids. The isoparaffin content of vaseline varies according to its source. If the n-paraffins predominate, the substance tends to be more crystalline than where iso-paraffins or branched chain paraffin are the dominant

types. Some cyclic compounds, including aromatic compounds, in petroleum jelly can be reduced in number (although not entirely removed) by a bleaching process¹⁷.

There have been concerns about using petroleum jelly since this product and paraffin wax are derived from crude oil and therefore contain an admixture of aromatic, including polycyclic aromatic, molecules. Generally speaking, rendering paraffin or petroleum jelly entirely free of aromatic content is not feasible. Furthermore, there is considerable variation in the composition of gels and paraffin waxes from different manufacturers, leading to varying levels of aromatic compounds. These formulations have been noted to cause irritation of the skin and may cause other skin reactions. Polycyclic aromatic hydrocarbons are known carcinogens, and some concerns about using such products may raise the risk of skin cancer. This is especially concerning when the level of ultraviolet radiation to which individuals are exposed is increasing, which is predicted to cause a raised incidence of dermatological neoplasia¹⁷.

The study presented here examined how topically applied agents (dexpanthenol or vaseline) affect nasal epitheliocytes in cell culture. In particular, the study aimed to identify any alterations to epithelial cells which might indicate toxicity.

Materials and Methods

The study was undertaken under the auspices of the Otorhinolaryngology Department at Eskisehir Osmangazi University, with the assistance of the Department of Biology of Eskisehir Technical University, within the Faculty of Science. The nasal epithelial cells for culture were sourced from surplus tissue remaining after routine ENT septorhinoplasty operations on individuals who had provided written consent for such use to be made of their tissue. The tissue obtained in this way was taken to the Cell Culture Laboratory of Eskisehir Technical University in a preservative transport medium.

Primary Cell Culture

The nasal epithelial cells were sourced from mucosal tissue fragments left over the following septorhinoplasty on five patients not suffering from rhinosinusitis. The first step was to dissect the mucosal fragments into smaller pieces on a

sterilized Petri dish. These fragments were then placed into DMEM-F12 cell culture medium, which had been freshly prepared. The medium also contained 1% penicillin-streptomycin and 10% fetal bovine serum. The surrounding atmosphere was humidified, and the carbon dioxide level was 5%. The temperature was maintained at 37°C. On day 7 of the experiment, the excess tissue was removed from the culture plates. Epithelial cells adhering to the plate were then rinsed with phosphate-buffered saline (PBS) and separated by exposure to trypsin before passing to T25 cell culture plates. The experimenters then waited until 85% of the culture was confluent before proceeding with the following experimental stage¹⁸.

MTT Assay Used to Assess the Toxicity of Applied Dexpanthenol or Vaseline

Having been treated with trypsin, the epithelial cells were transferred to plates with 96 separate wells. The number of cells placed in each well was 5×10^3 . The reagents utilized for the experiment varied in concentration between 0.15 and 5 mg/mL. As before, the atmosphere of the culture was kept at 37°C, with an atmosphere containing 5% carbon dioxide and additional moisture.

The dexpanthenol and vaseline were diluted in dimethylsulfoxide (DMSO) to a concentration of 5 mg/mL. The cells in the wells were exposed to varying concentrations of dexpanthenol or vaseline. The exposure period was 24 hours.

Following this procedure, the researchers added 20 μ L of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) in phosphate-buffered saline (PBS, Invitrogen) at a concentration of 5 mg/mL to the wells. The incubation then lasted a further 4 hours without changing the atmospheric condition of the plates. When the 4-hour incubation was finished, the media were replaced with 200 μ L DMSO. The ELISA plate reader was used with a wavelength of 570 nm. This reader was employed in the evaluation of all three plates. The absorbance value was then used to calculate the viability percentages and IC_{50} (half maximal inhibitory concentration)¹⁸.

Confocal Microscopy

Nasal epithelial cells were exposed to dexpanthenol or vaseline over 24 hours, with the temperature kept at 37°C. The cells were seeded on coverslips placed in 6-well plates. There were around 3×10^5 cells in each well. The concentra-

tion of dexpanthenol or vaseline was either the IC_{50} or the highest concentration of either agent. Control wells contained cells without exposure to either agent. Once the period of exposure had elapsed, the medium was removed, and the cells were washed with PBS. There followed a 15-minute-long fixation procedure in which the cells were immersed in 2% glutaraldehyde at ambient temperature, after which the cells were again washed with PBS. The epithelial cells then underwent staining with Alexa Fluor-488 phalloidin plus acridine orange.

The cells were finally examined using a Leica SP5II confocal microscope. The features sought were DNA fragmentation, condensation of the nuclei, changes in the outer membrane, or cytoskeletal abnormality. These features, if present, indicate cytotoxicity¹⁸.

Wound Healing Assay

Primary nasal epithelial cells underwent a 24-hour incubation on a plate containing six separate wells. Each well-held 3×10^5 epithelial cells. Areas on the plate where the cells had formed a confluent layer, received a vertical scratch injury with a 20-200 μ L pipette tip. This was followed by washing in PBS and adding either fresh culture medium or medium plus dexpanthenol or vaseline. The appearances at the start were examined with an ordinary light microscope. This examination was repeated at 0. and 24 hours after the scratch injury was made. Unscratched nasal epithelial cells were used to act as controls¹⁹.

Statistical Analysis

All the data gathered were analyzed statistically. One-way analysis of variance (ANOVA) was chosen to perform repeated comparisons. The analyses were all carried out with the GraphPad Prism 6.0 for Windows application (GraphPad Software Inc., La Jolla, CA, USA).

A p -value of no more than 0.05 was considered to indicate statistical significance.

Results

Results of the MTT Assay

The viability of the cultured nasal epithelial cells was unaltered by a 24-hour exposure to dexpanthenol, nor was the cellular proliferation rate affected at the level of statistical significance (Figure 1).

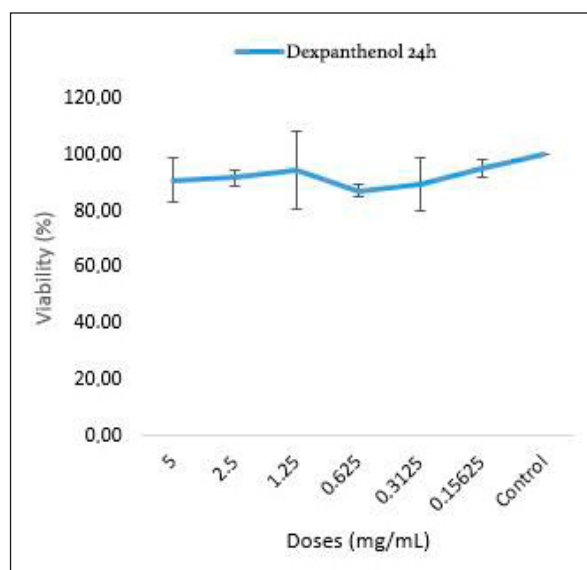


Figure 1. Viability percentages of cultured primary nasal cells treated with different concentrations of Dexpanthenol for 24 hours.

There was evidence of a cytotoxic effect from exposing nasal epithelial cells to vaseline in liquid form for 24 hours. There was a reduction in cellular viability in the plates where the highest dose of vaseline (5 mg/mL) was used. Cellular viability was not affected significantly at any of the doses below 5 mg/mL (Figure 2).

Results from Confocal Microscopy

The confocal microscopic findings are in accord with the findings from the MTT assay. The control epithelial cells were compact in shape, with a well-delineated, fusiform outline and distinct nuclear boundary (Figure 3 A). The cells exposed to dexpanthenol did not exhibit any

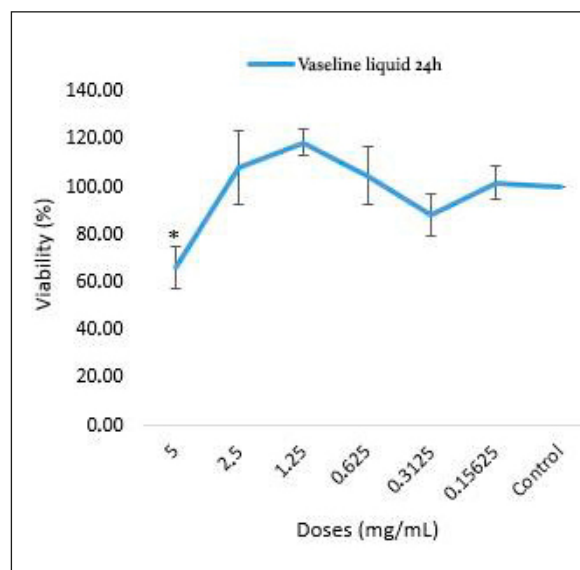


Figure 2. Cell viability of primary cells applied with liquid vaseline for 24 hours.

morphological changes from the controls, indicating the absence of cytotoxicity (Figure 3 B). By contrast, the epithelial cells exposed to liquid vaseline did have features indicating cytotoxicity, namely cellular shrinkage and condensed nuclear chromatin (Figure 3 C).

Results from the Wound Healing Assay

Microscopy was used to assess how broad the scratch injury was following a 24-hour recovery period. The epithelial cells exposed to dexpanthenol were compared with those exposed to vaseline. In the cells incubated with dexpanthenol, the denuded part of the plate noted at the beginning had been entirely re-epithelialized after 24 hours

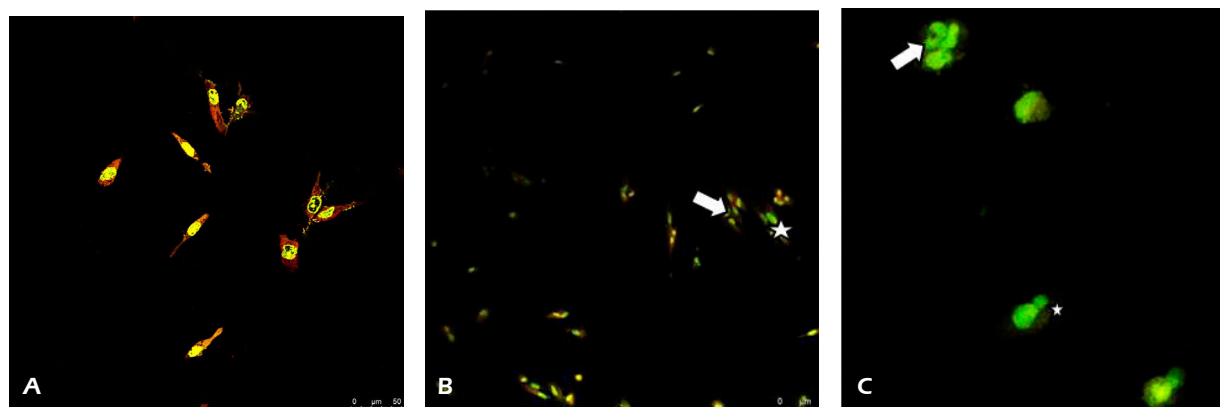


Figure 3. Confocal microscopy images of primary cultured nasal cells. A, Control group and test cells exposed to Dexpanthenol (B), and to Vaseline liquid (C). Arrow: nuclei, Asterisk: Cytoskeleton.

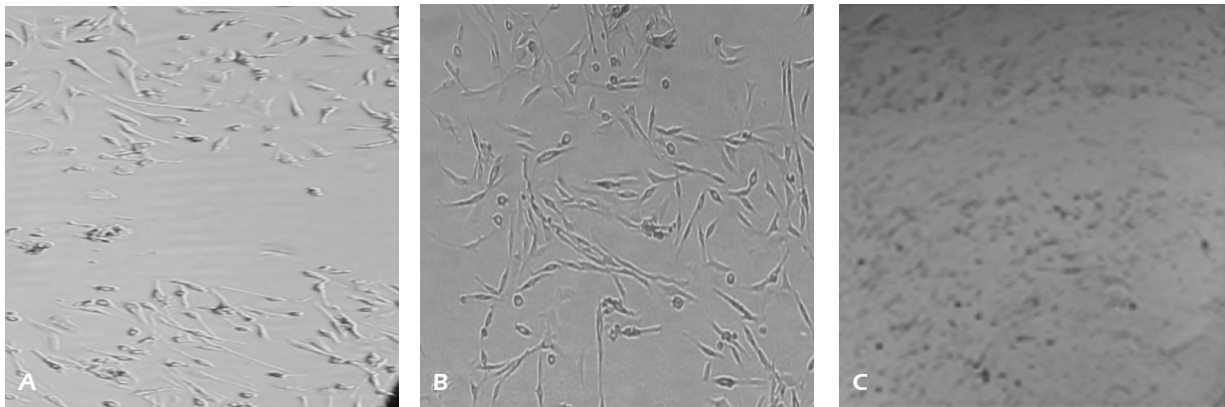


Figure 4. Wound healing images of primary nasal cells at the initial stage (0th hour). **A**, Untreated (Control) cells; **B**, Cells exposed to Dexpanthenol; **C**, Cells exposed to Vaseline liquid.

(Figure 4 A-B). In contrast, the re-epithelialization of the denuded area in the liquid vaseline plates was incomplete (Figure 4 C). Thus, at a point 24 hours after injury, it was clear that dexpanthenol neither increased nor decreased epithelial proliferation, whereas liquid vaseline had decreased the proliferative capability of the cells (Figure 5 A-C).

Discussion

The nose plays several physiological roles, including conditioning air during inspiration by warming it, adding moisture, and removing foreign particles. The nose also directs inspired air toward the olfactory mucosa, which allows odors to be sensed. This function is an essential component in a good quality of life²⁰. Although breathing can occur *via* the nasal or oral cavity, the latter fails to condition and clean inspired air,

which is less optimal for normal physiology²¹. The mucosal lining of the respiratory tract (including the nose) possesses several types of glands capable of generating nasal mucus. This mucus performs a protective role. The tubuloalveolar glands in the nasal lining are stimulated in response to input from the tenth cranial nerve, parasympathomimetic agents, and specific peptides. Secretion also increases in response to molecules that stimulate alpha- or beta-adrenoceptors or following irritation of the lining²².

One of the most straightforward and essential steps in treating symptoms of a dry nose is the prescription of a topical intranasal spray or an ointment since these can moisten the mucosa and ease symptoms. Sprays for intranasal use dispensing isotonic saline are frequently used for this purpose, although there are other pharmaceutical preparations with hyaluronic acid or dexpanthenol, for which superior efficacy has been claimed⁴.

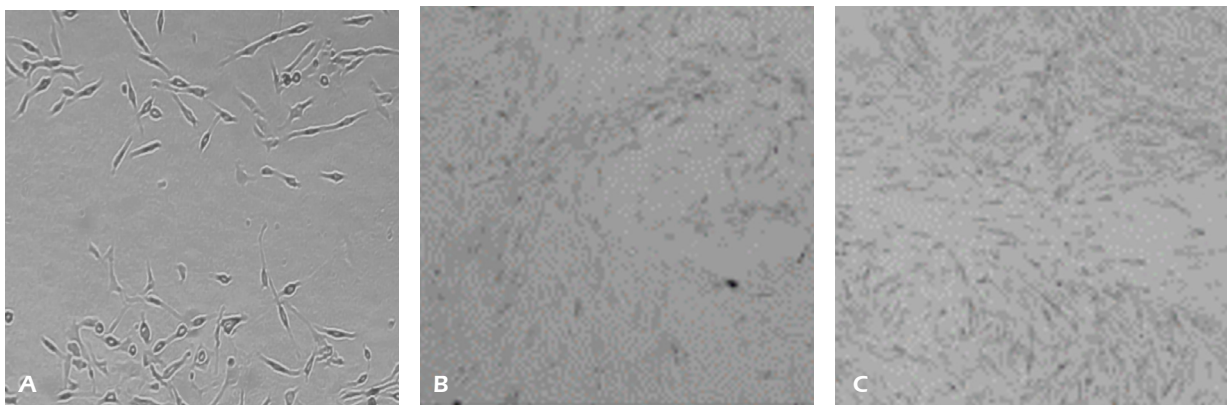


Figure 5. Wound healing images of primary nasal cells at the end of incubation period, i.e., at 24th hour. **A**, Untreated (Control) cells; **B**, Cells exposed to Dexpanthenol; **C**, Cells exposed to Vaseline liquid.

The European Pharmacopeia describes vaseline as composed of several solid or nearly solid hydrocarbon compounds at room temperature. It is obtained from crude oil. Alternative names for this preparation are soft paraffin, vaseline, or petroleum jelly²³. It is frequently employed as the basis for an ointment and may be used dermatologically for its emollient effects. Absorption through the skin is minimal, and few side effects have been reported when employed topically. It may be ignited by applying a heat source between 182-221°C, or it will auto-ignite if the ambient temperature reaches 290°C^{24,25}.

Dexpanthenol is an analog of pantothenic acid containing hydroxyl groups. When dexpanthenol is applied to the skin or another mucosal surface, it enters the epithelium and converts into pantothenic acid. This is then used to form coenzyme A. The latter is a vital co-factor for many enzymatically catalyzed cellular pathways, such as those involved in catabolism and anabolism of lipids, carbohydrates, and amino acids. The cell population containing the most elevated level of coenzyme A are the epidermis stem cells. It has been recognized for decades that dexpanthenol increases the epithelium's regrowth following skin injury that is not due to infection or trophic alterations²⁶. Dexpanthenol absorbs and retains a high-water level, i.e., it exhibits hygroscopy. This property is beneficial for prompt repair of the mucosa²⁷⁻²⁹, as formulations containing dexpanthenol improve epithelial hydration²⁷.

The objective of the present study was to ascertain whether direct topical application of either dexpanthenol or vaseline in liquid form causes any features indicative of cellular toxicity. The study's findings are that the viability of primary nasal epithelial cells directly exposed for 24 hours to dexpanthenol was not altered, nor was this result in any significant alteration in their proliferative capabilities. The epithelial cells exposed to liquid vaseline, in contrast, did exhibit changes indicative of cytotoxicity. At a dose of 5 mg/mL and with an exposure period of 24 hours, the viability of the nasal epithelial cells was decreased at a level found to be statistically significant. This was the highest dose tested. There was no significant alteration in cellular viability at the other applied doses. The MTT assay and confocal microscopy point to the same conclusion: topically applied liquid vaseline is cytotoxic at a high dose. The epithelial cells to which dexpanthenol was applied did not exhibit morphological changes, which indicates an absence of cytotoxicity for

epithelial cells in cell culture. However, the cytomorphological alterations seen in epithelial cells to which liquid vaseline was applied, namely condensed nuclear chromatin and shrinkage of the cell, are indications of a cytotoxic effect.

Standard light microscopy was used to assess the outcome of the wound healing assay. The primary outcome was the degree of re-epithelialization 24 hours after scratch injury in the presence of topically applied vaseline or dexpanthenol. Again, there were significant differences between the epithelial cells exposed to dexpanthenol and those exposed to liquid vaseline. The cells exposed to dexpanthenol could recover the denuded area within the 24-hour incubation period, whereas this was not the case with the cells to which vaseline had been applied. The result indicates that dexpanthenol does not affect the rate of re-epithelialization (i.e., proliferation). Vaseline does, however, impair this proliferative ability.

Dexpanthenol is structurally related to pantothenic acid. Pantothenic acid is a B-vitamin vital for the healthy physiology of epithelial surfaces. Dexpanthenol is converted to pantothenic acid by an enzymatically catalyzed reaction. The acid is then used to form Coenzyme A, a vital co-factor in multiple steps in synthesizing proteins by the epithelium^{14,15}.

When used on the skin, dexpanthenol promotes fibroblast proliferation and increases the rate at which epithelial regrowth occurs to cover damage to the skin. Moreover, it is topically protective, adds moisture, and has been shown^{14,16} to decrease the inflammatory response.

There is a variety of topical treatments suitable for cases of nasal dryness, including intranasal sprays, rinses, ointments, oils, and inhalations. The main therapeutic objectives when using such preparations are to moisten the lining of the nose, soften any crusted areas and promote nasal mucosal regeneration⁴.

A study³⁰ found that applying dexpanthenol to the nasal lining prior to using xylometazoline caused a significant reduction in cytotoxicity ($p < 0.001$). Removing benzalkonium chloride from sprays intended for nasal use was also associated with improved cellular proliferation ($p < 0.001$). Notably, when dexpanthenol does not precede xylometazoline, but is used afterward, it achieves only 50% of the pro-growth effects seen when used prior to applying xylometazoline. The study³⁰ concluded that prior application of dexpanthenol 5% both increases tolerability of other nasal agents and reduces potential toxicity.

The mechanism by which dexpanthenol is converted to pantothenic acid involves oxidation within the tissues³¹. Several studies³²⁻³⁴ have concluded that dexpanthenol offers benefits as an antioxidant agent. For example, a model of kidney reperfusion injury following ischemia found benefit, as did a similar model for the testis. Moreover, dexpanthenol has been shown³²⁻³⁴ to reduce oxidative stress secondary to gamma radiation and triggering apoptosis. Literature has already established that dexpanthenol delivered *via* an intranasal spray increases epithelial proliferation and is protective. A study³⁵ examining the effects of dexpanthenol on the repair of injured paranasal sinus tissue found benefits in terms of more rapid tissue repair. Klöcker et al³⁶ showed that adding dexpanthenol to a nasal decongestant resulted in significantly less impairment of ciliary action and cellular proliferation³⁶.

It was demonstrated³⁷ that adding dexpanthenol to xylometazoline produced more significant symptomatic relief in terms of nasal discharge, nasal blockage, swollen conchae, and hyperemia of the nasal lining than the preparation of xylometazoline alone. The researchers³⁶ hypothesized that the symptomatic benefits of acute rhinitis were explicable by a protective action of dexpanthenol on the nasal lining. Jagade et al³⁷ conducted a randomized trial prospectively involving blinding, which allocated 100 patients to receive either xylometazoline 0.1% nasal drops or oxymetazoline 0.05% combined with dexpanthenol 5%. The patients receiving the combined preparation reported more significant symptomatic benefits in less nasal stuffiness. This result was statistically significant.

Furthermore, rhinorrhea and sternutation were each reduced in the patients receiving the combined preparation. Additionally, this added benefit from the combined preparation was seen for irritation to the lining of the nose, and the symptomatic duration was around 40% lower, a finding of clinical significance. Hahn et al³⁸ examined the benefit of three different pharmaceutical preparations in patients with a dry nose: isotonic saline spray for nasal, a liposome-based spray, and a dexpanthenol-containing ointment. The best product for moisturizing the nasal interior was found to be the liposome-based product³⁸.

There have been several reports^{17,23} concerning cases where an individual's hair caught fire after being coated in paraffin-based hair products, leading to burns to the scalp, face, and hands. Following an incident in which a patient, who had

bandages over a vaseline ointment, accidentally set himself on fire while smoking and subsequently died, the UK National Patient Safety Agency issued a warning that patients should avoid all contact with naked flames if using emollients containing paraffin²³.

It has also been recorded^{39,40} that the use of paraffin mesh or vaseline-soaked gauze after the reduction of a broken nose may be linked to various complications, such as blockage of the nose, adhesions of the mucosa, disturbed sleep, headaches, oral dryness and difficulty swallowing. Patients are especially prone to discomfort due to nose blockage following nasal surgical procedures. Accordingly, the nose should ideally be packed so that the airway is splinted open, so any discomfort related to a blocked nose will be greatly lessened⁴¹.

The conventional approach to controlling hemorrhage after paranasal sinus operations is to pack the nose. Packing has been viewed as a way to stop adhesions from developing, the middle turbinate from being displaced laterally, or restenosis from occurring. However, this procedure has a significant disadvantage; patients find it the most distressing element when undergoing endoscopic sinus surgery^{42,43}. The opinion is divided about whether to avoid packing in the middle meatus⁴⁴ or whether the complete packing is essential to prevent the middle turbinate from being displaced laterally^{45,46}.

A vital factor to consider when trying to prevent adhesion formation is that methods that work by activating the intrinsic coagulation cascade will, at the same time, trigger an inflammatory response^{47,48}. There are multiple interactions between the coagulation cascade and the immune system. One such point of interaction is the various protease factors acting to produce coagulation and fibrin dissolution. Over-activity of the coagulation cascade can impair effective wound healing. Numerous studies^{46,49} have advanced knowledge of how the injury is repaired in the paranasal sinuses using animal models, particularly sheep, rabbits, or mice. The use of an ovine model is often preferred due to the animal's large size, which allows sinus surgery to be performed with minimum adaptation from human techniques, and the similarity of the paranasal mucosa between the two species at the histological level.

Before this study, no researchers have reported on how dexpanthenol or liquid vaseline affects nasal epithelial cells and how this may affect the choice to include these agents as excipients in na-

sal, topical preparations. Epithelial cells exposed to dexpanthenol retained the same viability, and no morphological alterations indicated toxicity. The proliferative behavior of these cells also did not change. The cells exposed to liquid vaseline, in contrast, did exhibit changes indicative of toxicity. For those epithelial cells exposed to the highest dose of vaseline (i.e., 5 mg/mL over 24 hours), morphological alterations consistent with toxicity were noted. In particular, the chromatin increased in density, and the cells decreased in size. These epithelial cells were also less viable.

Therefore, the authors recommend dexpanthenol as a suitable agent to use when packing the nose, as it exhibits no signs of localized toxicity. The use of liquid vaseline on nasal packing materials is best avoided as it has been shown to cause a cytotoxic effect on nasal epithelial cells.

Conclusions

The absence of cytotoxic effects from the application of dexpanthenol to the nasal mucosa indicates that this agent may be safely used within the nose. The cytotoxic effects of liquid vaseline observed in this trial (condensed nuclear chromatin, loss of cellular volume) indicate that this agent may be harmful when used intranasally. For patients who require nasal packing due to nose bleeds or following endoscopic sinus surgical procedures, dexpanthenol should be preferred to vaseline from the point of view of maximizing healing of the nasal injury.

ORCID ID

Omer Necati Develioglu: 0000-0001-6725-1013.
Muhammet Dilber: 0000-0001-5835-3181.
Nuray Bayar Muluk: 0000-0003-3602-9289.
Canan Vejselova Sezer: 0000-0002-3792-5993.
Hatice Mehtap Kutlu: 0000-0002-8816-1487.
Vedat Topsakal: 0000-0003-0416-4005.
Cemal Cingi: 0000-0003-3934-5092.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Contributions

Omer Necati Develioglu: Planning, designing, literature survey, interpretation of the results, active intellectual support, submission.
Muhammet Dilber: Planning, designing, literature survey, interpretation of the results, active intellectual support.

Nuray Bayar Muluk: Planning, designing, literature survey, interpretation of the results, active intellectual support, writing.

Canan Vejselova Sezer: Planning, designing, data collection, literature survey, interpretation of the results, active intellectual support.

Hatice Mehtap Kutlu: Planning, designing, data collection, performing the study, literature survey, interpretation of the results, active intellectual support, writing.

Vedat Topsakal: Planning, designing, literature survey, interpretation of the results, active intellectual support.

Cemal Cingi: Planning, designing, literature survey, performing the study, interpretation of the results, active intellectual support, English editing.

Ethics Approval

This is a cell-culture study. Ethics committee approval was not needed.

Informed Consent

Human primary nasal epithelium was obtained from healthy tissue removed routinely as part of surgery (septorhinoplasty) from individuals who gave written consent for their tissue to be used in scientific research.

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