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An evaluation of ketoprofen as an intranasal anti-inflammatory agent

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Abstract. – OBJECTIVE: The objective of the study was to evaluate the effect of ketoprofen when locally applied to tissue-cultured nasal epithelium.

MATERIALS AND METHODS: Healthy primary nasal epithelial cells were grown in a tissue culture medium. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was used to evaluate cytotoxicity. Markers of cellular injury revealed by the MTT assay include fragmentation of DNA, condensed nuclei, and changes affecting the cellular outer membrane and cytoskeleton. Epithelial cells at body temperature in cell culture were exposed over a 24-hour period to ketoprofen. Following the MTT assay, the confocal microscopic examination was performed. The extent to which epithelial cells remained capable of proliferating was evaluated by inducing a scratch injury, waiting for the repair to occur, and then examining the result with the ordinary light microscope.

RESULTS: Topically applied ketoprofen does not affect the viability of tissue-cultured nasal epithelial cells within a 24-hour period. Furthermore, there were no cellular morphological alterations observed which would indicate toxicity from ketoprofen. In the scratch assay, the cells regained a normal confluent appearance within 24 hours. Thus, ketoprofen neither increases nor alters the rate at which nasal epithelial cells proliferate.

CONCLUSIONS: Ketoprofen, when applied topically for 24 hours to nasal epithelial cells in cell culture, does not cause any alterations in cellular appearance which would suggest impairment of the ability to proliferate or indicate a cytotoxic effect. Extrapolating from these results, it appears acceptable to use ketoprofen topically within the nose in cases of rhinosinusitis (acute or chronic) or nasal pain since there is minimal risk of local toxic injury.

Key Words:
Ketoprofen, Cultured human nasal epithelial cells, Confocal microscopy, Viability, Toxicity.

Introduction

The use of systemic non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a high degree of clinical efficacy in several painful conditions, both acute and chronic. However, these agents also frequently cause severe side effects, especially within the gut. One way to reduce the severity of these adverse effects is to apply the agent locally, thereby avoiding systemic effects. A variety of preparations exist to deliver NSAIDs topically, in the form of gels, creams, or sprays. These agents cross the skin and achieve penetration into the subcutaneous adipose and muscle at levels sufficient to exert a local therapeutic effect without raising the circulating level of the agent in serum. There is evidence to confirm the analgesic efficacy of topically applied NSAIDs for a variety of painful conditions, both acutely and chronically[1].

The epithelium within the nose, however, presents a formidable barrier to the entry of most topical agents, especially when applied as an aqueous solution[2]. To overcome this issue, a number of technologies[3-6] have been investigated to see if they can improve local delivery and thus avoid the need for systemic administration. Several pharmaceutical preparations have been produced to increase the level of local absorption, e.g., chitosan-based *in situ* hydrogels, mucoadhesive nanostructured lipid carriers, and chitosan nanoparticles[3-6]. Topical delivery does, however, have some associated disadvantages; notably a toxic effect on the nasal lining and damage to the cellular outer membrane, including integral proteins, which can trigger an inflammatory response at the site of application[7]. Cell culture is valuable in the early assessment of novel drugs, as it may reveal both how efficacious a pharmaceutical agent is, and whether it results in toxic effects.

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Ketoprofen is a derivative of 2-aryl propionic acid. It is an NSAID with high potency, which has been in European clinical use for more than 15 years. It has recently entered the US market. The molecule exhibits chirality and exists in both R and S-enantiomers. Despite only the S-enantiomer being pharmacologically active, all forms of ketoprofen currently marketed exist as racemic mixtures. Both enantiomers undergo near identical metabolism in the body. Their concentrations in plasma do not greatly differ and there is an absence of apparent interaction between the isomers. It is thus methodologically sound to extrapolate from the overall pharmacokinetics of the racemate to the stereospecific situation. Ketoprofen is absorbed swiftly and virtually completely from the gut. There are enteric-coated preparations on the market, which have a role since the elimination half-life of the drug is no longer than 1 to 3 hours. Enteric-coated preparations may also cause less irritation to the gut. The enteric-coated forms have a lower peak concentration in plasma and build up more slowly in the plasma. However, they possess identical bioavailability to non-modified release preparations. The agent is extensively protein-bound in the circulation, the exact degree depends on the enantiomer, however. It has been ascertained that ketoprofen penetrates in high levels into the synovial fluid, which is beneficial clinically[8]. Gel forms of ketoprofen are also used in musculoskeletal conditions[9].

This study looks at how ketoprofen affects nasal epithelial cells in cell culture, when applied topically. Specifically, the aim is to look for any indications that this agent produces a toxic effect on the nasal epithelium.

Materials and Methods

The present study was undertaken jointly by the ENT Department at Eskişehir Osmangazi University and the Department of Biology of the Faculty of Science at Eskişehir Technical University, Turkey. Human tissue of an appropriate type (healthy nasal epithelial cells) was sourced from volunteer donors undergoing septorhinoplasty, where epithelium needs to be removed as an integral part of the procedure. These volunteers all provided written consent for the tissue to be used scientifically. Harvested tissues were preserved in a suitable medium before arrival at the Eskişehir Technical University Cell Culture facility.

Primary Cell Culture

Nasal epithelial fragments obtained in the course of septorhinoplasty from five patients provided healthy epithelial cells for cell culture. None of the donors had a diagnosis of rhinosinusitis. The epithelium was dissected into small fragments on sterile Petri dishes to obtain the epithelial cells. These cells were next placed in a complete DMEM-F12 medium, which contained 1% penicillin-streptomycin. Ten percent of the medium was made up of fetal bovine serum. This culture was maintained at 37 Celsius in moist air with 5% carbon dioxide. Any non-confluent tissue was separated from the main culture on day 7. Then the confluent cell mass was rinsed with phosphate-buffered saline (PBS), manufactured by Invitrogen (Waltham, MA, USA). Trypsinisation preceded passage to T25 cell culture plates. The cells were then left until the cell mass was 85% confluent, at which point the culture was appropriate for use in the next stage of the investigation[10].

MTT Assay to Assess Cytotoxic Effects from Topical Ketoprofen

The trypsinized primary epithelial cells were transferred to a 96-well plate, such that there were $5x10^3$ epithelial cells within each well. When the assay was performed, a variety of concentrations was required, ranging from 0.15 to 5 mg/mL. The cultures were maintained at 37 Celsius in moist air with 5% carbon dioxide.

Dimethylsulfoxide (DMSO) was used to dilute ketoprofen to a concentration of 5 mg/mL. Ketoprofen was added to each well in varying quantities, to ensure that the level of exposure varied systematically from 1 µg/mL to 500 µg/mL. The exposure period was 24 hours.

Once the period for which the epithelial cells were exposed to the agent had elapsed, the MTT assay was performed. Twenty microlitres of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) dissolved in PBS was placed in each well, after which the plate remained for a further 4 hours under the same conditions as in the preceding stage. Once this stage was complete, 200 µL of DMSO was used to replace the medium and the plate was evaluated using an ELISA plate reader operating at a wavelength of 570 nm. The absorbances obtained allowed the calculation of the viability percentage and the half-maximal inhibitory concentration (IC_{50}) of ketoprofen[10].

Confocal Microscopic Examination

For this part of the experiment, epithelial cells also underwent exposure to ketoprofen over a 24-hour period. The cells were kept at a steady 37 Celsius. The epithelial cells were put into 6-well plates and a coverslip was applied. The number of cells in each well was arranged to be $3x10^5$. The IC_{50} had previously been ascertained, and either this or the maximum ketoprofen concentration was used for those epithelial cells exposed to the agent. The unexposed epithelial cells acted as experimental controls. After exposure to the drug, the cells were washed with PBS and the medium removed. The cells were fixed using glutaraldehyde 2% at room temperature for the quarter of an hour. These cells were then washed a further time with PBS and stained with Alexa Fluor-488 phalloidin and acridine orange.

For the confocal microscopic examination, a Leica SP5II microscope was employed. The examiner assessed cytopathological changes implying cellular toxicity, in particular fragmented DNA, condensed nuclear appearances, cellular membranous alterations, and cytoskeletal injury[10].

Wound Healing Assay

For this part of the experiment, epithelial cells from cell culture were transferred into plates of 6 wells, after which the incubation continued for 24 hours. In the plates where the cells had formed a confluent mass, the tip of a sterile pipette (normally used to measure out 20-200 µL of a liquid) was employed to make a vertically oriented scratch, after which the plate was washed with PBS. Control wells had just fresh cell medium added to them, whilst the test wells had medium plus ketoprofen added. At this point, the light microscopic appearances were noted. The cells returned to the incubator but were examined at 8-hour intervals with the microscope, and the degree of re-closure was noted. The wells not subjected to scratching were used as controls[11].

Statistical Analysis

The data obtained at each stage of the experiment were analyzed statistically, for which purpose the GraphPad Prism 6.0 for Windows application (GraphPad Software Inc., San Diego, CA, USA) was employed. One-way analysis of variance (ANOVA) was performed where multiple comparisons were needed. The level of statistical significance was defined as a *p*-value lower than 0.05.

Results

Results Obtained with the MTT Assay

It was noted that the cells underwent no alteration in viability over the 24-hour period during which they were exposed directly to ketoprofen (See Figure 1).

Results of Confocal Microscopic Examination

The confocal microscopic examination produced results consistent with those from the MTT assay. The epithelial cells not exposed to the agent (control epithelial cells) had a compact morphological structure. These cells preserved their overall fusiform shape, and the nucleus had a clear outline (Figure 2A). When the treated epithelial cells are compared, it is seen that their morphological features are the same as the controls, implying that ketoprofen does not cause toxic cellular alterations (Figure 2B).

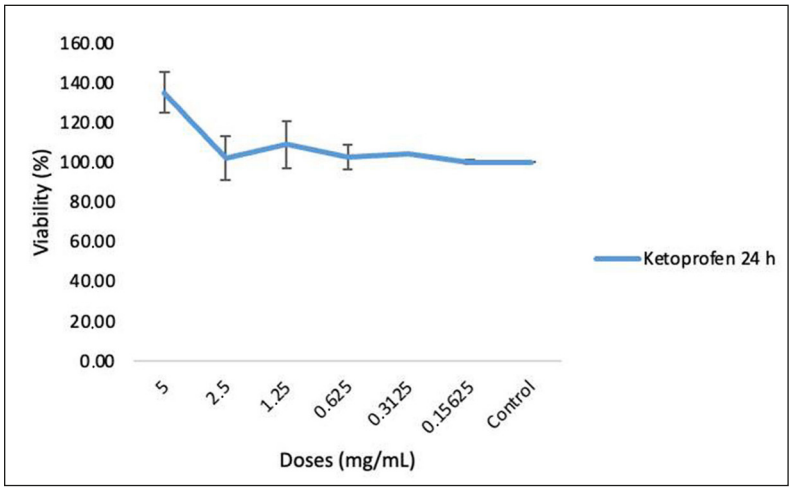

Figure 1. Graph indicating the viability of nasal epithelial cells following 24-hour exposure to ketoprofen.

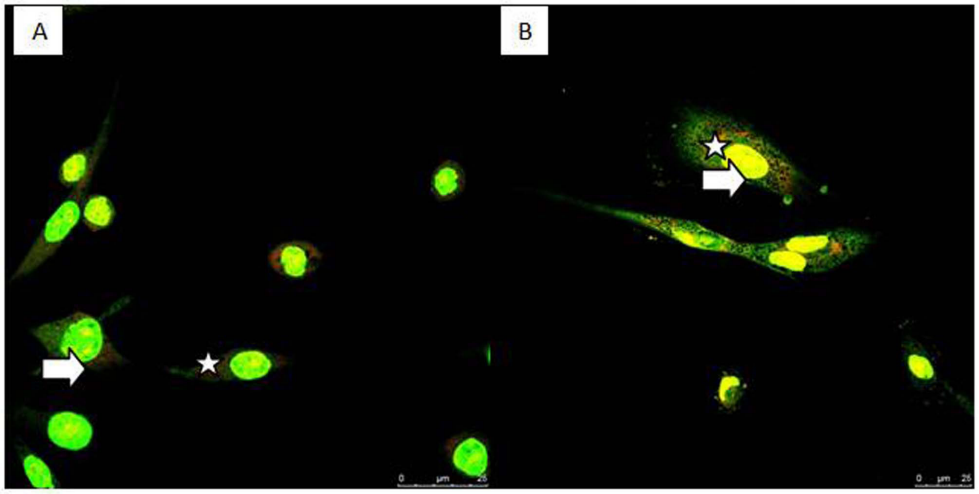

Figure 2. Images obtained during confocal microscopic examination of cell-cultures epithelial cells from the nasal interior. **A**, Untreated (control) epithelial cells. **B**, Epithelial cells exposed to ketoprofen. Arrows indicate nucleus, whereas asterisks indicate the cytoskeleton. Magnification: 40X.

Results Obtained from the Scratch Assay

A light microscopic examination was performed on the epithelial cells with the induced scratch injury. This assessed the size of the injury before and after exposure to ketoprofen. By the time the cells had been exposed for 24 hours to ketoprofen, they had proliferated to the extent that the open area had been completely covered by confluent epithelial cells. Figure 3A shows the appearances at the start and Figure 3B shows those at the end of the 24-hour period. These appearances indicate that ketoprofen does not affect cellular proliferation by epithelial cells when the exposure time is 24 hours (see Figures 4A and 4B).

Discussion

There is considerable debate about how effective NSAIDs are when used topically for pain relief. In certain regions, notably most countries in Western Europe, it has long been possible to obtain topical NSAID preparations, even as over-the-counter products. There is extensive advertising for such products, and they are widely used, with few reservations about their efficacy or lack thereof. However, in other regions, the consensus has held that their efficacy is primarily due to the rubbing action used during application and is therefore a placebo action. Indeed, in certain countries, notably the USA, the use of such topi-

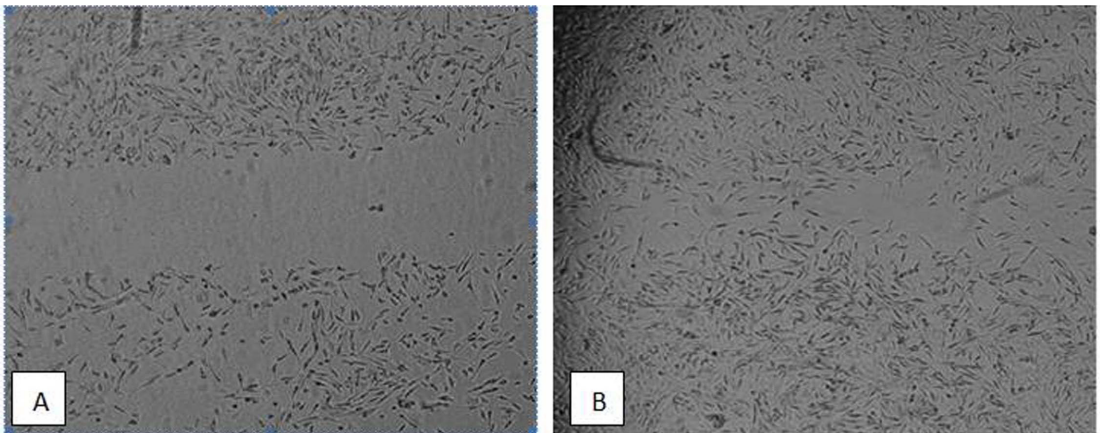

Figure 3. Images showing initial appearances of nasal epithelial cells after induced scratch trauma. **A**, shows how the control epithelial cells appeared, whilst **B**, shows the cells exposed to ketoprofen. Magnification: 40X.

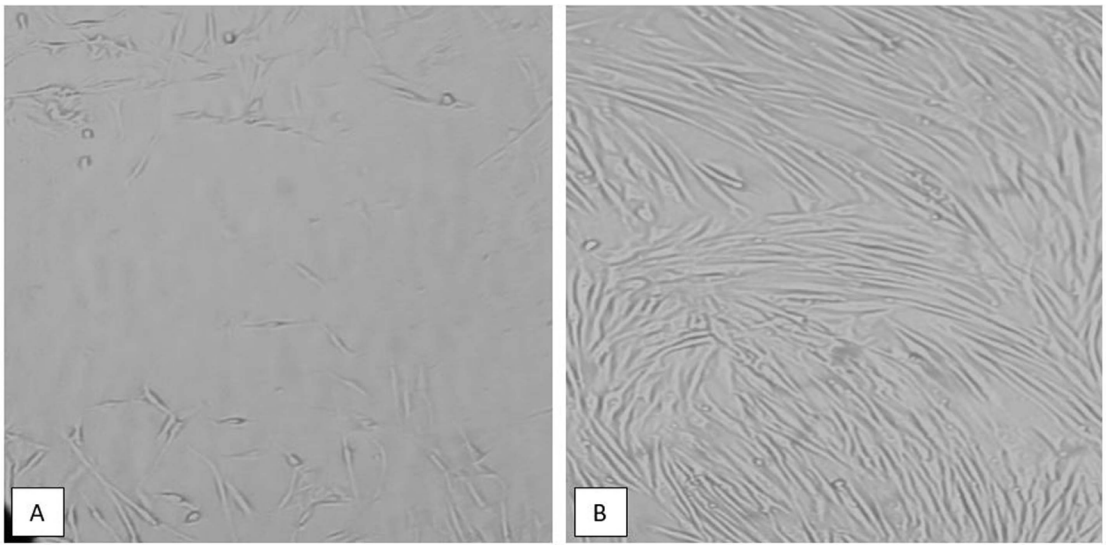

Figure 4. Images showing proliferation of nasal epithelial cells 24 hours after induced scratch trauma. **A**, shows how the control epithelial cells appeared, whilst **B**, shows the cells exposed to ketoprofen. Magnification: 40X.

cal agents was very rare, at least prior to around the year 2015. In England, by contrast, about 5.2 million topical NSAID preparations were prescribed in 2013[12].

The drug delivery method for topical agents has also been the subject of research. One approach involves the use of nanovesicles to deliver painkillers not subject to special legal restrictions. Thus, ketoprofen, butorphanol, and tramadol have all been incorporated into nanovesicular delivery systems (NVS), which can be used in the nasal interior. A study involving ketoprofen[13] delivered in this way noted that ten minutes after application in the nose, the C_{max} was three times higher than that expected when the agent was given by mouth. It was noted that administration of ketoprofen intranasally by NVS led to swift and superior pain relief. This painkilling effect was superior to that obtained with ketoprofen delivered by a conventional topical technique or by mouth. The authors recommend that administering specific analgesic agents *via* NSV into the nose may lead to superior pain control in severe cases and notes that it is less invasive than current techniques[13].

Ketoprofen is an NSAID that has systemic effects when administered orally[14]. It has proven efficacy in treating the pain associated with malignancy in patients within the hospital, is well tolerated, and is similar in benefit to that obtained by providing aspirin and codeine together[15]. In such patients, however, especially at a late stage in malignancy, it may be challenging to administer drugs by mouth, since the symptomatic burden increases and they are physically weakened. Thus, alternative routes of administration are called for. Moselli et al[16] looked at benefits of long-term subcutaneous administration of ketoprofen in combination with morphine to patients with malignancy-associated pain. The authors report that this technique is a practical, low risk and efficacious way to provide analgesia in such situations. If ketoprofen can be delivered effectively *via* the nose, this would provide a swift, non-invasive way to provide analgesia to patients with malignancy-associated pain.

The objective of the present study is to evaluate the toxic potential of ketoprofen when used topically, by observing its effect on nasal epithelial cells, to which it was directly applied. Our results show that ketoprofen when applied for up to 24 hours, does not affect how viable epithelial cells are. There was no loss of cells observed during the exposure period. This finding was confirmed by both the MTT assay and confocal microscopy. The latter technique was able to demonstrate that both the control and treated nasal epithelial cells retained a compact morphological appearance with a clear fusiform cellular boundary and a distinct nuclear outline. Thus, the exposure to ketoprofen did not cause cytopathological changes and this indicates that the drug is not toxic to primary nasal epithelial cells in culture.

A conventional light microscopic examination was undertaken on the plates where the scratch

injury had been induced. This revealed that the area opened up by the injury had been recovered by confluent epithelial cells within 24 hours. Since this occurred in both the control wells and the wells where ketoprofen was added, it is clear that the drug does not have an effect on cellular proliferation.

Patients suffering from acute rhinosinusitis (ARS), whether of viral or bacterial cause, experience nasal symptoms (blocked nose and nasal discharge) in addition to systemic symptoms, e.g., pyrexia and lassitude. Treatment calls for the relief of these symptoms. In appropriate cases, the authors recommend the use of over the counter (OTC) painkillers and antipyretic agents, irrigating the nasal interior with saline, and use of a topical intranasal steroid spray[17]. To relieve pain and reduce pyrexia, the use of OTC medications, namely NSAIDs and paracetamol, can be suggested[18,19].

For topical application directly to areas of trauma, a ketoprofen-containing patch has now been developed, which utilizes innovative technology to ensure drug delivery. It has been found that the ketoprofen patch results in a plasma concentration of the drug that exceeds that seen when ketoprofen gel is used. However, ketoprofen 100 mg p.o. results in a circulating plasma level at least ten times higher than that of the ketoprofen patch. The patch ensures that ketoprofen is continuously delivered for the 24 hours of its application, and thus guarantees the drug is present in the injured area at all times. In this way, the technology ensures high levels of the drug in the area where it exerts beneficial effects but sufficiently low circulating levels to prevent the occurrence of adverse events associated with high plasma concentrations of NSAIDs[1].

Superior clinical efficacy to placebo has been demonstrated for topical preparations of diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin, although not for benzydamine. To achieve a clinically successful outcome, the numbers needed to treat (NNTs) in trials of three topical agents were less than 4. Two trials[20,21] involving a topical preparation of diclofenac (Emulgel®) used the criterion that pain intensity reduces by a half to define success. With the exception of Flector®, plasters with integrated diclofenac resulted in an NNT of 3.2 (CI 2.6-4.2) in a high-quality trial. An NNT of <4 is considered a good result. The evidence for topical ketoprofen is less robust (moderate quality) from an evidential point of view due to the unclear outcome measures chosen by some studies, and dates back to the 1980s, however, the NNT was still only 2.5 (CI 2.0-3.4)[20].

High-quality trial evidence concerning NSAIDs used topically indicates that the rate of skin-related side effects does not significantly differ between preparations containing an active agent and those containing a placebo, nor do the rates of treatment discontinuation. Indeed, whilst placebo did occasionally cause mild irritation to the skin, in few cases this led to stopping the treatment. High-quality evidence indicates that systemic side effects rarely occurred and were at the same level for active agents and placebo. In two individuals administered diclofenac in plaster or gel form, there were serious adverse events recorded, but these were felt to be unrelated to the use of diclofenac[20]. The localized side effects involved skin irritation at the site of application, which caused erythema and/or pruritus. In the majority of such occurrences, the effect was mild and of brief duration[20].

One trial compared nimesulide 200 mg b.d. with ketoprofen 100 mg b.d., both of which were administered by suppository. The participants in this randomized trial featuring double blinding were all individuals who underwent major otorhinolaryngological surgical procedures. Forty-five individuals were operated on for malignancy. Either drug produced a significant reduction in the severity of pain from baseline, and the results were similar (p=0.0001). For participants treated with nimesulide, swelling and hyperemia decreased significantly on day 2, the same effect is seen on day 3 in participants treated with ketoprofen. Virtually the entire group of participants reported complete pain relief by day 5[21]. Governali and Casalini[22] undertook a trial comparing ketoprofen administered as a cream with a gel preparation[17]. Some 93% of those using cream reported benefits (14 out of 15 participants), whereas, with gel, the rate of response fell to 27% (4 out of 15 individuals).

To date, there have been no studies reported in the literature which specifically addressed the use of ketoprofen within the nasal cavity nor investigated possible toxic effects on the nasal epithelium. The present study shows that, for up to 24 hours, the viability of nasal epithelial cells is unaffected by the application of ketoprofen. The absence of cytopathological changes indicates that toxicity does not occur to epithelial cells in culture. In the scratch injury assay, the epithelial cells had completely re-covered the area within 24 hours. Ketoprofen does not, therefore, alter

the proliferative activity of epithelial cells. These findings mean that ketoprofen can be recommended as a topical agent to use in rhinosinusitis (acute or chronic) for analgesia. There are no concerns about local toxic effects.

Conclusions

Ketoprofen, when applied topically for 24 hours to nasal epithelial cells in cell culture, does not cause any alterations in cellular appearance which would suggest impairment of the ability to proliferate or indicate a cytotoxic effect. Extrapolating from these results, it appears acceptable to use ketoprofen topically within the nose in cases of rhinosinusitis (acute or chronic) or nasal pain, since there is minimal risk of local toxic injury.

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

Ethics Approval
This is a cell-culture study. Therefore, the Ethics Committee is not required.

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.

Authors' Contributions
Mustafa Altıntaş: 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, submission.
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.
Cemal Cıngı: Planning, designing, literature survey, performing the study, interpretation of the results, active intellectual support, English editing.

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