The Effects of Topical Intranasal Mometasone Furoate on Nasal Septal Tissues: An Experimental Study

Topikal İntranazal Mometasone Furoatın Nazal Septal Dokular Üzerine Etkileri: Deneysel Çalışma

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ABSTRACT

Objective: This study analyzed the effects of topical mometasone furoate, which is a synthetic glucocorticoid, on rabbit nasal septal tissues in relation to the mode of administration.
Material and Methods: The study was carried out on 35 New Zealand mature male rabbits. The animals in the study were divided into subgroups: the control group in which nothing was administered, the groups in which mometasone furoate or ringer lactate were applied directly to the nasal septum, to the lateral nasal wall and to the nasal passage between nasal septum and lateral nasal wall. After three months, 5 μm thick sections were taken from all animals' nasal septums and the sections were evaluated histopathologically in terms of mucosal ulceration, cartilage damage, goblet cell loss, mucopericchondrium and cartilage thickness, fibrosis, cilia loss, mucosal thickness, submucosal vascularity and the severity of inflammatory cell infiltration.
Results: There was a statistically significant difference between the control group and the group in which mometasone furoate was applied to the nasal septum ($p< 0.05$). However, in all mometasone furoate applied groups, goblet cell and cilia loss were observed. Seventy five percent of the rabbits with severe cilia loss were from the group in which mometasone furoate was applied directly to the nasal septum.
Conclusion: The results indicate that cilia loss, goblet cell loss and submucosal vascularity occurred depending on the mode of administration of mometasone furoate, and were seen particularly in the group in which mometasone furoate was applied directly to the nasal septum.

Keywords
Rabbit; mometasone furoate; nasal septum; cilia loss

ÖZET

Amaç: Çalışmamızda sentetik bir glukokortikoid olan topikal mometazon furoatın kullanım şekline bağlı olarak tavşan nazal septal dokularında oluşturduğu etkiler incelendi.
Gereç ve Yöntemler: Çalışma 35 Yeni Zellanda türü erişkin erkek tavşan üzerinde yapıldı. Çalışmadaki hayvanlar hiçbir ilaç uygulanmayan kontro grubu, direkt nazal septuma mometazon furoat ve ringer laktat uygulanan grup, lateral nazal duvara mometazon furoat ve ringer laktat uygulanan grup ve nazal septum ile lateral nazal duvar arasından nazal pasaja mometazon furoat ve ringer laktat uygulanan grup olmak üzere alt gruplara ayrıldı. Üç ay sonunda tüm gruplardaki tavşanların nazal septumlarından 5 μm kalınlığında kesitler alındı ve histopatolojik olarak mukozal ülserasyon, kartilaj hasarı, goblet hücre kaybı, mukoperikondrium ve kartilaj kalınlığı, fibrozis, silya kaybı, mukozal kalınlık submukozal damarlanma, inflamatuvar hücre infiltrasyonunun şiddeti yönünden değerlendirildi.
Bulgular: Kontrol grubu ile septuma mometazon furoat uygulanan grup arasında istatistiksel olarak anlamlı farklılık saptandı ($p< 0.05$). Ancak mometazon furoat uyguladığımız grupların tümünde goblet hücre kaybı ve silya kaybı olduğu görüldü. Şiddetli silya kaybı olan tavşanların %75'ini ise direkt olarak septuma mometazon furoat uygulanan grup oluşturuyordu.
Sonuç: Bulgular mometazon furoat kullanımına bağlı oluşan silya kaybı, goblet hücre kaybı ve submukozal damarlanma artışının özellikle mometazon furoatın direkt nazal septuma uygulanan grupta olduğunu ortaya koymaktadır.

Anahtar Sözcükler
Tavşan; mometazon furoat; nazal septum; silya kaybı

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INTRODUCTION

Corticosteroids (CS) are used intravenously, orally, as an inhaler, intranasally and dermatologically. Intranasal topical CSs are rapidly metabolized, they have a high effectiveness and low systemic bioavailability. They were first used in 1973 for perennial allergic rhinitis and were found to be as effective as systemic CSs.[1] Topical CSs were shown to be effective in allergic rhinitis and they were shown to inhibit the early and late phases of response to the allergen.[2] Subsequently, the second generation steroid compounds were introduced. These include mometasone furoate (MF), budesonide (BUD), beclomethasone dipropionate (BDP), fluticasone propionate (FP) and triamcinolone acetonide (TAA).

Apart from allergic rhinitis, the indications of topical CSc include non-allergic rhinitis, chronic rhinosinusitis, rhinitis medicamentosa and nasal polyps.[3-6]

Topical steroids are widely used to control inflammation in rhinitis and sinusitis. The clinical effects of topical steroids can be associated with the prevention of accumulation of inflammatory cells in the respiratory tract, selective inhibition of local cytokine production, inhibition of mediator secretion and rehabilitation of nasal mucosa structure.[7]

Many people use topical CSs continuously for months and years. Although rare, it may cause local irritations in Kiesselbach's plexus of the nasal septum as well as drying, crusting, hemorrhage and septal perforation. These adverse effects can be reduced with a more careful application.[8]

The aim of this study was to analyze the effects of topical mometasone furoate, which is a synthetic glucocorticoid on rabbit nasal septal tissues in terms of dosage and administration.

MATERIAL AND METHODS

The study was carried out on 35 New Zealand mature male rabbits with body weights of 2500-3500g (average 3000g). The subjects were supplied by the Faculty of Medicine Experimental Research Center, Fırat University (FUDAM). Prior consent for the study was obtained from the Ethics Committee of Fırat University Faculty of Medicine. The rabbits were randomly divided into four groups. The animals in the study group were further divided into subgroups. The subgroups were as follows: The group in which MF or Ringer Lactate (RL) were applied directly to the nasal septum; the group in which MF or RL were applied to the lateral nasal wall; and the group in which MF and RL were applied to the nasal passage between the nasal septum and lateral nasal wall. The groups formed according to application type were organized as follows. Applications continued for a period of three months:

Group 1 (Control group, n= 5): No topical MF and RL was applied

Group 2 (n= 10):

- Group 2a (n=5): 5 µg/kg/day MF was applied directly to the nasal septum in both nostrils once a day, using a special applicator.
- Group 2b (n= 5): 5 µg/kg/day RL was applied directly to the nasal septum in both nostrils once a day, using a special applicator.

Group 3 (n= 10):

- Group 3a (n= 5): 5 µg/kg/day MF was applied to the lateral nasal wall to the nostrils once a day, using a special applicator.
- Group 3b (n= 5): 5 µg/kg/day RL was applied once a day to the lateral nasal wall in both nostrils, using a special applicator.

Group 4 (n= 10):

- Group 4a (n= 5): 5 µg/kg/day MF was applied once a day to the nasal passage between the nasal septum and lateral nasal wall in both nostrils, using a special applicator.
- Group 4b (n= 5): 5 µg/kg/day RL was applied once a day to the nasal passage between the nasal septum and lateral nasal wall in both nostrils, using a special applicator.

The rabbits in the groups were administered drugs once a day by using a special applicator fitted on a spray pump. At the end of the 3-month period, the rabbits in all groups were sacrificed using ketamine hydrochloride (Ketalar, Eczacıbaşı Medicine, Turkey), in accordance with National Research Council, guidelines from the Institute for Laboratory Animals Rights. The nasal septums of the rabbits were totally removed using the lateral rhinotomy technique.

After removing cartilaginous nasal septum of each animal, specimens were prepared from a similar septal region. The cross sections were stained with hematoxylin -eosin and Masson-trichrome. All specimens were evaluated by the same pathologist, using a light microscope (Olympus, BX51, Japan), and the following parameters were evaluated:

1. Mucosal ulceration
2. Cartilage damage
3. Goblet cell loss
4. Mucoperichondrium and cartilage thickness
5. Fibrosis
6. Cilia loss
7. Mucosal thickness
8. Submucosal vascularity
9. Severity of inflammatory cell infiltration

Mucosa, mucoperichondrium and cartilage thicknesses were evaluated by measuring a X100 objective micrometer. Other parameters were evaluated semi-quantitatively with the following scoring system: no change (0), mild change (1), moderate change (2), significant change (3).

Data were uploaded to the SPSS program and Kruskal-Wallis analysis of variance was used to compare all groups in terms of the analyzed parameters. Mann-Whitney U test was used to compare paired groups. $P< 0.05$ was considered as statistically significant.

RESULTS

Changes in septal tissues after 3 months nasal MF and RL application were analyzed histopathology and the following findings were obtained.

Following 3-month MF or RL application, there was no histopathological difference between the basal group and other groups in terms of mild, moderate, severe mucosal ulceration, cartilage damage, mucoperichondrium and cartilage thickness, fibrosis, mucosal thickness and the severity of inflammatory cell infiltration ($p> 0.05$) (Figure 1).

Cilia Loss

At the end of 3 months, two animals in group 2a (40%) were found to have mild cilia loss, and three animals (60%) were found to have severe cilia loss (Figure 2). It was found that one animal (20%) in group 2b had no cilia loss, while four animals had a mild degree of cilia loss. Cilia loss in the other groups was summarized in Table 1.

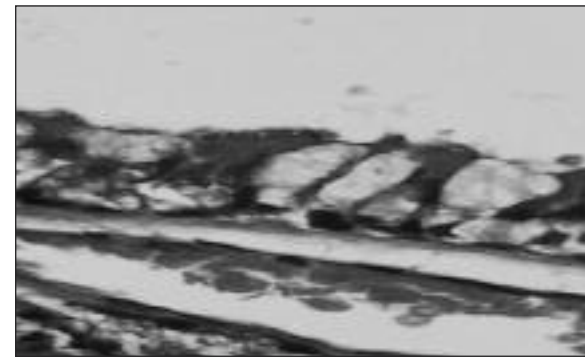

Figure 1. The histopathological appearance of control group's septal tissues (HE, x100).

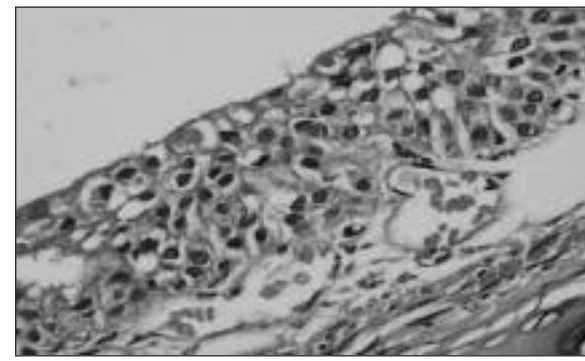

Figure 2. Following 3-month MF application; severe cilia loss (HE, x100).

When the control group was compared with the other groups in terms of cilia loss, a statistically significant difference was found between the control group and groups 2a, 2b, 3a, 4a ($p< 0.05$).

When the groups were compared with each other in terms of cilia loss, it was found that there was a statistically significant difference between group 2a and group 2b; and group 3a and group 3b ($p< 0.05$); however, there was no significant difference between group 4a and group 4b ($p> 0.05$).

Submucosal Vascularity

Submucosal vascularity changes of the each group after 3 months were summarized in Table 2. When the control group was compared to other groups in terms of submucosal vascularity, it was found that there was a statistically significant difference only between the basal group and group 2a ($p< 0.05$) (Figure 3).

Table 1. Cilia loss results after 3 months.

Groups	Cilia loss								
	n	No change	%	Mild change	%	Moderate change	%	Significant change	%
1	5	4	80	1	20	(-)	(-)	(-)	(-)
2a	5	(-)	(-)	2	40	(-)	(-)	3	60
2b	5	1	20	4	80	(-)	(-)	(-)	(-)
3a	5	1	20	1	20	2	40	1	20
3b	5	5	100	(-)	(-)	(-)	(-)	(-)	(-)
4a	5	2	40	2	40	1	20	(-)	(-)
4b	5	3	60	2	40	(-)	(-)	(-)	(-)
Total	**35**	**16**	**45.7**	**12**	**34.3**	**3**	**8.6**	**4**	**11.4**

Table 2. Submucosal vascularity results after 3 months.

Groups	Submucosal vascularity								
	n	No change	%	Mild change	%	Moderate change	%	Significant change	%
1	5	2	40	3	60	(-)	(-)	(-)	(-)
2a	5	(-)	(-)	(-)	(-)	4	80	1	20
2b	5	(-)	(-)	3	60	2	40	(-)	(-)
3a	5	1	20	2	40	1	20	1	20
3b	5	2	40	3	60	(-)	(-)	(-)	(-)
4a	5	3	60	1	20	1	20	(-)	(-)
4b	5	1	20	3	60	1	20	(-)	(-)
Total	**35**	**9**	**25.7**	**15**	**42.9**	**9**	**25.7**	**2**	**5.7**

When the groups were compared with each other in terms of submucosal vascularity, it was seen that there was no statistically significant difference between group 2a and group 2b; group 3a and group 3b; group 4a and group 4b ($p > 0.05$).

Mucosa, Mucoperichondrium and Cartilage Thickness

Following 3-month MF and RL applications, each of the subjects in the groups were statistically evaluated in terms of nasal mucosa, mucoperichondrium and cartilage thickness using X100 magnification. There was no statistical difference between the groups ($p>0.05$) (Tables 3 and 4).

Goblet Cell Loss

Goblet cell loss changes of each group after 3 months were summarized in Table 5.

There was a statistically significant difference between the control group and groups 2a, 2b, 3a and 4a in terms of goblet cell loss ($p< 0.05$) (Figure 4).

When the groups were compared with each other in terms of goblet cell loss, there was no statistically significant difference between group 2a and group 2b; group 3a and group 3b; group 4a and group 4b ($p> 0.05$).

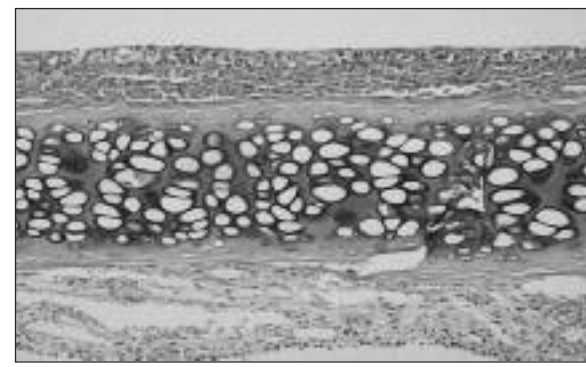

Figure 3. Following 3-month MF application; increase in submucosal vascularity (H.E. X40).

DISCUSSION

Corticosteroids (CSs) are used in various forms as intravenous, oral, inhaler, intranasal and dermatological preparations. Due to adverse effects of systemic use of CSs in allergic rhinitis, topical CSs were started to be used. Topical application was used to restrict the region affected by the CSs, to reduce total dose and to limit

Table 3. Mean values of mucosal thickness (μm).

		Mucosal thickness		
Groups	**n**	**Minimum**	**Maximum**	**Mean**
1	5	76.00	176.00	141.0 ± 38.7
2a	5	83.00	123.00	99.8 ± 15.2
2b	5	73.00	110.00	97.6 ± 14.6
3a	5	43.00	173.00	99.0 ± 50.9
3b	5	66.00	116.00	92.0 ± 20.7
4a	5	83.00	143.00	117.2 ± 22.6
4b	5	76.00	103.00	93.6 ± 10.5
Total	**35**	**43.00**	**176.00**	**105.7 ± 30.5**

Table 4. Mean values of mucoperichondrium and cartilage thickness (μm).

		Mucoperichondrium and cartilage thickness		
Groups	**n**	**Minimum**	**Maximum**	**Mean**
1	5	176.00	460.00	279.8 ± 111.6
2a	5	123.00	246.00	197.8 ± 53.8
2b	5	140.00	250.00	204.6 ± 44.6
3a	5	196.00	310.00	243.6 ± 44.7
3b	5	213.00	260.00	234.4 ± 20.8
4a	5	186.00	213.00	202.4 ± 13.2
4b	5	153.00	260.00	211.0 ± 40.4
Total	**35**	**123.00**	**460.00**	**224.8 ± 57.6**

Table 5. Goblet cell loss results after 3 months.

Groups		**Goblet cell loss**							
	n	**No change**	**%**	**Mild change**	**%**	**Moderate change**	**%**	**Significant change**	**%**
1	5	4	80	1	20	(-)	(-)	(-)	(-)
2a	5	(-)	(-)	2	40	2	40	1	20
2b	5	1	20	2	40	2	40	(-)	(-)
3a	5	1	20	2	40	2	40	(-)	(-)
3b	5	3	60	2	40	(-)	(-)	(-)	(-)
4a	5	1	20	2	40	2	40	(-)	(-)
4b	5	3	60	1	20	1	20	(-)	(-)
Total	**35**	**13**	**37.1**	**12**	**34.3**	**9**	**25.7**	**1**	**2.9**

possible adverse effects.[9] CSs are more effective than oral antihistamines, effective on all nasal symptoms and beneficial in allergic asthma treatment. In addition, CSs have a positive effect on conjunctivitis symptoms that generally accompany allergic rhinitis.[9] The disadvantages of topical CSs, on the other hand, include potential adverse effects such as the time required to show their effect, the necessity of regular use, mucosal irritation and hemorrhage.[9,10] An ideal topical CS should generally have a high effectiveness against all nasal symptoms, its effect should start earlier, one dose a day should be enough and should not cause local or systemic adverse effects.[9]

Topical corticosteroids are anti-inflammatory agents that show a multi-factorial effect by bonding to specific cytoplasmic glucocorticoid receptors such as eosinophils, mast cells, basophils, T lymphocytes and antigen-presenting cells, and by reducing the number, lifespan and activity of these cells. Irrespective of the etiology, cytokines have the most important role in the onset of inflammation. These mediators can activate inflammatory cells and perpetuate their survival.[11] Topical CSs inhibit antigen-presenting cells, reduce cytokine (IL-3, IL-4, IL-5, IL-13) and chemokine secretion, cell infiltration in nasal mucosa and mediator secretion from these cells, and show a strong anti-inflammatory effectiveness.[7,10]

While appropriate use of topical CSs can lead to highly favorable results, inappropriate use of these agents might sometimes cause irritation-induced burning or stinging sensation, crusting and hemorrhage in nasal mucosa.[8] Since nasal respiratory epithelium is very important for the mucociliary defense system, changes in epithelial cover should be avoided. The use

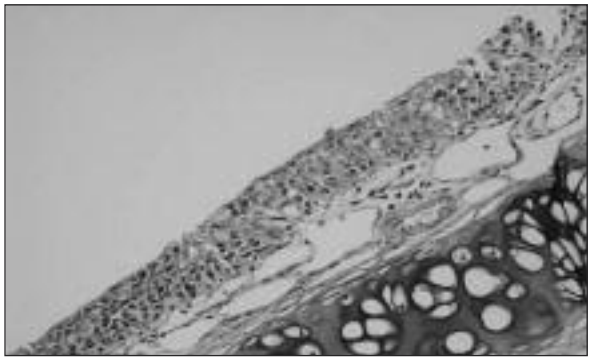

Figure 4. Following 3-month MF application; severe goblet cell loss (HE, x40).

of aqueous forms, separate lateral nasal wall away from the septum and avoiding direct trauma of the applicator on the nasal septum prevents these effects.[11] In addition, the application of spray forms on the nasal wall away from the septum increases the anti-inflammatory effect on nasal mucosa.[12]

Recent studies indicated that, in some patients, nasal septum perforation and mucosal ulceration can be associated with the use of topical nasal steroids.[8,12] It was reported that although rare, septal perforation can occur after the use of intranasal steroids, although the mechanism is not clear.[13] Cervin et al.[13] analyzed 32 patients with septum perforation and found that 11 were using intranasal steroids. Their study emphasized that intranasal topical steroids may play a role in the etiology of septal perforation, and it was indicated that the risk of septal perforation was higher during the first 12 months and in females.

In the present study, no septal perforation was observed during a 3-month period in MF applied groups. In addition, the present study statistically evaluated the mucosa, mucoperichondrium and cartilage thickness of each rabbit in all groups by X100 magnification after 3 months MF application. No statistically significant difference was found between the groups ($p> 0.05$).

The majority of the formulas applied to the nasal mucosa via a spray pump contain substances to prevent bacterial reproduction. Benzalkonium chloride, which is among these preventive substances, is an antimicrobial quaternary ammonium used in various nasal solutions such as topical CSs, for preventing bacterial contamination. However, there are still different views about the effects of benzalkonium chloride on nasal mucosa. The most discussed toxic effect of benzalkonium chloride is the effect on mucociliary clearance.[14, 15] In vitro evidence indicates that benzalkonium chloride inhibits ciliary function and potentially affects mucociliary clearance. This adverse effect might result in local irritation and recurring infections in the long term.[16,17]

Steinsvag et al.[18] used BDP, FP, FLU, and BUD on a study group and physiological serum in the control group. The researchers found that cilia structure was completely destroyed in the tissue surfaces on which benzalkonium chloride containing preparations were used. The study found that there were occasional ruptures and detachments in cells and nuclear membranes in stroma, where cilia and basal corpuscles were rarely observed. The researchers suggested that these morphological changes were caused by benzalkonium chloride.

In the present study, the MF preparation used contained benzalkonium chloride. It was observed that MF caused cilia loss in all study groups. When the control group and the study groups were compared in terms of cilia loss, a statistically significant difference was found ($p< 0.05$). seventy five percent of the rabbits with severe cilia loss were from the group in which MF was applied directly on the septum.

Minshall et al.[7] evaluated the effect of MF on the histopathologic properties of nasal mucosa in 69 allergic rhinitis patients. They found no atrophic change or local adverse effects in nasal mucosa. They did not observe any difference in epithelium thickness, goblet cell distribution and density, morphological properties of the veins and glands in lamina propria and in basal membrane integrity. However, it was found that expansion of inflammatory cells, particularly eosinophils and mast cells, was reduced.

Similar to the findings of Minshall et al.,[7] no change was observed in epithelial thickness and basal membrane integrity in the present study. However, when the control group was compared to other groups in terms of submucosal vascularity, it was found that there was a significant difference only between the control group and the group in which MF was applied to the septum ($p< 0.05$). When the control group was compared to other groups in terms of submucosal vascularity no statistical difference was found ($p> 0.05$).

Bende and Mark[8] analyzed a control group consisting of patients using no topical steroids and a study group consisting of 10 patients using budesonid and 11 patients using beclomethasone. In biopsies, the researchers histopathologically evaluated inflammation findings, basal membrane thickness, fibrosis and squamous epithelium metaplasia, extending from Kiesselbach's

plexus to the perichondrium. However they found no significant difference between the study and control groups in terms of the mentioned parameters.

Consistent with the findings of Bende and Mark, the present experimental study found no statistically significant difference between the groups in terms of inflammatory cell infiltration and fibrosis ($p > 0.05$).

CONCLUSION

This study analyzed the effects of topical mometasone furoate, which is a synthetic glucocorticoid, on rabbit nasal septal tissues in relation to administration type. When the control group was compared with other groups in terms of mucosal ulceration, cartilage damage, mucoperichondrium and cartilage thickness, fibrosis, mucosal thickness and the severity of inflammatory cells, no histopathologic difference was found. However, the results indicated that cilia loss, goblet cell loss and increase of submucosal vascularity were highest in the group in which topical CSs were applied to the septum. Therefore patients should be specifically warned and informed about the appropriate dosage and administration of the drug. Patients should be informed that topical CS aqueous spray applicators should be used by the left hand to the right nostril and by the right hand to the left nostril, in such a way as to apply the spray towards the lateral nasal wall, away from the nasal septum. Furthermore, to avoid erosion, which is a local adverse effect caused by contact of the applicator with the septum, patients should be instructed how to use the applicator.

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