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Effects of Nasal Topical Corticosteroids on Nasal Secretory Immunoglobulin A in Allergic Rhinitis Patients

ABSTRACT

Background: Recently, there has been interest in the immunoregulatory and preventative effects of immunoglobulin A (IgA) in individuals with allergic rhinitis (AR). Topical corticosteroids are one of the main treatment options for AR. The purpose of this study was to investigate the secretory IgA (sIgA) levels in the nasal fluid of healthy people and people who had received intranasal beclomethasone dipropionate (BD) and triamcinolone acetonide (TA) treatment.

Methods: There were 29 newly diagnosed AR patients and 29 healthy control individuals in the study. Group 1 (n = 13) treated with BD and group 2 (n = 16) treated with TA were included. Blood samples were collected to measure IgE levels. Nasal secretions were collected through nasal packing and evaluated by enzyme-linked immunosorbent assay.

Results: The mean nasal fluid sIgA level was 573.7 ± 192.2 µg/mL in group 1, 564.8 ± 270.8 µg/mL in group 2, and 559.7 ± 241.9 µg/mL in the control group. The difference in baseline sIgA levels between groups was not statistically significant. After 1 month of nasal steroid treatment, sIgA levels in groups 1 and 2 increased significantly.

Conclusion: It was found that adult AR patients who were being treated with 2 types of intranasal corticosteroids (BD and TA) have significantly higher levels of sIgA in their nasal secretions.

Keywords: Rhinitis, allergic, adult, immunoglobulin A, beclomethasone, triamcinolone

Deniz Kocaoz[1]
Emre Ocak[2]
Muhammed Sefa Uyar[2]
Emre Mirici[1]
Sevinc Bayrak[1]
Elif Dagli[1]
Aydin Acar[1]

[1]Department of Otolaryngology-Head and Neck Surgery, Health Sciences University, Kecioren Research and Training Hospital, Ankara, Turkey
[2]Department of Otolaryngology-Head and Neck Surgery, Ankara University School of Medicine, Ankara, Turkey

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Corresponding author:
Muhammed Sefa Uyar
E-mail: *drsefauyar@gmail.com*
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INTRODUCTION

Allergic rhinitis (AR) is one of the most common diseases in the adult population. It is the fifth most common chronic disease seen in the adult population in the USA.[1] Many treatment options are available for AR patients. But recently published guidelines stand out for the use of nasal topical corticosteroids.[1,2]

Corticosteroids have an immunosuppressive effect by affecting many stages of the immune system.[3] Because of the frequent side effects associated with systemic use, topical applications for the final organ to minimize these side effects are available for many diseases.[4,5] There are plenty of intranasal forms of corticosteroids in use that have almost the same clinical efficacy.[6] High concentrations on the target organ with minimal local side effects, possible use in pregnancy, short onset of action, and cost-effectiveness are some important advantages for the intranasal route of administration of corticosteroids.[7]

Antigens' main route is the penetration of mucosal surfaces. Secretory immunoglobulin (sIgA) is the first line of defense to intercept this penetration by binding soluble or particulate antigens and making these antigens excluded by the immune system. Bacterial agglutination, endotoxin, and virus neutralization by sIgA inhibit pathogens' epithelial adherence and invasion.[8,9] The role of secretory immunoglobulins in different forms of allergies has been studied recently. Patients with IgA deficiency tend to be more prone to allergic diseases.[10] Insufficient sIgA-dependent function at the intestinal surface barrier decreases an individual's threshold for food allergy.[11] Compared to healthy individuals, asthmatic patients' bronchoalveolar lavage fluid had lower sIgA levels.[12]

Despite all the growing data investigating the relationship between sIgA and allergy, there is conflicting and insufficient knowledge about the effects of nasal topical corticosteroids on nasal sIgA levels in AR patients. For this reason, we aimed to investigate the levels of total sIgA in adult AR patients and healthy subjects' nasal secretions and the change of total nasal sIgA levels after treatment with 2 different nasal topical corticosteroids.

MATERIAL AND METHODS

Patients

This prospective case–control study was conducted between November 2016 and June 2017 in the Otorhinolaryngology Head and Neck Surgery Department of Kecioren Research and Training Hospital. The research was carried out in compliance with the Good Clinical Practice guidelines outlined in the Declaration of Helsinki and received approval from the Kecioren Research and Training Hospital Health Sciences University Kecioren Research and Training Hospital Ethics Commission (date: 28.12.2016 decision number: 1276). Written informed consent was received from each participant.

A total of 58 patients were enrolled in the study. Twenty-nine newly diagnosed adult AR patients were included in the study group whereas 29 healthy adult subjects formed the control group. Inclusion criteria were: (1) age 18 years or older and (2) AR diagnosis confirmed according to criteria defined in the AR and its Impact on Asthma (ARIA) Guidelines.[2] Exclusion criteria were: (1) use of any medications, including other intranasal, inhaled or oral corticosteroids, montelukast, other anti-inflammatory drugs, antihistamines, vitamins, and food supplements; (2) acute/chronic infections or inflammatory diseases; (3) previous history of adverse effects seen after the use of triamsinolon acetate (TA) and beclomethasone dipropionate (BD); (4) non-compliance with nasal topical corticosteroid therapy; (5) any intranasal pathology like nasal septal deviation or synechiae which prevent the distribution of drug to nasal cavities; (6) previous history of nasal surgery; and (7) smoking.

Patients who presented with allergic symptoms to the outpatient clinic and who had not received prior treatment for AR underwent a complete otorhinolaryngological examination. Skin prick tests were performed on the patients who were thought to have AR in the light of ARIA guideline.[2] The diagnosis of AR was confirmed in all patients with clinical history (at least 1-year history of symptoms of sneezing, watery rhinorrhea, and nasal blockage), physical examination, positive skin prick testing, and positive serum total IgE.

According to the criteria and test results, 29 patients were diagnosed with AR and included in the study group. After the sIgA samples were collected from the nasal secretions of the patients and the blood was taken for serum total IgE levels; they were randomly divided into 2 groups. The randomization was made according to the computer-generated lists. Nasal topical sprays containing BD (Rinoclenil®, CHIESI Farmaceutici SpA, Parma, Italy) were given to group 1 (n=13) and TA (Nasacort®; Sanofi-Aventis, Paris, France) to group 2 (n=16). At the control examination after 1 month of continuous treatment, a complete otorhinolaryngological examination and sample collection for sIgA measurement from nasal secretions were repeated for all patients.

Non-allergic 29 healthy adults with negative skin prick tests were included in the control group according to the criteria. All individuals in the control group underwent a complete otorhinolaryngological examination, and samples for sIgA measurement were taken from their nasal secretions.

Obtaining and Evaluation of Nasal Secretions

The secretions of the nasal cavity were collected by a sterile polyvinyl acetate nasal packing (Steridea, Sassari, Italy) placed between the inferior concha and the nasal septum in a single nasal cavity of the patients. The nasal packing was divided into 2 equal parts to produce 4 cm long pieces (Figure 1). The nasal packing was kept for 30 minutes in the inferior meatus and then sent to the laboratory in sterile urine containers after being removed from the nasal passage with sterile forceps. The nasal packings were separated into 2 parts again and placed in the 2 mL Eppendorf tube (Eppendorf AG, Hamburg, Germany).

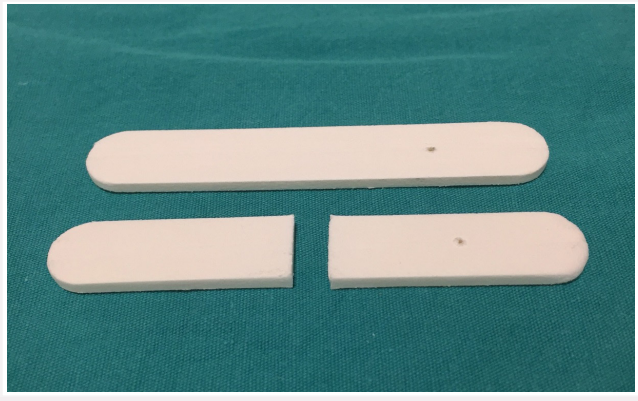

Figure 1. Preparation of nasal packing.

MAIN POINTS

- Topical corticosteroids are one of the main treatment options for AR.
- Corticosteroids have an immunosuppressive effect by affecting many stages of the immune system. Because of the frequent side effects associated with systemic use, topical applications for the final organ to minimize these side effects are available for many diseases.
- Despite all the growing data investigating the relationship between sIgA and allergy, there is conflicting and insufficient knowledge about the effects of nasal topical corticosteroids on nasal sIgA levels in AR patients.
- The outcomes of this study highlight the effect of certain topical corticosteroids on one of the major immunologic defense mechanisms in the upper airways.
- The levels of sIgA in nasal fluids are significantly increased in AR patients treated with 2 different intranasal corticosteroids (BD and TA).

Figure 2. Preparation for centrifugation.

Totally, 10-15 holes were opened up to the inferior end of this tube with a 21-gauge needle. Then, these Eppendorf tubes were placed in 2 larger outer tubes for proper insertion in the centrifuge device (Figure 2). They were centrifuged at 4000 rpm for 6 minutes. The collected fluids were frozen at -80°C for analysis.

Measurement of the Levels of Secretory Immunoglobulin A

The sIgA levels were assessed using the enzyme-linked immunosorbent assay (ELISA) technique. The sIgA ELISA kit (Immundiagnostic AG, Bensheim, Germany) was used for the quantitative determination of sIgA in nasal secretions. The resulting color was measured at a wavelength of 450 nm (Spectrophotometer, µQuant, BioTek Instruments Inc., Winooski, Vermont, USA). The obtained optical density values were calculated by the optical density–absorbance graph obtained from the standards. Results are reported in µg/mL.

Skin Prick Test

Prick-Test Diagnostic (ALK, Madrid, Spain) was used as a skin-prick test for allergens and lancets. A total of 13 different allergens including trees, weeds, cereals, mites, and animals were used. The skin prick test was accepted as positive when the wheals of ≥3 mm in diameter measured 15 minutes after the performance of the test and the control site was completely negative in accordance with the Global Allergy and Asthma European Network's recommendations.[13]

Statistical Analysis

Statistical Package for Social Sciences (SPSS®) for Windows 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used to analyze the research data. Mean ± standard deviation (minimum–maximum), distribution of frequencies, and percentage were presented for the descriptive statistics. Categorical variables were tested using Pearson's chi-square and Fisher''s exact tests. Visual (histograms and probability graphs) and analytical (Shapiro–Wilk test) methods were used to assess the suitability of variables to a normal distribution. The Wilcoxon signed-rank test was used to compare statistical variables between 2 dependent groups, while the Mann–Whitney *U*-test was used to compare between 2o independent groups. For the variables with a normal distribution, Student's *t*-test was used between 2 independent groups. Paired sample *t*-test was used between 2 dependent groups and one-way analysis of variance (ANOVA) between 3 independent groups. Statistical significance was accepted as $P < .05$.

RESULTS

A total of 58 subjects were examined. Of these, 13 (22.4%) were treated with BD and 16 (27.6%) with TA, while 29 (50.0%) were healthy individuals without treatment as the control group. The demographics of all participants are summarized in Table 1. Control groups, BD (group 1), and TA (group 2) were accepted as the 3 groups that were evaluated in this study. There was no statistically significant difference in age and gender between the 3 groups ($P > .05$).

The mean baseline sIgA values of patients who were treated with BD, TA, and the control group were 573.7 ± 192.2 (minimum: 210.0; maximum: 881.5) µg/mL, 564.8 ± 270.8 (minimum: 182.3; maximum: 929.5) µg/mL, and 559.7 ± 241.9 (minimum: 190.8; maximum: 989.3) µg/mL, respectively. There was no statistically significant

Table 1. The Demographics of all Participants

	Group 1 (n = 13)	Group 2 (n = 16)	Control (n = 29)	F/χ^2	*P*
Age (year), mean ± SD (minimum–maximum)	36.5 ± 13.6 (18-59)	32.5 ± 10.0 (18-50)	32.0 ± 9.3 (18-50)	0.870	.424*
Sex, n (%)					
Male	2 (15.4)	6 (37.5)	8 (27.6)	1.756	.416**
Female	11 (84.6)	10 (62.5)	21 (72.4)		

SD, standard deviation.
*One-way analysis of variance.
**Chi-square test.

Table 2. Distribution of Basal Secretory Immunoglobulin A Values Between Study Groups

	Group 1 (n = 13)	Group 2 (n = 16)	Control (n = 29)	*F*	*P*
Basal sIgA (µg/mL)					
Mean ± SD	573.7 ± 192.2	564.8 ± 270.8	559.7 ± 241.9	0.015	.985*
(minimum–maximum)	(210.0-881.5)	(182.3-929.5)	(190.8-989.3)		

*One-way analysis of variance.

Table 3. Distribution of Skin Prick Test Results Among Patients

	Group 1 (n = 13)	Group 2 (n = 16)	χ^2	*P*
Skin prick test results, n (%)				
Tree pollen	9 (69.2)	7 (43.8)	1.883	.170*
Weed pollen	13 (100)	10 (62.5)	–	**.020****
Cereals pollen	6 (46.2)	0	–	**.004****
Mites	4 (30.8)	9 (56.3)	1.883	.170*
Animals	8 (61.5)	7 (43.8)	0.909	.340*

Values in bold indicate statistical significance.
*Chi-square test.
**Fisher's exact test.

difference between the study groups in terms of basal sIgA value ($F = 0.015$, $P = .985$; one-way ANOVA) (Table 2).

Among the patients in the study, skin prick test results were significantly different in terms of weed pollen and cereal pollen ($P = .020$; .004, respectively). The percentage of those who have grass and cereal pollen allergies in group 1 was significantly higher than that in group 2 (Table 3).

On the other hand, there was no statistically significant difference between the skin prick test results of group 1 and group 2 patients in terms of tree pollen, mites, and animal allergies ($P > .05$) (Table 3).

There was no statistically significant difference between group 1 and group 2 patients in terms of serum IgE, basal, and first-month sIgA values ($P > .05$) (Table 4).

When the changes in sIgA values of patients in groups 1 and 2 were taken into consideration, the mean sIgA values of both groups were significantly increased ($P = .042$ for group 1; $P < .001$ for group 2) when compared to the baseline value (Table 4).

The amount of increase was calculated by subtracting the baseline value of sIgA from the first month sIgA values. No statistical significance was found in the levels of sIgA increase between group 1 and group 2 ($t = 0.959$, $P = .346$; Student's *t*-test) (Table 5).

DISCUSSION

Secretory immunoglobulin A has a key role in the struggle against allergens and pathological microorganisms in the mucosal immunological function of the upper airways.[14] Competent sIgA secretion in saliva was found to be related to fewer allergic symptoms in children.[15] On the other hand, insufficient sIgA secretion is associated with allergic disorders.[10] Cortesina et al[17] showed that nasal fluid sIgA was significantly lower in allergic patients than in healthy individuals.[16] In a recent study with pediatric AR patients, similar results were concluded. Hsin et al[18] studied the nasal secretory immunoglobulin (sIgA, total IgA, IgG1, IgG2, IgG3, and IgG4) levels of AR and chronic rhinosinusitis patients and they reported no significant change in sIgA levels. In our study, we found no decrease in nasal fluid sIgA levels in study groups (groups 1 and 2) when compared with the control group.

It has been shown that sIgA secretion has a circadian rhythm.[19,20] This secretion is affected by different factors and conditions.[21-23] Contradictory results in the literature about sIgA levels between patients and control groups may be related to these different factors.

Table 4. Distribution of Immunoglobulin E, Basal, and 1-Month Secretory Immunoglobulin A Values in Patients

	Group 1 (n = 13)	Group 2 (n = 16)		
	Mean ± SD (Minimum–Maximum)	Mean ± SD (Minimum–Maximum)	*z/t*	*P*
IgE (IU/mL)	167.2 ± 192.5 (14.8-677.0)	163.1 ± 213.0 (9.5-828.0)	−0.219	.826*
Basal sIgA (µg/mL)	573.7 ± 192.2 (210.0-881.5)	564.8 ± 270.8 (182.3-929.5)	−0.100	.921**
First month sIgA (µg/mL)	758.8 ± 307.2 (175.9-1410.1)	839.1 ± 242.3 (437.4-1217.4)	0.788	.438**
	$t = -2.270$ $P*** = .042$	$t = -5.318$ $P*** < .001$		

*Mann–Whitney *U*-test.
**Student's *t*-test.
***Paired samples *t*-test.

Table 5. Distribution of the Increase in Secretory Immunoglobulin A in the First Month According to the Baseline Among Study Groups

	Group 1 (n = 13)	Group 2 (n = 16)	*t*	*P*
Increase in sIgA (IU/mL)				
Mean ± SD (min-max)	185.2 ± 294.1 (−314.7-941.5)	274.4 ± 206.4 (−180.1-544.6)	0.959	.346*

*Student's *t*-test.

Immunoglobulin E is an important immunoglobulin in AR pathophysiology. It has inflammatory effects on the nasal mucosa.[24] Its serum levels in IgE-mediated allergies may increase up to 10 times the normal values. At the same time, the decrease in IgE levels in these patients correlates with clinical improvement.[25] In our study, all study group patients have elevated serum total IgE levels, but there is no significant difference in terms of serum total IgE levels when compared within study groups.

One limitation of this study was the absence of symptom scores. Although assessment of symptom scores would have increased the clinical value of the study, many publications investigating the use of topical corticosteroids indicated high quality of life scores and acceptable medical adherence.[6,26]

The effect of topical corticosteroids on nasal sIgA levels is controversial. In a study with pediatric AR patients, Dilek et al[17] reported that the mean nasal fluid sIgA level is significantly lower in patients treated with topical mometasone furoate. Another study by Aksoy et al[27] investigated the effect of topical mometasone furoate on nasal fluid sIgA levels in rats. A statistically significant increase is reported in nasal sIgA levels after the use of nasal topical mometasone furoate. Kita et al[28] analyzed the effect of topical budesonide on nasal fluid sIgA levels in adult AR patients and reported that nasal sIgA levels increased during both budesonide and placebo use, but there was no statistically significant difference between the 2 groups, and budesonide did not affect nasal sIgA levels.

In our study, baseline sIgA levels were similar between the study groups and the control group. After a treatment period of 1 month, nasal sIgA levels showed a statistically significant increase in groups 1 and 2.

The results of similar studies are controversial, as indicated before. This conflict may be due to the age and demographic differences of the study groups. New prospective studies with more comprehensive and homogenized groups with large numbers are needed to clarify this contradiction.

The outcomes of this study highlight the effect of certain topical corticosteroids on one of the major immunologic defense mechanisms in the upper airways. Prospective studies with different molecules will pave the way for more comprehensive knowledge on this issue.

Ethics Committee Approval: This study was approved by the Ethics Committee of Health Sciences University (approval no: 1276; date: 28.12.2016).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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