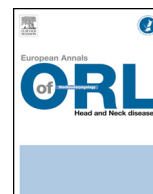




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Original article

Comparison of the effects of nasal steroids and montelukast on olfactory functions in patients with allergic rhinitis[☆]

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ARTICLE INFO

Keywords:

Montelukast
Mometasone furoate
Allergic rhinitis
Sniffin' Sticks test

ABSTRACT

Objective: Olfactory dysfunction is one of the comorbidities associated with allergic rhinitis (AR) and AR is one of the common causes of olfactory problems. We aimed to evaluate by the Sniffin' Sticks test the effects on olfactory functions of nasal steroids and leukotriene antagonists used for allergic rhinitis.

Methods: Thirty patients with seasonal rhinitis were included in this study. Patients were randomly divided into three groups of 10 patients; group 1 received montelukast sodium and mometasone furoate (MF) therapy, group 2 received only montelukast, and group 3 only MF. Patients' olfactory functions were determined using the Sniffin' Sticks olfactory test before and after a month treatment.

Results: Threshold, discrimination, identification, and the sum of threshold, discrimination, and identification (TDI) values were not significantly different among the groups before treatment. For Group 1 and Group 3 patients, there were statistically significant differences in threshold, discrimination, identification, and TDI values before and after treatment ($P < 0.05$) (Wilcoxon signed ranks analysis). For Group 2 patients, the before and after treatment values of threshold, discrimination, identification, and TDI showed no significant difference ($P > 0.05$).

Conclusion: According to the findings of our study, MF is superior to montelukast in improving olfactory function. Although montelukast has been shown to be effective against AR symptoms, its effect on olfactory function was not demonstrated in this study.

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1. Introduction

Olfactory dysfunction is one of the comorbidities associated with allergic rhinitis (AR) [1–3], and AR is one of the common causes of olfactory problems [4]. Hyposmia is often neglected by patients and overlooked by physicians. Clinical studies have stated that 60% of patients with AR have olfactory abnormality even if they have no nasal polyps or septum deviation [5]. Olfactory disorders affect the quality of life and job performance of AR patients. Olfactory dysfunction in AR may be explained by obstruction of airflow to the olfactory cleft due to nasal mucosal swelling from inflammation [6–8]. However, it has been shown that the degree of airflow obstruction in AR is not directly linked with olfactory dysfunction [9–12]. Also, it has been shown that inflammatory mediators play an important role in olfactory dysfunction in AR patients [13,14].

Nasal steroids, antihistamines and immunotherapy are usually used for treatment of AR symptoms. It is recommended that montelukast is used, if AR is together with asthma in the patients. Although olfactory effects of nasal steroids, antihistamines, and immunotherapy have been demonstrated [15–17], leukotriene antagonists have not been thoroughly investigated to date. The Sniffin' Sticks olfactory test has been used to assess olfactory function in many studies related to AR. In this study, we aimed to evaluate by the Sniffin' Sticks test the effects on olfactory functions of nasal steroids and leukotriene antagonists used for AR.

2. Materials and methods

This was a prospective, randomized, parallel-group (three groups) study. The study was conducted in the Department of ENT Clinic of Gaziosmanpaşa-Taksim Training and Research Hospital. The Gaziosmanpaşa-Taksim Training and Research Hospital Ethical Board approved the protocol and informed consent forms. Thirty patients (ages 18 to 65) with a clinical history of seasonal AR for at least 1 year were included in this study. This study was conducted during the pollinic season.

[☆] This manuscript was presented at the 37th Turkish National Congress of Otorhinolaryngology Head and Neck Surgery 2015, Antalya, Turkey.

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2.1. Assessment of allergic rhinitis

AR was diagnosed using ARIA criteria: a positive skin test to grass and/or tree pollens in patients with clinical history of seasonal AR for at least 1 year [18]. Patients who had received drug treatment (corticosteroids, antihistamines, antidepressants, antihypertensive, etc) or immunotherapy before the study were excluded. Patients with asthma, deviated nasal septum, history of nasal operation, turbinate hypertrophy, nasal polyposis or chronic nasal disorders (Chronic sinusitis with or without polyps, fungal sinusitis, nasal masses, chronic nasal infections, etc), pregnancy, smoking or upper airway infections were also excluded. After a thorough ear, nose, and throat examination and nasal endoscopy, patients were randomly divided into three groups of 10 patients; group 1 received montelukast sodium (10 mg once daily) and mometasone furoate (MF) (200 µg/day) therapy, group 2 received only montelukast, and group 3 only MF.

2.2. Olfactory evaluation

Patients' olfactory functions were determined using the Sniffin' Sticks olfactory test. The test was performed (with both nostrils simultaneously) to obtain the TDI score (the sum of threshold, discrimination, and identification) for each patient.

Sniffin' Sticks is a validated test that examines olfactory threshold (n-butanol), discrimination, and identification with good test-retest reliability. Odorants were presented in commercially available felt-tip pens (Sniffin' Sticks', Burghart GmbH, Wedel, Germany) [19]. For odor presentation, the pen cap was removed by the experimenter for approximately 3 s and the tip of the pen was placed approximately 1–2 cm in front of the nostrils. For odor thresholds, three pens were presented in a randomized order, one containing n-butanol in different dilutions (with an increasing dilution ratio of 1:2), and two containing the solvent. When the patient identified the pen with the odorant twice, the next lower concentration was presented, until the patient could not identify the pen with the odorant (scale of 1 to 16). This miss triggered a reversal of the staircase, so the pen with a one-step higher concentration was administered until the pen with the odorant was identified correctly. The test finished when seven reversals of the staircase had been found. The threshold is the mean of the last four reversals of the staircase. For identification, 16 common odorants were presented. To prevent olfactory desensitization, an interval of at least 30 s was maintained between exposures. Patients were asked to identify each odor on an odorant form by selecting four odorants, and correct answers were recorded. Odor discrimination was made using 16 triplets of odorant pens in which the odor in one pen differs from that of the other two.

The results of the TDI tests were considered separately and summarized in an overall TDI score. Results from olfactory testing can be analyzed separately from each other.

After 4 weeks of drug therapy, the Sniffin' Sticks test was applied again to assess olfactory function. Pre- and post-therapy results were compared among the three groups.

2.3. Statistical analysis

Statistical analysis of the data was performed using the SPSS 15.0 for Windows software. The Mann-Whitney U test was used for comparisons between the two groups, and the Kruskal-Wallis H test (Mann-Whitney U with post hoc Bonferroni correction) was used for comparisons between more than two groups. The Wilcoxon signed-ranks test was used for comparisons of data obtained before and after treatment. In post hoc tests $P < 0.10$ and in other analyses $P < 0.05$ were considered to indicate statistical significance.

Table 1

The ratio of age and sex in three groups.

Group	Sex	n	%	Age		P^a
				Mean $\pm$ SD	Min.–Max.	
Group 1	Male	3	30	25.33 $\pm$ 7.57	20–34	0.425
	Female	7	70	30.71 $\pm$ 7.91	18–41	
	Total	10	32.3	29.1 $\pm$ 7.82	18–41	
Group 2	Male	3	30	29.67 $\pm$ 11.5	18–41	0.909
	Female	7	70	27.86 $\pm$ 9.82	19–42	
	Total	10	32.3	28.4 $\pm$ 9.72	18–42	
Group 3	Male	1	9.1	60	60–60	0.096
	Female	10	90.9	32.5 $\pm$ 6.19	23–43	
	Total	11	35.5	35 $\pm$ 10.16	23–60	
Total	Male	7	22.6	32.14 $\pm$ 14.79	18–60	0.849
	Female	24	77.4	30.63 $\pm$ 7.77	18–43	
	Total	31	100	30.97 $\pm$ 9.51	18–60	

^a Mann-Whitney U analysis.

3. Results

There was no statistically significant difference in the age and sex of the patients among the three groups (Table 1) ($P = 0.849 > 0.05$). Threshold, discrimination, identification, and TDI values were not significantly different among the groups before treatment. For Group 1 and Group 3 patients, there were statistically significant differences in threshold, discrimination, identification, and TDI values before and after treatment ($P < 0.05$) (Wilcoxon signed ranks analysis) (Tables 2 and 3). For Group 2 patients, the before and after treatment values of threshold, discrimination, identification, and TDI showed no significant differences (Table 3) ($P > 0.05$).

4. Discussion

The most widely drugs used in AR treatment are nasal steroids, antihistamines, and the montelukast group of drugs [18,20,21]. These drugs have been shown to reduce inflammation in the allergic nasal mucosa and to increase the patient's quality of life. One of the important symptoms in patients with AR is hyposmia or olfactory dysfunction [12]. When we reviewed the effect of various treatments on olfactory dysfunction in patients with AR, we found reports in the literature indicating that intranasal steroids, antihistamines, and immunotherapy increase olfactory function [12,15].

We determined olfactory function using the Sniffin' Sticks test. The Sniffin' Sticks test is a convenient and reliable method for determining olfactory dysfunction. The Sniffin' Sticks test has been suggested and widely accepted as a standard test. It has been used to quantitatively evaluate olfactory functions by measuring TDI, identification, and threshold values. Although the test results may be affected by various factors such as age, sex, environmental factors, smoking, and the person who conducts the test, use of this test has become popular. We used the Sniffin' Sticks test for this study because it provides a quantitative assessment of olfactory function in patients with AR.

In patients with AR, there are studies on the use of MF to treat olfactory dysfunction [12,16]. MF has been shown to reduce inflammation and to improve the smell function by increasing nasal airflow and decreasing inflammation of the olfactory region [12]. However, the mechanism for these effects is unknown. Although obstruction of airflow to the olfactory cleft secondary to nasal mucosal swelling from inflammation may contribute to loss of olfaction in AR, the normal cyclic variations in the nasal cycle are not associated with olfactory loss [7,8,12]. Additionally, treatment that improves symptoms of obstruction and reduces nasal edema can fail to improve hyposmia. Studies have suggested that intranasal corticosteroids may be effective in improving olfactory loss in AR.

Table 2

The distribution of the average value according to the group of patients before and after treatment.

	Group 1	Group 2	Group 3	P^a	Comparisons between two groups ^b		
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		Groups 1–2	Groups 1–3	Groups 2–3
T (before)	6.73 $\pm$ 2.33	7.88 $\pm$ 2.19	6.05 $\pm$ 1.92	0.147	–	–	–
T (after)	9.52 $\pm$ 2.05	7.98 $\pm$ 2.55	7.73 $\pm$ 1.62	0.116	–	–	–
I (before)	11.91 $\pm$ 0.7	12.2 $\pm$ 0.42	12.09 $\pm$ 0.54	0.515	–	–	–
I (after)	13.09 $\pm$ 0.7	12.4 $\pm$ 0.52	12.73 $\pm$ 0.47	0.048	0.025	–	–
D (before)	12.64 $\pm$ 0.67	12.5 $\pm$ 0.53	12.45 $\pm$ 0.69	0.518	–	–	–
D (after)	13.73 $\pm$ 0.65	12.5 $\pm$ 0.53	13.45 $\pm$ 0.52	0.001	0.001	–	0.002
TID (before)	31.27 $\pm$ 3.24	32.58 $\pm$ 2.74	30.59 $\pm$ 2.57	0.221	–	–	–
TID (after)	36.36 $\pm$ 3.07	32.88 $\pm$ 3.33	33.91 $\pm$ 2.16	0.022	0.026	0.019	–

^a Kruskal-Wallis H analysis.^b Mann-Whitney U test with Bonferroni's adjustment.**Table 3**

The averages of value threshold (T), discrimination (D), identification (I) and TDI value of groups before and after treatment.

	Group 1		Group 2		Group 3	
	Mean $\pm$ SD	P^a	Mean $\pm$ SD	P^a	Mean $\pm$ SD	P^a
Before T	6.73 $\pm$ 2.33	0.003	7.88 $\pm$ 2.19	0.607	6.05 $\pm$ 1.92	0.026
After T	9.52 $\pm$ 2.05		7.98 $\pm$ 2.55		7.73 $\pm$ 1.62	
Before I	11.91 $\pm$ 0.7	0.002	12.2 $\pm$ 0.42	0.157	12.09 $\pm$ 0.54	0.020
After I	13.09 $\pm$ 0.7		12.4 $\pm$ 0.52		12.73 $\pm$ 0.47	
Before D	12.64 $\pm$ 0.67	0.001	12.5 $\pm$ 0.53	1.000	12.45 $\pm$ 0.69	0.018
After D	13.73 $\pm$ 0.65		12.5 $\pm$ 0.53		13.45 $\pm$ 0.52	
Before TDI	31.27 $\pm$ 3.24	0.003	32.58 $\pm$ 2.74	0.352	30.59 $\pm$ 2.57	0.010
After TDI	36.36 $\pm$ 3.07		32.88 $\pm$ 3.33		33.91 $\pm$ 2.16	

^a Wilcoxon Signed Ranks analysis.

Meltzer et al. examined that the effects on olfaction of intranasal MF in AR and they have shown that MF could be a reduction of edema resulting in restored airflow/odorant access to the olfactory cleft or a resolution of inflammation in the olfactory mucosa itself [16]. Also glucocorticoid receptor mRNA is expressed in mammalian olfactory epithelium, suggesting a potential direct role for steroids in this tissue [22].

It has been shown that the inflammatory process caused olfactory dysfunction in patients with AR [14]. Intranasal steroids may improve olfactory function by decreasing inflammation, especially eosinophil cells in the nasal region [5,12]. Thus, MF provides significant improvements in olfactory function directly (by reducing inflammation in the olfactory region) and indirectly (by increasing nasal airflow), and relieves symptoms of AR by preventing inflammation [5,12]. As expected, after 1 month of treatment there was a significant improvement in olfactory function in the MF group in this study. It has been demonstrated that intranasal steroids improve olfactory function quantitatively and qualitatively [5,16]. Also, due to direct contact with the olfactory region (such as spraying toward the olfactory region), MF may be more effective in improving olfaction [23].

Cysteinyl leukotrienes (CysLTs) are involved in the pathophysiology of AR and have receptors in the nasal mucosa [24]. Various mediators such as histamine and CysLTs have important roles in AR [13]. Cysteinyl-leukotriene receptor antagonists such as montelukast are also potent drugs for AR [25]. Leukotriene receptors are present in nasal tissue and the lower airway, and therefore these drugs may also affect the nasal and olfactory mucosa [25].

A number of studies have reported that CysLT antagonists have positive results in AR [25]. However, clinical studies related to the effects of leukotriene antagonists on olfactory functions are lacking. There are only a few animal studies on the effects of CysLTs antagonists in the olfactory region. Rubuni et al. [26] showed that CysLTs antagonism did not affect olfactory system histology and had a negligible effect on olfactory function in mice. We also examined quantitatively the effect of montelukast and MF on olfactory

function. In the montelukast group, values of TDI, threshold, and identification were not significantly improved. Montelukast was expected to improve olfactory function because of its effects on the pathophysiology of AR. However, it was demonstrated that CysLTs antagonists were ineffective in the olfactory region [26]. We believe that montelukast did not significantly improve TDI, identification, and threshold for this reason.

We deduced that the absence of a significant improvement in olfactory function in the montelukast group and the presence of a significant improvement in the MF and montelukast group were related to the effect of MF.

The efficiency and reliability of montelukast in patients with AR has been demonstrated [25]. Nevertheless, it has not yet been demonstrated that montelukast significantly improves olfactory functions. Our results were in agreement with those of other studies [26]. It is necessary to conduct histopathological studies on the olfactory region or bulb related to CysLTs or montelukast to elucidate the precise effect of montelukast on olfactory function.

Quantitative analysis of olfactory functions can be performed with the Sniffin' Sticks test. Olfactory functions were evaluated with the Sniffin' Sticks test in this study. We did not question how the patients perceived their own ability to smell before and after treatment. Although the ability to smell was not significantly improved in the montelukast group, identification, and threshold were slightly improved. Therefore, it cannot be claimed that montelukast has no effect on olfactory function. The number of patients in this study was small. Studies with larger numbers of patients would be valuable.

Finally, according to the findings of our study, MF is superior to montelukast in improving olfactory function. Although montelukast has been shown to be effective against AR symptoms, its effect on olfactory function was not demonstrated in this study.

Disclosure of interest

The authors declare that they have no competing interest.

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