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Investigation of the effects of intranasal botulinum toxin type a and ipratropium bromide nasal spray on nasal hypersecretion in idiopathic rhinitis without eosinophilia*

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SUMMARY

Idiopathic rhinitis without eosinophilia is a group of frequently observed diseases, the aetiopathogenesis of which is not yet well known. One of the most disturbing symptoms for patients within this disease group is nasal hypersecretion. Although many different treatments have been tried for hypersecretion, nasal topical drugs form the basis of any such therapy today.

Ipratropium bromide (IB) is a drug of first choice in nasal hypersecretion therapy. It displays a parasympatholytic effect in topical use and antagonizes acetylcholine transport in efferent parasympathetic nerves, thus decreasing submucosal gland secretion, which is the cause of hypersecretion. Botulinum toxin type A (BTX-A) is among the alternative treatment choices that is increasingly used in symptomatic treatment of nasal hypersecretion.

Our study was planned with the aim of comparing the effect of these two groups of drugs on nasal hypersecretion. Thirty-eight patients who were diagnosed with idiopathic rhinitis without eosinophilia were included in the study and were divided in 3 different groups: In the first group, a total of 10 units of BTX-A were injected into both nasal cavities. In the second group, 3x2 IB was injected into both nasal cavities for 4 weeks. The third group received intranasal physiologic saline as placebo.

The patients were evaluated in terms of nasal hypersecretion with visual analogue scale prior to the treatment and at weeks 1, 2, 4, 8, and 12 during the follow-up period. Throughout the 8 weeks follow-up period, the patient complaints displayed a 41.2% decrease in the group that received BTX-A and a 61.4% decrease in the group which received IB, while no change was observed in the control group. Both drug groups were well tolerated by the patients, with no serious adverse or systemic effects.

As a result, while IB and BTX-A differ in terms of method of application, they display a similar degree and duration of efficiency in hypersecretion therapy.

Key words: botulinum toxin, ipratropium bromide, idiopathic rhinitis without eosinophilia, secretion, hypersecretion

INTRODUCTION

Rhinitis arises due to inflammation in the nasal mucosa, characterized by occurrence of two or more of the following symptoms: nasal obstruction, nasal discharge, sneezing, and nasal itching, recurrently or for more than one hour [(1)]. It is one of the most frequent groups of diseases in the community. The frequency of rhinitis was reported as 10-40% in epidemiologic studies held in various countries [(1,2)]. When allergy, infection and other causes are excluded as aetiologic factors, the remaining cases are grouped under NARES (non-allergic rhinitis with eosinophilic syndrome) and idiopathic (vasomotor or intrinsic) rhinitis without eosinophilia. Classification and terminology of rhinitis excluding infectious and allergic rhinitis has changed over time, and has become a source of confusion. To be able to talk about specific hyperactivity, the stimulant causing rhinitis has to be known. Otherwise, non-specific hyperactivity is the case. Non-allergic, non-infectious rhinitis forms are generally named as 'intrinsic rhinitis' [(3)]. The prevalence of NARES

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and idiopathic rhinitis without eosinophilia is thought to range between 7 and 21%. Roughly one third of the patients in this group suffered from NARES, and two thirds had idiopathic rhinitis without eosinophilia [4]. Idiopathic rhinitis without eosinophilia is a hyperactive nasal mucosal disease characterized by inflammation, which follows a perennial course, with a sudden initiation and a short duration. Patients present with nasal obstruction and watery nasal or postnasal discharge, while allergy tests are negative and there is no increase in the number of eosinophils in nasal secretions. Personal physiological state, psychological status, and autonomic nervous system balance are thought to modulate the severity of this reaction [5]. NARES is a typical nasal hyperactivity syndrome, which has been known since early nineteen eighties, starting with sneezing crisis and very watery nasal discharge, where nasal obstruction and hyposmia are rapidly added to the clinical picture, and where the number of eosinophils in the nasal secretions increases to reach 20% of the total leukocyte count, with no IgE dependent allergy [2].

Ipratropium bromide (IB) a topical medication that has a cholinergic antagonistic effect, is a first choice drug in the treatment of nasal hypersecretion [6,7]. Used topically, it decreases submucosal gland secretion, which is the cause of hypersecretion, by antagonizing acetylcholine transmission in efferent parasympathetic nerves, as it has a parasympatholytic effect [8,9]. Botulinum toxin type A (BTX-A), which has been used in various areas of medicine in the recent years, is among the treatment choices that are increasingly being used in the symptomatic treatment of nasal hypersecretion [8,10]. BTX-A, which blocks acetylcholine release in neuromuscular joint and cholinergic autonomic nerves by binding peripheral cholinergic terminals, causes flacid paralysis and autonomic symptoms. BTX-A does not kill neurons, but provides a transient and reversible blockage of cholinergic transmission [11].

This study aimed to assess the effects of IB and BTX-A in nasal hypersecretion by comparing them with a placebo control group, in idiopathic rhinitis without eosinophilia patients with primary complaints of nasal and postnasal hypersecretion, with no subjective or objective nasal obstruction\.

MATERIALS AND METHODS

Study Design

This study was planned as a prospective randomized placebo-controlled study to include 40 patients who received a diagnosis of idiopathic rhinitis without eosinophilia in between November 2003 and August 2005. The study was completed with 38 patients (18 male, 20 female), as two patients were excluded from the study due to lack of compliance in their follow up appointments. All patients gave their written informed consent before being included in the study, which was approved by the Ethics Committee. All procedures were performed by two of the authors (T.S, S.Y).

Patients

Patients with previous turbinate surgery, septal deformities, nasal polyps or tumor, nasal radiotherapy, or recurrent sinusitis were excluded. Additional exclusion criteria included glaucoma, prostate hypertrophy, which could be influenced negatively by the anticolinergic therapy, hyperthyroidism and hypothyroidism, pregnancy, serious systemic disease and being on antihypertensive, antidepressive or sedative drugs. Examination included anterior rhinoscopy and nasal endoscopy in all patients. The presence of eosinophilia was assessed in all patients, while multi-puncture skin prick test and radioallergosorbent test (RAST) for specific allergens were performed using a standard screening panel including the local antigens, for allergy evaluation. Patients with positive skin test and RAST were classified as suffering from allergic rhinitis, and were excluded from the study. Nasal cytology was performed, as NARES and idiopathic rhinitis without eosinophilia have similar clinical symptoms, and the patients negative for eosinophils in cytology were classified suffering from idiopathic rhinitis without eosinophilia and included in this study.

Patients who were included in the study consisted of those with a history of idiopathic rhinitis without eosinophilia (patients with persistent rhinitis with nasal and postnasal hypersecretion occurring more than 4 days a week and 3 months a year); having no history of asthma and contact dermatitis; who were negative for eosinophils in skin tests, RAST, and nasal cytology; who did not benefit from the medical therapies they received before; and in whom eosinophilia was less than 3%.

Thirty-eight patients were randomly assigned into three groups (groups A, B, and C). Group A included 15 patients, whereas Group B included 15, and Group C included 10 patients. Two patients included in Group B were excluded from the study, as they did not regularly attend the follow up clinic. The patients were chosen to be put into a particular group simply by drawing lots.

Of the group A patients, 6 were female and 9 were male. The mean age of the patients was 51.53 years (± 22.6 y Standard deviation [SD]). BTX-A (Botox, Allergan Inc., Irvine, CA, USA) was diluted with physiological serum to reach a final concentration of 25 units/ml. A dental injector was used to inject 2,5 units (0,1 ml) of BTX-A in the middle turbinate anterior region under 0° rigid telescope guidance, whereas 2,5 units (0,1 ml) were injected into the inferior turbinate medial region, which made a total of 5 units injected into each nasal cavity (a total of 10 units) of the patients. After the application, the patients were reminded they should not use additional allergic therapies, they were given no antibiotics and nasal pack was not used.

Of the group B patients, 5 were male and 8 were female. The mean age was 44.69 years (± 20.44 y Standard deviation [SD]). IB (Atrovent 0,03%, Boehringer-Ingelheim Inc, France) nasal

spray was applied to both nasal cavities as 3 x 2 times/day for 4 weeks. Following the treatment, the patients were reminded they should not use additional allergic treatments.

Group C was the control group, made up of 4 male and 6 female patients; the mean age of the patients was 42.9 years (± 20.06 y = Standard Deviation [SD]). These patients declared that they had been receiving medical treatment for 12 weeks for their complaints but that these had not diminished. One ml of 0.9 % NaCl was injected into the middle turbinate anterior region, while another 1 ml was injected into the inferior turbinate medial region, with a dental injector, under 0° rigid telescope image. After the application, the patients were reminded they should not use additional allergic therapies; they were given no antibiotics; and nasal pack was not used.

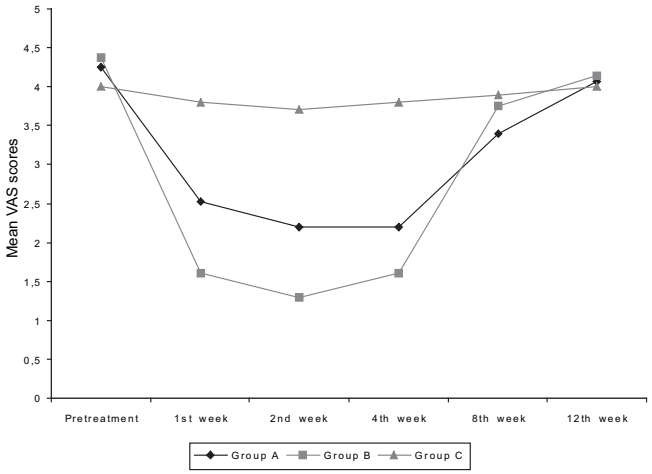

Figure 1. Distribution of the groups according to mean VAS scores.

Table 1. Comparison of group A (BTX-A) and group C (Control) according to VAS.

	Group A		Group C		*p*
	Mean	***SD***	**Mean**	***SD***	
Pretreatment	4,26	*0,70*	4,00	*0,66*	*0,394*
1st week	2,53	*1,35*	3,80	*1,03*	*0,023***
2nd week	2,20	*1,32*	3,70	*1,15*	*0,009***
4th week	2,20	*1,42*	3,80	*0,91*	*0,007***
8th week	3,40	*0,98*	3,90	*0,87*	*0,423*
12th week	4,06	*0,79*	4,00	*0,81*	*0,943*

Kruskal Wallis test ***p < 0,01*

Table 2. Comparison of group B (IB) and group C (Control) according to VAS.

	Group B		Group C		*p*
	Mean	***SD***	**Mean**	***SD***	
Pretreatment	4,38	*0,65*	4,00	*0,66*	*0,382*
1st week	1,61	*1,12*	3,80	*1,03*	*0,001***
2nd week	1,30	*0,75*	3,70	*1,15*	*0,001***
4th week	1,61	*1,12*	3,80	*0,91*	*0,001***
8th week	3,76	*0,92*	3,90	*0,87*	*0,358*
12th week	4,15	*0,68*	4,00	*0,81*	*0,825*

Kruskal Wallis test ***p < 0,01*

Evaluation

Subjective symptoms including severity of nasal and postnasam hypersecretion were measured by a standard 6-cm visual analogue scale (VAS). The patient's assessments of the degree of nasal and postnasal hypersecretion were recorded. A score of 0 represented no secretion,\ and a score of 6 indicated severe nasal and postnasal hypersecretion (0-`none, 1-mild, 2-mild-intermediate, 3-intermediate, 4-intermediate-severe, 5-severe). The evaluations were made prior to the therapy and at 1, 2, 4, 8, and 12 weeks after the therapy, under anterior rhinoscopic examination.

Statistical Analysis

Statistical analysis was performed by a specialized company using the statistical software package SPSS for Windows, version 10.0. One-way ANOVA test, Kruskal-Wallis test, Mann-Whitney U test, Wilcoxon-Signed Rank Test, Chi-square Test were used, and a p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Thirty-eight patients (20 female, 18 male) were enrolled in the present study. None of the patients had a history of allergy and acute infection. The results of skin-prick test, radioallergosorbent test for specific allergens, eosinophilia and eosinophil in nasal cytology were all negative for all the patients. All patients had a diagnosis of idiopathic rhinitis without eosinophilia. None of the three groups displayed any uncontrolled hemorrhage, pain, crusts, and infection following the treatment, as an early or late complication of the treatment.

Subjective Change of Symptoms

A significant decrease in secretion was observed in Group A, upon comparison of the mean secretion rates before and after the therapy, as 31.6% (z: 3.086; p= 0.002) in the first week; 41.2% (z: 3.097; p = 0.002) in the second week; and 41.2% (z: 3.082; p = 0.002) in the fourth week. The decrease rate was observed to have regressed to 17.2% (z: 2.598; p = 0.009) in the eighth week, and to 4% (z: 1.732; p = 0.083) in the twelfth week. Maximum effect appeared to be at weeks 2 and 4. Although BTX-A had a prominent effect for 4 weeks, its effect, while continuing in a statistically significant level, decreased at week 8, and ended at week 12 (Table 1 and Figure 1).

A significant decrease in secretion was detected in Group B, upon comparison of the mean secretion rates before and after the therapy, as 55.2% (z: 3.247; p = 0.001) in the first week; 61.4% (z: 3.270; p = 0.001) in the second week; and 55.2% (z: 3.115; p = 0.002) in the fourth week. The decrease rate was observed to have regressed to 12.2% (z: 1.994; p = 0.046) in the

eighth week, and to 4.4% (z: 1.134; p = 0.257) in the twelfth week. IB was detected to have the maximum efficiency at week 2. It was observed that IB, like BTX-A, was quite prominently effective for 4 weeks, and that the effect decreased at week 8, while continuing in a statistically significant level, and ended at week 12 (Table 2 and Figure 1).

In Group C, the decrease in secretion was detected to be 4% at week 1; 6% at week 2; 4% at week 4 and 2% at week 8. The values before the therapy were reached at week 12. No statistically significant difference was observed in this group in comparison of the amount of secretion, between the period before the therapy and at weeks 1, 2, 4, 8, and 12 in the follow-up period ($p > 0.05$) (Figure 1).

DISCUSSION

Submucosal secretion glands in the nose are the main source of nasal secretion [12]. Nasal hypersecretion develops due either to hyperfunction of the parasympathetic nervous system in the nasal or paranasal sinuses, or to the imbalance between the parasympathetic and sympathetic nervous system [13-15]. Jaradeh et al. [16] have reported that the problem regarding autonomic nervous system was due to hypoactive sympathetic system or to the imbalance between the two systems, rather than to the parasympathetic system. Therefore, the effect of sympathetic nervous system on nasal function can be more important than previously known. Parasympathetic effect is negatively influenced by drugs (such as those containing estrogen), some physiological conditions (such as pregnancy, stress, hypothyroidism), and external factors (such as cigarette smoke, industrial chemicals, and cold weather) [17].

Development of hypersecretion in the idiopathic rhinitis without eosinophilia is thought to be due to mucosal edema and to the glandular secretion mechanism with plasma exudation into the interior nasal area [18]. In this disease, patients usually complain from watery nasal discharge or persistent nasal obstruction, usually throughout the year. Many clinicians attribute these complaints to allergy. While headache and sneezing can occur, itching is not a prominent symptom. The symptoms may be triggered by non-specific irritants such as cigarette smell, perfume, changes in temperature, and humidity. It is most of the time not possible to distinguish the picture from allergic rhinitis solely by the symptoms. Physical findings are also very important in distinction. However, erythema, congestion, and pallor of the turbinates, and humid or dry mucosa can also make differential diagnosis difficult [13]. In this group of diseases, in which the symptoms or the physical examination is inadequate by itself in diagnosis, diagnosis is usually made by eliminating other causes, as there are no objective tests to support the diagnosis [19].

In idiopathic rhinitis without eosinophilia, as the patients have many symptoms such as sneezing, rhinorrhea, and nasal congestion, the therapy is applied against the dominant symptom, and there is no perfect therapy [20]. As very few of the hypersecretion therapies are satisfactory, search for novel treatment methods continues. Current therapy is based on topical drugs [20].

The idea that BTX-A can be effective on rhinorrhea was first suggested in the study by Shaari et al. [21] held on 4 dogs, in 1995. Later on, Kim et al. tried BTX-A in their double-blind, placebo-controlled study on 43 patients whom they diagnosed with intrinsic rhinitis in 1998 [8], and found that it effectively decreased rhinorrhea, but had no effect on nasal obstruction and sneezing. Rohrbach and Laskawi [10] applied BTX-A to one patient in their study published in 2001 as a case report, and found that it was effective for both rhinorrhea and nasal congestion and sneezing. Again, Rohrbach et al. in another controlled study held in 2001 on 10 pigs, detected that BTX-A induced apoptosis of the nasal secretion glands in pigs [22]. Later on in 2003, Unal et al. used BTX-A in their randomized, placebo-controlled study on 34 patients with allergic rhinitis and found that it was effective for rhinorrhea, nasal obstruction, sneezing, and itching [23].

Kim et al. have shown that BTX-A effectively decreased rhinorrhea in 43 patients, but did not affect nasal obstruction and sneezing, and suggested that this could be explained by the innervation pattern of the autonomic nervous system [8]. They stated that, as the vascular muscarinic receptor was atropine-resistant, the therapeutic potential of the anticholinergic drugs were in treating hypersecretion, as cholinergic blockage decreased secretion, rather than improving nasal obstruction or sneezing [24].

Ipratropium bromide, which is a topical drug with cholinergic antagonistic effect, is another first choice drug for rhinorrhea. Every dose contains 21 micrograms of ipratropium bromide in a concentration of 0,03%. Ten percent of the active substance passes on to the systemic circulation following intranasal application [25]. The pharmacokinetics of the drug was investigated by Deckers [6] in 1975, and by Rominger [7] in 1979. Borum et al.[26] and Mygind and Borum [27], in their studies where they investigated the clinical efficacy of IB, have shown a significant decrease in rhinorrhea as assessed by subjective symptom scores of the 14 patients included in the study. 0,03% IB nasal spray has been shown to be effective and safe in rhinorrhea with by PNAR in 285 patients who received treatment for 1 year in a study by Grossman et al.[28]. In the study, 0,03% IB nasal spray was used in a 3x2 dosing schedule for the first 6 months, and the treatment continued after 6 months with the lowest dose that could control rhinorrhea, according to the preference of the clinician. The original 3x2 dosing schedule was continued in the majority of the patients. Consequently, the drug was found to be well-tolerated and thus suitable for long term use. In a multi-centered study organized by Kim et

al. [24], 230 children between the ages of 2 to 5 who had rhinitis due to common cold and allergy, 0,06% IB nasal spray was given for 4 days in a 3x1 pattern, and the drug was found to be well-tolerated, without causing any serious systemic anticholinergic side effects. In a controlled, double blind study by Diamond et al. in 955 common cold patients, topical use of IB was shown to decrease glandular secretion [29].
IB has been shown not to affect nasal obstruction and/or sneezing in a number of studies [9,27,30,31], and has been found to be 70% effective on nasal obstruction and sneezing, in long-term use for one year, in another study [32].

Although the efficiency of BTX-A and IB on hypersecretion has been proved in various studies, there are no controlled studies in literature comparing the effects of the two drugs. In this study, we aimed to compare the effects of IB nasal spray and intranasal BTX-A on nasal hypersecretion with placebo control groups, in patients who were diagnosed as idiopathic rhinitis without eosinophilia yet not having subjective symptoms or objective evidence of nasal obstruction, with the most disturbing symptom being rhinorrhea. We needed to decide on the amount and application method of BTX-A before initiating the study, as although the toxic dose of BTX-A is known to be 2500-3000 units [33], there is no absolute consensus on the application method and the suitable dose to be used in the nasal cavity. Kim et al. have compared application of a total of 8 units, each nostril receiving 4 units, with a total of 12 units, each nostril receiving 6 units [8]. They used 8 units in their study, as they detected no significant difference between the effectiveness of the two doses. They used a dilution of twenty units/ml (2 units in 0.1 ml), and performed injection under 0° endoscope, 2 units to the middle of the lower turbinate, and 2 units to the anterior of the intermediate turbinate. Shaari et al.[21] have applied 50 units of BTX-A soaked into a sterile tissue to the nasal cavity of dogs, and Rohrbach and Laskawi [10] have used BTX-A soaked sterile tissues, 20 units to each nasal cavity. Unal et al. have injected a total of 40 units, each nasal cavity receiving 20 units to a group of patients, and a total of 60 units, each nasal cavity receiving 30 units to another group of patients [23]. They found no significant difference between the two groups, in terms of improvement in the symptoms. We diluted BTX-A with physiologic saline to a final concentration of 25 units/ml (2.5 units in 0.1 ml), and performed injection under guidance of a 0 degree endoscope, applying 2.5 units to the intermediate section of the lower turbinate, and 2.5 units to the anterior part of the intermediate turbinate, each nasal cavity receiving a total of 5 units (10 units in total). The reason we chose the injection method was that we could control the amount of the drug better this way, and that this application method did not require long waiting times for the patients. We used IB in a 3x2 dosing schedule, which was the generally accepted form of use [25,28,34].
We detected that both BTX-A and IB displayed their maximum effects in the 2nd week, however IB was found to be more effective (41.2% to 61.4%). Both drugs were effective for 8 weeks, yet whereas the effect was almost constant until the 4th week, and although there appeared a prominent decrease in the effect of both drugs at week 8, there was still a statistically significant difference compared to prior to the therapy. Neither of the drugs was effective anymore at week 12. Both drugs were statistically significantly more effective than placebo throughout the follow-up period until week 8.

Kim et al. have detected the maximum effect of BTX-A as 41.5% at week 1, and have reported that the effect of the drug gradually decreased throughout the follow-up period, lasting for 4 weeks [8]. They attributed the short duration of the effect to the fast distribution of the toxin due to the intense vascular network in the nasal cavity. Shaari et al. demonstrated that BTX-A have decreased rhinorrhea by an average of 41% in dogs [21]. Rohrbach and Laskawi have detected the maximum effect at week 4, however they have not checked its effect in the later weeks [10]. Unal et al. have demonstrated that the effect appeared at week 1 of the follow-up period, and lasted in the same levels until week 8 [23]. They attributed the long term effect to the high dose they have used. In a study by Rohrbach et al. the recovery of the degeneration in the nasal secretion glands in pigs took 12 weeks, and the authors claimed that BTX-A could be effective until week 12 [22].

In our study, the effect of BTX-A prominently decreased after the 4th week, yet lasted for 8 weeks. These results are in accordance with those of Unal et al. [23]. Although Unal et al. [23] have attributed the long duration of BTX-A effect to the high dosage used, we think that the effect observed was dosage-independent, as we detected the same duration of effect with the 10 unit dosage in our study. In a study held on pigs by Rohrbach et al. [22], although the recovery period of the degeneration in the nasal secretion glands has been detected as 12 weeks, we think that the recovery period of the degeneration in the nasal secretion gland in humans may be shorter than in pigs, as we detected in our study that the effect did not continue in the 12th week and was detected to last for a maximum of 8 weeks. Histopathological investigations on humans are needed to confirm this.

In our study, an average of 38% decrease in rhinorrhea and/or postnasal discharge scores was observed until the 4th week during the follow-up period in the BTX-A group. These results were in accordance with the literature [8,21,23].

In the placebo-controlled study by Bronsky et al., which included 224 patients with Perennial non-allergic rhinitis (PNAR), 0.03% ipratropium bromide nasal spray was applied in a 3x2 pattern for 8 weeks [34]. They observed that the effect displayed an increase starting from the first week and increasing more in the second week, which followed a constitutively increasing pattern for the 8 weeks the drug was being used.

These results are in accordance with the results in our study. In the same study, VAS scores displayed a 30% decrease compared to pre treatment values, and the effect of IB on rhinorrhea was reported as 'excellent' or 'good' by 60-70% of the patients and the physicians. In another placebo-controlled study which included 152 patients with PNAR-dependent nasal hypersecretion, held by Druce et al., IB was applied in each nostril twice daily for 4 weeks of follow-up period, as 21 microgram and 42 microgram to two different groups, and VAS scores showed an average of 30% decrease in both groups independent from the dosage [31].

In our study, a mean decrease of 57% was observed in the VAS scores, during the 4 weeks of drug use. The results revealed that IB was more effective compared to the other studies. This may be due to the average pre-treatment VAS scores being intermediate-severe rhinorrhea (4.38) in our study, while being mild-intermediate in other studies (2.76, 2.87) [31,34]. The patients with severe rhinorrhea may have found the response to the therapy more effective. The results may have been different with objective evaluation criteria, as VAS is a subjective criterion.

Although IB spray use was discontinued on the 4th week in our study, its effect continued with a prominent decrease in the 8th week as well. This effect was thought to depend on the decrease in the number or activity of the nasal secretion glands following IB treatment, as was stated by Mygind and Borum [35]. Although this effect was revealed after 6 to 12 months of IB use in Mygind and Borum's study, similar nasal changes may occur in short term use also [35].

While Kim et al. [8] and Unal et al. [23], who used BTX-A in their study stated that no local or systemic adverse effects were observed in their patients, Rohrbach and Laskawi have reported nasal dryness in a single patient whom they presented as a case report [36]. Grossman et al., who used IB in their study, have detected 10% nasal dryness and 4% epistaxis in the 285 patients included in their study, who were followed-up for 1 year [26]. Bronsky et al. in their series, which included 24 patients who received IB nasal spray application for 28 weeks, have reported an incidence of 9.4% epistaxis, and 5% nasal dryness [34]. None of their patients displayed rebound rhinitis or systemic side effects. In another study on healthy volunteers, a single dose of 80 micrograms of IB nasal spray did not impair mucociliary clearance, compared to placebo [36]. Knight et al. have not detected rebound phenomenon in 18 of the 26 patients included in their study, although sense of dryness in the throat and sense of burning in the nose were present [9].

A patient on BTX-A in our study described a burning sensation in his nose. This effect lasted for 2 weeks following the application of BTX-A. One patient on whom IB spray was used complained from nasal dryness, which lasted for 4 weeks. Anterior rhinoscopic evaluation was normal in both patients. None of our patients suffered from epistaxis, atrophic rhinitis, rebound rhinitis or systemic side effects.

As a conclusion from our study, IB was found to decrease rhinorrhea in various rates ranging from 12.2% to 61.4%, and BTX-A in rates ranging from 17.2% to 41.2%. BTX-A was found to be equally effective compared to IB. This effect was shown statistically to continue for 8 weeks in both drug groups.

The fact that BTX-A and IB have a limited effect on rhinorrhea can be due to neurotransmitter mechanisms other than acetylcholine playing a role in the nasal secretory mechanism, as stated by Rohrbach et al. [23] Parasympathetic system is stimulated not only by the vidian nerve but also by the anterior ethmoid nerve through the ciliary ganglion, and this may be another reason for the limited effect of BTX-A [37].
Although ipratropium bromide has proved its efficacy and safety in long-term use [28,32], there is no literature on long-term use of BTX-A on rhinorrhea therapy, but it has been shown that its application was successful for at least 4 weeks with a single application in low dose [8,10,23]. Whether sensitization will develop or not following long duration recurrent injections, as stated by Borodic et al., will be revealed only after studies to be held [38]. Kim et al. have attributed the limited effect duration to the acceleration of toxin absorption and distribution by the extensive vascular network of the nasal cavity [8]. On the other hand, it is doubtful that the injection reached sphenopalatine ganglion. Although Kim et al. [8] has claimed that it was possible for the injection to reach sphenopalatine ganglion, based on the study by Bushara and Park [39], where an injection at a single point in the back of the hand has showed an effect in an area with a 5-6 cm diameter, the difference between the back of the hand and the nasal cavity should also be kept in mind. Similarly, the level of intranasal distribution of the drug when IB is used in the intranasal spray form is not known.

Other botulinum toxin types other than BTX-A have not been tried on rhinorrhea yet. Even though particularly BTX-D is known to be more effective on autonomic neuroglandular joint [21], further studies are required on its use in the nasal cavity.

Although there is a need for studies to let us understand the pathophysiology of idiopathic rhinitis without eosinophilia completely, and for objective evaluation methods of the therapy efficiency, both BTX-A and IB are efficient and safe therapeutic choices on rhinorrhea and/or postnasal discharge, in the light of the current data.

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