

Effect of Botulinum Toxin Type A on Nasal Symptoms in Patients with Allergic Rhinitis: A Double-blind, Placebo-controlled Clinical Trial

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Objective—To investigate the possible beneficial effects of botulinum toxin type A (BTX-A) on nasal symptoms in patients with allergic rhinitis (AR).

Material and Methods—Thirty-four patients (21 females, 13 males; mean age 28 years) were included in the study. AR was diagnosed by means of history, clinical examination and skin prick test. Patients were randomly divided into 3 subgroups as follows: in Group A, 20 units of BTX-A was injected into each nasal cavity (total 40 units); in Group B, 30 units of BTX-A was injected into each nasal cavity (total 60 units); and in Group C, 2 ml of isotonic saline was injected as placebo. The symptoms of AR (rhinorrhea, nasal obstruction, sneezing, itching) were scored by the patient on a six-point scale (from 0 to 5). All of the patients were followed up at Weeks 1, 2, 4, 6 and 8; at each visit an anterior rhinoscopic examination was done and symptom scores were recorded.

Results—There was no statistically significant difference between Groups A and B in terms of average symptom scores. Rhinorrhea, nasal obstruction and sneezing scores in Groups A and B were significantly better than those in Group C at all time points. Although itching scores were significantly lower at Weeks 1 and 2, there was no difference in the Week 4, 6 and 8 scores in Groups A and B. When total symptom scores were evaluated, the results for Groups A and B were similar but significantly better than those for Group C.

Conclusion—In selected cases, injection of 40 units of BTX-A into the turbinates, as a single agent, may help the symptomatic control of AR for up to 8 weeks. *Key words:* botulinum toxin, nasal allergy, rhinitis, rhinorrhea.

INTRODUCTION

Rhinitis is a common, heterogeneous disorder characterized by nasal symptoms such as rhinorrhea, sneezing, nasal congestion and itching. About 50% of cases of rhinitis are caused by allergy and symptoms arise as a result of inflammation induced by an IgE-mediated immune response to specific allergens such as pollens, molds, animal dander and dust mites (1). The incidence of allergic rhinitis (AR) is increasing, especially in industrialized countries, and constitutes a major health problem (2).

Nasal patency and secretion are mainly controlled by the autonomic nervous system. Sympathetic activity decreases nasal airway resistance by constricting the capacitance vessels and venous sinusoids; however, parasympathetic activity induces nasal mucus secretion from submucosal seromucinous glands and excessive activity produces a copious watery mucus discharge (3, 4). Nasal symptoms in AR are caused by histamine and other mediators, which increase vascular permeability and edema in the submucosal secretory glands and lead to an alteration in the balance of the autonomic nervous system (3, 4). Serous discharge is one of the most prominent features of the disease.

Botulinum toxin (BTX) is a lethal neurotoxin purified from *Clostridium botulinum* and has at least seven antigenically different serotypes (types A–G) (5). This neurotoxin inhibits the release of acetylcholine from presynaptic neurons at the neuromuscular

junctions (6). In the field of otolaryngology it has been used therapeutically for many entities, such as spasmodic dysphonia, dysphagia, oromandibular dystonia, palatal myoclonus, achalasia, hemifacial spasm, torticollis, gustatory sweating, sialorrhea and intrinsic rhinitis (6–11). Shaari et al. (3) demonstrated a reduction of rhinorrhea in experimentally induced nasal hypersecretion in dogs after nasal application of BTX type A (BTX-A). Kim et al. (10) and Rohrbach and Laskawi (11) applied BTX-A to patients with intrinsic rhinitis and obtained satisfactory results. In the light of the above studies, we hypothesized that BTX-A could be used to decrease the intensity of nasal symptoms in patients with AR. Our study mainly focused on the evaluation of the subjective symptomatic relief of rhinorrhea, nasal obstruction, sneezing and itching.

MATERIAL AND METHODS

Thirty-four cases with nasal allergy complaints were included in the study, all of whom gave their informed consent. AR was diagnosed by means of history, clinical examination and skin prick test. Exclusion criteria were pregnancy or the possibility of pregnancy, gross nasal anatomical abnormality (polyp or septal deviation), acute rhinosinusitis, accompanying diseases such as glaucoma or prostate hypertrophy that might be aggravated by anticholinergic therapy and serious systemic diseases. Patients were randomly

divided into three subgroups. All of the participants had similar socioeconomic and environmental backgrounds. The study was conducted between the last week of August and the first week of November 2002 among inhabitants of Mersin, a city on the Mediterranean coast of Turkey with a population of ≈ 1 million. The allergen load was abundant during this period and approximately stable.

The allergen solutions used for the skin prick test were as follows: positive control (histamine); negative control (serum physiologic); *Dermatophagoides farinea*; *Dermatophagoides pteronyssinus*; mold mixture (*Cladosporium* and *Alternaria*); tree pollens (*Betula*-*cea* and *salicacea*); a mixture of cereals; grass pollens; weed pollens; a feather mixture; and animal epithelia (cat and dog hair) (Stallergene S.A., France).

BTX-A (Botox®; Allergan Inc., Irvine, CA) was distilled to a concentration of 20 units/ml. In Group A, 20 units of BTX-A was injected into each nasal cavity (total 40 units); in Group B, 30 units of BTX-A was injected into each nasal cavity (total 60 units); and in Group C, 2 ml of isotonic saline was injected as placebo. BTX-A was applied to the inferior and middle turbinates using a standard dental injector under direct vision (anterior rhinoscopy) at equal doses. The symptoms of AR (rhinorrhea, nasal obstruction, sneezing, itching) were scored by the patient on a six-point scale (0 = none, 1 = mild, 2 = mild to moderate, 3 = moderate, 4 = moderate to severe, 5 = severe). All patients were advised not to take any additional allergy therapy. They were followed up at Weeks 1, 2, 4, 6 and 8; at each visit an anterior rhinoscopic examination was done and symptom scores were recorded.

The difference between the BTX groups and the placebo group for each symptom was statistically analyzed using the Kruskal–Wallis test. Total symptomatic scores (the sum of the four symptom scores) were compared using ANOVA and a post-hoc Tukey test. $p < 0.05$ was considered significant.

RESULTS

The study groups were comprised as follows: Group A, $n = 12$ (7 females, 5 males; mean age 28 years; range 18–44 years); Group B, $n = 12$ (8 females, 4 males; mean age 28.9 years; range 19–42 years); and Group C, $n = 10$ (6 females, 4 males; mean age 26.8 years; range 18–38 years). Twenty-five of the patients had perennial complaints and none of them kept animals in their houses.

The skin prick test results of the 34 patients were as follows. *D. farinea* and *D. pteronyssinus* sensitivities were present in 16 and 15 patients, respectively. Three patients were sensitive to mold mixture. Sensitivities to

tree pollens were present in five and three patients, respectively. Sensitivities to the mixture of cereals and the grass pollens were present in 10 and 13 patients, respectively. Five patients were sensitive to the weed mixture and eight to the feather mixture. There was no statistically significant difference between the three groups in terms of symptom scores before BTX-A injection.

Rhinorrhea scores in Groups A and B were significantly different from those in Group C at Weeks 1 ($p = 0.001$), 2 ($p = 0.001$), 4 ($p = 0.001$), 6 ($p = 0.002$) and 8 ($p = 0.009$). Nasal obstruction scores in the BTX-A groups were significantly better than those in the placebo group at Weeks 1 ($p = 0.016$), 2 ($p = 0.025$), 4 ($p = 0.049$), 6 ($p = 0.040$) and 8 ($p = 0.048$). Sneezing scores in the BTX-A groups were significantly lower than those in the placebo group at Weeks 1 ($p = 0.002$), 2 ($p = 0.028$), 4 ($p = 0.028$), 6 ($p = 0.025$) and 8 ($p = 0.045$). Although itching scores were significantly lower at Weeks 1 and 2 ($p = 0.024$, $p = 0.021$), there was no significant difference in the scores at Weeks 4 ($p = 0.087$), 6 ($p = 0.152$) and 8 ($p = 0.317$) in Groups A and B. When total symptom scores were evaluated, the results for Groups A and B were similar but significantly lower than those in Group C (Table I, Fig. 1).

DISCUSSION

The effects of BTX-A on the nasal cavity have been postulated to occur via three mechanisms: (i) inhibition of the release of acetylcholine from the cholinergic nerve endings in the nasal mucosa; (ii) inhibition of the release of acetylcholine from pre-ganglionic cholinergic nerve endings in the sphenopalatine ganglion; and (iii) induction of apoptosis of nasal glands (10, 12). According to Shaari et al. (3), this anticholinergic effect is partial: they obtained an average decrease in rhinorrhea of 41% in their experimental study. They suggested that this partial effect might be related to the release of other non-cholinergic secretory neurotransmitters, such as vasoactive intestinal polypeptide.

BTX-A has been introduced into the nasal cavity via direct injection into the inferior and middle turbinates or via a gauze or sponge soaked with toxin. We preferred the injection method instead of using toxin-soaked sponges because of the shorter application time and the ease of controlling the dose and placement of the toxin. To date, there is no accepted dosage of BTX-A for AR. The toxic dose of BTX-A is in the range 2500–3000 units (13). Shaari et al. (3) applied 50 units using a soaked sterile gauze to one nasal cavity; Kim et al. (10) injected 4 units into each nasal cavity (total 8 units); and Rohrbach and Laskawi (11) introduced 20 units BTX-A in a soaked sponge to

Table I. Mean total symptom scores in the study groups

Week	Group A		Group B		Group C		<i>p</i>
	Score	SD	Score	SD	Score	SD	
0 ^a	16.4	2.5	17.3	1.7	16.5	2.2	0.12
1	8.4	5.8	9.8	5.9	17.7	1.4	0.000
2	8.6	6	8.2	6.1	17	1.2	0.001
4	8.3	6.2	7.8	6.5	16.9	1.4	0.001
6	9	5.4	7.3	6.8	16.8	1.1	0.000
8	9.7	6.5	9.2	7.2	17.1	1.3	0.007

^aBefore BTX-A injection.

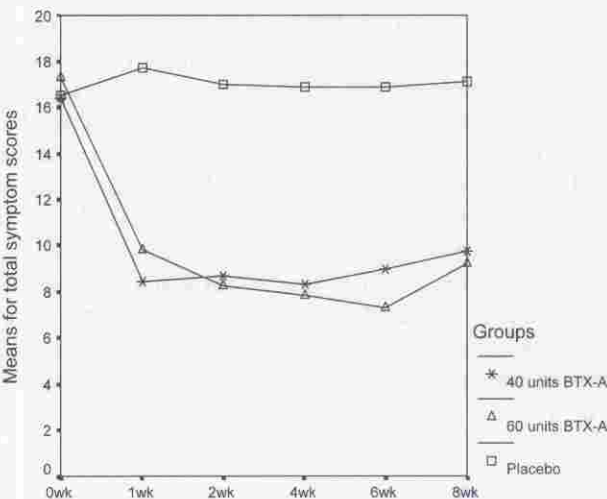


Fig. 1. Comparison of mean total symptom scores among the three groups.

each nasal cavity (total 40 units). We applied BTX-A in two different total dosages—40 and 60 units—in order to determine an optimum therapeutic level for a safe, long-lasting effect. We did not find any statistically significant difference in symptomatic relief between the two dosage groups.

The symptoms associated with AR are predominately related to the release of histamine and other mediators from the IgE–mast cell complex (1). These mediators cause leakage from blood vessels, produce mucosal edema and serous rhinorrhea, dilate the blood vessels to cause congestion and stimulate sensory nerves, resulting in the sensation of itching and congestion (1). Moreover, histamine induces orthodromic sensory impulses resulting in reflex parasympathetic activation (14). Previous authors who applied the toxin in human beings used subjective symptomatic scores and calculated the number of paper tissues used per day. For a more comprehensive assessment, we evaluated the effect of toxin on each symptom score and on the total symptom score. Kim et al. (10) found a significant reduction in rhinorrhea ($\approx 40\%$) but not in sneezing and nasal obstruction in

43 patients with intrinsic rhinitis. Rorhbach and Laskawi (11) also obtained a satisfactory reduction in rhinorrhea and nasal obstruction in their patients. Similarly, Shaari et al. (3) demonstrated a reduction in rhinorrhea (41%) in experimentally induced nasal hypersecretion in dogs. We observed that BTX-A significantly lessened rhinorrhea, sneezing, nasal obstruction and itching (although this effect was seen only for 2 weeks); furthermore, it lowered the total symptom scores significantly throughout the 8-week follow-up period. According to Rorhbach and co-workers (11, 12), a reduction in glandular volume or a decrease in nasal fluids is responsible for the change in nasal obstruction. We did not encounter any side-effects, such as dry nose, epistaxis or systemic reaction. Although Kim et al. (10) did not report any complications, Rorhbach and Laskawi (11) encountered dry nose occasionally.

The duration of effect of BTX-A is not known exactly in intrinsic rhinitis, although Kim et al. (10) reported a figure of 4 weeks. They speculated that the nasal cavity has abundant blood vessels, so that absorption and clearance of the toxin occur more rapidly. However, we observed that symptomatic relief lasts for at least 8 weeks and this result may be the result of our higher dosage (40 or 60 units in total versus 8 units). Rorhbach et al. (12) showed that 20 units of BTX-A induces apoptosis in the nasal glandular compartment of adult guinea pigs; however, this degeneration improves within 3 months. Given these data and our results, it can be speculated that BTX-A at the dosages used in the current study may be effective for 8–12 weeks.

Therapeutic efforts to lessen the symptoms of AR include avoiding the specific allergen, antihistaminic drugs, nasal corticosteroid sprays, immunotherapy and surgical interventions to the turbinates. All of these treatment methods have both advantages and disadvantages. In this respect, use of BTX-A, as a single agent, may produce additional long-lasting relief of AR symptoms in selected cases and may be especially useful in patients whose symptoms are more

difficult to control with standard therapeutic regimens. However, this is an area where further comparative studies are needed (e.g. BTX-A versus local corticosteroid therapy, etc.). Although long-term repetitive therapeutic injections do not produce permanent denervative effects in human muscle specimens, we do not have any experience of long-term, repetitive treatment for AR (15). Moreover, it is speculated that immunological sensitization to BTX may occur after repeat injections, leading to poor responses (15). BTX-A has its greatest effect at the neuromuscular junction; however, BTX type D has been shown to have a greater anticholinergic effect at the autonomic neuroglandular junction in experimental studies and thus its use in the nasal cavity may be expected to be more effective (3).

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