

The effect of intranasal injection of botulinum toxin A on the symptoms of vasomotor rhinitis

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Abstract

Purpose: Vasomotor rhinitis (VMR) is a common disease that is unrelated to allergy, infection, structural abnormalities, and systemic diseases. Patients with VMR usually complain of nasal obstruction accompanied by profuse watery nasal discharge. The exact pathophysiologic mechanisms of VMR are not known. Some studies suggested that it results from an autonomic nervous system dysfunction. No effective long-term treatment modalities exist for the VMR.

Materials and methods: Thirty patients with VMR were randomly and equally divided into 2 groups. The mean age was 38.46 years (range, 18–59 years; 1 men, 14 women) for group 1 and 41.60 (range, 29–62 years; 4 men, 11 women) for group 2. Five patients with VMR were accepted as a control group. Fifteen patients were injected 10 U of botulinum toxin A (BTX-A) (group 1) and patients in group 2 were injected 20 U to inferior and middle turbinates. Control patients were injected with saline solution into the inferior and middle turbinates.

Results: Total symptom scores generally decreased after the first week and increased after the eighth week. The symptoms of patients (nasal obstruction, sneezing, nasal discharge, and nasal itching) were scored from 1 to 5, with 1 as less severe and 5 as most severe. The statistical significance of the results was analyzed using Kruskal-Wallis and Mann-Whitney *U* test. When total symptom scores of group 1 (10 U BTX-A) were compared with the control group, there was a statistically significant difference regarding symptoms scores at all control weeks. There was also a statistically significant difference for total symptom scores between group 2 and control group, except for the first control week.

Conclusion: Intranasal injection of BTX-A is a highly effective, safe, and simple symptomatic treatment modality with a long-lasting effect for patients with VMR. Botulinum toxin A may be a good alternative especially for the treatment of resistant VMR cases.

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1. Introduction

Rhinitis is known as inflammation of nasal mucous membranes, characterized by nasal discharge, itching, and congestion, and affects approximately 20% of the popula-

tion [1,2]. According to latest consensus report on the diagnosis and management of rhinitis, rhinitis is divided into allergic rhinitis, infectious, and other rhinitis. “Other” rhinitis is further subdivided into idiopathic rhinitis, nares, occupational rhinitis, and so on [3]. In this study, the term *vasomotor rhinitis* (VMR) was used instead of idiopathic rhinitis. It is also known as nonallergic noninfectious perennial rhinitis, or intrinsic rhinitis. Vasomotor rhinitis, almost 50% of chronic rhinitis, is unrelated to allergy, infection, structural lesions, systemic disease, or drug abuse. It is a diagnosis of exclusion and is likely to result from

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many different etiologies. Its symptoms range from nasal blockage to rhinorrhea; sneezing and nasal pruritus are less common [1,4,5].

The nasal airway is under the control of the autonomic nervous system. Sympathic nervous system decreases nasal airway resistance; parasympathic system produces nasal discharge [4,6]. The precise pathogenesis of VMR is unknown, but it is suggested to be the result of autonomic imbalance with a relative dominance of the parasympathetic nervous system in the nasal mucosa [7–9]. Several factors including emotional disturbance, hormones, physical agents, and trauma are suggested as predisposing factors [7,10]. The medical treatment of VMR including decongestants, nasal ipratropium bromide, and antihistamines needs long time usage and has some potential side effects. Nasal steroids may be appropriate treatment option, but the efficacy of these drugs has been not consistent [1,11]. Surgical treatment (concha resections, vidian nerve section, etc) of VMR generally has short-term effect and some complications.

Botulinum toxin is a neurotoxin that inhibits the release of acetylcholine from the presynaptic nerve terminal. Strains of *Clostridium botulinum* produce 7 antigenically distinct neurotoxins designated types from A through G [12]. Botulinum toxin A (BTX-A) has the greatest anticholinergic effect at the neuromuscular junction. Botulinum toxin A is widely used in the treatment of a wide spectrum of conditions characterized by overactivity of one or a few muscles such as focal dystonia and spasticity [13,14]. It has also been used in cases of sialorrhea, Frey syndrome, and salivary and pharyngocutaneous fistulas [13–16]. It was reported that BTX-A showed potent anticholinergic effect in nasal mucosa regarding nasal discharge [6]. It was suggested that local BTX-A injection may have a potential role in the treatment of intrinsic rhinitis [17].

In this study, we aimed to investigate the effect of intranasal injection of 2 different doses of BTX-A on the symptoms of patients with VMR.

2. Patients and methods

Thirty patients with VMR with the symptoms of nasal blockage and rhinorrhea for at least 3 months were enrolled in the present study. Patients were randomly and equally divided into 2 groups. The mean age was 38.46 years (range, 18–59 years; 1 men, 14 women) for group 1 and 41.60 years (range, 29–62 years; 4 men, 11 women) for group 2. Five patients with VMR were accepted as a control group. The mean age was 34.40 years (2 men, 3 women) for the control group.

Anterior rhinoscopy and nasal endoscopy using rigid telescopes were done for all patients. Skin prick and specific blood immunoglobulin E (IgE) tests were performed on all patients. We used 16 allergens in the prick test and 35 allergens in the specific blood IgE test. Nasal smears of all patients were also evaluated. Skin prick- and

specific IgE test-positive patients, patients with high blood level IgE, and patients with high eosinophil in nasal smear (<20% of cell population) were excluded from the study. Patients with structural deformities (deviated septum, adenoid hypertrophy, nasal valve pathology, etc), nasal polyps, maxillofacial trauma, and nasal infection signs were also excluded from the study. The symptoms of patients (nasal obstruction, sneezing, nasal discharge, and nasal itching) were scored through 1 to 5 with 1 as less severe and 5 as the most severe.

Fifteen patients from group 1 were injected with 10 U BTX-A (Botox, Allergan Inc, Irvine, Ca), whereas fifteen patients from group 2 were injected with 20 U. One box of BTX-A was diluted in 4 mL saline solution, and 1 mL of final solution was equal to 25 U BTX-A. After the application of topical lidocaine spray, one quarter of total BTX-A doses (10 U for group 1 and 20 U for group 2) were injected to one point of anterior side of the inferior and middle turbinates of left and right nasal cavities in patients with VMR using 1-mL syringe and 30-gauge needle (Fig. 1). Control patients were injected with saline solution into the inferior and middle turbinates.

The symptoms of patients were evaluated and scored in the first, second, fourth, sixth, eighth, and 12th weeks during their control examinations in our outpatient clinic after the intranasal BTX-A injection. The results for the 3 groups were analyzed using Kruskal-Wallis and Mann-Whitney *U* tests for the statistical significance (Fig. 2).

3. Results

All patients completed the study. No patient complained about any side effects and allergic reactions, that is, epistaxis and intranasal crusting. In general, total symptom scores decreased after the first week and increased after the eighth week. The symptoms of 3 patients (2 from group 1 and 1 from group 2) were not changed at all control week examinations.

When the total symptom scores of group 1 (10 U BTX-A) were compared with the control group, there was a

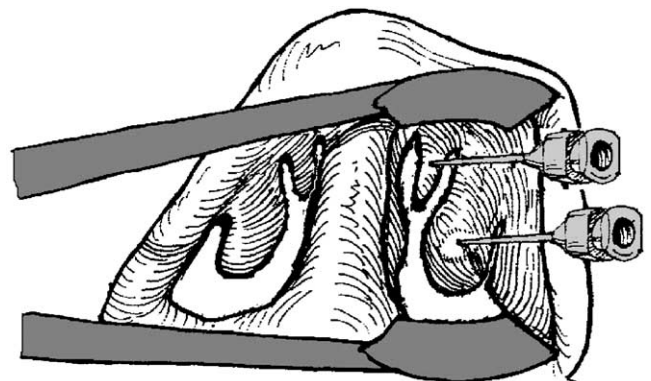


Fig. 1. Schematic drawing of intranasal BTX-A injection sites.

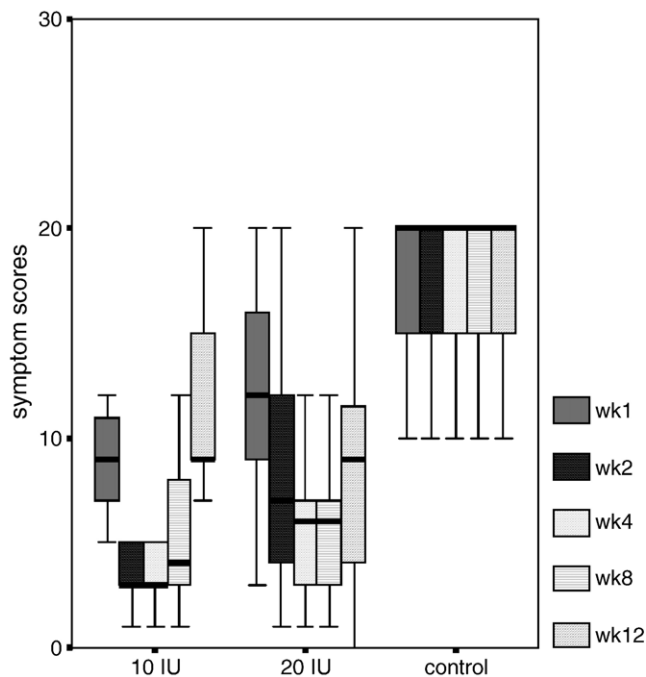


Fig. 2. Comparison of treatment and control groups regarding symptom scores.

statistically significant difference in symptoms scores in all the control weeks ($P = .013, .007, .007, .009, .009$, and $.0031$). There was also a statistically significant difference for total symptom scores between group 2 (20 U BTX-A) and the control group, except for the first control week ($P = .111, .01, .04, .004, .004$, and $.008$) (Table 1). There was no statistically significant difference except in the 12th week ($P = .045$) between group 1 and group 2 regarding symptom scores (Table 2). Regarding nasal discharge, sneezing, and itching at the 12th week, there was also a statistically significant difference ($P = .026, .004$, and $.060$, respectively) when compared with groups 1 and 2. There was no statistically significant difference between group 1 and the control group regarding itching scores at the 12th control week ($P = .121$). There was also no difference between group 2 and the control group

Table 1
 P values of comparison of control and treatment groups regarding symptom scores

	Symptoms	Weeks					
		1	2	4	6	8	12
Group 1 (10 IU BTX-A)	Discharge	0.003	0.003	0.003	0.002	0.002	0.004
	Sneezing	0.007	0.006	0.006	0.005	0.005	0.017
	Obstruction	0.003	0.006	0.006	0.006	0.006	0.008
	Itching	0.064*	0.063*	0.063*	0.059*	0.059*	0.121*
Group 2 (20 IU BTX-A)	Discharge	0.006	0.001	0.000	0.000	0.000	0.002
	Sneezing	0.011	0.004	0.001	0.001	0.001	0.001
	Obstruction	0.004	0.038	0.003	0.003	0.003	0.005
	Itching	0.092*	0.032	0.017	0.017	0.017	0.024

* Statistically nonsignificant (Mann-Whitney U test).

Table 2

P values for comparison of effectiveness of 2 BTX-A doses (10 and 20 IU) regarding symptom scores

Symptoms	Weeks					
	1	2	4	6	8	12
Discharge	0.586	0.135	0.551	0.701	0.293	0.026*
Sneezing	0.454	0.135	0.551	0.701	0.306	0.004*
Obstruction	0.424	0.826	0.549	0.549	0.549	0.125
Itching	0.178	0.121	0.378	0.957	0.957	0.060*

* Statistically significant (Mann-Whitney U test).

regarding itching symptom scores at the first week control ($P = .092$).

4. Discussion

Vasomotor rhinitis indicates the diagnosis of idiopathic perennial nonallergic rhinitis associated with negative allergy skin tests, normal serum IgE levels, and a lack of identifiable inflammation signs on nasal cytology [1]. The exact pathomechanism of VMR is not properly known, but some studies showed that it is caused by an autonomic nervous system dysfunction (relative parasympathetic hyperactivity) as a result of sympathetic hypoactivity [18–20]. Parasympathetic hyperactivity in the nasal cavity causes clear nasal discharge from submucosal glands; on the other hand, sympathetic hypoactivity can give rise to nasal blockage [6]. Although several treatment modalities are available for VMR, no single one has been proved to be significantly superior to the others [19]. Therapeutic efforts to decrease rhinorrhea in human beings have attempted to either cut the parasympathetic nerve supply through vidian neurectomy or chemically block the receptors with the short-acting, topical ipratropium. Either therapy options produce only partial relief of nasal symptoms [6].

Botulinum toxin A selectively inactivates peripheral cholinergic nerve terminals by blocking the release of acetylcholine. Its most important effect is at the neuromuscular junction where it causes temporary and reversible weakness and atrophy of striated muscle. Botulinum toxin A also provokes autonomic dysfunction by blocking sympathetic and parasympathetic ganglion cells and postganglionic parasympathetic neurons. It exerts action at the molecular level by selectively cleaving the protein SNAP-25 (synaptosomal-associated protein with a molecular weight of 25 kd). When the BTX-A damages SNAP-25, the most obvious effect is on regulated exocytosis, the release of synaptic vesicles in response to electrical depolarization [12,14]. Blocking the release of acetylcholine from the cholinergic nerve terminal in the nasal mucosa or preganglionic cholinergic nerve endings in sphenopalatine ganglion are the 2 suggested mechanisms of BTX-A action in the nasal cavity [17]. Rohrbach and colleagues demonstrated a degeneration of nasal glands and ducts in addition to diffuse glandular apoptosis in guinea pigs after nasal

application of 20 U BTX-A. They also observed the absence of necrosis or inflammation after application of BTX-A [21]. Wang and colleagues also demonstrated induction of glandular cell degeneration in guinea pig nasal mucosa after topical BTX-A application [23].

Shaari and colleagues [6] suggested that BTX-A might be injected into the sphenopalatine ganglion alone or in combination with the topical nasal application to reduce nasal discharge. Sphenopalatine ganglion injections are technically easy and may possibly be very effective, but they may be complicated by epistaxis or lacrimation problems.

Rohrbach and Laskawi [22] reported that intranasal 20 U BTX-A application reduced the nasal secretion in 1 patient with VMR. Topical application of BTX-A alone to the nasal mucosa is less invasive, but this method may not equally distribute it to all areas of the nasal cavity. Kim and colleagues [17] reported that BTX-A injected into the middle and inferior concha could widely spread the sphenopalatine ganglion and result in blocking the preganglionic cholinergic nerve terminal as well as the postganglionic nerve terminal in nasal mucosa. Wang and colleagues [23] also reported that 10 U of BTX-A injection into the nasal mucosa of patients with VMR reduced the symptom scores. These reports encouraged us to apply BTX-A via intratubal injection in patients with VMR.

Shaari and colleagues [6] reported that intranasal BTX-A application decreased 41% of the nasal discharge in 3 of the 4 dogs after the sphenopalatine ganglion stimulation using needle electrode. The partial response was explained by that a low-rate blockage of some noncholinergic neurotransmitters, such as vasoactive intestinal peptide, may have been released after sphenopalatine ganglion stimulation. They also reported that type D botulinum toxin might have a more complete anticholinergic effect [6].

The duration of BTX-A effect on the autonomic nervous system was very long (6 months for lacrimation and 11 months for salivation in salivary fistula) [13,15,21]. The duration of BTX-A effect in our patients with VMR (generally the eighth week) is longer than that in the study of Kim and colleagues [17]. Higher BTX-A dose injections might be the explanation of long duration in our study. The lower duration of BTX-A effect might be explained by rich blood vessels in nasal mucosa leading to more rapid absorption and clearing [17].

There are rare reports about transient or permanent visual loss after intratubal steroid injections. The estimated incidence rate of visual loss was approximately 0.006%. Embolization and vasospasm of retinal artery were the possible causes of visual loss. Small-particle drugs must be used to minimize this complication [24,25]. There was no reported visual loss complication after intratubal BTX-A injection [17–22].

The cost-effectiveness is an important issue in the management of chronic diseases such as VMR. The price of the treatment of VMR with nasal steroids or oral antihistamines was approximately \$45 for 3 months in our

country. Nasal ipratropium bromide and antihistamines were not available in Turkey. The price of Botox was approximately \$40 to \$80 (10 and 20 IU) for one person. Health insurance companies also do not pay the price of BTX-A for the VMR treatment in Turkey.

In conclusion, intranasal injection of 10 or 20 U BTX-A is a highly effective, safe, and simple symptomatic treatment option with a long-lasting effect for patients with VMR. Botulinum toxin A is a good alternative for the treatment of resistant VMR cases.

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