

Comparing the Effects of Botulinum Toxin-A and Cetirizine on the Treatment of Allergic Rhinitis

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ABSTRACT

Background: There are few reports on the effects of intranasal Botulinum Toxin-A (BTX-A) as a treatment of allergic rhinitis (AR). In this study, we compared the efficacy of intranasal BTX-A to cetirizine in the treatment of AR.

Methods: Fifty AR patients at the age of 26.2 ± 9.1 years (64% females), were recruited to the trial according to the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria. Participants randomly received either intranasal injection of BTX-A (75 IU Dysport®) or cetirizine (10 mg/day). Symptoms (based on the ARIA) and side effects were assessed every two weeks for two months. Quality of life was evaluated before and after the study using the Rhinasthma questionnaire.

Results: Total symptom severity score of patients significantly decreased ($P < 0.001$) and quality of life significantly improved ($P < 0.001$) at the same level in both groups. Side effects included nasal dryness (4%) and epistaxis (4%) in the BTX-A group. In the cetirizine group 44% sleepiness and 4% blurred vision was reported.

Conclusions: Nasal injection of BTX-A shows the same therapeutic effects as cetirizine in the management of AR. Since BTX is expensive, we do not suggest it in the first line of treatment for AR. However, BTX-A is a potential treatment for patients who are resistant or not compliant to the routine medications of AR. Further studies are required to investigate implications and limitations of BTX-A in the treatment of AR.

KEY WORDS

allergic rhinitis, botulinum toxin type A, histamine H1 antagonist

INTRODUCTION

Allergic rhinitis (AR) is a common disease with a high prevalence of about 24% in Iranian population in 2003.¹ The prevalence of AR has increased over the last decade in several Middle East countries.² The upper respiratory symptoms of AR include nasal congestion, itching, rhinorrhea, and sneezing. These symptoms are caused by the release of granular-associated mediators due to the activation of mast cells residing in nasal tissue. Mast cells of the respiratory mucosa and basophiles in the blood coated by IgE are said to be sensitized. These mechanisms are responsible for respiratory symptoms after exposure

to the allergen in atopic individuals. There are also other proposed mechanisms to explain non-allergic rhinitis including those that are not related to mucosal impairment by inflammation, such as autonomic imbalance and hyper-responsiveness of the sensory nerves.³⁻⁵

Depending on the pathogenesis of rhinitis and patient's complaints, several treatment strategies are recommended, such as intranasal and systemic corticosteroids, histamine H1 antagonists, decongestants, cromolyn sodium, antileukotrienes, anticholinergics, capsaicin, anti-IgE agents, and intranasal saline.⁶ However, the conventional medications are not able to completely control the symptoms in most of the pa-

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tients. Another limitation to conventional treatments is side effects associated with medications e.g. drowsiness with histamine H1 antagonists.

Botulinum toxin (BTX) is a natural neuromuscular agent, extracted from the purified toxin of clostridium botulinum bacteria. There are eight types of BTX from A to G, with different immunological specificity.⁷ BTX inhibits the function of acetylcholine in presynaptic area of neuromuscular junctions and consequently blocks the cholinergic pathways.⁸ Currently in otolaryngology, BTX is administered to achieve various therapeutic goals including treatment of spasticity, dystonia, strabismus and other face movement disorders. Recently, innovative usage of BTX in cosmetic procedures, pain relief, involuntary muscle contractions and glandular hypersecretion has been suggested.⁹ Findings by other studies emphasize the efficiency of BTX type A (BTX-A) in the treatment of rhinitis. Rohrbach *et al.* demonstrated that BTX-A sponge (Botox®) could reduce the symptoms of rhinitis in individuals resistant to other medications.¹⁰ Another study showed that 25 units (IU) of injected BTX-A (Botox®) is more effective than injected triamcinolone in relieving AR symptoms.¹¹ Also, injection of 20 IU BTX-A (Botox®) into each nasal cavity has been shown to be an appropriate method in controlling the symptoms of rhinitis.¹² However, with all the valuable data available, there are still few reports on the effects of BTX-A and histamine H1 antagonists in controlling AR symptoms. The aim of this study was to compare the effects of intranasal BTX-A injection versus cetirizine administration in relieving the symptoms of AR.

METHODS

PATIENTS AND SETTINGS

This randomized, controlled trial was conducted on patients with AR referred to the outpatient otolaryngology clinics in Alzahra and Kashani university hospitals of Isfahan (Iran), between 2010 and 2012. Diagnosis of AR was made by an otorhinolaryngologist based on a comprehensive assessment of symptoms and physical examination and according to the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria. Participants had three upper respiratory symptoms including sneezing, nasal obstruction and discharge.⁵ Patients with the history of rhinoplasty, nasal anatomic abnormality (i.e. nasal polyp or septal deviation), persistent asthma, long use of systemic corticosteroids, malignancy, tuberculosis, diabetes mellitus and other chronic systemic disease as well as pregnant females were excluded from the study. Patients on local corticosteroids at the time of the study were not included. Calculated sample size was 25 cases in each group with type I error (alpha) of 0.05 and study power of 80%. We expected at least one score difference between the two groups in ARIA total score. The ethics committee of the Isfahan Univer-

sity of Medical Sciences approved the study and all patients signed a consent form before participating in the trial. The trial has also been registered at Iranian Registry for Clinical Trials: IRCT201208261579N3.

INTERVENTION

Using random table numbers, patients were randomly assigned into two groups of BTX-A and cetirizine. In the BTX-A group, participants were treated with a single dose intranasal injection of BTX-A (Dysport®, Ipsen Biopharm, Wrexham, UK) and the other group were treated with cetirizine (Abidi Co., Tehran, Iran) 10 mg once daily. In the BTX-A group, the procedure was applied while the patients were in sitting position. Local intranasal anesthesia was conducted with 10% lidocaine sprayed 10 minutes before the injection. Each vial of 495 IU BTX-A was diluted with 3.3 cc of distilled water (150 IU/cc), and 0.5 cc (75 IU each nasal cavity) of this solution was slowly injected into the anterior part of each inferior turbinate via insulin needle.

ASSESSMENTS

Patients were visited every two weeks for two months. In each visit, questionnaires including symptoms and side effects were filled out by the same otolaryngologist throughout the study. Clinical symptoms were evaluated according to the ARIA criteria.⁵ The questionnaire in this section evaluated five major symptoms including sneezing, rhinorrhea, nasal congestion, nasal itching, and eye redness/itching/waterness. Severity of each symptom was graded from 0 (no symptom) to 3 (severe). Patient's quality of life was evaluated before and after the study using the Rhinasthma questionnaire that is designed to evaluate the quality of life in rhinitis/asthma or both and includes 30 items; each question scored from 0 (none) to 2 (moderate to severe).¹³

STATISTICAL ANALYSIS

Data were analyzed using the SPSS software for windows version 16.0. Independent sample t-Test and Chi-square test were used for comparing quantitative and qualitative variables between the two groups. Repeated Measures test was used to analyze the trend of changes within and between the groups. Multivariate analyses conducted where needed. *P* value of <0.05 was considered significant.

RESULTS

During the course of the study, 50 AR patients at the age of 26.2 ± 9.1 years (64% female) were included and all of them completed the study. The two groups were similar with regards to demographic and baseline clinical variables. Trend of changes in total symptom severity score is presented in Table 1. At the end of the trial, the total symptom severity score was significantly reduced in both groups ($P < 0.001$). Re-

Table 1 Symptom severity score from baseline to the end of study

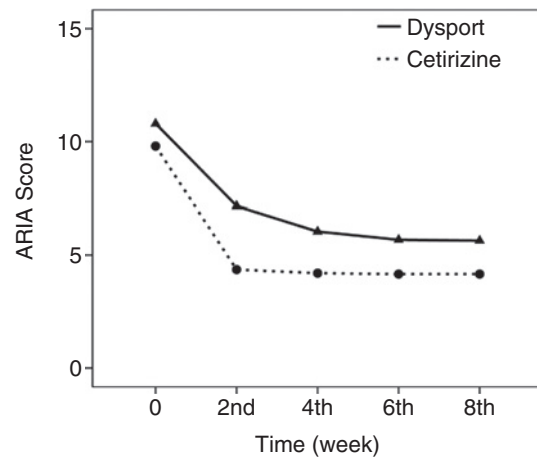
	Dysport <i>n</i> = 25	Cetirizine <i>n</i> = 25	<i>P</i> *
Baseline	10.8 ± 2.4	9.8 ± 3.1	0.213
2nd wk.	7.1 ± 3.7	4.3 ± 3.3	0.007
4th wk.	6.0 ± 3.9	4.2 ± 3.2	0.077
6th wk.	5.6 ± 4.1	4.1 ± 3.2	0.152
8th wk.	5.6 ± 4.0	4.1 ± 3.2	0.161
<i>P</i> **	<0.001	<0.001	
<i>P</i> ***	0.045		
Score change	5.1 ± 4.0	5.6 ± 3.4	0.656

Data are presented as mean ± SD.

*Independent sample t-Test.

**Repeated measure within group.

***Repeated measure between group.

**Fig. 1** Trend of change in ARIA score during the study.**Table 2** Comparison of each symptom severity score and quality of life from baseline to the end of study in the two groups

	BTX-A <i>n</i> = 25		<i>P</i> *	Cetirizine <i>n</i> = 25		<i>P</i> *
	Before	After		Before	After	
Sneezing	2.48 ± 0.87	1.24 ± 1.05	<0.001	2.32 ± 0.80	0.76 ± 0.92	<0.001
Rhinorrhea	2.60 ± 0.64	1.28 ± 1.06	<0.001	2.44 ± 0.58	0.80 ± 1.00	<0.001
Nasal congestion	2.60 ± 0.76	1.48 ± 0.87	0.001	1.96 ± 0.73	1.32 ± 0.80	0.004
Nasal itching	1.68 ± 1.10	1.04 ± 1.09	0.014	1.92 ± 0.95	0.52 ± 0.77	<0.001
Irritated eye	1.44 ± 0.76	0.60 ± 0.81	<0.001	1.16 ± 0.85	0.76 ± 0.72	0.089
QOL	43.9 ± 14.0	20.1 ± 15.1	<0.001**	28.7 ± 13.1	15.8 ± 11.3	<0.001**

Data are presented as mean ± SD. BTX-A, Botulinum toxin A; QOL, Quality of life.

*Wilcoxon test.

**Paired t-Test.

peated measures analysis showed a significant difference in symptom severity trend between the two groups ($P = 0.045$); however, there was no difference between the two groups regarding the amount of change in total symptom severity score (pre-to-post difference = 5.1 ± 4.0 vs. 5.6 ± 3.4 , $P = 0.656$); Table 1 and Figure 1.

Severity scores of each symptom before and after the study are presented in Table 2. All symptoms were significantly improved in both groups, except irritated eye symptoms in the cetirizine group ($P = 0.089$). Comparing the two groups regarding the amount of change revealed a non-significant greater improvement in nasal congestion ($P = 0.06$) and more decrease in eye irritation ($P = 0.013$) among those who received BTX-A, and a greater improvement in nasal itching among those who received cetirizine ($P = 0.019$), compared with each of the other group. Because there was a difference between the two groups in baseline nasal congestion score ($P = 0.002$), we conducted a multivariate analysis. Results showed no difference between the BTX-A and cetirizine in decreasing the severity of nasal congestion ($P = 0.742$).

Quality of life was improved in both groups (Table 2), but more improvement observed in the BTX-A group (pre-to-post difference = 23.8 ± 15.6 vs. 12.8 ± 9.3 , $P = 0.004$). Considering the baseline difference between the two groups in quality of life score ($P < 0.001$), a multivariate analysis was performed that showed no difference between the two groups in improvement of quality of life ($P = 0.300$).

In overall, side effects included nasal dryness (4%) and epistaxis (4%) in the BTX-A group, sleepiness (44%) and blurred vision (4%) in the cetirizine group.

DISCUSSION

Allergic rhinitis is a common and disturbing disorder that affects patients' quality of life. AR causes a great economic burden on the health care system, therefore finding a cost effective treatment for AR is becoming increasingly important.¹⁴ We compared the effect of intranasal injection of BTX-A to cetirizine usage in the management of AR. Our results demonstrate that after two months of therapy, the overall severity of rhinitis decreased at the same level when participants received either BTX-A or cetirizine.

Symptoms were comparably improved in both groups, with cetirizine more effective for nasal itching and BTX-A for irritated eye. The quality of life was also improved in both groups. Despite the similar effects of BTX-A and cetirizine on patient symptoms and quality of life, BTX-A was injected only once and thus, higher tolerance (compliance) can be achieved by such treatment. The findings of our study show that BTX-A causes less frequent irritations and side effects compared to cetirizine. The epistaxis caused by BTX-A injection was mild and manageable using local compression. However, drowsiness/sleepiness occurred in about 50% of the participants receiving cetirizine, highlighting a better compliance in BTX-A group. A single dose of BTX-A may seem more expensive than daily use of cetirizine during two months of therapy; however side effects and long term use of antihistamines impose a higher economic burden with a high costs for indirect expenses due to patients disability and drowsiness in cetirizine group. A review by Thorn *et al.* showed that there is a remarkable decrease in work productivity among patients treated with antihistamines such as cetirizine or loratadine.¹⁵ Although our study showed similar effects of treatments on quality of life, longer follow-ups are required to investigate if the long-term benefits of treatment with BTX-A is higher than cetirizine (or other antihistamines) regarding quality of life and daily function of the patients.

Mechanisms that explain therapeutic effects of BTX-A on AR nasal symptoms include anticholinergic and apoptotic signaling. BTX-A has an anti-cholinergic effect by inhibiting the acetylcholine release from presynaptic neurons and cholinergic nerve endings in the sphenopalatine ganglion. It also induces vasodilatation in nasal vessels that leads to the blockage of vasoactive intestinal polypeptide. Additionally, it can cause apoptosis in nasal glands tissue.^{16,17} The beneficial effects of BTX-A on rhinitis have also been shown by previous studies. Rohrbach *et al.* used BTX-A sponge (Botox®) and compared its effect to saline as a control. Their findings show that this non-invasive method can reduce the symptoms of AR in patients with resistant idiopathic rhinitis.¹⁰ In a placebo-controlled trial, two units of BTX-A was injected into the middle turbinate and two units into the inferior turbinate of each nasal cavity. Results demonstrated that rhinitis symptoms were significantly diminished in BTX-A group compared to the control.¹⁶ Another study showed decrease in vasomotor rhinitis using 10 and 20 IU of BTX-A (Botox®) injected into the inferior and middle turbinates.¹⁸ A recently published study also showed that septal injection of BTX-A in patients with idiopathic rhinitis could effectively control the symptoms.¹⁹ These studies, however, did not compare the effect BTX-A with conventional treatments for AR. In this regard, one study compared the effect of injected BTX-A to ipratropium

bromide nasal spray. Investigators reported that these two reagents display a similar degree and duration of efficiency in upper respiratory symptoms.²⁰ Another placebo-controlled trial compared the injected BTX-A (Botox®) with injected triamcinolone and found that BTX-A may provide a better treatment for AR symptoms.¹¹

Uses different doses of Botox® from 5 to 40 units for each turbinates^{10,18,20} as well as routes of application (inferior vs. middle turbinate¹⁶) and different methods (injection or applying with sponge) for BTX-A administration can explain the differences found between findings of other studies and our results. We applied 75 IU of a different trade (Dysport®) equal to 25-30 units of Botox® for each turbinate and it seems that lower doses of BTX-A can be as effective. A well designed comparative study is required to demonstrate the minimum effective dose and compare the invasive vs. non-invasive methods of BTX-A administration. Another important point is that in some studies the effect of BTX-A was compared to saline as a control,^{11,21} showing a significant improvement in AR symptoms; however, comparing the effectiveness of BTX-A with other medications showed equivocal results indicating that BTX-A may not replace the previous treatment strategies in uncomplicated cases.

The limitation of our study is a difficulty to conduct a real double-blinded study by injecting normal saline in the control group because it is an invasive procedure. Although the two groups were matched in demographic and baseline clinical variables, they were differences regarding baseline quality of life that can be explained by small samples size. We suggest long time follow up of patients to demonstrate long-term effects of BTX-A injection.

Nasal injection of BTX-A has the same therapeutic effect as cetirizine in the management of allergic rhinitis. Since BTX is expensive, we cannot consider nasal injection of BTX-A as the first lines of allergic rhinitis management. However, it may be helpful to use the BTX-A in patients who are resistant to other treatments or those who have intolerance to current treatments including nasal corticosteroids or systemic antihistamines. Further studies with longer follow-ups are required to find long-term effects of BTX-A injection compared to other medications.

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