

## Botulinum Toxin Type A on an Intranasal Sponge for Chronic Allergic Rhinitis: Randomized Clinical Trial

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**Objectives:** In this study, we examined the effect of botulinum toxin A (BTA) on chronic allergic rhinitis (CAR). We tested the effects of BTA, applied to an intranasal sponge, on patients who had CAR for a minimum of three years and had been treated unsuccessfully with conventional medications.

**Method:** The study was an interventional case-control single-blind randomized clinical trial. Forty-four male and female CAR patients who were referred to Tehran's Saeed & Pasargad Hospitals, and Saadat-Abaad, Sarv and Karimkhan Clinics in 2012; aged 20-40 years were selected on the basis of inclusion and exclusion criteria. The subjects were randomly assigned to the intervention (n=22) or control group (n=22). The intervention group received BTA (100 IU/ml; Dysport), on a 5cm nasal sponge retained in each nasal cavity for 30 minutes. The control group received normal saline. The groups were evaluated by the same examiner. Pre- and post-tests (1, 3, 6, and 12 weeks) were performed according to the authors' pre-designed checklist, the validity and reliability of which was previously established. The symptoms scored from none (0) to severe (10) at the test points. The statistical analysis was conducted with SPSS-19, with a significance level of 0.05.

**Results:** Based on ANOVA, there was a significant difference ( $P<0.05$ ) in symptomatic relief between the intervention and control groups. No marked adverse effects were observed during the study.

**Discussion:** An intranasal 5cm sponge impregnated with 100 IU/ml BTA, retained in each nasal cavity for 30 minutes, may alleviate CAR symptoms with no significant adverse effects.

**Keywords:** Botulinum Toxin-A, disease rehabilitations, chronic allergic rhinitis, intranasal sponge, conventional medications, unsuccessful treatments, Botox, Dysport, Antihistamine, Corticosteroids, Intranasal injection

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### Introduction

Chronic allergic rhinitis (CAR) is an uncomfortable malady that affects many people around the world (1, 2). In the USA, the prevalence of CAR is 10%-20% and up to 2% of these cases are accompanied by other signs and sometimes fatal respiratory manifestations, including asthma (3). Several other studies have reported that CAR may be even more prevalent in other industrialized countries, including countries or states in the American continent, such as New York, Atlanta, New Mexico, USA, São Paulo in Brazil, and Toronto in Canada. In these places, the prevalence of CAR has been attributed to environmental triggering factors, such as Bioaerosols and ambient pollutants, including NO<sub>2</sub> particles (4). Similar meta-analytical research has

suggested that these environmental factors are the exacerbating causes (14) of allergic rhinitis in industrialized regions of the world (5). CAR may be associated not only with different geographic locations, but also with socioeconomic status in some populations (3). In several countries, CAR has been linked to genetic, familial, and cultural factors. The prevalence of this disorder in the Gulf States (15) is reported to be as high as 36% in all populations living in this region (6).

Because CAR disrupts the state of well-being (16), it influences many basic elements of an individual's life. The malady can affect some important daily activities, impairing school performance, various tasks, (17) productivity at work, and other normal duties, thereby diminishing the individual's quality

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of life (7). These effects clearly impose a high economic burden on countries in which the health status of the population is affected (18). A study has shown that in 2002, in the USA alone the economic burden directly attributable to CAR was \$4.195 billion, with an indirect cost of \$665 million (8). Therapies for CAR have been developed to reduce or even eliminate the symptoms that create the associated health problems. During attacks, symptoms appear and discomfort occurs. These symptoms have been categorized as A, B and C for ease of reference. Symptom A is itching (of the nose, eyes, or ears), symptom B is sneezing, and symptom C is a runny nose (rhinorrhea). These symptoms constitute the classical presentation of CAR (9). Because the ultimate etiology of CAR is unclear, different theories have been proposed, including autoimmune imbalance, airway hyper-reactivity, unidentified environmental allergens, and lack of nasal resistance in the sympathetic nerve endings (19), which are regulated by adrenaline and nor-adrenaline neurotransmitters (10). Some patients respond to conventional medical therapies, regardless of the pathogenesis of CAR.

Most traditional medical treatments, such as topical or systemic anticholinergic drugs (ipratropium) (20), short-term topical or systemic steroid therapies (fluticasone) (21), mast cell stabilizers (topical cromoglycate solution), and anticholinergic sympathomimetic drugs (imipramine), are accompanied by mild, moderate, and even severe or life-threatening adverse effects (11, 12).

There are many alternative treatments, including chemosurgery (22), beentrichloricmpted (23) such as chemosurgery with tricimmuno therapy (24), ultrasound immuno-intranasal rhino-surgery (25), ear acupuncture, and inferior turbinectomy (11-19). The continual repetition of these therapeutic modalities in response to the expected relapses in symptoms (although to different degrees), is part of the clinical profile of CAR. Most researchers seek a better remedy for CAR patients, with fewer adverse effects.

In the present study, we investigated the effects of botulinum toxin A (BTA) on CAR, the extent of these effects, and any undesirable adverse events that might exacerbate the existing symptoms in these patients. BTA, is a toxin produced by an anaerobic Gram-positive rod-shaped microorganism and is considered to be naturally potent (26). The refinement of this toxin and its formulation as a drug is considered an amazing medical breakthrough.

BTA offers extensive benefits to many people as a cosmetic pharmaceutical (20, 21) and to patients throughout the world with specific medical needs (22, 27). Its specific applications, especially in otorhinolaryngology, are noteworthy. The use of this toxin for disorders such as gummy smile, blepharospasm, bruxism, deglutition problems, sialorrhea, and voice disorders has been reported (28) by several investigators (21, 23-26). BTA therapy has also recently been proposed as a new treatment for CAR (27, 28) that may alleviate CAR symptoms without marked adverse effects. Its injection into the intranasal turbinates (29) and septal zones has been tested, and BTA injections into the intranasal covering mucosa, specifically in the septal region, have reduced the symptoms of CAR (27, 29). Other studies have shown that BTA injection into the middle and inferior turbinates can also ease CAR symptoms (28). Because these injections can be very painful, we administered BTA on intranasal sponges, and retained them in each nasal cavity for 30 minutes. This is an acceptable, easier (30) and painless mode of medicinal administration, which may therefore encourage clients to undertake therapeutic treatment. So intranasal sponges were used instead of injections in this study. Investigation was also undertaken to evaluate the effects of BTA as a remedy for patients who had suffered CAR for a minimum of three years, and to determine whether any adverse effects accompany this therapeutic modality or not (10,30,31).

## Methods

This was a case-control single-blind placebo-controlled randomized clinical trial. Initially, this clinical trial was registered at the Iranian Registry of Clinical Trials (IRCT registration code: irct201206079963N1) of the Ministry of Health and Medical Education.

The study subjects were CAR patients who had been referred to Tehran's *Sae & Pasargad* Hospitals, and *Saadat-Abad, Sarv & Karimkhan* Clinics in 2012. The initial sample selected for the study consisted of 84 patients. However, after the inclusion criteria were considered (age 20-40 years; sex distribution; CAR suffered for a minimum of three years; previous failure of conventional medication) and the exclusion criteria were applied to the initial sample (no informed consent; age below 20 or above 40 years; having other major systemic illness; history of oronasal surgery; having

other extranasal allergic manifestations such as asthma; history of allergy to BTA) as shown in Table (1), 44 patients were selected (22 men and 22 women, age 20-40 years). After permission was obtained from our institution's Research Ethics Committee and the research goals were explained to the patients, informed consents were obtained. The subjects were then randomly assigned to either the intervention (n=22) or control group (n = 22). The intervention group was treated with two standard, 5

cm nasal sponges, each impregnated with 100 IU/ml BTA (Dysport, Ipsen Ltd. -Burkshire, UK), inserted into both nasal cavities (200 IU/2ml BTA in total) for 30 minutes. The BTA (Dysport) dose was determined based on the average values determined in previous investigations (26,27,28 and 31) and after considering the potency of BTA (Botox) which is 3-4 times stronger (20) than in our country's available BTA (Dysport).

**Table 1.** Patients' inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Age	20-40	Below 20, above 40
Sex	Male=Female	
Chronic Allergic Rhinitis	Minimum of 3 years	Less than 3 years
Extra oronasal allergic manifestations	No	Yes
Systemic diseases	No	Yes
Unsuccessful traditional treatments	Yes	No
Informed consent (signed voluntarily)	Yes	No

The control group was treated with a placebo (normal saline). Both groups underwent pre- and post-tests, administered with the same method by the same examiner. None of the participants knew who was receiving BTA and who was receiving the normal saline treatments. CAR symptoms were evaluated in the pretest and in the post-tests after intervals of 1, 3, 6, and 12 weeks using a predefined symptom chart, designed and standardized by the authors. The content validity and reliability of the checklist was determined via a test-retest in two weeks apart, with a correlation coefficient of (r=80%). Symptoms A (itching of the nose, eyes, or ears), symptoms B (sneezing), and symptoms C (rhinorrhea) were ranked from none (0) to severe (10). The scores were collected and analyzed with SPSS version 19.

## Results

The mean ages of the men in the intervention and control groups were  $29.91 \pm 7.43$  and  $31.45 \pm 5.66$  years, respectively. Significant differences were found in the responses of the intervention and control groups at the time points tested ( $P < 0.001$ ). Overall significant differences were also found during the whole study period ( $P < 0.001$ ), but there were no significant differences in the responses of the sexes at any point ( $P = 0$ ). The statistical results are shown for symptoms A Table (2), symptoms B Table (3), and symptoms C Table (4) for the pretest and post-tests at 1, 3, 6, and 12 weeks.

**Table 2.** A1 scores at pre-test, post-test (1-week) and three follow-ups

		pre-test	1-week	3-week	6-week	12-week
<b>group case</b>	<b>gender (N)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
	<b>male (11)</b>	9.64 (0.505)	7.55 (1.036)	5.55 (1.293)	3.09 (0.944)	0.55 (0.522)
	<b>female (11)</b>	9.27 (0.647)	6.64 (0.809)	4.45 (0.934)	2.45 (1.128)	0.55 (0.522)
	<b>total (22)</b>	9.45 (0.596)	7.09 (1.019)	5.00 (1.234)	2.77 (1.066)	0.55 (0.510)
<b>control</b>	<b>male (11)</b>	9.64 (0.505)	9.64 (0.505)	9.45 (0.688)	9.36 (0.809)	9.36 (0.674)
	<b>female (11)</b>	9.64 (0.674)	9.64 (0.674)	9.64 (0.674)	9.45 (0.688)	9.36 (0.809)
	<b>total (22)</b>	9.64 (0.581)	9.64 (0.581)	9.55 (0.671)	9.41 (0.734)	9.36 (0.727)
<b>Time effect</b>			<b>F statistic</b>	458.570		
			<b>P-value</b>	<0.001		
<b>Time*group effect</b>			<b>F statistic</b>	398.989		

	pre-test	1-week	3-week	6-week	12-week
<b>Time*gender effect</b>		<b>P-value</b>	<0.001		
		<b>F statistic</b>	1.300		
<b>Time*group*gender effect</b>		<b>P-value</b>	0.277		
		<b>F statistic</b>	2.108		
<b>Post Hoc (group=case) Comparison of time points</b>					
			<b>Mean of difference</b>	<b>t statistic</b>	<b>P-value</b>
		<b>Pre-test vs. 1-week</b>	2.364	12.289	<0.001
		<b>1-week vs. 3-week</b>	2.091	11.300	<0.001
		<b>3-week vs. 6-week</b>	2.227	11.327	<0.001
		<b>6-week vs. 12-week</b>	2.227	9.069	<0.001

1: Itching (eyes, ears and nose) graded as none (0), to severe (10)

**Table 3.** B1 scores at pre-test, post-test (1-week) and three follow-ups

Group	Gender (N)	pre-test Mean (SD)	1-week Mean (SD)	3-week Mean (SD)	6-week Mean (SD)	12-week Mean (SD)
Case	Male (11)	9.09 (0.539)	6.82 (1.168)	5.09 (1.044)	2.45 (1.293)	0.55 (0.688)
	Female (11)	8.91 (0.701)	6.00 (0.894)	3.55 (0.820)	2.00 (0.894)	0.64 (0.505)
	Total (22)	9.00 (0.617)	6.41 (1.098)	4.32 (1.211)	2.23 (1.110)	0.59 (0.590)
Control	Male (11)	9.27 (0.647)	9.27 (0.647)	9.18 (0.603)	9.00 (0.447)	8.91 (0.539)
	Female (11)	9.18 (0.751)	9.09 (0.701)	9.09 (0.701)	9.00 (0.632)	9.00 (0.632)
	Total (22)	9.23 (0.685)	9.18 (0.664)	9.14 (0.640)	9.00 (0.535)	8.95 (0.575)
<b>Time effect</b>			<b>F statistic</b>	443.841		
			<b>P-value</b>	<0.001		
<b>Time*group effect</b>			<b>F statistic</b>	387.056		
			<b>P-value</b>	<0.001		
<b>Time*gender effect</b>			<b>F statistic</b>	4.598		
			<b>P-value</b>	0.004		
<b>Time*group*gender effect</b>			<b>F statistic</b>	3.145		
			<b>P-value</b>	0.025		
<b>Post Hoc (group=case) Comparison of time points</b>						
				<b>Mean of difference</b>	<b>t statistic</b>	<b>P-value</b>
			<b>Pre-test vs. 1-week</b>	2.591	10.655	<0.001
			<b>1-week vs. 3-week</b>	2.091	11.300	<0.001
			<b>3-week vs. 6-week</b>	2.091	12.090	<0.001
			<b>6-week vs. 12-week</b>	1.636	6.521	<0.001

1: Sneezing graded as none (0), to severe (10)

**Table 4.** C1 scores at pre-test, post-test (1-week) and three follow-ups

Group	Gender (N)	pre-test	1-week	3-week	6-week	12-week
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Case	male (11)	9.09 (0.831)	6.73 (1.272)	4.55 (1.440)	1.64 (1.027)	0.55 (0.522)
	female (11)	9.00 (0.775)	6.27 (0.905)	4.18 (1.250)	1.91 (1.136)	0.45 (0.522)
	total (22)	9.05 (0.785)	6.50 (1.102)	4.36 (1.329)	1.77 (1.066)	0.50 (0.512)
Control	male (11)	9.00 (0.775)	9.00 (0.775)	9.09 (0.701)	8.91 (0.701)	8.91 (0.701)
	female (11)	9.09 (0.831)	9.09 (0.831)	9.09 (0.831)	9.09 (0.831)	9.00 (0.894)
	total (22)	9.05 (0.785)	9.05 (0.785)	9.09 (0.750)	9.00 (0.756)	8.95 (0.785)
<b>Time effect</b>			F statistic	336.519		
			P-value	<0.001		
<b>Time*group effect</b>			F statistic	323.649		
			P-value	<0.001		
<b>Time*gender effect</b>			F statistic	0.782		
			P-value	0.511		
<b>Time*group*gender effect</b>			F statistic	0.385		
			P-value	0.772		
<b>Post Hoc (group=case)</b>						
<b>Comparison of time points</b>						

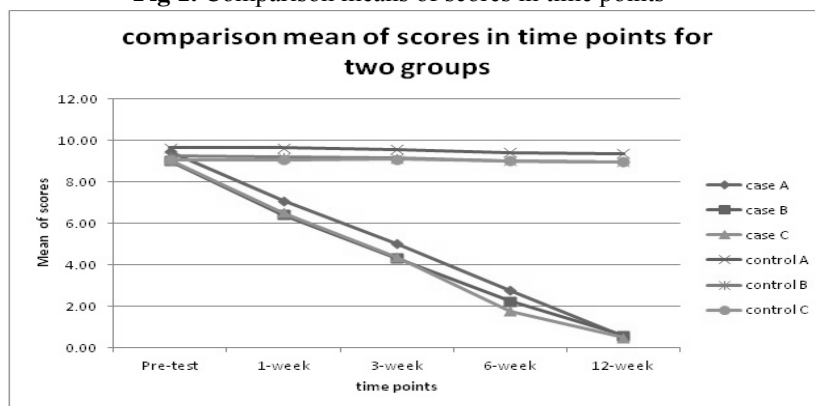
	Mean of difference	t statistic	P-value
Pre-test vs. 1-week	2.545	8.710	<0.001
1-week vs. 3-week	2.136	8.044	<0.001
3-week vs. 6-week	2.591	9.951	<0.001
6-week vs. 12-week	1.273	5.785	<0.001

1: Rhinorrhea graded as none (0), to severe (10).

When the mean scores for the intervention and control groups were compared at each time point, it was clear that BTA had alleviated symptoms A (itching of the nose, eyes, or ears), symptoms B (sneezing), and symptoms C (rhinorrhea) in the intervention group. These effects were more

pronounced for symptoms B and C than for symptoms A at the 6-week time point, but after 12 weeks, the effects on all symptoms were identical Fig (1). No significant adverse effects were noted during the period of the trial.

**Fig 1.** Comparison means of scores in time points



## Discussion

CAR is a difficult problem that affects many people around the world. Because it influences the quality of life of individuals and affects many of the basic elements of life, different remedies based on diverse conventional medical approaches have been tested. Some of these therapies have failed and have even had undesirable effects, and some patients have relapsed, with adverse effects too. In these circumstances, patients must take a variety of medicines repeatedly.

Recently, various investigations have examined the effects of BTA on CAR, after its injection into the intranasal middle and inferior turbinates. Other studies have administered BTA into the intranasal mucosal surface and the septal zones by injections. Because these injections are painful, a less invasive mode of treatment has been investigated, such as the application of BTA into each nasal cavity via intranasal sponges.

In the present study, we used this painless approach to observe the effects of BTA, applied to an intranasal sponge, on selected patients who had suffered CAR for a minimum of three years and had been treated unsuccessfully with conventional medical therapies. After assessing the doses of BTA used in other studies, and taking into

consideration that BTA in the form of Botox is 3-4 times more potent than BTA (Dysport), we chose 100 IU of available BTA (Dysport), applied to intranasal sponges placed in each nasal cavity for 30 minutes.

We compared the results of this more convenient and less irritating method with those of other therapeutic modalities, such as BTA injection, and found that BTA (Dysport) may be used safely and effectively in selected patients with CAR, who had been treated with conventional medications with no clinical improvement and who still felt unwell. The major limitation of this therapeutic approach is the high cost of the BTA medication. Further research in different geographic regions is recommended.

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