The Effect of Turbinate Injection of Botulinum Toxin A on the Symptoms of Idiopathic Rhinitis

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Abstract

Introduction Idiopathic rhinitis is a nonallergic and noninfectious rhinitis characterized mainly by nasal obstruction and rhinorrhea, resulting from an autonomic imbalance. Botulinum toxin type A (BTX-A) demonstrated its action in reducing rhinorrhea and nasal obstruction when injected into the nasal turbinates or septum.

Objective To analyze the effects of intranasal BTX-A injection to control the symptoms of idiopathic rhinitis and its possible adverse effects.

Method Patients with idiopathic rhinitis were divided into two groups. Group A had 15 participants (8 female and 6 male), of ages from 47 to 84 years (mean 66.57 years), and these received 60 U of Dysport (Ipsen Ltd, Maidenhead, Berkshire, UK) in each inferior nasal turbinate; group B had 12 participants (1 male and 11 female), of ages from 50 to 76 years (mean 60 years), and they received 1 ml of 0.9% saline. The individuals were reevaluated in the 1st, 2nd, 4th, 8th, and 12th weeks after injection by a questionnaire, accompanied by nasal inspiratory peak flow and acoustic rhinometry.

Results Group A showed significant improvement, mainly regarding the symptoms of sneezing/itching and nasal obstruction, over time and when compared to group B. Acoustic rhinometry confirmed the improvement in nasal obstruction. There was no relationship between the nasal peak flow data and the nasal obstruction score. No major adverse effects have been reported.

Conclusion The injection of botulinum toxin in the inferior nasal turbinates of patients with idiopathic rhinitis reduces the symptoms of sneezing, itching, nasal obstruction, and runny nose without significant adverse effects, suggesting that it is an option in the treatment of these patients.

Keywords
- rhinitis
- botulinum toxin
- nasal obstruction
- pruritus
- acoustic rhinometry
- therapeutics

Introduction

Rhinitis is defined as inflammation of the nasal mucosa, which is characterized by nasal discharge, itching, sneezing, and nasal obstruction and affects approximately 30% of the population.[1,2] Classically, rhinitis is classified as allergic, infectious, nonallergic noninfectious, or mixed rhinitis.[2,3] Idiopathic rhinitis, known in the past as vasomotor rhinitis, is a type of non-allergic and non-infectious rhinitis, and it is not related to systemic diseases, structural injuries, or drug abuse. Therefore, its diagnosis is based on the exclusion of all other groups of rhinitis, through clinical history, allergic test, nasal cytological examination and rhinoscopy.[2–4] The main symptoms are nasal obstruction and

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rhinorrhea, with no evidence of allergic sensitization, which can be perennial/persistent and/or with recognized triggering factors.

Idiopathic rhinitis still does not have its pathophysiology completely elucidated; however, some studies suggest the existence of an autonomic imbalance with inhibition of the sympathetic nervous system response in the nose and hyperactivity of the parasympathetic system leading to nasal obstruction and increased glandular secretion.[5,6] Other mechanisms found in idiopathic rhinitis include the participation of the nonadrenergic, noncholinergic system (NANC). Nonspecific stimuli in the nasal mucosa can activate nonmyelinated sensory C-fibers, releasing neuropeptides, thus contributing to the symptoms of patients with idiopathic rhinitis.[6] Some authors suggest that nasal hyperreactivity may be related to the release of substance P through trigeminal terminations, leading to vasodilation and increased vascular permeability.[7]

The treatment of idiopathic rhinitis includes long-term use of decongestants, intranasal ipratropium bromide, and antihistamines, and there are some potential side effects. Nasal steroids may be a treatment option, but their effectiveness is not consistent.[3] Azelastine has shown a reduction in nasal sensitivity to odors in patients with nonallergic rhinitis.[8] Capsaicin can be used in the treatment of idiopathic rhinitis, although there is still no standardization regarding its form of use.[3,9] The vidian neuroctomy nerve can be used to treat refractory rhinitis, especially nonallergic rhinitis; nonetheless, it has a high rate of complications, especially when not performed by the endonasal route.[10]

Botulinum toxin is a neurotoxin produced by *Clostridium botulinum* that inhibits the release of acetylcholine from presynaptic nerve fibers. There are seven antigenic types of botulinum toxin, divided from A to G.[11] Due to its great anticholinergic action at the neuromuscular junction, botulinum toxin type A (BTX-A) is used in a wide spectrum of conditions characterized by muscle hyperactivity or by increased glandular secretion.[11,12] Botulinum toxin has been used in the treatment of several non-cosmetic conditions in the head and neck area, such as laryngeal dystonia, headache, cervical dystonia, masticatory myalgia, drooling, temporomandibular joint disorders, bruxism, blepharospasm, and hemifacial spasm, with level 1 evidence of effectiveness.[12]

The effect of BTX-A on glandular secretion is well demonstrated through its use in Frey syndrome, hyperhidrosis, and sialorrhea.[13] Some studies have shown the action of BTX-A on the nasal mucosa with reduced rhinorrhea and nasal obstruction, suggesting an important role in the control of symptoms of rhinitis when injected into the nasal turbinates or septum. The aim of the present study was to analyze the effects of intranasal injection of BTX-A on the control of idiopathic rhinitis symptoms, as well as to evaluate some objective patterns such as nasal peak flow and acoustic rhinometry and possible adverse effects.

Method

The study was approved by the research ethics committee under the number 0333/09, and all individuals received and signed a free and informed consent form. Patients with clinical symptoms suggestive of idiopathic rhinitis were selected. All patients underwent nasal endoscopy, immediate hypersensitivity skin test (prick test) with common inhaled antigens in our environment, listed on ►**Table 1**, and nasal cytological examination.

Table 1 Inhaled antigens tested

Mites	- *Dermatophagoides pteronyssinus* - *Dermatophagoides farinae* - *Blomia tropicalis*
Mold	- *Alternaria alternata* - *Cladosporium herbarum* - *Aspergillus fumigatus*
Cockroaches	- *Blatella germânica* - *Periplaneta americana*
Animal antigens	- *Canis familiaris* - *Felis domesticus*
Pollens	- *Phleum pratense* - *Lolium perenne* - *Dactylis glomerata* - *Festuca pratensis*

The inclusion criteria were:

A) Patients over 18 years old who signed the free and informed consent form and understood the explanation of the study, carried out by the researcher himself.
B) Patients of both sexes, regardless of race.
C) Patients diagnosed with idiopathic rhinitis for at least 1 year, that is, patients in whom other rhinitis etiologies (allergic rhinitis, non-allergic eosinophilic, medication, hormonal, drug and occupational) were excluded through clinical history, physical examination, nasal cytological examination with eosinophils below 2% and skin test for immediate hypersensitivity to negative inhalants.

The exclusion criteria were:

A) Patients with other nasal anatomical abnormalities, such as nasal polyposis or obstructive nasal septum deviation.
B) Patients with acute or chronic rhinosinusitis.
C) Patients with severe systemic diseases, glaucoma, or prostatic hypertrophy that can be aggravated by anticholinergic therapy.
D) Patients with positive immediate hypersensitivity skin test for inhalants, and nasal cytological exam with eosinophilia greater than 2%.
E) Patients who received rhinitis medications before the immediate hypersensitivity skin test for inhalants according to ►**Table 2**.
F) Patients with possibility of pregnancy.

The patients were randomly divided into two groups, the group that received BTX-A and the control group. Each BTX-A bottle (Dysport, Ipsen Ltd, Maidenhead, Berkshire, UK) contains a 500 U dose, which was diluted in saline. After topical nasal injection of lidocaine with soaked cotton, a 60 U dose of Dysport was injected, equivalent to 20 U of BTX-A Botox, diluted in 1 ml and divided into the head and body of the

Table 2 Drugs that affect the efficiency of skin prick tests

	Supression		
	Degree	Duration (days)	Clinical significance
H1 antihistamines			
Cetirizine	++++	3-10	Yes
Chlorferinamine	++	1-3	Yes
Desloratadine	++++	3-10	Yes
Ebastine	++++	3-10	Yes
Hydroxyzine	+++	1-10	Yes
Levocabastine (topical)	Possible		Yes
Levocetirizine	++++	3-10	Yes
Loratadine	++++	3-10	Yes
Mequitazine	++++	3-10	Yes
Mizolastine	++++	3-10	Yes
Promethazine	++	1-3	Yes
Ketotifen	++++	> 5	Yes
H2 antihistamines			
Imipramines	++++	> 10	Yes
Phenothiazines	++	?	Yes
Glucocorticosteroids			
Systemic, short period	0		
Systemic, long period	Possible		Yes
Inhaled	0		
Topic (skin)	0 to ++		Yes
Cromolyn	0		
β2 agonists			
Formoterol	Unknown		
Dopamine	Unknown		
Clonidine	++		
Montelukast	0		

inferior nasal turbinate of each nasal cavity in group A (total of 40 U/subject). In group B, after topical nasal application of lidocaine, 1 ml of 0.9% saline solution was injected, divided into the head and body of the inferior nasal turbinate of each nasal cavity. Simple randomization and preparation of the syringe were performed by another professional who performed the injection. Neither the professional who performed the injection nor the research subjects knew the syringe content.

The individuals were reevaluated in the 1st, 2nd, 4th, 8th and 12th weeks after the injection of BTX-A, according to the schedule detailed in ►**Table 3**. At each visit, they answered a questionnaire about the symptoms (nasal obstruction, rhinorrhea, pruritus, and sneezing) which were classified from 0 to 3, according to the score of signs and symptoms proposed by Mello Jr.,[14] described in ►**Table 4**, accompanied by nasal inspiratory peak flow and acoustic rhinometry. The professional who performed the evaluations did not have the information of which group the subject belonged to.

An Eccovision Acoustic Rhinometry System (Eccovision Nasal Version 4.40; Hood Laboratories, Pembroke, MA, USA) was used. The measurements were made according to the guidelines recommended by the Standardization Committee on Objective Assessment of the Nasal Airway.[15] The nose piece did not enter the vestibule.

The nasal inspiratory peak flow was measured 3 consecutive times with a 1-minute interval between them. The examination technique consisted of measuring the nasal inspiratory flow of the seated patient, with the device positioned on the face, completely covering the nose through a small, well-sealed mask connected to a plastic cylinder through which the forced inspired air passes. The measurement was performed on a scale with the mark on the cylinder surface that varies between 30 to 370 liters/minute.

Statistical analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (GraphPad Software, Inc, La Jolla, CA, USA). The Mann-Whitney test was used to compare the groups, and linear regression was used to assess the evolution of symptoms over time. The repeated measures test was used to analyze the changes within and between the groups. Multivariate analyses were conducted where needed. A p-value of < 0.05 was considered significant.

Results

Group A (BTX-A) had 15 participants (8 female and 6 male), of ages from 47 to 84 (mean 66.57 years). Group B (control) had 12 participants (1 male and 11 female) of ages from 50 to 76 (mean 60 years), presented in ►**Table 5**. We noticed a

Table 3 Schedule

	Physical examination	Skin prick test	Peak flow	Nasal cytology	VAS	Acoustic rhinometric
Day 0	+	+	+	+	+	+
Week 1	+		+		+	+
Week 2	+		+		+	+
Week 4	+		+		+	+
Week 8	+		+		+	+
Week 12	+		+		+	+

Table 4 Score of nasal signs and symptoms

Symptoms	Signs
Sneezing/itching 0- Absent 1- 1 to 4 per day/occasional itching 2- 5 to 10 per day/sporadic itching for 30 minutes 3- 11 or more/interferes with sleep and/or concentration Runny nose 0- Absent 1- Cleaning 1 to 4 times a day 2- Cleaning 5 to 10 times a day 3- Constant cleaning Nasal obstruction 0- Absent 1- Small and not disturbing 2- Mouth breathing most of the day 3- Does not breathe through the nose / interferes with sleep, smell or voice Retro-nasal secretion 0- Absent 1- Sensation of secretion in the throat 2- Frequent throat cleaning 3- Cough and discomfort when speaking oropharynx	Nasal secretion 0- Absent 1- The mucosa appears moist 2- Visible secretion in the turbinates or nasal floor 3- Profuse/draining Color of the nasal turbinates 0- Rosy 1- Reddish/pale pink 2- Red/pale 3- Anemic/bluish Edema of the nasal turbinate 0- Absent 1- Hypertrophy of the inferior or middle turbinate with small nasal block 2- Congestion compromising breathing in one or both nasal cavities 3- Congestion preventing breathing in one or both nasal cavities Posterior wall of the oropharynx 0- Normal 1- Discreetly red 2- Hyperemic and apparent lymphoid follicles 3- Visible mucus

Adapted from Mello Jr 2002.

Table 5 Sample descriptive

	Group A (n = 15)	Group B (n = 12)	*p*-value
Gender			
Female	8	11	*
Male	6	1	
Age[a] (years)	47–84	50–76	
Mean[b]	66.57 ± 10.2	60 ± 7.88	0.0996

[a]Teste de Wilcoxon.
[b]Data are presented as mean ± standard deviation.
*As the contingency table has a value less than 5, it was not possible to do the chisquare test.

Table 6 Symptom score from baseline to 12th Week.

Week	TXB-A N = 15	Control N = 12	*p*-value[a]
Baseline	10.9 ± 3.65	10.9 ± 2.31	0.9892
1	8.87 ± 4.21	8.73 ± 2.41	0.9225
2	6.50 ± 3.03	9.33 ± 2.87	0.0121
4	6.14 ± 2.44	8.64 ± 2.46	0.0087
8	6.08 ± 2.47	7.75 ± 2.05	0.0695
12	5.53 ± 1.68	9.00 ± 2.93	0.0008
p-value[b]	< 0.001	< 0.001	
p-value[c]	0.0252		

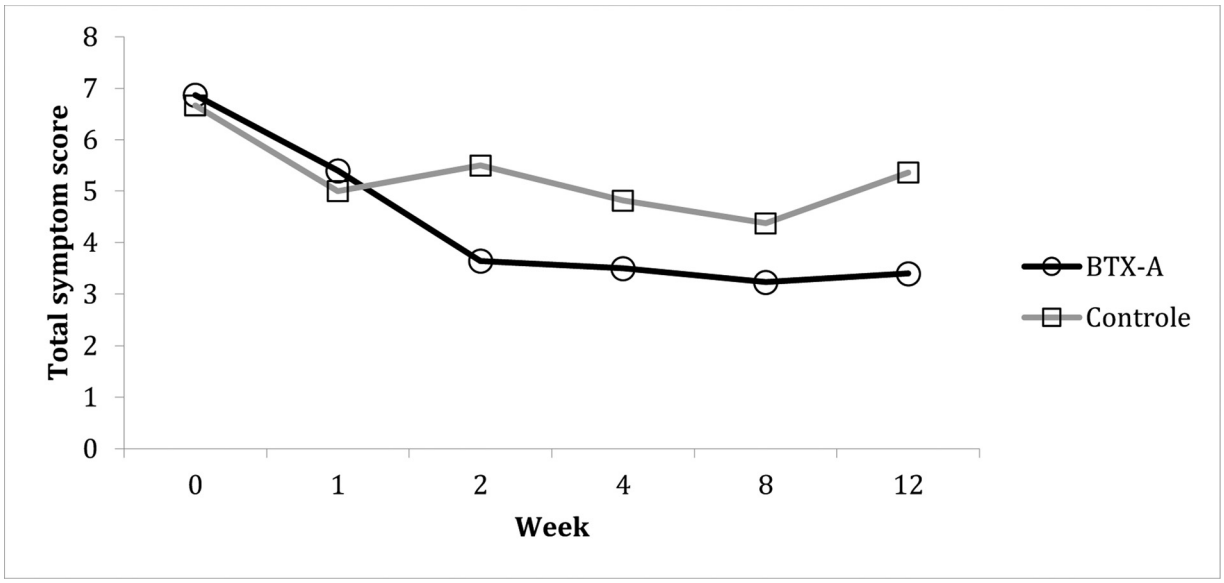
Data are presented as mean ± standard deviation.
[a]Mann-Whitney test.
[b]Repeated measure within group.
[c]Repeated measure between group.

difference between the groups in terms of gender but not in terms of ages. As the contingency table has a value < 5, it was not possible to perform the chi-squared test. However, linear regression shows that age and gender are not significant determining the score difference between the groups in the 12th week (p-value = 0.0241, adjusted R-squared = 0.2745).

The two groups were similar with regards to nasal signs and symptoms score at baseline, as shown in ►**Table 6**. The symptoms showed improvement after 1 week, but the statistical difference between the 2 groups appeared only in the 2nd week. The improvement in the score was due to the symptoms of sneezing/itching and runny nose. In the 12th week, group A still showed improvement in scores when compared to baseline and to the control group.

Graph 1 shows the evolution of total symptoms throughout the study, and it was found that the group that received the injection of botulinum toxin showed a statistically significant improvement, according to the Mann-Whitney test and presented in ►**Table 6**. Comparison of each item of the nasal signs and symptoms score from baseline to the 12th week in the 2 groups is presented in ►**Table 7**. The symptoms of sneezing/itching and nasal obstruction showed significant improvement when compared to the control group, shown in **Graphs 2** and **3**. In the botulinum toxin group, we observed an important improvement in rhinorrhea over 12 weeks. However, when we analyzed the placebo group using the Mann-Whitney test ($p = 0.048$), the statistical difference appeared only in the 12th week, represented in **Graph 4**. There was no difference between the groups nor over the 12 weeks in the score of retro nasal secretion.

Acoustic rhinometry confirmed the improvement in nasal obstruction over the 12 weeks ($p = 0.002$), even when compared to the control group, shown after the 2nd week ($p = 0.014$). There was no relationship between the nasal peak flow data and the nasal obstruction score. No major adverse effects were reported, only mild burning during



Graph 1 Comparison of the total symptom score between the group that received BTX-A and the control group over the 12 weeks.

Table 7 Comparison of each item of nasal signs and symptoms score from baseline to the 12th Week in the two groups.

		BTX-A		p^*	Control		p^*
		N = 15			N = 12		
		Baseline	12th Week		Baseline	12th Week	
Symptom	Sneezing/itching	1.87 ± 1.13	0.87 ± 0.64	0.092	1.92 ± 0.90	1.82 ± 0.98	0.897
	Runny nose	2.53 ± 0.83	1.13 ± 0.64	< 0.001	2.17 ± 1.03	1.82 ± 0.75	0.270
	Nasal Obstruction	1.20 ± 1.15	0.40 ± 0.51	< 0.05	1.42 ± 1.00	0.82 ± 0.98	0.147
	Retro-nasal secretion	1.27 ± 1.03	1.00 ± 0.85	0.4822	1.17 ± 0.83	0.91 ± 0.54	0.490
Total (symptoms)		6.47 ± 2.50	3.40 ± 1.30	< 0.001	6.67 ± 1.44	5.36 ± 2.29	0.127
Signs	Color of the nasal turbinates	1.87 ± 0.52	1.27 ± 0.46	< 0.01	1.83 ± 0.39	1.82 ± 0.40	0.963
	Edema of the nasal turbinate	1.07 ± 0.70	0.2 ± 0.41	< 0.001	1.00 ± 0.60	0.82 ± 0.40	0.447
	Nasal secretion	0.67 ± 0.62	0.40 ± 0.51	0.2396	0.83 ± 0.58	0.64 ± 0.67	0.422
	Posterior wall of the oropharynx	0.47 ± 0.52	0.27 ± 0.46	0.2745	0.58 ± 0.67	0.36 ± 0.50	0.459
Total (signs)		4.07 ± 1.44	2.13 ± 0.99	< 0.001	4.25 ± 1.42	3.64 ± 1.12	0.343
Total score:		10.53 ± 3.11	5.53 ± 1.68	< 0.001	10.92 ± 2.31	9.00 ± 2.93	0.087

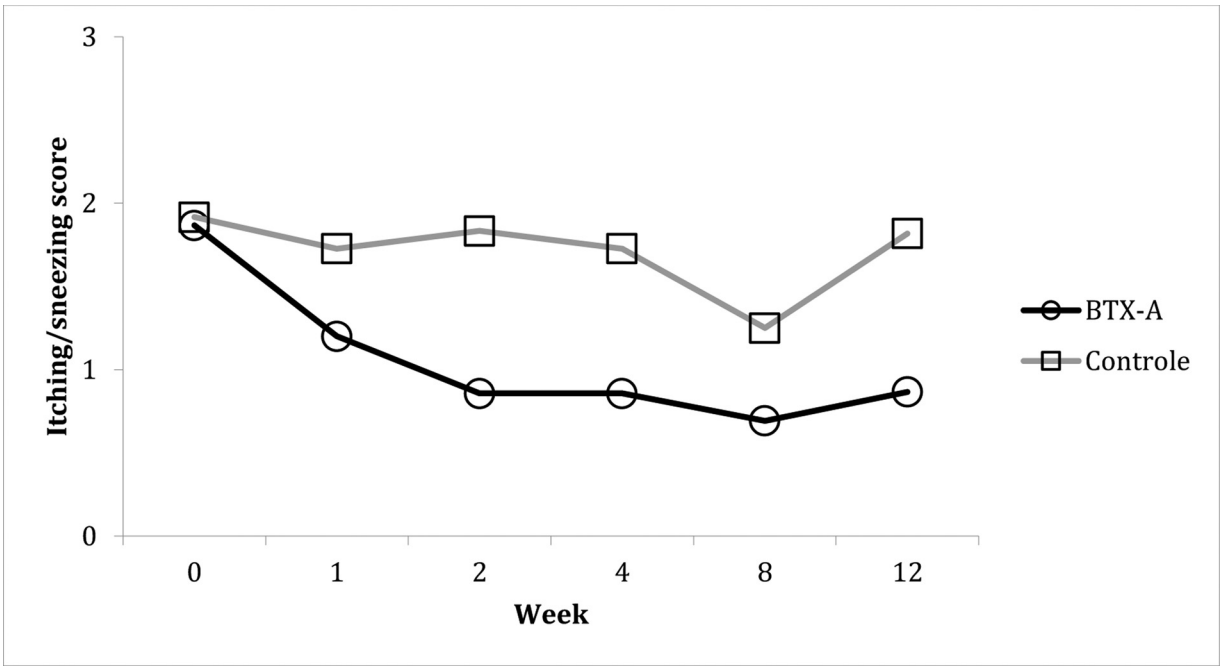
Data are presented as mean ± standard deviation.
BXT-A, botulinum toxin A.
*Wilcoxon test.

injection in four patients and mild self-limited bleeding in two patients.

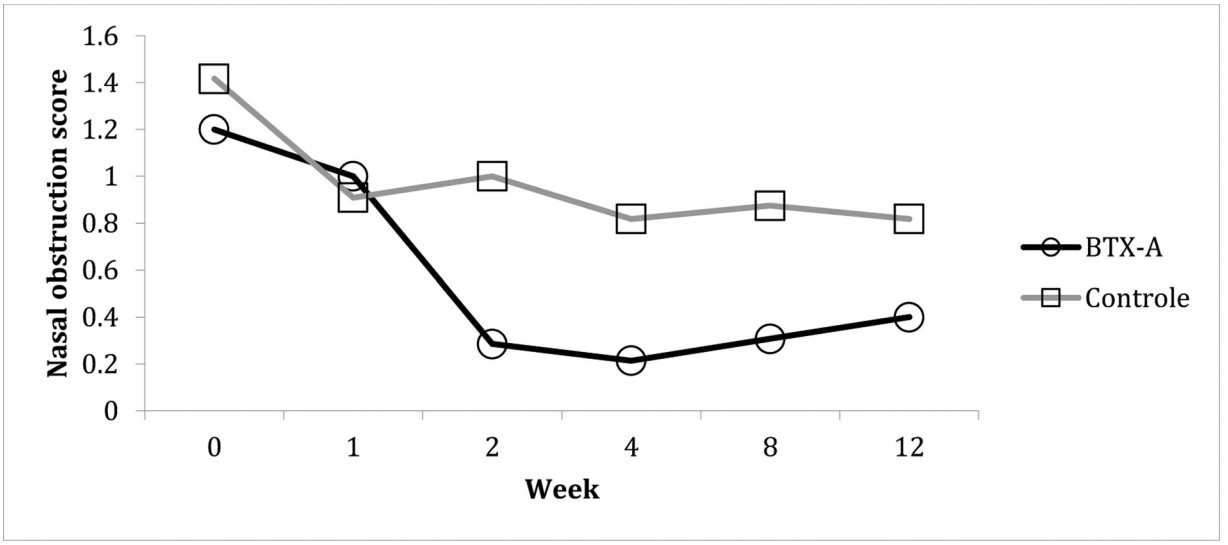
Discussion

We demonstrated a decrease in nasal symptoms of patients with idiopathic rhinitis after the injection of botulinum toxin in the inferior nasal turbinates without showing significant adverse effects. Botulinum toxin type A has been tested for idiopathic rhinitis since 1998,[16] under different regimens, all with favorable results. The topical route uses a greater amount of toxin (20-50U/nostril x 4-30U/nostril) and does not allow quantifying the medication absorbed. When the injectable route was used, the sites chosen were the inferior turbinate, the middle turbinate and the anterior portion of the septum. Braun et al., in 2012, carried out a pilot study with 5 patients who received 80 U of BTX applied to the septum, obtaining symptom improvement without significant discomfort during injection.

Considering that the anterior portion of the inferior turbinate has more mucous glands, and the anterior portion of the septum has more serous glands,[17] the hypothesis of different results was raised according to the application site. Abtahi et al., in 2013, observed an improvement in symptoms



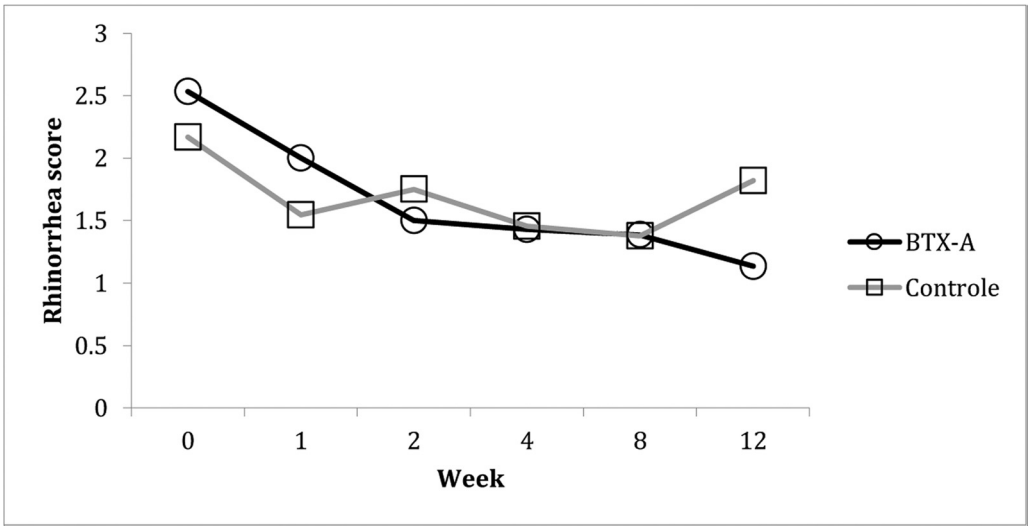
Graph 2 Comparison between the group that received BTX-A and the control group regarding itching and sneezing over the 12 weeks.



Graph 3 Comparison between the group that received BTX-A and the control group regarding nasal obstruction over the 12 weeks.

both in the group that received the injection in the turbinates and in the septum, showing that there was no difference in effectiveness. However, the occurrence of adverse effects (epistaxis) reported was greater when the application was in the turbinate. The same author considered septal injection to be safer and technically easier.[18] Mozafarinia et al., in 2015, also suggested that the subperichondrial septal injection could have a more prolonged effectiveness due to the lower clearance of the drug, obtaining the peak of symptom improvement in the 4th week, with gradual return to the initial levels in the 12th week. Nevertheless, these results were not superior to the studies that applied the substance to the inferior turbinates,[19,20] including the present study, in which the effects lasted until the 12th week.

The symptoms involved in rhinitis are assessed with subjective tests using symptom scores and visual analog scales. Rohrbach et al., in their 2001 case report, counted the tissues used to assess rhinorrhea and rhinomanometry to quantify nasal permeability, noting an improvement in all parameters.[21] In 2009, these same authors, now with 17 patients, used the tissue count and obtained an improvement in the complaint of rhinorrhea and a decrease in the number of tissues.[20] The other studies used symptom scales to assess the subjects' evolution. The improvement in nasal obstruction has been observed in most studies, which has led us to introduce two objective measures of nasal permeability: nasal peak flow and acoustic rhinometry. In the present study, a significant improvement in nasal obstruction was



Graph 4 Comparison between the group that received BTX-A and the control group regarding rhinorrhea over the 12 weeks.

observed, confirmed by acoustic rhinometry. This improvement in nasal obstruction can be attributed to the parasympathetic nervous system block, a greater manifestation of sympathetic stimuli (vasoconstriction) resulting in a decrease in the volume of the turbinates.

We observed improvement in other symptoms such as itching and sneezing, which also occurred in most studies. In 1998, Kim et al. injected 4 U of BTX-A per nostril, observing a reduction in rhinorrhea, but it did not improve nasal obstruction and sneezing.[16] Unal et al., in 2003, conducted a randomized, placebo-controlled study with 34 patients that showed improvement in sneezing and itching only in the first 2 weeks, using 20 and 30 U BTX-A infiltration.[22] In 2006, a randomized, placebo-controlled study was conducted in 30 patients with idiopathic rhinitis divided into 2 groups, 1 and 2, that received infiltration of 5 and 10 U of BTX-A respectively, in which only group 2 showed improvement in nasal itching for 8 weeks.[23] The effect on sneezing and itching may be related to the dose applied.

Comparison with other medications has shown the superiority of botulinum toxin. In 2008, a prospective, randomized, placebo-controlled study of 38 patients with idiopathic rhinitis compared the effectiveness of applying BTX-A (5 U per nostril) with the use of topical nasal ipratropium bromide and observed an improvement in symptoms and duration of similar effect in both groups.[24] However, botulinum toxin showed a more comfortable dosage, with a single dose and lasting 8 to 12 weeks, while ipratropium bromide requires 2 to 3 daily applications and is not available in Brazil. Still in 2008, Yang et al. showed better results when compared to injectable triamcinolone in the inferior turbinates.[19]

Allergic rhinitis patients have also shown significant improvement in symptoms after receiving botulinum toxin. In 2003, a randomized, placebo-controlled study of 34 patients with allergic rhinitis showed improvement in rhinorrhea, nasal obstruction, sneezing and itching using 20 and 30 U BTX-A infiltration.[22] In 2008, another study compared the infiltration of 25 U of BTX-A in each nostril with the infiltration of triamcinolone in 39 patients with allergic rhinitis and observed a significant improvement in rhinorrhea and nasal obstruction in the BTX-A group, including superior to that of steroid.[19] In 2013, Hashemi et al. compared the effects of applying intranasal BTX-A with the use of 10 mg/day cetirizine in patients with allergic rhinitis and observed similar improvement in symptoms in both groups. However, there was a high rate of drowsiness (44%) in the group that received cetirizine.[25] Abtahi et al., in 2013, demonstrated an improvement in nasal symptoms after the injection of 40U of intranasal BTX-A (Dysport) in patients with allergic rhinitis, both when applied to the anterior septum and the lower turbinate.[18]

Studies with injection of botulinum toxin in other places for different conditions have shown variable adverse effects, in some cases severe.[11] Nevertheless, botulinum toxin has been shown to be very safe for nasal use, both topically and injectable septal or in the turbinates, with no significant adverse effects reported in any of the studies. The main adverse effects described were mild epistaxis and nasal dryness. In the present study, we observed only mild burning sensation at the time of application (4 subjects) and mild, self-limited bleeding (2 subjects).

Apoptosis of nasal secretory glands observed in guinea pigs 10 days after receiving BTX-A and no longer after 3 months suggests a transient effect.[26] Histological changes and clinical improvement show that BTX-A has some effects on the pathophysiology of idiopathic rhinitis and allergic rhinitis.

To reduce the risk of bias, we observed the limitations of previous studies. As for the route of administration, we opted for the injectable method for better control of the therapeutic dose when compared to topical administration with soaked sponges. In addition, the topical route requires a higher dose of BTX-A, which is a relatively expensive medication. We tried to match the control group as precisely as possible, using the same type of syringe and needle, with the same volume, injecting in the same places. Furthermore, both the patient and the professional who applied the injection were blinded to

the contents of the syringes. The follow-up time was 12 weeks, longer than most previous studies, to try to better estimate the duration of the effect of BXT-A. The limitation of the present study is regarding the randomization process. We used simple randomization to divide the groups, which is a method that has some limitations.[27] Block randomization, computer-generated randomization list, or a randomized numbers' list to divide the research groups is more advisable.[27] Despite the difference between the groups in terms of gender, it was not a significant factor in determining the scores of the groups.

Conclusion

The injection of botulinum toxin in the inferior turbinates of patients with idiopathic rhinitis reduces the symptoms of sneezing, pruritus, nasal obstruction, and runny nose, with no significant adverse effects, suggesting that it is an option in the treatment of these patients. However, further studies are needed to assess the type of toxin to be used (since BTX-D has a greater effect on the neuro glandular junction), form of application (topical or injectable), local (middle, inferior, or septal turbinate), dose, and what would be the expected effects (runny nose, obstruction, itching, sneezing).

Conflict of Interests
The authors have no conflict of interests to declare.

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