Effect of combined septal and turbinate injection of botulinum toxin type A in allergic rhinitis

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Objective
Allergic rhinitis (AR) has increased in prevalence recently, and traditional treatment strategies sometimes show limited effectiveness for patients with intractable AR. Botulinum toxin type A (BTX-A) is among the increasingly used alternative treatment options. This study was carried out with the aim of performing a clinical assessment of the effect of combined septal and turbinate injection of BTX-A for the management of uncontrolled AR.

Materials and methods
A single-arm pilot study enrolled 40 patients with moderate to severe uncontrolled AR recruited between October 2018 and August 2019. Each patient received 45 units of BTX-A injected into three fixed points of each side of the nose: inferior turbinate (15 IU), middle turbinate (15 IU), and nasal septum (15 IU). All patients were evaluated in terms of nasal hypersecretions, congestion, and sneezing with a visual analog scale before treatment and at weeks 1, 2, 4, 8, and 12 during the follow-up period.

Results
Throughout the 12-week follow-up period, a significant difference in the degree of nasal hypersecretions could be identified before and after BTX-A injection. Sneezing differed significantly only in the first 4 weeks, while nasal congestion did not differ significantly before and after BTX-A injection. BTX-A was well tolerated by the patients, with no serious adverse or systemic effects.

Conclusion
Combined septal and turbinate injection of BTX-A, in patients with uncontrolled AR, may be a long-lasting therapeutic option for the treatment of nasal hypersecretions, but not as effective as for sneezing and nasal congestion.

Keywords:
allergic rhinitis, botulinum toxin, intranasal injection, nasal congestion, nasal hypersecretions, sneezing

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Introduction

Allergic rhinitis (AR) is a common disease with a high prevalence that has increased in prevalence over the last few decades [1]. Depending on the pathogenesis of AR and patient complaints such as nasal hypersecretions, sneezing and nasal congestion, several treatment strategies have been performed [2]. Conventional medications are not able to completely alleviate the symptoms in most patients with severe AR, in addition to the possible side effects and the financial burden [3].

Botulinum toxin type A (BTX-A) inhibits the release of acetylcholine in the presynaptic area of the neuromuscular junction and consequently blocks the cholinergic pathway. Therefore, intranasal administration of BTX-A through different methods and doses had been reported as a safe and effective therapeutic option for controlling AR symptoms [4]. BTX-A is expected to suppress nasal hypersecretions by blocking the cholinergic pathway in the nasal mucosa. However, the effects of BTX-A on sneezing and nasal congestion remain controversial. Some previous reports described the beneficial effects of BTX-A on all nasal allergic symptoms [5–8], although other reports failed to observe an effect of BTX-A on sneezing and nasal congestion [3,9].

The aim of this study was to determine the possible therapeutic effects of the combined nasal septum, inferior and middle turbinate injection of BTX-A on AR symptoms over a period of 12 weeks and to report any possible side effects.

Materials and methods

This prospective single-arm pilot study was planned to include 40 adult patients who received a diagnosis

of moderate to severe uncontrolled AR and were recruited between December 2018 and October 2019 in a single institution. The study was approved by the Committee for Medical Research Ethics in Minia University, Faculty of Medicine, Egypt. All patients signed a written consent before being included in the study.

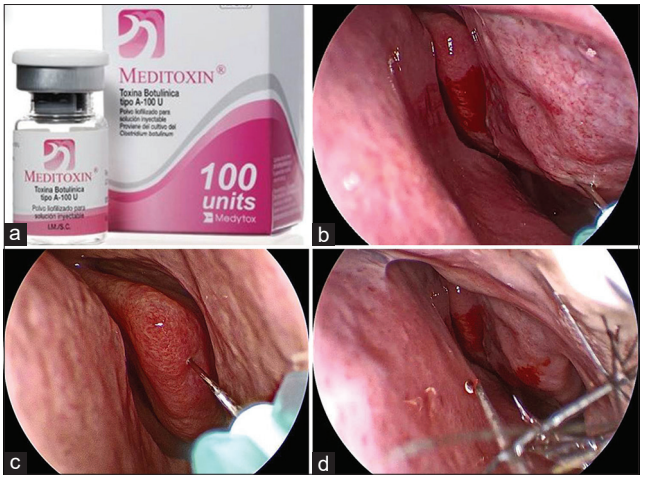
Patients with AR as described in the Allergic Rhinitis and its Impact on Asthma guidelines based on history, clinical findings and a positive skin prick test were recruited. Inclusion criteria included moderate to severe AR, initial mean five-point visual analog scale (VAS) score above three for all three cardinal symptoms of AR (nasal hypersecretions, nasal congestion, and sneezing) and uncontrolled disease (defined as insufficient control of allergic symptoms with VAS scores for nasal symptoms remaining higher than 3 after 4 weeks of regular medical treatment). According to Allergic Rhinitis and its Impact on Asthma, intranasal steroids complemented by antihistamines as an add-on treatment are recommended for the treatment of severe persistent AR.

Patients who had undergone previous turbinate surgery and patients who had marked septal deviation, nasal polyps, or tumors were excluded. Additional exclusion criteria included pregnancy patients, lactating patients and patients receiving treatment with oral corticosteroids, anticholinergics and drugs affecting hypothyroidism or hyperthyroidism during the 2 months before the initiation of the study.

Each patient underwent assessment of complete medical history and complete endoscopic examination. Local anesthesia of the nasal mucosa was administered using a ribbon gauze soaked with ephedrine: saline (1: 1000)+xylocaine in both nasal cavities for 15 min before the injection. 100 units of diluted BTX-A (Medytox Inc., South Korea) in normal saline to a final concentration of 100 units/ml (15 units in 0.15 ml) was slowly injected using a long needle syringe. Injection was administered at three fixed points: first, intermediate part of the inferior turbinate; second, anterior end of the middle turbinate; and three, submucoperichondrial at the anterior part of the nasal septum (Fig. 1a-d). Each patient received 45 IU in each side of the nose (90 IU, in total) divided as follows: 15 IU in the inferior turbinate, 15 IU in the middle turbinate and 15 IU in the nasal septum. After the injection, patients were reminded that they should not use additional allergic therapies.

Subjective symptoms including severity of nasal hypersecretions, congestion and sneezing were determined by a five-point VAS. The evaluations were performed before the therapy and at 1, 2, 4, 8, and 12 weeks after the therapy. Each symptom was evaluated according to the following scale: 0=no, 1=mild, 2=moderate, 3=moderate to severe, and 4=severe.

Figure 1



(a-d) Endoscopic view of the left nasal cavity showing the location of the botulinum toxin type A injection, (b) intermediate part of the inferior turbinate, (c) anterior end of the middle turbinate, and (d) submucoperichondrial at the anterior part of the nasal septum.

The software package SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA) was used to carry out the statistical analysis of the data. The Wilcoxon signed-rank test for nonparametric quantitative data was used to compare the mean preinjection and postinjection scores. A value of *P* less than 0.05 was considered to be statistically significant.

Results

Forty patients (22 males, 18 females) were enrolled in the current study. The mean age of the participants was 31.7±9.5 years, ranging from 19 to 52 years. None of the patients recorded any postinjection hemorrhage, pain or infection as side effects or complications.

Nasal hypersecretions

A significant reduction in nasal hypersecretions was observed after BTX-A injection started by the second week. Upon comparison of the mean nasal hypersecretion rate before and after the injection, the nasal hypersecretions reduced by 27.5% (*P*=0.083) in the first week. The reduction rate of nasal hypersecretions decrease rate was increased to 62.5% (*P*=0.001) in the second week, 57.5% (*P*=0.002) in the fourth week, and 42.5% (*P*=0.025) in the eighth week. Then it was regressed to 32.5% in the 12th week, but still remained statistically significant. The maximum

effect was reached in the second and fourth weeks. Although BTX-A had a major effect for 8 weeks, its effect remained at a statistically significant level until the 12th week (Table 1 and Fig. 2).

Sneezing and nasal congestion

A significant decrease in the severity of sneezing was detected upon comparison of the mean scores before and after injection at the first three follow-up points. It was 37.5% (P=0.035) at week 1; 47.5% (P=0.016) at week 2; and 40% (P=0.031) at week 4. The values before therapy were reached at week 8 (Table 2 and Fig. 3). The severity of nasal congestion decreased after injection at the first three follow-up points, but without showing a significant difference. It was 12.5% (P=0.059) at week 1; 17.5% (P=0.071) at week 2; and 7.5% (P=0.083) at week 4 (Table 3 and Fig. 4).

Discussion

Various medical protocols for the management of AR have been formulated in a stepwise manner. The mainstay of all treatments has always been conservative including antihistamines and intranasal steroids [10].

Table 1 Effect of botulinum toxin type A injection on nasal hypersecretions

	Mean±SD
Pretreatment	3.7±0.5
Week 1	2.6±0.7
Week 2	1.2±1.1
Week 4	1.4±1
Week 8	2±1.1
Week 12	2.4±0.5
P (preinjection vs. postinjection)	
Pre. vs. week 1	0.083
Pre. vs. week 2	0.001*
Pre. vs. week 4	0.002*
Pre. vs. week 8	0.025*
Pre. vs. week 12	0.048*

A *P*-value less than 0.05 (typically ≤ 0.05)

Table 2 Effect of botulinum toxin type A injection on sneezing

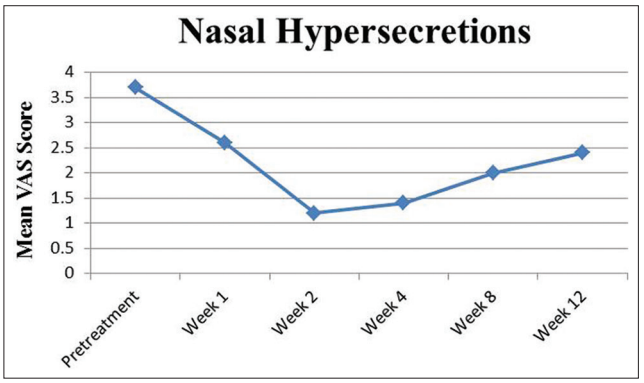
	Mean±SD
Pretreatment	3.6±0.6
Week 1	2.1±0.7
Week 2	1.7±0.5
Week 4	2±0.7
Week 8	3.6±0.5
Week 12	3.6±0.6
P (preinjection vs. postinjection)	
Pre. vs. week 1	0.035*
Pre. vs. week 2	0.016*
Pre. vs. week 4	0.031*
Pre. vs. week 8	1
Pre. vs. week 12	1

A *P*-value less than 0.05 (typically ≤ 0.05)

However, for patients with AR refractory to medication therapy, a novel form of pharmacological treatment has been attempted, for controlling allergic symptoms, in the form of intranasal injection of BTX-A.

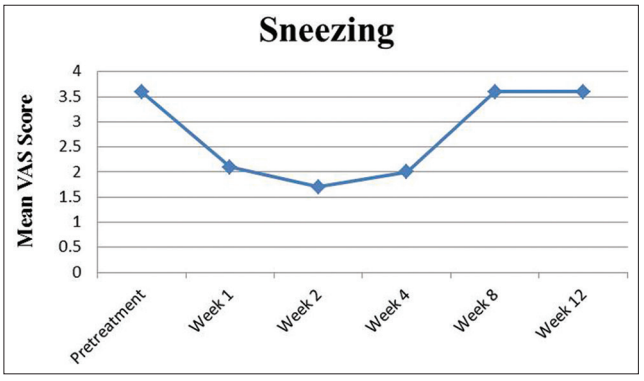
Since it provides a transient and reversible blockage of cholinergic transmission [11], BTX-A has been used recently in the symptomatic treatment of nasal hypersecretions [3,9], which is controlled primarily by

Figure 2



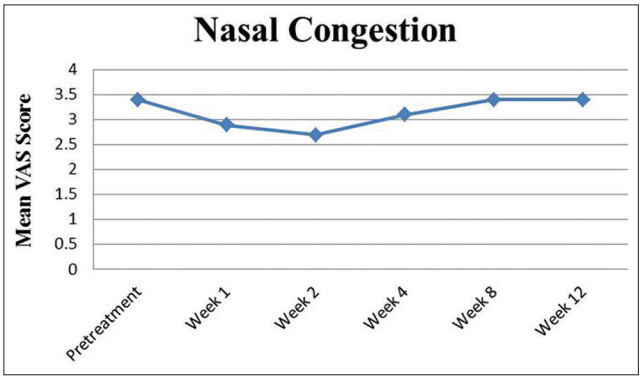
Mean visual analog score for nasal hypersecretions after botulinum toxin type A injection.

Figure 3



Mean visual analog score for sneezing after botulinum toxin type A injection.

Figure 4



Mean visual analog score for nasal congestion after botulinum toxin type A injection.

Table 3 Effect of botulinum toxin type A injection on nasal congestion

	Mean±SD
Pretreatment	3.4±0.5
Week 1	2.9±0.7
Week 2	2.7±1.1
Week 4	3.1±0.7
Week 8	3.4±0.5
Week 12	3.4±0.5
P (preinjection vs. postinjection in group A)	
Pre. vs. week 1	0.059
Pre. vs. week 2	0.071
Pre. vs. week 4	0.083
Pre. vs. week 8	1
Pre. vs. week 12	1

the parasympathetic nervous system [12]. However, the effects of BTX-A on the suppression of sneezing and nasal congestion remain controversial as, besides the autonomic control of nasal mucosa, some sensory neuropeptides and sensory branches of the trigeminal nerve are also responsible for itching, sneezing and nasal congestion in allergic patients [13,14].

Kim *et al.* [3] showed that BTX-A effectively decreased nasal hypersecretions for 4 weeks, but did not affect nasal congestion and sneezing. Sapci *et al.* [9] recorded a longer effect on nasal hypersecretions lasting for 8 weeks. The overall total nasal symptom score determined by Zhang *et al.* [15] showed the greatest effect of BTX-A in subscales of nasal hypersecretions, followed by sneezing, nasal congestion, and itching, all lasting for 4 weeks. In contrast, recent reports demonstrated the effectiveness of intranasal BTX-A in improving all cardinal symptoms of AR including nasal hypersecretions, congestion and sneezing, with an effect lasting from 4 to 8 weeks [5–8]. The Yang *et al.* [16] study reported the longest effect of BTX-A injection, lasting for 20 weeks for all the allergic symptoms.

There is no universally accepted site of administration for intranasal BTX-A usage; submucoperichondrial of the nasal septum, inferior, middle turbinate, and posterior lateral nasal wall injections have been applied for the relief of allergic symptoms in different studies [2]. Although the inferior turbinate has been the most common site for intranasal injection of BTX-A, some recent reports suggested that intraseptal injection had prolonged effects. This could return to the lower blood flow in the submucoperichondrium of the nasal septum, which may lead to lesser clearance of BTX-A by the bloodstream [6,8]. Ineffective infiltration of the area supplied by the anterior ethmoidal nerve has been postulated to be another reason for the limited effect in turbinate injections as compared to the anterior nasal septum [9,17]. In contrast, Abtahi *et al.* [8] concluded, in their clinical trial, that no differences in efficacy were noted between inferior turbinate and septal injections of BTX-A, except for a lower epistaxis rate in septal injections. A novel injection technique into the posterior lateral nasal wall, targeting parasympathetic innervation at the sphenopalatine ganglion, was described by Zhang *et al.* [15]; however, the efficacy and safety of this technique require more investigations.

Although 2500 3000 units of BTX-A is known to be a toxic dose [18], 25–150 U is the range of BTX-A doses used in AR. There is no absolute agreement on the most suitable and effective dose for the intranasal injection. The efficacy of an intraturbinate injection of 40 U and 60 U of BTX-A did not differ significantly in their effectiveness in improving allergic symptoms, lasting for 8 weeks [5]. Although Mozafarinia *et al.* [6] and Hashemi *et al.* [7] recorded improvements in allergic symptoms lasting for 4 and 8 weeks, after an intraseptal injection of 80 U and an intraturbinate injection of 150 U of BTX-A, respectively, a long-lasting effect for 20 weeks had been reached in the Yang *et al.* [16] study using a lower dose of 50 U injected solely intraturbinate. These results confirmed our hypothesis that the effect of BTX-A in the nose is dose independent and could be site dependent.

In our study, we proposed a different technique of combined intraseptal and intraturbinate injection of BTX-A as the intermediate part of the inferior turbinate, the anterior end of the middle turbinate and submucoperichondrial at the anterior part of the nasal septum. A dose of 90 units was selected in this study as an average dose between the effective doses utilized for AR in the preceding studies. It was considerably lower than the dose selected by Hashemi *et al.* [7] (150 U). The reason we chose this combined injection method was to reduce the parasympathetic tone to the whole nasal mucosa. A recent anatomic study has redefined the nasal parasympathetic innervation, suggesting that two main rami project from the sphenopalatine ganglion to innervate the nasal mucosa. The sphenoethmoidal ramus gains access to the nasal cavity through the sphenopalatine foramen to innervate the posterolateral part of the nasal mucosa, blocked by the intraturbinate injection, and the orbitonasal ramus gains access to the nasal cavity through the anterior ethmoidal foramen to innervate the anterosuperior part of nasal mucosa, blocked by the intraseptal injection [19].

In our study, the combined injection method of BTX-A effectively reduced nasal hypersecretions at rates ranging from 27.5 to 62.5%. An increase was observed starting from the first week and showed further increase, reaching the maximum in the second and fourth weeks, which followed a statistically significant

pattern for 12 weeks. These results are in accordance with those of Özcan *et al.* [20] in a clinical study and Rohrbach *et al.* [21] in an animal model; they have attributed the long duration of the effect of BTX-A to the recovery period of the degeneration in the nasal mucus glands that has been detected at 12 weeks. Another explanation for the durable effect of BTX-A on nasal hypersecretions, in the current study, was that the multiple and different intranasal injections enabled extensive distribution of the toxin to the nasal mucosa and nasal glands, resulting in a greater reduction of secretomotor innervation.

Although the combined injection method, in our study, effectively suppressed nasal hypersecretions, it lacked similar efficacy on other allergic symptoms such as sneezing and nasal congestion. The significant effect of BTX-A on sneezing prominently decreased after the fourth week, while it was insignificantly different throughout the 12-week follow-up period for nasal congestion. The most likely explanation for these findings is that BTX-A does not play an essential role in the histamine-mediated allergic reactions [22]. Minor sensory and parasympathetic efferent pathways exist in the nasal mucosa that may not be affected by the injected BTX-A; this may be another reason for the limited effect of BTX-A on nasal congestion and sneezing [19,22].

Our study revealed the effect of combined septal and turbinate injection of BTX-A on the symptoms of AR. The greatest effect was observed in nasal hypersecretions that lasted for 12 weeks; however, the effect on sneezing lasted only 4 weeks. The most important limitation of this study was that a subjective analysis was carried out after BTX-A injection. Therefore, further studies are required for the objective evaluation of the efficacy of therapy. Moreover, further studies are required to compare the combined injection technique with the other techniques reported in previous studies, to evaluate the effect of repetitive injections of BTX-A in the same patient and to evaluate the optimal dose of BTX-A in AR.

Conclusion

In the light of this results, combined septal and turbinate injection of BTX-A seems to be a safe and efficient therapeutic choice for controlling AR symptoms, especially nasal hypersecretions with a long-lasting effect. Further studies with extended follow-ups are needed to objectively evaluate the injection effect and to determine the efficacy duration and the optimal dose of BTX-A in AR.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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