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The Effect of Combined Septal and Turbinate Injection of Botulinum Toxin Type A in Allergic Rhinitis

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Abstract

Objectives: Allergic rhinitis (AR) has been recently increasing in prevalence, 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 conducted aiming at clinical assessment of the effect of combined septal and turbinate injection of BTX-A for management of uncontrolled AR. Design and setting: A single-arm pilot study enrolled 40 patients having moderate to severe uncontrolled AR were recruited in between October 2018 and August 2019. Each patient received 45 units of BTX-A injected in 3 fixed points of each side of the nose: inferior turbinate (15IU), middle turbinate (15IU) and nasal septum (15IU). All patients were evaluated in terms of nasal hypersecretions, congestion and sneezing with visual analogue scale prior to treatment and at weeks 1, 2, 4, 8 and 12 during the follow-up period. Results: Throughout the 12 weeks 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.

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Results: Throughout the 12 weeks 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.

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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, Nasal hypersecretions, Sneezing, Nasal congestion, Intranasal injection.

Key points

* Uncontrolled severe allergic rhinitis.

* Intranasal injection of Botulinum toxin type A.

* Combined septal and turbinate injection.

* Nasal hypersecretions.

* Sneezing and nasal congestion.

Introduction

Allergic rhinitis (AR) is a common disease with a high prevalence that has been increased over last decades (1). Depending on pathogenesis of AR and patients complaints such as nasal hypersecretions, sneezing and nasal congestion, several treatment strategies had been conducted (2). Conventional medications are not able to completely control symptoms in most of patients with severe AR, other than the possible side effects and the financial burdens (3).

Botulinum toxin type A (BTX-A) inhibits release of acetylcholine in presynaptic area of neuromuscular junction and consequently blocks cholinergic pathway. Therefore, intranasal administration of BTX-A through different ways 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),(6),(7),(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 assess the possible therapeutic effects of the combined nasal septum, inferior and middle turbinates 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 in 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 prior being included in the study.

Patients with AR as described in the ARIA guidelines based on history, clinical findings and positive skin prick test were recruited. Inclusion criteria included moderate to severe AR, initial mean five-point visual analogue scale (VAS) score above 3 for all the 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 remained higher to 3 after 4 weeks of regular medical treatment). According to ARIA, intranasal steroids complemented by antihistamines as add-on treatment are recommended for treatment of severe persistent AR.

Patients with previous turbinate surgery, marked septal deviation, nasal polyps or tumors were excluded. Additional exclusion criteria included pregnancy, lactation, patients receiving treatment with oral corticos-

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teroids, anticholinergics, drugs affecting hypothyroidism or hyperthyroidism during the 2 months before the beginning of the study.

Each patient had complete medical history and complete endoscopic examination. Local anesthesia of nasal mucosa was carried out using a ribbon gauze soaked with ephedrine: saline (1:1000) + Xylocaine in both nasal cavities for 15 minutes before the injection. A diluted 100 units of 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 done in 3 fixed points: 1- Intermediate part of inferior turbinate, 2- Anterior end of middle turbinate, and 3- Submucoperichondrial at the anterior part of nasal septum *(Fig.1.A,B,C,D).* Each patient received 45IU in each side of the nose (90IU, in total) divided as: 15IU in inferior turbinate, 15IU in middle turbinate and 15IU in the nasal septum. After the application, patients were reminded they should not use additional allergic therapies.

Subjective symptoms including severity of nasal hypersecretions, congestion and sneezing were measured by a five-point visual analogue scale (VAS). The evaluations were made prior to the therapy and at 1, 2, 4, 8 and 12 weeks after the therapy. Each symptom was evaluated according the scale as follow; (0= no, 1= mild, 2= moderate, 3= moderate to severe and 4= severe).

Software package SPSS® version 16.0 (Chicago, U.S.) was used in the statistical analysis of the data. Wilcoxon signed-rank test for nonparametric quantitative data was used upon comparing the pre- and post-injection mean scores. A value of $p < 0.05$ was considered to be statistically significant.

Results

Forty patients (22 male, 18 female) were enrolled in the current study. The mean age overall of participants was 31.7±9.5 years, ranging from 19 to 52 years. None of patients recorded any post injection 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 hypersecretions rate before and after injection, the reduction in nasal hypersecretions was as 27.5% (p= 0.083) in the first week. The decrease rate was observed to have 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. The decrease rate was observed to have regressed to 32.5% in the twelfth week but still statistically significant (p = 0.048). Maximum effect was reached in the second and fourth weeks. Although -A had an eminent effect for 8 weeks, its effect was continued in a statistically significant level till the twelfth week

(Table 1 and Figure 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 in 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 the therapy were reached at week 8 *(Table.2, Figure.3).* Severity of nasal congestion decreased after injection in the first three follow-up points but without 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, Figure.4).

Discussion

Various medical protocols for management of allergic rhinitis (AR) have been formulated in a stepwise manner. The mainstay of all treatments have been always conservative including antihistamines and intranasal steroids (10). However, for patients with AR refractory to medication therapy, a novel form of pharmaco-

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logical treatment has been attempted, for controlling allergic symptoms, in form of intranasal injection of Botulinum toxin type A (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), that is controlled primarily by 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. showed that BTX-A effectively decreased nasal hypersecretions for 4 weeks, but did not affect nasal congestion and sneezing (3). Sapci et al. recorded a longer effect on nasal hypersecretions lasting for 8 weeks (9). The overall total nasal symptom score conducted by Zhang et al. showed greatest effect of BTX-A in subscales of nasal hypersecretions, followed by sneezing, nasal congestion, and itching, lasting all for 4 weeks (15). On the other hand, recent reports demonstrated 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),(6),(7),(8). Yang et al. study had the longest effect of BTX-A injection lasting for 20 weeks for all the allergic symptoms (16).

There is no universally accepted site of administration for the intranasal BTX-A usage; submucoperichondrial of 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 inferior turbinate has been the commonest site for intranasal injection of BTX-A, some recent reports suggested that intraseptal injection had prolonged duration of effect. This could return to the lower blood flow in the submucoperichondrium of nasal septum that may lead to lesser clearance of BTX-A by 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 anterior nasal septum (9),(17). On contrary, Abtahi et al. concluded in their clinical trial that no differences in efficacy were noted between inferior turbinate and septal injections of BTX-A except a lower epistaxis rate in septal injections (8). 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 the toxic dose of BTX-A is known to be 2500-3000 units (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 intra-turbinate injection of 40 U and 60 U of BTX-A did not differ significantly in their effectiveness on improving allergic symptoms, lasting for 8 weeks (5). Although Mozafarinia et al. (6) and Hashemi et al. (7) recorded improvement in allergic symptoms lasting for 4 and 8 weeks, after intraseptal injection of 80 U and intra-turbinate injection of 150 U of BTX-A, respectively, a long-lasting effect for 20 weeks had been reached in Yang et al. study using a lower dose of 50 U injected purely intra-turbinate (16). These results indorsed our praise to think that the effect of BTX-A in the nose is dose independent and it could be site dependent.

In our study, we proposed a different technique of combined intraseptal and intra-turbinate injection of BTX-A as; the intermediate part of inferior turbinate, anterior end of middle turbinate, and submucoperichondrial at the anterior part of 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 safely below the dose selected by Hashemi et al. (150 U), (7). The reason we chose this combined injection method was to reduce the parasympathetic tone to 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 gain access to the nasal cavity via the sphenopalatine foramen to innervate the posterolateral part of nasal mucosa, blocked by the intra-turbinate injection and the orbitonasal ramus gain access to the nasal cavity via the anterior ethmoidal foramen to innervate the anterosuperior part of nasal mucosa, blocked by the intraseptal injection (19).

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In our study, the combined injection method of BTX-A effectively reduced nasal hypersecretions in rates ranging from 27.5% to 62.5%. The effect displayed an increase starting from the first week and increased more 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 Ozcan et al. in a clinical study (20), and Rohrbach et al. on an animal model (21), they have attributed the long duration of BTX-A effect to the recovery period of the degeneration in the nasal mucus glands that has been detected as 12 weeks. Another explanation for the long effect of BTX-A on nasal hypersecretions, in current study, was attributed to the multiple and different intranasal injections that enabled extensive distribution of the toxin to nasal mucosa and nasal glands, resulting in a more reduction of secretomotor innervation.

Although the combined injection method, in our study, effectively suppressed nasal hypersecretions, it lacked a similar efficacy on other allergic symptoms such as sneezing and nasal congestion. The significant effect of BTX-A on sneezing prominently decreased after the 4th week, while it was insignificantly different throughout the 12 weeks follow-up period for nasal congestion. The most likely explanation for these findings is that BTX-A does not have 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 seen in nasal hypersecretions lasted for 12 weeks, however effect on sneezing lasted only 4 weeks. The most important limitation of this study; that it was a subjective analysis after BTX-A injection, so further studies are required for the objective evaluation of the therapy efficacy. 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 allergic rhinitis.

Conclusion

In the light of the current results; combined septal and turbinate injection of BTX-A seems to be a safe and efficient therapeutic choice for controlling allergic rhinitis 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 allergic rhinitis.

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Figure legends

Fig.1A,B,C,D. Endoscoic view of Lt nasal cavity showing the location of -A injection; (B) Intermediate part of inferior turbinate, (C) Anterior end of middle turbinate, and (D) Submucoperichondrial at the anterior part of nasal septum.

Fig.2. Mean visual analogue score (VAS) for nasal hypersecretions after BTX-A injection.

Fig.3. Mean visual analogue score (VAS) for sneezing after BTX-A injection.

Fig.4. Mean visual analogue score (VAS) for nasal congestion after BTX-A injection.

Table 1. Effect of BTX-A injection on nasal hypersecretions

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	(Mean ± SD)	
	3.7 ± 0.5	**Pretreatment**
	2.6 ± 0.7	**Week 1**
	1.2 ± 1.1	**Week 2**
	1.4 ± 1	**Week 4**
	2 ± 1.1	**Week 8**
	2.4 ± 0.5	**Week 12**
p-value (pre. vs. post. injection)	**p-value (pre. vs. post. injection)**	**p-value (pre. vs. post. injection)**
0.083	0.083	**Pre. vs. Week 1**
0.001*	0.001*	**Pre. vs. Week 2**
0.002*	0.002*	**Pre. vs. Week 4**
0.025*	0.025*	**Pre. vs. Week 8**
0.048*	0.048*	**Pre. vs. Week 12**

Table 2. Effect of BTX-A injection on sneezing

	(Mean ± SD)	
	3.6 ± 0.6	**Pretreatment**
	2.1 ± 0.7	**Week 1**
	1.7 ± 0.5	**Week 2**
	2 ± 0.7	**Week 4**
	3.6 ± 0.5	**Week 8**
	3.6 ± 0.6	**Week 12**
p-value (pre. vs. post. injection)	**p-value (pre. vs. post. injection)**	**p-value (pre. vs. post. injection)**
0.035*	0.035*	**Pre. vs. Week 1**
0.016*	0.016*	**Pre. vs. Week 2**
0.031*	0.031*	**Pre. vs. Week 4**
1	1	**Pre. vs. Week 8**
1	1	**Pre. vs. Week 12**

Table 3. Effect of BTX-A injection on nasal congestion

	(Mean ± SD)	
	3.4 ± 0.5	**Pretreatment**
	2.9 ± 0.7	**Week 1**
	2.7 ± 1.1	**Week 2**
	3.1 ± 0.7	**Week 4**
	3.4 ± 0.5	**Week 8**
	3.4 ± 0.5	**Week 12**
p-value (pre. vs. post. in Group A)	**p-value (pre. vs. post. in Group A)**	**p-value (pre. vs. post. in Grou**
0.059	0.059	**Pre. vs. Week 1**
0.071	0.071	**Pre. vs. Week 2**
0.083	0.083	**Pre. vs. Week 4**
1	1	**Pre. vs. Week 8**
1	1	**Pre. vs. Week 12**

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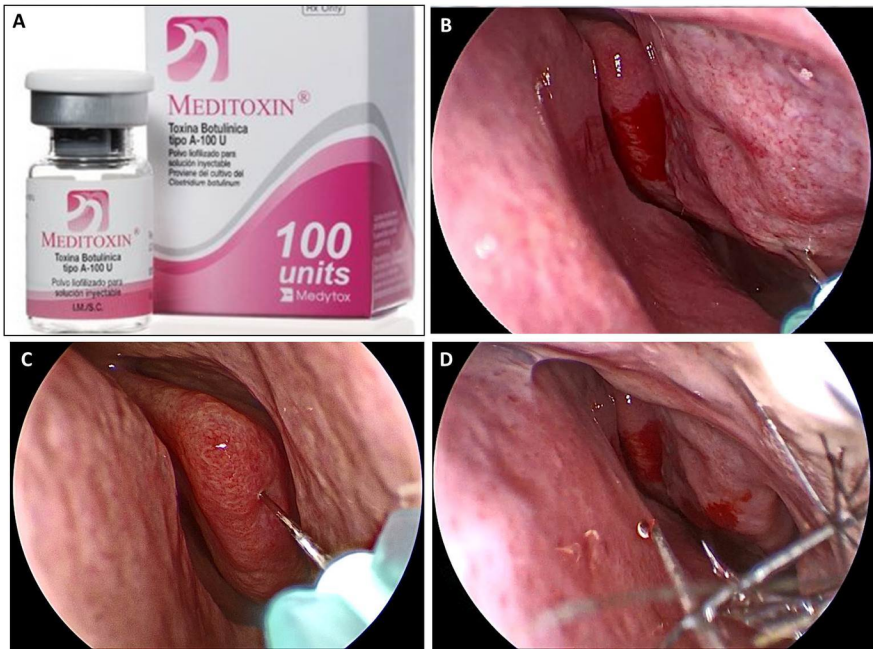

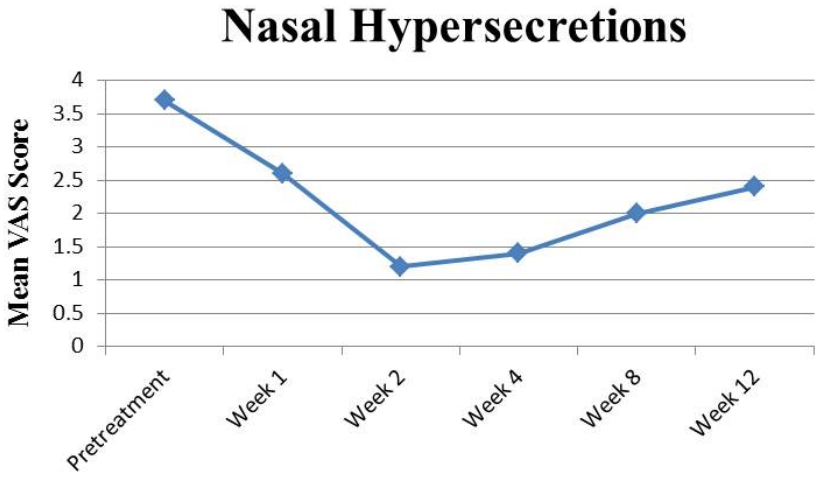

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