ORIGINAL ARTICLE

Septal injection in comparison with inferior turbinates injection of botulinum toxin A in patients with allergic rhinitis

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Background: Botulinum toxin A (BTA) is a promising therapeutic option in the treatment of allergic rhinitis (AR). Although recent studies have introduced BTA septal injection as an alternative method, the conventional localization for the injection of BTA in patients with AR is still the nasal turbinates. This study was designed to compare the effectiveness and safety of septal BTA injection with turbinal BTA injection in patients with AR. **Materials and Methods:** This open-label study was performed on 50 patients with AR who were randomly allocated to septal and turbinal BTA injection groups. All patients received an injection of 40 U of BTA (Dysport®, Ipsen Ltd, Maidenhead, UK) in each side of the nose and were followed for 8 weeks. Prior to the intervention and 8 weeks later, symptom severity and quality of life scores were calculated using the AR symptom severity and Rhinasthma questionnaires respectively. **Results:** Comparison of pre- and post-treatment symptom severity scores within each group showed a significant reduction of total symptom severity score and severity of sneezing, rhinorrhea, and congestion in both groups ($P < 0.05$). However, post-treatment symptom severity scores were not significantly different between two groups ($P > 0.05$). Both methods have improved the quality of life of subjects significantly ($P < 0.05$). Significantly more patients in the turbinal injection group reported adverse effects (four patient's vs. one, $P < 0.05$). **Conclusion:** Although both septal and turbinal BTA injections are effective on patients with AR, septal administration of BTA could be safer and easier method. However, further investigations are required to achieve more accurate results.

Key words: Allergic rhinitis, botulinum toxin A, quality of life

INTRODUCTION

Allergic rhinitis (AR) is a common immunoglobulin-E-mediated disease of the nasal mucosa that usually occurs after exposure to various indoor and outdoor allergens including dust mites, insects, animal dander, molds, and pollens. AR is characterized by nasal congestion, paroxysmal repetitive sneezing, watery rhinorrhea, and pruritus.[1,2] These bothersome symptoms may have negative effects on daily activities, quality of sleep, and productivity.[3] AR affects up to 40% of the general population,[4-6] and imposes a considerable burden both on patients and society.[7] Although the quality of life of patients with AR is significantly impaired,[8,9] it can be improved by appropriate treatment.[10]

Therefore, depending on the pathogenesis of the particular type of rhinitis and symptoms of the patient, several therapeutic options are available for the treatment of nasal hyperreactivity.[11] Various pharmacologic options including intranasal corticosteroids, oral and topical antihistamines, decongestants, intranasal cromolyn, intranasal anticholinergics, and leukotriene receptor antagonists have been widely used for the treatment of AR.[12,13] However, few of these conventional methods lead to significant symptom relief.[11] For this reason, novel therapeutic methods have to be developed.

Botulinum toxin A (BTA) is a neurotoxin with metalloproteinase activity that inhibits the release of acetylcholine from the presynaptic nerve endings at the neuromuscular and neuroglandular junctions.[11,14,15] Based on the anticholinergics activities of BTA, it has been used in the treatment of patients with idiopathic rhinitis[16-19] or AR,[20,21] and has reduced its symptoms effectively.[16-21] Although initial investigations have described the nasal turbinates as the site of BTA injection,[16-19] recent studies have suggested that the nasal septum could be more suitable alternative site for BTA injection.[22] However, no study has compared the effectiveness and safety of BTA injection into the nasal turbinates with those of BTA injection into the nasal septum.

In light of the above, this comparative study was designed to determine the safer and more suitable site for BTA injection in patients who suffer from AR.

MATERIALS AND METHODS

Study population and design

After approval of the study by the Ethic Committee

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of Isfahan University of Medical Sciences and obtaining informed consent, this open-label randomized clinical trial was performed on patients who were referred to the ENT outpatient clinics of "Al-zahra" and "Kashani" hospitals. This investigation was performed in Isfahan, Iran, between March 2011 and April 2012.

A convenience sample of 50 patients of both genders was entered into this study. Participants were included in this study if they fulfilled the criteria of AR according to the allergic rhinitis and its Impact on Asthma (ARIA).[23]

Any anatomic abnormality of the nasal cavities such as nasal septal deviation and nasal polyp, previous rhinoplasty or septoplasty, pregnancy, history of persistent asthma, systemic corticosteroid therapy, malignancy, diabetes mellitus or other significant medical diseases were considered as the exclusion criteria. In addition, participants who received any medication for AR over 2 months prior to the study were excluded.

Using simple randomization, patients who met all criteria for enrollment were randomly allocated into 2 treatment groups of inferior turbinate injection and septal injection [Figure 1].

Data collection

In addition to demographic data, patients' information was collected using reliable and valid Persian editions of 2 questionnaires including AR symptom severity questionnaire and Rhinasthma questionnaire for quality of life.[24]

The AR symptom severity questionnaire consists of 5 items according to ARIA criteria (sneezing, watery runny nose, nasal obstruction, nasal itching, conjunctivitis) and asses the severity of each symptom on a 4 point scale (0: No symptom, 1: Mild, 2: Moderate, 3: Severe).

The Rhinasthma is a 42 item quality of life questionnaire. Patients were asked to indicate items they had directly experienced, and to indicate the importance of each of them on a 4 point scale (1 = not important; 4 = very important).[25]

Before and 8 weeks after the intervention (at the last follow-up session), all patients answered the Rhinasthma questionnaire, and the symptom severity questionnaire was filled by the investigator based on the patients' history.

Intervention and follow-up

In order to make a BTA solution with a concentration of 100 U/ml, each 500 U BTA vial (Dysport®, Ipsen Ltd., Maidenhead, UK) was diluted with 5 ml sterile water. Ten min prior to the injection, local anesthesia was applied using 10% lidocaine spray. While patients were in the sitting position, they received an injection of 40 U BTA (0.4 ml) in each side using a 27 G hypodermic needle. In the first group, BTA was injected into the bilateral inferior turbinates (in the anterior tip of turbinate). In the second group, patients underwent bilateral subperichondrial septal injection of BTA (in the anterior 1 cm submucoperichondrial of septum). BTA was injected very slowly. All injections were performed by a single otolaryngologist.

Follow-up visits were arranged on a 2 weekly basis for 8 weeks (4 follow-up visits with a 2 week interval). On each follow-up session, patients were asked about the symptom severity and possible adverse effects.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA). Independent *t*-test, Mann-Whitney *U*-test, Wilcoxon test and Chi-square were used when appropriate. $P < 0.05$ were considered statistically significant.

Sample template for the Consort diagram showing the flow of participants through each stage of a randomized trial

RESULTS

Baseline and demographic data

There was no significant differences between 2 groups regarding baseline data [Table 1].

Efficacy

Effects on symptom severity score.

Comparison of pre- and post-treatment total symptom severity score within each group showed that BTA injection into both sites has significantly reduced the symptom severity score ($P < 0.0001$). However, post-treatment symptom severity score was not significantly different between two groups (P: 0.18) [Table 2].

Table 1: Baseline characteristics of two groups

Variables	Turbinal injection (*N*=25)	Septal injection (*N*=25)	Total (*N*=50)	*P* value
Age (year)	26.25±9.33	27.14±7.78	26.70±8.84	0.83
Sex (male/female) (%)	9 (36)/16 (64)	11 (44)/14 (56)	20 (40)/30 (60)	0.67
Pre-treatment symptom severity score	10.83±2.41	9.74±1.98	10.28±2.01	0.33
Pre-treatment Rhinasthma score	36.75±11.03	31.33±12.79	34.06±11.91	0.41

Age is presented as mean±SD; Sex is presented as number (%); Pre-treatment symptom severity score and Pre-treatment Rhinasthma score are presented as mean score±SD; *N*=Number of patients

Comparison of pre- and post-treatment severity score of each symptom within 2 groups revealed that both methods of BTA injection have significantly improved the severity of sneezing, rhinorrhea and congestion; however, they have not been effective on nasal itching and conjunctivitis. No significant differences were found between the treatment groups in any of post-treatment severity scores [Table 2].

Effects on quality of life

Participants of both treatment groups have experienced significant improvement in their quality of life. However, there was no statistically significant differences between two groups regarding the post-treatment Rhinasthma score [Table 3].

Table 2: Comparison of symptom severity score between and within 2 groups

Variables	Turbinal injection (*N*=25)	Septal injection (*N*=25)	*P* value
Sneezing			
Pre-treatment	2.01±0.74	1.95±0.33	0.67
Post-treatment	1.12±0.22	0.99±0.12	0.49
P value	<0.0001	0.01	
Watery runny nose			
Pre-treatment	2.31±0.81	2.01±0.45	0.57
Post-treatment	1.22±0.31	1.01±0.23	0.19
P value	<0.0001	<0.0001	
Nasal obstruction			
Pre-treatment	1.86±0.23	1.83±0.11	0.96
Post-treatment	1.01±0.11	1.02±0.17	0.90
P value	0.02	0.04	
Nasal itching			
Pre-treatment	2.36±0.34	2.11±1.01	0.81
Post-treatment	2.02±0.43	1.91±0.87	0.72
P value	0.58	0.14	
Conjunctivitis			
Pre-treatment	2.25±0.97	1.99±0.34	0.43
Post-treatment	2.13±0.71	1.89±0.33	0.19
P value	0.71	0.82	
Total score			
Pre-treatment	10.83±2.41	9.74±1.98	0.33
Post-treatment	5.63±4.09	4.88±1.33	0.41
P value	<0.0001	<0.0001	

Data are presented as mean score±SD; *N*=Number of patients

Table 3: Comparison of Rhinasthma quality of life score between and within 2 groups

Variables	Turbinal injection (*N*=25)	Septal injection (*N*=25)	Total (*N*=50)	*P* value
Rhinasthma score				
Pre-treatment	36.75±11.03	31.33±12.79	34.06±11.91	0.41
Post-treatment	21.23±10.07	19.83±11.54	20.57±10.99	0.59
P value	<0.0001	<0.0001	<0.0001	

Data are presented as mean score±SD; N=Number of patients

Adverse effects

During the follow-up sessions, 4 (16%) patients in the inferior turbinate group reported adverse effect (3 subjects had epistaxis, and 1 had nasal mucosa dryness). The number of subjects who developed adverse effect was significantly lower in the nasal septum group and only 1 (4%) patient complained of epistaxis (*P* value: 0.03). All adverse effects were mild-moderate and were treated appropriately.

DISCUSSION

AR is a common systemic inflammatory condition[24] that was first defined in 1929.[26] Since then, it has been a global health problem that causes major illness and disability world-wide.[24] AR affects various aspects of daily-life of people regardless of their sex, age, ethnicity or country.[7]

Because AR usually imposes indirect costs, its economic impact is often underestimated.[7] Given the high prevalence of AR and its substantial effects on quality of life of patients, several therapeutic strategies have been developed to improve the quality of life and reduce the symptom severity.

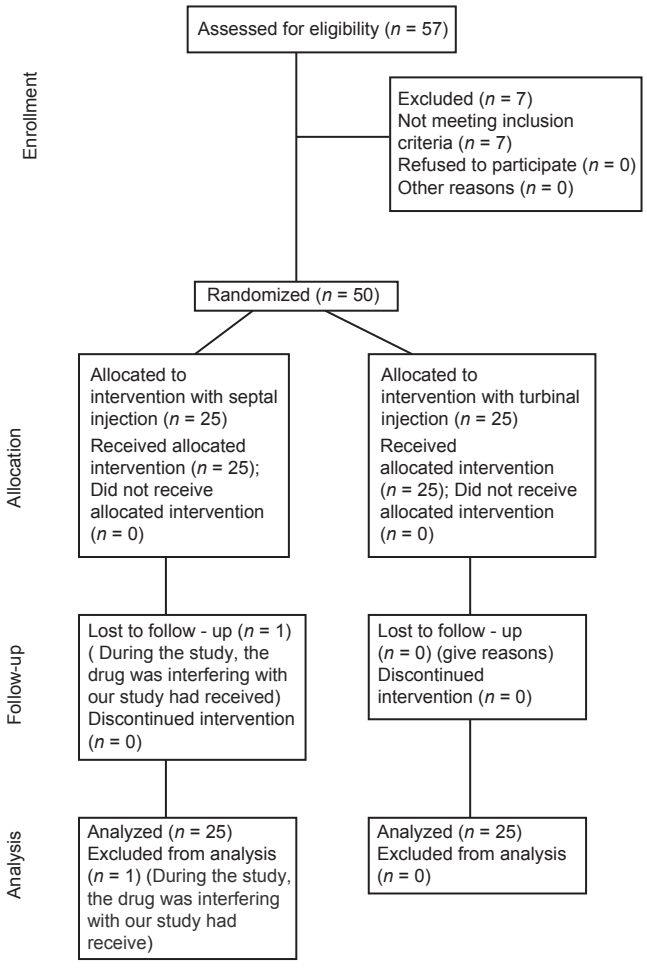

Figure 1: Consort diagram of participation

BTA has recently emerged as a promising new treatment for different types of rhinitis.[11,16-18,20-22] The role of BTA in the treatment of idiopathic rhinitis was first described by Kim *et al*.[16] Then, Wen *et al*. performed a study on rats, and reported that local BTA treatment could be a long lasting method to reduce symptoms of AR.[27]

Ozcan *et al*.[17] and Sapci *et al*.[18] confirmed the effectiveness of BTA as a therapeutic option for idiopathic rhinitis in human subjects, and Unal *et al*. reported the same result for patients with AR;[21] however, all these investigations used the technique of injection of BTA into the inferior or middle turbinates.

Recently, Braun *et al.* described the new technique of BTA injection into the nasal septum in patients with idiopathic rhinitis. They concluded that this new method can achieve good symptom control and patient comfort. In addition, they suggested comparison of nasal septal injection with the conventional turbinal injection technique.[22]

To the best of our knowledge, this is the first study that has compared the effectiveness and safety of BTA injection in different sites in patients with AR.

Present study demonstrated that both turbinal and septal injection of BTA can significantly improve the average of symptom severity and quality of life of patients with AR.

When a treatment can improve bothersome symptoms such as rhinorrhea, nasal congestion and sneezing, it would not be surprising to find it effective on the quality of life of patients. Laskawi also demonstrated that intranasal injection of BTA is a helpful option to improve the quality of life in patients with various head and face disorders such as AR.[28]

In addition to the total symptom severity score, BTA injection reduced the severity of all symptoms except nasal itching and conjunctivitis.

These findings match with the results that Ozcan *et al*. have reported. They demonstrated that intranasal BTA injection improves nasal discharge, nasal obstruction and sneezing, whereas it has no effect on itching.[17] Unal *et al*. also described a significant reduction of sneezing and nasal congestion in patients with AR after treatment with BTA.[21]

It is well-known that the nasal secretory activity is under parasympathetic control.[17,22] Moreover, it has been suggested that acetylcholine may play an significant role in the sneezing reflex.[11]

The effectiveness of intranasal injection of BTA in the treatment of AR symptoms can be attributed to the anticholinergics properties of BTA that affect the large number of serous glands in the nasal cavity, and result in decreased nasal secretory response.[22,29] BTA selectively inactivates peripheral cholinergic nerve terminals by blocking the release of acetylcholine from the cholinergic nerve endings in the nasal mucosa or preganglionic cholinergic nerve terminals in sphenopalatine ganglion. These two mechanisms have been considered as the main mechanisms of action of BTA in the nasal cavity.[16,17]

Furthermore, Rohrbach *et al*. demonstrated that nasal application of BTA in pigs can lead to a degeneration of nasal glands and ducts and a diffuse glandular apoptosis. However, they did not observe any necrosis or inflammation following the application of BTA.[30]

Similar to the previous studies, we have found no complications of intranasal injection of BTA.[16-18,22]

Our experience demonstrated that septal BTA injection could be an easier technique than the septal injection. The nasal septum can usually be visualized without any difficulty. Similarly, Braun *et al*. has reported septal injection as an easy and well-tolerated intranasal BTA injection technique.[22]

We also observed significantly lower rate of adverse effect in patients treated with septal injection of BTA. The rich vascular supply of the inferior turbinate[31] may increase the risk of adverse effects. When BTA is injected into the nasal septum, the injection is performed by the submucoperichondrial approach. Submucoperichondrial injection could be associated with a lower systemic absorption of BTA, and therefore lead to a lower rate of systemic adverse effects.

Kim *et al*. has reported that rich blood vessels in the mucosa of the inferior turbinate might lead to more rapid absorption and clearing of the BTA.[16] Hence, submucoperichondrial injection of BTA in the nasal septum may result is more duration of BTA effect. However, long-term follow-up is needed to compare these 2 methods regarding the duration of effects on AR symptoms.

When two treatment methods have similar efficacy, their other characteristics play a more important role in the process of technique selection. Safety and ease of administration are among the most important characteristics that significantly affects the success of a treatment. Injection of BTA into the septum was easier than turbinal injection and caused significantly fewer adverse effects. Given these two important factors and the equal efficacy of septal and turbinal BTA injection, it seems that septal BTA injection could be a more suitable technique.

Since, this study was conducted with an open-label design; re-investigation of this study with a double-blind study design may lead to more accurate results. In addition, we used a subjective method to assess the severity of symptoms; therefore, using rhinomanometry, rhinoresistometry and acoustic rhinometry to objectify the severity of nasal discharge and nasal patency can increase the reliability of findings.

CONCLUSION

Although both septal and turbinal BTA injections are effective on symptom severity and quality of life of patients with AR, septal administration of BTA could be safer and easier technique. However, further investigations are required to achieve more accurate results.

LIMITATIONS OF THE STUDY

The sample size may be not enough to mention definitely about "Adverse Reactions" and Safety of this treatment option.

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