

ORIGINAL RESEARCH—ALLERGY

A comparison of the effects of botulinum toxin A and steroid injection on nasal allergy

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OBJECTIVES: To compare the effects of botulinum toxin A (BTX-A) with intranasal steroid injections on nasal symptoms in patients with allergic rhinitis (AR).

STUDY DESIGN: A randomized, placebo-controlled, single-blinded clinical trial (patients were blinded).

MATERIAL AND METHODS: Thirty-nine patients were included in the study. AR was diagnosed by means of history, clinical examination, and skin prick test. Patients were randomly divided into three subgroups as follows: in group A, 25 units of BTX-A were injected into each inferior turbinate (total 50 units); in group B, 1 cc (20 mg/mL) of triamcinolone was injected into each inferior turbinate; and in group C, 1 cc of isotonic saline was injected as placebo. The symptoms of AR were scored by the patient on a six-point scale.

RESULTS: At all time points, group A was significantly better than group C. In the nasal obstruction and rhinorrhea scores, group A was significantly better than group B after 8 weeks.

CONCLUSION: BTX-A may provide better AR symptom relief in terms of duration and degree than a steroid injection.

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The incidence of allergic rhinitis (AR) is increasing and constitutes a major health problem.¹ Nasal symptoms in AR are caused by both inflammatory mediators, which increase vascular permeability and edema in the secretory glands and cause alterations in the balance of the autonomic nervous system. Furthermore, serous secretions are under parasympathetic control and, therefore, should be sensitive to anticholinergic substances.²

Botulinum toxins are powerful neuroparalytic agents naturally synthesized by various strains of the spore-forming, obligate anaerobic bacterium *Clostridium botulinum*. Its exotoxin is divided into several types, A through G, depending on the immunological specificity of the toxin.³ This neurotoxin inhibits the release of acetylcholine from presynaptic neurons at the neuromuscular junctions. In addition, this toxin can block vasoactive intestinal polypeptide, the potent vasodilator,⁴ possibly yielding an additional effect on relieving nasal symptoms such as nasal congestion

and nasal discharge. The clinical effects of botulinum toxins are dose-related and transient, usually diminishing several months after the natural regeneration of new nerve terminals at the treated site. Because of their powerful anticholinergic effects, botulinum toxins have been used therapeutically for many entities in the field of otolaryngology, such as Frey syndrome, hyperhidrosis after parotid surgery, spasmodic dysphonia, voice tremor as laryngeal motion disorder, oromandibular dystonia, and cervical dystonia.⁵

Recent studies have suggested that botulinum toxin can relieve rhinitis symptoms. Shaari et al⁶ demonstrate a reduction in rhinorrhea in experimentally induced nasal hypersecretion in dogs after nasal application of botulinum toxin type A (BTX-A). Kim et al⁷ and Rohrbach et al⁸ administered BTX-A to patients with intrinsic rhinitis and obtained satisfactory results. Murat et al⁹ reported subjective symptomatic relief in AR patients after injection of BTX-A. Although the relationship between BTX-A and AR symptom relief has been described, there have been no comparative studies that describe the effect of BTX-A versus local steroid therapy. Therefore, this study focused on the comparisons of the effects of BTX-A and local steroid therapy, and the evaluation of the subjective symptomatic relief of rhinorrhea, nasal obstruction, sneezing, and itching at 1, 4, 8, 12, 16, and 20 weeks after treatment.

MATERIAL AND METHODS

This study was conducted at the In-Ha University Hospital. This protocol was reviewed and accepted by the ethics committee under the In-Ha University Research Grant #07-175. The author obtained informed consent from all patients. Thirty-nine patients who had perennial nasal allergy complaints and visited the In-Ha University Hospital Otolaryngology Center between April and August 2007 were included in the study. Patients were all recruited in the city of Incheon from the In-Ha University Hospital ENT outpatient clinic. For the purpose of eliminating patient bias, we

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Table 1
Severity of symptoms before treatment

	Nasal obstruction		Rhinorrhea		Sneezing		Itching	
	Mean (SD)	F value	Mean (SD)	F value	Mean (SD)	F value	Mean (SD)	F value
BTX-A	4.50 (0.51)	1.780	4.28 (0.83)	0.073	4.11 (0.68)	0.514	3.27 (1.02)	4.406*
TCA	4.33 (0.78)		4.33 (0.49)		4.00 (0.74)		2.83 (0.94)	
Placebo	4.00 (0.71)		4.22 (0.44)		3.78 (1.09)		4.00 (0.71)	

BTX-A, Botulinum toxin type A; TCA, triamcinolone; placebo, normal saline.

There are no statistically significant differences ($P > 0.05$) except for itching ($P = 0.026$) (Kruskal-Wallis ANOVA test).

* $P < 0.05$.

selected only patients who had not taken antiallergic medication 2 months prior to the study. Because many patients with nasal allergy in the Korean population tend to visit a primary physician first, doctors of tertiary medical centers seldom meet patients with allergy who have not received an antiallergic medication. For that reason, we chose only 39 patients in this preliminary study. Initially, 46 patients who had only positive skin test results for *Dermatophagoides farinae* or *D pteronyssinus* were included in this study. Of these patients, seven were excluded (three patients with acute rhinosinusitis, two with glaucoma, and two with benign prostate hyperplasia). AR was diagnosed by means of history, clinical examination, and skin prick test. Exclusion criteria were pregnancy or possibility of pregnancy, gross nasal anatomical abnormality, acute rhinosinusitis, and any accompanying disease such as glaucoma or prostate hyperplasia that might be aggravated by anticholinergic therapy. We also excluded patients who had prior nasal surgery and who took antiallergic medication 2 months prior to study. The patients, who were not aware of the treatment, were randomly divided into three groups. Mean age was 37.3 years (range 14–62 years; 17 men, 22 women). Group A was injected with BTX-A (Botox; Allergan Inc, Irvine, CA); mean age was 36.4 years (range 16–59 years; 8 men, 10 women). Group B was injected with the steroid triamcinolone acetonide (40 mg/mL; Dong Kwang, Pharm, Korea); mean age was 43.8 years (range 19–53 years; 5 men 7 women). Group C, the control group, was injected with isotonic saline; mean age was 32.6 years (range 14–62 years; 4 men, 5 women). There was no statistically significant difference among the three groups (Table 1). Anterior rhinoscopy and nasal endoscopy using a rigid telescope were conducted for all patients. A skin prick test was performed on all patients, and only patients who were positive for *D farinae* or *D pteronyssinus* were included in this study.

Group A was injected with 25 units of BTX-A into each nasal cavity (total of 50 units). One box of BTX-A was diluted in 4 mL saline solution; 1 mL of final solution was equal to 25 units of BTX-A. After application of a topical lidocaine spray, BTX-A was injected slowly (1-mL syringes, 30-G needles) over 5 minutes into one point of the anterior side of the inferior turbinate and middle turbinates of both the left and right nasal cavities of the patients (Fig 1).

Group B was injected with 1 mL (20 mg/mL) of triamcinolone into each nasal cavity (total of 2 mL; 40 mg/mL) by using the same method for group A. Group C was injected with 1 mL of an isotonic saline solution into the inferior and middle turbinates of each nasal cavity (total 2 mL). The patients' symptoms were evaluated and scored in the outpatient clinic at 1, 4, 8, 12, 16, and 20 weeks after the injections. Symptoms of AR (rhinorrhea, nasal obstruction, sneezing, itching) were scored by the patient on a six-point scale (0 = none, 1 = mild, 2 = mild to moderate, 3 = moderate, 4 = moderate to severe, and 5 = severe). All patients were advised not to take any additional antiallergy drugs or to have surgery. The differences among the groups were analyzed with the Kruskal-Wallis analysis of variance (ANOVA) test; $P < 0.05$ was considered significant.

RESULTS

All patients completed the study during the 20-week time period. No patients complained of any side effects, such as epistaxis or muscular palsy. The three groups were not statistically different before treatment except for the itching

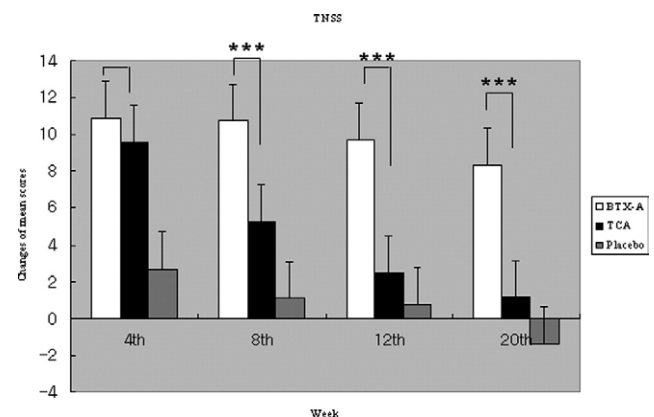


Figure 1 Comparison of changes in mean scores in three groups with respect to total nasal symptoms. Scores (TNSS) obtained via Kruskal-Wallis ANOVA test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. BTX-A, Botulinum toxin type A; TCA, triamcinolone; placebo, normal saline.

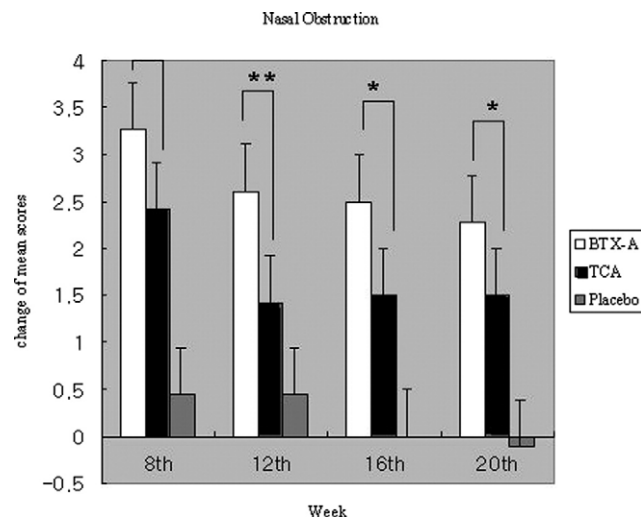


Figure 2 Comparison of changes in mean scores in three groups with respect to nasal obstruction scores via Kruskal-Wallis ANOVA test. $P < 0.05$; $**P < 0.01$; $***P < 0.001$. BTX-A, Botulinum toxin type A; TCA, triamcinolone; placebo, normal saline.

symptom. Group B showed a significantly lower mean score (2.8 points before beginning the treatment) than did the other groups for itching (Table 1). When total nasal symptom scores (TNSS) were evaluated, TNSS decreased after the first week in groups A and B, but in group B almost all of the symptoms recurred after 8 weeks. Therefore, the mean change of TNSS in group A was significantly higher than in group B after 8 weeks. TNSS in group C were not significantly changed during examinations for any week (Fig 1).

Nasal obstruction scores in group A showed a significant difference from group B after 12 weeks (Fig 2). With regard to rhinorrhea, group A showed a significant statistical difference in comparison with group B from 4 weeks (Fig 3).

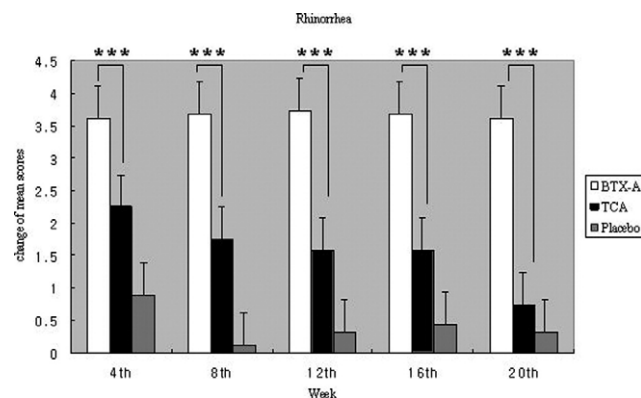


Figure 3 Comparison of changes in mean scores in three groups with respect to rhinorrhea scores via Kruskal-Wallis ANOVA test. $P < 0.05$; $**P < 0.01$; $***P < 0.001$. BTX-A, Botulinum toxin type A; TCA, triamcinolone; placebo, normal saline.

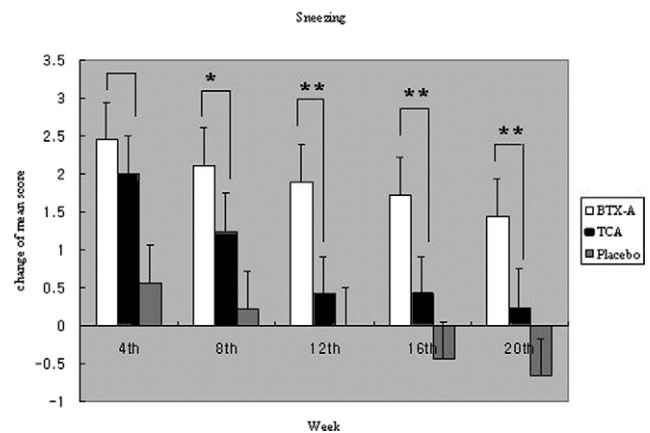


Figure 4 Comparison of changes in mean scores in three groups with respect to sneezing scores via Kruskal-Wallis ANOVA test. $P < 0.05$; $**P < 0.01$; $***P < 0.001$. BTX-A, Botulinum toxin type A; TCA, triamcinolone; placebo, normal saline.

With regard to sneezing, group A showed a more significant change in this symptom compared with group B; this change appeared from week 8 onward (Fig 4).

With regard to itching, even though group B showed a lower average score before treatment, the change in this symptom was greater in group B than in group A from week 8 (Fig 5). However, after week 8, group B showed a recurrence of the itching symptom.

Comparison of group A with group C showed a statistically significant greater change in all symptoms. Moreover, when we compared the two groups, group A showed a significantly greater change in all symptoms than the other two groups; group B did not show a statistically significant difference from the control group for rhinorrhea, itching, and sneezing symptoms after 20 weeks ($P > 0.05$; Table 2).

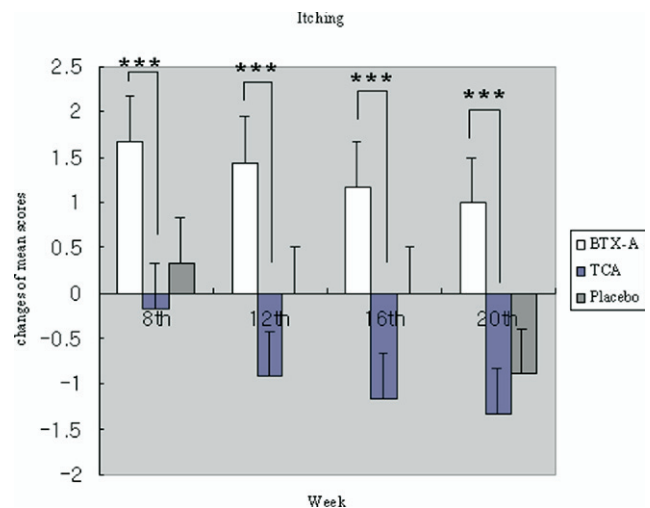


Figure 5 Comparison of changes in mean scores in three groups with respect to itching scores via Kruskal-Wallis ANOVA test. $P < 0.05$; $**P < 0.01$; $***P < 0.001$. BTX-A, Botulinum toxin type A; TCA, triamcinolone; placebo, normal saline.

Table 2
Symptom change 20 weeks after treatment

	Nasal obstruction		Rhinorrhea		Sneezing		Itching	
	Mean (SD)	F value	Mean (SD)	F value	Mean (SD)	F value	Mean (SD)	F value
BTX-A	2.27 (0.67)	24.172*	3.61 (0.85)	66.375*	1.44 (0.98)	14.099*	1.00 (0.97)	29.736*
TCA	1.50 (1.09)		0.75 (0.45)		0.25 (0.45)		−1.33 (0.78)	
Placebo	−.11 (0.78)		0.33 (1.12)		−.66 (1.50)		−.15 (1.38)	

BTX-A, Botulinum toxin type A; TCA, triamcinolone; placebo, normal saline.

In all four symptoms, there was strong statistical significance between the three groups. Group A showed a significantly greater change in all symptoms than did the other two groups, and group B did not show a statistically significant difference from the control group for rhinorrhea, itching, and sneezing symptoms after 20 weeks ($P > 0.05$; Kruskal-Wallis ANOVA test).

* $P < 0.001$.

DISCUSSION

Therapeutic efforts to lessen the symptoms of AR include avoidance of the specific allergen, use of antihistaminic drugs and nasal corticosteroid spray, immunotherapy, and surgical interventions. All of these treatment methods have advantages and disadvantages. In this respect, the use of BTX-A as a single agent may produce long-standing relief of AR symptoms and may be especially useful in patients whose symptoms are more difficult to control with standard therapeutic regimens.⁹ The effects of BTX-A on the nasal cavity have been postulated to occur through three mechanisms: 1) inhibition of the release of acetylcholine from the cholinergic nerve endings in the nasal mucosa; 2) inhibition of the release of acetylcholine from preganglionic cholinergic nerve endings in the sphenopalatine ganglion; and 3) induction of apoptosis in the nasal gland.^{7,8} BTX-A selectively inactivates peripheral cholinergic nerve terminals by blocking the release of acetylcholine. It exerts action at the molecular level by selectively cleaving the protein SNAP-25 (synaptosomal-associated protein with a molecular weight of 25 kD). When the BTX-A damages SNAP-5, the most obvious effect is on regulated exocytosis, that is, the release of synaptic vesicles in response to electrical depolarization.^{10,11} To date, there is no accepted dosage of BTX-A for AR; however, many study dosages range from 8 to 50 units. The toxic dose of BTX-A is 3000 units.¹² Shaari et al⁶ administered 50 units of BTX-A into one nasal cavity using soaked sterile gauze; Kim et al⁷ injected 4 units into each nasal cavity (total of 8 units); and Rohrbach et al¹³ administered 20 units into each nasal cavity using soaked sponges (total of 40 units). In this study, 25 units of BTX-A were injected into each nasal cavity (total of 50 units) to optimize the therapeutic level and give a safe and long-lasting effect.

The group with BTX-A injection showed the greatest change in rhinorrhea compared with other symptoms, confirming previous findings. Group A showed alleviation from week 1, with a significant change in rhinorrhea symptom, and steady alleviation was noted until week 20. The change in the symptom of sneezing was smaller than the changes in

nasal obstruction and rhinorrhea, and it gradually decreased further over time. The change in the symptom of sneezing was smaller than that of any other group every week. Although group B showed a greater change in the symptom of itching than group A before week 4 (although within a statistically insignificant range), this result seems meaningless because symptoms before treatment differed statistically.

In group B, although there was notable alleviation of the nasal obstruction, sneezing, and itching symptoms until the fourth week, all of the symptoms suddenly returned after the fourth week.

The duration of BTX-A effect among AR patients in this study (approximately 20 weeks) is longer than the duration of effect in other studies.¹⁴ The duration of effect and the occurrence of complications associated with the injection of BTX-A and the steroid were compared in medical literature. In accordance with other reports, BTX-A was most effective for treating rhinorrhea, but our study showed that it can also alleviate other allergic rhinitis symptoms, including nasal obstruction, sneezing, and itching. The difference in results may be attributed to the fact that we used a high dosage (total of 50 units) and injected the BTX-A slowly over 5 minutes. The higher BTX-A dose injections and the adequate time for distribution of local anesthesia might explain the long duration of symptom relief in this study. The relatively lower duration of BTX-A effect in other studies with quicker injection times might be attributed to rich blood vessels in the nasal mucosa, leading to more rapid absorption and clearing.

Intranasal steroid injection was originally attempted to treat AR without having to resort to surgery, but because of complications and short duration of the effect, this treatment has had limited use in clinical practice. There are rare reports about transient or permanent visual loss after intratubal steroid injections. The estimated incidence rate of visual loss was approximately 0.006 percent. Embolization and vasospasm of retinal artery were the possible causes of visual loss. Small-particle drugs must be used to minimize this complication.¹⁵ There was no reported visual

loss after intratubal BTX-A injection.^{16,17} In addition, BTX-A injection produced no complication such as dry eye, epistaxis, or systemic immune reaction.¹⁸ The dosage of 50 units was very effective in reducing AR symptoms in this study. During the observation period of 7 months to date, there have been no complications. This study was designed on the basis of subjective symptoms; thus, quantitative analysis was limited. A study using an objective method to measure the effects of BTX-A will be required.

CONCLUSION

Intranasal injection of 25 units (total 50 units) BTX-A is a highly effective and simple symptomatic treatment option with long-standing effects for patients with AR. BTX-A injection is superior to steroid injection for the treatment of AR symptoms.

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Tae Yong Yang: writer, study design, investigation; **Yoon Gun Jung:** English assistant; **Young Hyo Kim:** statistical analysis, data collection; **Tae Young Jang:** supervision.

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REFERENCES

1. Aberg N. Asthma and allergic rhinitis in Swedish conscripts. *Clin Exp Allergy* 1989;198:959–63.
2. Ayars G. Non allergic rhinitis. *Immunol Allergy Clin North Am* 2000; 20:283–302.
3. Schantz EJ, Johnson EA. Properties and uses of botulinum toxin and other microbial neurotoxins in medicine. *Microbiol Rev* 1992; 56:80–99.
4. Lance LS. Identification of the major steps in botulinum toxin action. *Annu Rev Pharmacol* 2004;44:16–193.
5. James K. Botulinum toxin-physiology and application in head and neck disorders. *Head Neck* 2005;27:525–35.
6. Shaari CM, Sanders I, Wu BL, et al. Rhinorrhea is decreased in dogs after nasal application of botulinum toxin. *Otolaryngol Head Neck Surg* 1995;112:566–71.
7. Kim KS, Kim SS, Yoon JH, et al. The effect of botulinum toxin type A injections for intrinsic rhinitis. *J Laryngol Otol* 1998;121:248–51.
8. Rohrbach S, Olthoff A, Laskwawi RG, et al. Botulinum toxin type A induces apoptosis in nasal glands of guinea pigs. *Ann Otol Rhinol Laryngol* 2001;110:1045–50.
9. Murat U, Serhan S, Okan D, et al. Effect of botulinum toxin type A on nasal symptoms in patients with allergic rhinitis: a double-blind, placebo-controlled clinical trial. *Acta Otolaryngol* 2003;123:1060–3.
10. Schantz EJ, Johnson EA. Properties and uses of botulinum toxin and other microbial neurotoxins in medicine. *Microbiol Rev* 1992;56: 80–99.
11. Dogu O, Apaydin D, Sevim S, et al. Ultrasound guided versus blind intraparotid injections of botulinum toxin-A for the treatment of sialorrhea in patients with Parkinson's disease. *Clin Neurol Neurosurg* 2004;106:93–6.
12. Scott AB, Suzuki D. Systemic toxicity of botulinum toxin by intramuscular injection in the monkey. *Mov Disord* 1982;170:149–59.
13. Rohrbach S, Olthoff A, Laskwawi RG, et al. Minimally invasive application of botulinum toxin type A in nasal hypersecretion. *ORL J Otorhinolaryngol Relat* 2001;63:382–4.
14. Ozcan C, Vayisoglu Y, Okan D, et al. The effect of intranasal injection of botulinum toxin A on the symptoms of vasomotor rhinitis. *Am J Otolaryngol* 2006;27:314–8.
15. Martin PA, Church CA, Petti GH, et al. Visual loss after intratubal steroid injection. *Otolaryngol Head Neck Surg* 2003;12:280–1.
16. Jaradeh SS, Smith TL, Torrico L, et al. Autonomic nervous system evaluation of patients with vasomotor rhinitis. *Laryngoscope* 2000; 110:1828–31.
17. Wilde AD, Cook JA, Jones AS. The nasal response to axillary pressure in non-eosinophilic intrinsic rhinitis. *Clin Otolaryngol* 1997;22: 219–21.
18. Unal M, Sevim S, Dogu O, et al. Effect of botulinum toxin type A on nasal symptoms in patients with allergic rhinitis: a double-blind, placebo-controlled clinical trial. *Acta Otolaryngol* 2003;123:1060–3.