Research Article

Intranasal injection of Botulinum toxin type A in treatment of allergic rhinitis.

Balegh H. Abdel-Hak, Osama G. and Alaa N. Alsaied.
Department of Otolaryngology, fucalty of Medicine, Minya university, Egypt .

Abstract
Objectives: We tested the effects of BTA injections in septum ,middle and inferior turbinates, on patients who had AR for a minimum of three years and had been treated unsuccessfully with conventional medications. **Method:** The study was an interventional case-control single-blind randomized clinical trial . 20 male and female AR patients who were referred to the hospital of Minya university ,in 2019; aged 15-52 years were selected on the basis of inclusion and exclusion criteria. The subjects were randomly assigned to the intervention (n=10) or control group (n=10). The intervention group received BTA (45 IU/ml; medytox), by injection intranasally in septum , middle and inferior turbinates. The control group received normal saline. The groups were evaluated by the same examiner. post-tests (1,4, and 12 weeks) were performed according to the authors' pre-designed checklist, the validity and reliability of which was previously established. The symptoms scored from none (0) to severe (10) at the test points. The statistical analysis was conducted with SPSS-19, with a significance level of 0.05. **Results:** Based on ANOVA, there was a significant difference ($P<0.05$) in symptomatic relief between the intervention and control groups. No marked adverse effects were observed during the study. **Discussion:** An intranasal injection of BTA, , may alleviate AR symptoms with no significant adverse effects.
Keywords: Botulinum Toxin type A(BTA), allergic rhinitis (AR),

Introduction
Allergic rhinitis (AR) is a common disease with high prevalence.
1- The upper respiratory symptoms of AR include nasal congestion, itching, anterior and posterior rhinorrhea and nasal sneezing. These symptoms are caused by the release of granular-associated mediators due to activation of mast cell residing in nasal tissue. Mast cell of respiratory mucosa and basophils in the blood coated by IgE are said to be sensitized. These mechanisms are responsible for respiratory symptoms after exposure to the allergen in atopic individuals.
2-3 Rhinorrhea in allergic rhinitis is under control demonstrated most readily by a unilateral antigen challenge, to one side of the nose, causing a bilateral increase in secretion response. Depending on pathogenesis of rhinitis and patients complains several treatment strategies are recommended such as in and intra nasal saline.
4- however the conventional medications are not able to completely control the symptoms in most of patients. Another limitation is the side effects of conventional treatments also financial problem.
5- Tranasal and systemic corticosteroid, histamine H1 antagonists, decongestants, cromolyn sodium, anti leukotrienes, anticholinergic, capsaicin, anti igE agent have been commonly used.
6- Botulinum toxin (BTX) is a natural neuroparalytic agent extracted from purified toxin of clostridium botulinum bacteria. There are eight types from A to G with different immunological spasticity. BTX inhibit the function of acetylcholine in presynaptic area of neurovascular `junction and consequently block cholinergic pathway Consequently, intranasal administration of BTX-A through different ways and doses seems to be a safe and effective treatment option for controlling rhinitis symptoms.

Patient and Methods
Study design
The current study is a prospective study for evaluation of the effect of injection of botulinum toxin type A on treatment of patients

with allergic rhinitis .The study was done at the department of Otorhinolaryngology, Minia University hospital from April 2018 to December 2018.

funding
The funding was afforded by the researcher herself with use of the facilities available in the hospital.

Ethical approval
Ethical permission was sought from a local ethics research committee (REC).
According to hospital protocol all patients consented for data retrieval for research purposes after ensuring the confidentiality so the study poses no harm regarding the safety issues to the patients.

participants
The study included 20 patients aged from 15-52 years old in both sexes.
In This study patients answered a survey to rate severity of allergic rhinitis symptoms (nasal secretions ,nasal obstruction, sneezing,) which graded according to kim et al., (2014).

classification as follow
0: no symptoms. I: Mild symptoms. II: Moderate symptoms. III: moderate to Severe symptoms. 1V: severe.

Inclusion criteria
We selected patients with long history of allergic rhinitis with former treatment with no control of symptoms. Allergic rhinitis was diagnosed by history, clinical and endoscopic examination and positive skin prick test.

Exclusion criteria
We excluded from the study any patient with the following exclusion criteria:
1- Patients with organic nasal obstruction ex: nasal polyposis
2- Patients with negative skin prick test
3- Pregnant and lactating women
4- Renal and hepatic patients.
5- Patients on antihistaminic drugs.

The patients were classified into 2 groups each group included 10 patients as follows:
1- BTA group (case group): included 10 allergic rhinitis patients with positive skin prick test which are injected by botulinum toxin type A (BTA) in inferior and middle turbinate and septum.
2- Saline group (study group): included 10 allergic rhinitis patients with positive skin prick test who have been injected by saline in middle, inferior turbinates and septum.
Patients were followed up one week, one month and 3 months post treatment.

Patients were evaluated for
Secretions, sneezing and obstruction& endoscopically. According to Kim et al each symptom was evaluated on a four point scale (0= no, 1 mild, 2 moderate, 3 moderate to severe, 4 sever) starting two weeks before the treatment and evaluation after treatment for week, one month, 3 month.

Evaluation and preparation of the patients
1- Detailed history of ear, nose and throat was taken from each patient.
2- Examination of the nose: By anterior rhinoscopy using simple nasal speculum.

Endoscopic examination
Examination was done under local anesthesia.
the examination was done by Nasal endoscopy (4-mm diameter, 0, 30° nasal endoscope, KARL STORZ, Germany) was used in both nasal cavities to assess the middle, inferior turbinates and septum

Clinical examination with nasal endoscopy using Freedman classification (2008) where: 0 equals no obstruction. 1mild obstruction. 2 in between means moderate obstruction. 3 sever obstruction.

4- Skin prick test (SPT)
The procedure was explained to the patient clearly SPT performed on the volar or inner aspect of the forearms. we cleaned the skin with 70% ethyl alcohol.
A grid is marked with a pen at 2 cm intervals (Future test sites 2 cm apart and a drop of the relevant allergen is placed on the arm at the end of each line. The pattern follows a corresponding list of allergens used for easy identification, Passing a lancet through a drop of allergen extract at a 45-degree angle to the surface of the skin. The needle is lightly pressed into the epidermis, and the tip of the needle is then lifted up, producing a pricking sensation, The lancet is wiped with a dry gauze between each prick, A 0.1% histamine solution is used

as a positive control, A negative control is included also using diluent solution to assess skin reactivity to mechanical trauma.
About 15-20 minutes after skin has been punctured, the test site is observed for erythema and wheal formation, We assessed a positive skin reaction in relation to size of histamine.

Botulinum toxin type A injection

We prepared the patient by informing him about the procedure, we put local anaethesia by ribbon gauze soaked with ephedrine: saline (1:1000) + xylocaine in both nasal cavities for 15 minutes.
We used insulin syringe for each patient to inject BTA in septum, middle and inferior turbinates, we diluted 100 units of BTA (Medytox, inc, south korea) in 5cm of sterilized water.
Patient were lying horizontally, Injection was in the anterior part of the septum and medial side of inferior turbinate and middle turbinate.
10 patients (group A) (study group) (BTA group) received 45U in each side of the nose divided as:15 in inferior turbinate, 15 in middle turbinate and 15 in the septum.
While the placebo group (group B) (control group) (saline group) received the same amount but from plain saline
No complications occurred, the procedure took about 10 minutes for each patient and they were discharged after it instantly.

In the follow up

A chart was made for every patient as the follow up was after one week, one month and 3 months .

A detailed history was taken and allergic rhinitis symptoms were graded according to kim et al., (2014) classification as follow:
0: no symptoms. I: Mild symptoms. II: Moderate symptoms.
III: moderate to severe symptoms. 1V: severe.

Also anterior rhinoscpy and endoscopic examination was done
And classified using Freedman classification (2008) where:
0 equals no obstruction, 1 mild obstruction, 2 in between means moderate obstruction,
3 severe obstruction

Results

This study included 20 patients (aged from 15-52 years old and of both sexes, 12 males and 8 females) divided into 2 groups:
Group (A), study group (BTA group): included 10 patients were injected by saline in inferior, middle turbinates and septum.
Group (B), control group (saline group): included patients were injected by BTA in inferior, middle turbinates and septum.

Statistical data

The study was done on 20 patients, 8 (40%) were females and 12 (60%) were males. Patients were in the age range of 15-52 years (mean 31.7± 9.5) with no significant difference regarding the age and sex distribution (Table).
The mean age ± SD of the studied cases was 36.2± 14.2 for group A, 37±12.4 for group B. 12cases were males while 8 cases were females. No significant associations were found between patients‘ age or sex and the effect of BTA on allergic rhinitis.

Table (1):Age & sex of the patient

Demographic data	BTA group N =10	Saline group N =10	P value
Age/years:			0.993
Range:	(17 – 50)	(15-52)	
Mean ± SD	36.2± 14.2	37±12.4	
Sex:			0.544
Male.	4 (40%)	6 (60%)	
Female	6 (60%)	4 (40%)	

Nasal obstruction

Table (2) : the effect of BTA and saline injection on nasal obstruction symptom

Nasal obstruction		BTA N=10	Saline N=10	P value
Pre-injection	Mean ± SD Median / IQR	3.4±0.5 3/(3-4)	3.5±0.5 3.5/(3-4)	0.661
1 week post-injection	Mean ± SD Median / IQR	2.9±0.6 3/(2.8-3)	3±0.7 3/(2.8-3.3)	0.721
1 month post-injection	Mean ± SD Median / IQR	2.1±0.7 2/(1.8-3)	2.5±0.5 2.5/(2-3)	0.208
3 months post-injection	Mean ± SD Median / IQR	1.6±1 1.5/(1-2.3)	2.1±0.6 2/(2-2.3)	0.177
P value (between different times)		<0.001*	<0.001*	
Pre vs 1w		0.025*	0.025*	
Pre vs 1m		0.010*	0.004*	
Pre vs 3m		0.007*	0.004*	
1w vs 1m		0.023*	0.025*	
1w vs 3m		0.009*	0.014*	
1m vs 3m		0.025*	0.046*	

• Mann Whitney test for non-parametric quantitative data between the two groups:
• Friedman's test for non-parametric quantitative data between the four times within each group.
• Wilcoxon signed rank test for non-parametric quantitative data between each two times within each group. *: Significant difference at P value < 0.05

In this study patients who injected with BTA in inferior and middle turbinates and septum showed significant improvement in the parameter of nasal obstruction more than the others who have been injected with saline however the improvement isn't very noticeable.

Table (3): the effect of BTA and saline injection on nasal secretions

Secretions		BTA N=10	Saline N=10	P value
Pre-injection	Mean ± SD Median / IQR	3.7±0.5 4/(3-4)	3.5±0.5 3.5/(3-4)	0.374
1 week post-injection	Mean ± SD Median / IQR	2.6±1.1 3/(1.8-3.3)	3.4±0.5 3/(3-4)	0.071
1 month post-injection	Mean ± SD Median / IQR	2.1±0.7 2/(1.8-3)	3±0.5 3/(3-3)	0.006*
3 months post-injection	Mean ± SD Median / IQR	1.2±1 1/(0-2)	3±0.7 3/(2.8-3.3)	0.001*
P value (between different times)		<0.001*	0.017*	
Pre vs 1w		0.016*	0.317	
Pre vs 1m		0.006*	0.025*	
Pre vs 3m		0.007*	0.059	
1w vs 1m		0.102	0.046*	
1w vs 3m		0.011*	0.046*	
1m vs 3m		0.011*	1	

- **Mann Whitney test for non-parametric quantitative data between the two groups:**
- Friedman's test for non-parametric quantitative data between the four times within each group.
- Wilcoxon signed rank test for non-parametric quantitative data between each two times within each group.
- *: Significant difference at P value < 0.05

So BTA shows highly significant results in reliving rhinorrhea (nasal secretions) in comparison with saline injection.

Table (4): the effect of BTA and saline injection on sneezing symptom

Sneezing		BTA N=10	Saline N=10	P value
Pre-injection	Mean ± SD	3.6±0.5	3.5±0.5	0.661
	Median / IQR	4/(3-4)	3.5/(3-4)	
1 week post-injection	Mean ± SD	2±0.8	3.2±0.8	0.007*
	Median / IQR	2/(1-3)	3/(2.8-4)	
1 month post-injection	Mean ± SD	1.7±0.5	3±0.7	0.001*
	Median / IQR	2/(1-2)	3/(2.8-3.3)	
3 months post-injection	Mean ± SD	0.7±0.5	2.6±0.8	<0.001*
	Median / IQR	1/(0-1)	3/(2-3)	
P value (between different times)		<0.001*	0.003*	
Pre vs 1w		0.016*	0.083	
Pre vs 1m		0.005*	0.025*	
Pre vs 3m		0.004*	0.014*	
1w vs 1m		0.083	0.157	
1w vs 3m		0.010*	0.034*	
1m vs 3m		0.008*	0.102	

• ***Mann Whitney test for non-parametric quantitative data between the two group.***
• Friedman's test for non-parametric quantitative data between the four times within each group.
• Wilcoxon signed rank test for non-parametric quantitative data between each two times within each group.
• *: Significant difference at P value < 0.05
So BTA shows highly significant results in reliving sneezing symptom in comparison with saline injection.

Table (5):the effect of BTA and saline injection on nasal endoscopy

Nasal endoscopy		BTA N=10	Saline N=10	P value
Pre-injection	Mean ± SD	3.5±0.5	3.5±0.5	1
	Median / IQR	3.5/(3-4)	3.5/(3-4)	
1 week post-injection	Mean ± SD	2.6±1	2.9±0.9	0.466
	Median / IQR	3/(1.8-3)	3/(2.8-3.3)	
1 month post-injection	Mean ± SD	2±0.7	2.7±0.8	0.043*
	Median / IQR	2/(1.8-2.3)	3/(2-3)	
3 months post-injection	Mean ± SD	1.4±0.8	2.5±0.7	0.007*
	Median / IQR	1/(1-2)	2/(2-3)	
P value (between different times)		<0.001*	0.004*	
Pre vs 1w		0.041*	0.063	
Pre vs 1m		0.007*	0.023*	
Pre vs 3m		0.007*	0.008*	
1w vs 1m		0014*	0.157	
1w vs 3m		0.010*	0.157	
1m vs 3m		0.014*	0.414	

Mann Whitney test for non-parametric quantitative data between the two groups*:*
- Friedman's test for non-parametric quantitative data between the four times within each group.
- Wilcoxon signed rank test for non-parametric quantitative data between each two times within each group.
- *: Significant difference at P value < 0.05.

In conclusion BTA injection has a significant effect on improvement of nasal endoscopy (chronic hypertrophic rhinitis) over saline.

Discussion

Studies conducted over the past 50 years have shown that there is a relationship between over-activity of the parasympathetic nervous system and reduced sympathetic activity of the nasal mucosa.

In the present study, we used this less invasive under local anesthesia approach to observe the effects of BTA, We compared the results of this

method with those of other therapeutic modalities, such as BTA injection in septum only or septum and inferior turbinates only or intranasal sponge, and found that BTA (Meditox) may be used safely and effectively in selected patients with chronic allergic rhinitis, who had been treated with conventional medications with no clinical improvement.

In Keramat Mozafarinia et al., study forty patients diagnosed with persistent AR or non-allergic rhinitis Patients received an injection of 80 units BTA (Dysport, Ipsen Ltd Company, UK) at a concentration of 200 mU/ml in normal saline on each side of the nasal septum and were followed for 12 weeks[6] .

The severity of rhinitis symptoms was reduced after 4 weeks of injections in the intervention group and then gradually decreased further until the 12th week. There was a statistically significant difference between the groups($P< 0.05$)[6]

According to Keramat Mozafarinia et al., treatment in improving symptoms appears to maximize at the fourth week and then gradually decreases after this time[6].

The advantage of mucopericondrial injection is It is an effective therapeutic method for the treatment of idiopathic non-allergic rhinitis and persistent AR as it leads to less drug clearance and greater efficacy of treatment Compared with intraturbinate injection also, there is a reduced risk of direct entry of the drug into the systemic circulation, resulting in fewer potential complications. In comparison with our study which we injected BTA intra-nasally in septum, middle and inferior turbinates the symptoms improvement started one week after injection also it was more effective as it was injected in 3 places on the contrary with Keramat Mozafarinia et al., study where the injection was in turbinate only and the efficacy appeared to be prominent 4 weeks later and started to decrease gradually while in our study the improvement started one week and the
improvement increased till it reached its maximum at 12th week and started to decrease but didn't return to the state before the injection.

In Kim et al., study 60 patients who diagnosed with idiopathic rhinitis were injected by 8U BTA(Botox®) in Inferior and middle turbinates on each side of the nose the result is decreased rhinorrhea for 4 weeks, but did not affect nasal obstruction or sneezing[7].
This study compared to our study there is low efficacy of BTA in kim et al., study may be due to the study was on different group of patients (idiopathic rhinitis patients) or due to low dose of BTA 8U in each side so the sneezing and obstruction symptoms didn't relief as in our study.

In Rohrbach et al., case report, a BTA(Botox®) soaked sponge was put in a case report who had idiopathic rhinitis his nose bilaterally and left for thirty minutes, BTA decreased both rhino-rrhea and nasal obstruction for 4 weeks but didn't have a significant effect on sneezing there was a side effect of nasal dryness[8].
In comparison with our study which was about allergic rhinitis may be the difference in results due to the difference in the disease nature as in

Rohrbach et al., case report it was about idiopathic rhinitis this agrees with kim et al., study as we saw BTA didn't relief sneezing symptom.

In Unal et al., study 34 allergic rhinitis patients were injected in Inferior and middle turbinate by BTA(Botox®),The unit number was 40–60 U on each side of the nose there was no side effects Both BTA doses were effective in decreasing symptoms for 8 weeks except itching symptom[9].
This study results in comparison to ours it appears to be the same.

Conclusion

- Our study showed that BTA could be a promising treatment for allergic rhinitis patients who had long term of ordinary treatment that is not very responsive to the ordinary treatment.
- While in BTA injection it is only single dose abolishing the patients burden to remember time for doses.
- Our study showed significant improvement in case of sneezing and rhinorrhea parameters and the improvement increased overtime.
- More studies including more number of patients with long term follow up should be performed,we need protocol for the dose and sites of injection of BTA, Longer duration for

evaluation is needed to measure the effet of BTA over time, the cost benefit relationship between BTA and medical therapy should be evaluated.

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