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ORIGINAL RESEARCH

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The minimum effective dose of abobotulinum toxin A injection for allergic rhinitis: A dose-escalation randomized controlled trial

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Abstract

Objective: To find the lowest effective injection dose of abobotulinum toxin A (Dysport) for allergic rhinitis.

Study Design: Dose-escalation randomized controlled trial.

Methods: We included all patients aged 18 years or older who had persistent allergic rhinitis and positive allergy skin prick test. The patients were randomly allocated to receive 40, 30, or 20 U of abobotulinum toxin A by injection at the inferior turbinate. We followed up on patients for 12 weeks to evaluate nasal symptoms, ocular symptoms, minimum nasal cross-sectional area as measured using acoustic rhinometry, and complications.

Results: Seventeen patients were included in this study, with 7 receiving 20 U of abobotulinum toxin A and 5 each receiving 30 U and 40 U. Abobotulinum toxin A significantly improved nasal congestion, rhinorrhea, sneezing, and loss of smell at 40 U ($P < .05$) and nasal congestion, sneezing, and loss of smell at 30 U ($P < .05$). However, at a dose of 20 U, only nasal congestion and loss of smell improved ($P < .05$). Nasal patency had also significantly improved two weeks after treatment at doses of 40 and 30 U ($P < .05$). Complications included epistaxis (11.8%) and nasal dryness (23.5%).

Conclusion: Abobotulinum toxin A at a dose of at least 30 U effectively reduced most nasal symptoms.

Level of Evidence: 2.

Trial registration: Clinicaltrials.in.th/ TCTR20200526014.

KEYWORDS

allergic rhinitis, botulinum toxin, nasal symptoms, ocular symptoms

1 | INTRODUCTION

Allergic rhinitis is a common problem, with a prevalence ranging from 10 to 40% depending on geographic location.[1,2] In Thailand, the prevalence of allergic rhinitis using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire in both children and adults can be as high as 50%. Around 30% of the participants who had rhinitis symptoms in the ISAAC questionnaire were positive for skin prick test. In the Thai community screening program for ear nose and throat diseases, the prevalence of allergic rhinitis diagnosed by the otolaryngologists ranging from 3 to 5%.[3-7] The main treatment options for allergic rhinitis include antihistamines, intranasal corticosteroids, and nasal irrigation.[1,8]

Botulinum toxin A was first used as a treatment for allergic rhinitis in 1998, in which the authors injected 20 U of onabotulinum toxin A (Botox) into the inferior and middle turbinate. The study found that this treatment reduced rhinorrhea by 24% to 41%, but had no effect on nasal congestion or sneezing.[9]

There are three types of botulinum toxin A approved by the US Food and Drug Administration: (a) Onabotulinum toxin A (eg, Botox /Vistabel; Allergan Inc., Dublin, Ireland), (b) Abobotulinum toxin A (Dysport/Azzalure; Ipsen, Paris, France/Galderma, Lausanne, Switzerland), and (c) Incobotulinum toxin A (Xeomin/Bocouture, NT 201; Merz Pharmaceuticals GmbH, Frankfurt, Germany).[10] Each of botulinum toxin A formulated differently, has a different manufacturing process, and demonstrates unique characteristics. Subsequently, these products are not interchangeable.[11] The molecular mass of the botulinum toxin A complexes is as follows: onabotulinum toxin A (900 kDa), abobotulinum toxin A (300-900 kDa), and incobotulinum toxin A (150 kDa). The lower molecular mass is associated with a longer diffusion distance, causing it to spread to a broader area after it is injected. However, in some areas, it can adversely cause a neurotoxin effect on unwanted structures. The optimal conversion ratio between onabotulinum toxin A and abobotulinum toxin A is still debated. The most accepted conversion ratio is 1:3. As a result, the number of units recommended for each indication is usually specific for each preparation.[10]

Minimum (lowest) effective dose is the smallest dose that will produce the desired outcome. The dose beyond the minimum effective dose may achieve more clinical efficacy. However, the risk of side effects of the toxin also increased. Furthermore, it may not be economically cost-effective. Various dose strategies of botulinum toxin A have been examined in the literature, ranging from 10 to 80 U of onabotulinum toxin A and 80 to 200 U of abobotulinum toxin A.[12] Based on the accepted conversion ratio, the minimum effective dose of abobotulinum toxin A should be around 30 U or lower.

To date, there is no study regarding the minimum effective dose of abobotulinum toxin A. This is the first dose-escalation trial conducted to determine the lowest effective injection dose of abobotulinum toxin A (Dysport) for allergic rhinitis.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This dose-escalation trial was conducted from August 2017 to December 2019 at the Khon Kaen University Faculty of Medicine's Department of Otorhinolaryngology (Thailand).

2.2 | Participants

We included all patients aged 18 years or older who had persistent allergic rhinitis and positive allergy skin prick test.

The allergic rhinitis was defined according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline.[13] The symptoms include rhinorrhea, nasal obstruction, nasal itching, sneezing, and post-nasal drip. Persistent allergic rhinitis was defined when the patient has symptoms more than four days a week.

Participants were tested for 12 inhaled allergens preserved in phenolated saline, negative (phenolated saline) and positive (histamine) control (Allertech Laboratories, Florida) using a 23G intravenous (IV) needle (Nipro Medical Corporation, Bridgewater, New Jersey)[14] at the volar aspect of the forearm with a distance of more than 2 cm between test locations.[15] A drop of each allergen was placed on the skin immediately before the prick was performed.

The results were read 15 to 20 minutes following application.[16] Negative and positive controls were inspected to confirm that the test was applied correctly. Reactions were recorded as positive when a wheal ≥ 3 mm greater than the negative control was found according to the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) practice parameter.[17,18]

The exclusion criteria were (a) having received allergy medication, including antihistamines, intranasal corticosteroids, and decongestants, 1 month prior to enrollment, (b) pregnancy, (c) rhinosinusitis, (d) deformed nasal cavity, such as significant nasal septum deviation, (e) tumor in the sinonasal tract, (f) history of sinus surgery, (g) conditions that carry a high risk of botulinum toxin side effects, such as glaucoma or prostate hypertrophy, and (h) having undergone immunotherapy treatment.

2.3 | Randomization

The randomization list was computer-generated by a statistician based on the block randomization method with randomly selected block sizes. The allocation assignment was sealed in opaque, sequentially numbered envelopes. Because of the nature of the interventions, it was not possible to conceal the group allocation from the physicians. However, participants and research assistant who help the participants to complete the questionnaire were blinded from the intervention.

2.4 | Procedure

The dose of abobotulinum toxin A (Dysport) was determined from a common conversion proportion of 1:3. From the literature, the lowest dose of onabotulinum toxin was 10 U. In theory, it should be comparable to abobotulinum toxin A 30 U. However, the lowest total dose of abobotulinum toxin A shown to be effective in treating allergic rhinitis in the literature was 80 U.[12] So, in this study, we started with half the known effective dose (ie, 40 U) in the first arm and two consecutively lower doses (30 U and 20 U) in the second and third arms.

Abobotulinum toxin A is supplied as a dry powder, in single-dose 300 Unit and 500 Unit vials, which must be reconstituted with preservative-free 0.9% Sodium Chloride Injection, USP using aseptic technique prior to injection. After reconstituted, it should be stored in the original container in a refrigerator at 2°C to 8°C and use within 24 hours.

Topical anesthesia (4% lidocaine) and decongestant (0.05% oxymetazoline) were sprayed into the patient's nostrils 15 minutes before injection. The total dose for each arm was divided at a 50:50 ratio and injected slowly over 5 minutes into the anterior part of the inferior turbinate on each side under a rigid endoscope.

The typical injection sites are inferior turbinate, middle turbinate, and nasal septum. The inferior turbinate plays a crucial role in the nasal patency. Injection of botulinum toxin to both inferior/middle turbinate and nasal septum may improve efficacy but also increase the risk of the toxin spreading to adjacent structures.

The molecular size of abobotulinum toxin A was relatively small amongst botulinum toxin A and tended to spread to the tissue more easily. All the previous studies of abobotulinum toxin A injected the toxin into the inferior turbinate or nasal septum only. A recent study comparing the efficacy between inferior turbinate and nasal septum injection site for abobotulinum toxin A and found no statistically difference.[19]

The patients were not allowed to use antihistamines, intranasal or systemic corticosteroids, or decongestants during the study.

2.5 | Follow-up

We followed-up on patients for 3 months. Outpatient evaluations were conducted at weeks 2 and 12 and telephone interviews at weeks 1, 4, and 8.

2.6 | Rescue procedure

The patients were advised to take loratadine if they developed severe allergies and to stop when the symptoms improved. They were instructed to record their usage of the rescue medication in their diary.

2.7 | Outcomes

A 5-point Likert scale (ranging from 0 to 4) was used to evaluate patients' symptoms including nasal obstruction, rhinorrhea, sneezing, nasal itching, inhibited sense of smell, and eye itching, redness, and watering.[20] Each question can be answered from "0" (not a problem) up to "4" (severe problems).

Likert scale was recommended as a method for assessing the severity of symptoms of allergic rhinitis by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology[21] and later adopted to Nasal Obstruction Symptom Evaluation (NOSE) score.[22]

The objective outcomes included findings from nasal endoscopy and acoustic rhinometry. Data regarding complications, including epistaxis, nasal dryness, and muscular palsy, were also collected.

2.8 | Statistical analysis

The sample size was based on the standard methodology for dose-escalation trials.[23] We expected the patients would experience more complications from higher doses of abobotulinum toxin, so five patients were given a 40 U dose, five were given 30 U, and 7 were given 20 U (5 + 5 + 7 design).

Statistical analyses were performed using the SPSS version 20 and Stata version 14. Data were described as either means (for continuous variables) or frequencies and percentages (for categorical variables). Significant differences between groups were determined using the one-way ANOVA, repeated measure ANOVA or Kruskal-Wallis test for continuous variables. The chi-square test or Fisher-exact test was used to determine whether there were significant differences between expected frequencies and observed frequencies. For all tests, $P < .05$ was considered statistically significant.

2.9 | Ethical considerations

This study was approved by the Khon Kaen University Ethics Committee in Human Research (HE601288). Written informed consent to participate was provided by all patients enrolled.

3 | RESULTS

There were 17 patients included in this study, 10 males (58.82%) and 7 females (41.18%) (Figure 1). The mean age of the patients was 33 years, ranging from 19 to 59. There was no difference in symptoms among groups, except with regard to ocular itching ($P = .017$). There was also no difference in terms of the nasal cross-sectional area among groups ($P > .05$; Table 1).

Follow-ups were conducted to examine patients' symptoms at weeks 1, 2, 4, 8, and 12. The score used to rate symptoms ranged from 0 to 4 (lower is better). Abobotulinum toxin A significantly improved nasal congestion, rhinorrhea, sneezing, and loss of smell at a dose of 40 U ($P < .05$) and nasal congestion, sneezing, and loss of

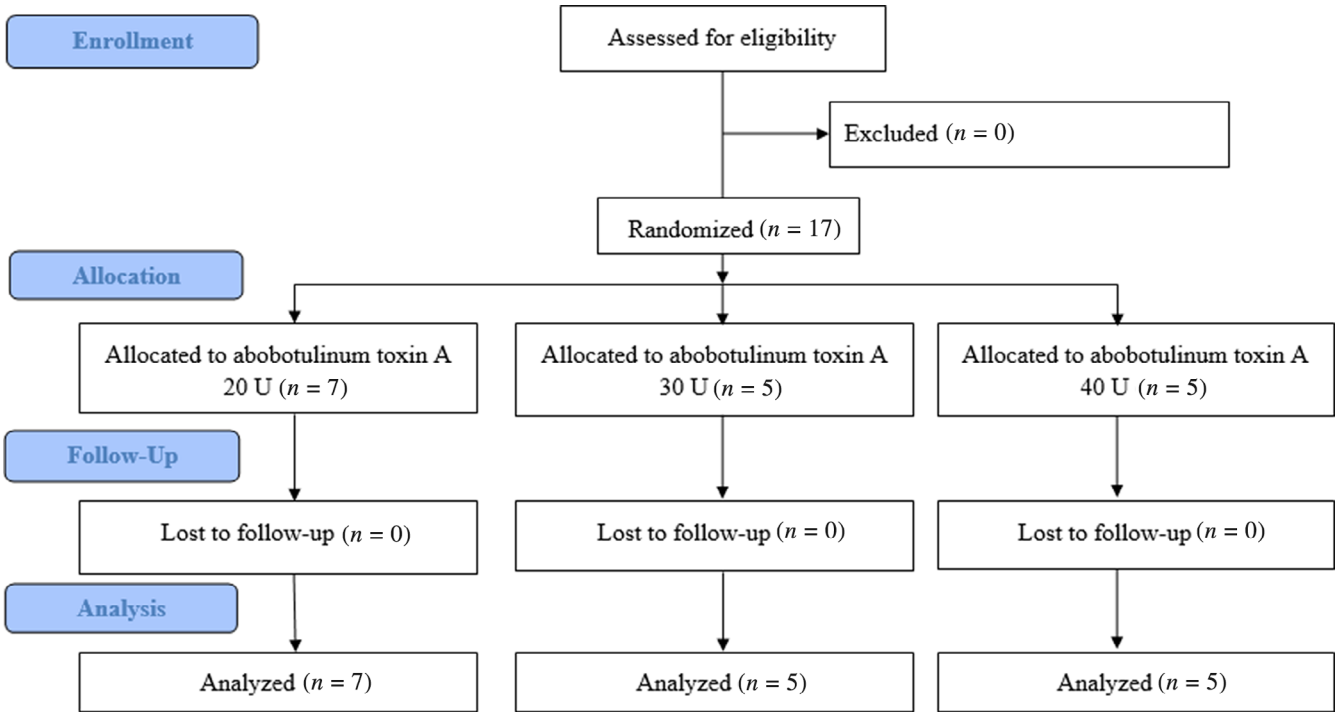

FIGURE 1 Participants flow diagram

TABLE 1 Demographic data

	40 U	30 U	20 U	*P*-value[a]
Sex				
Male	3	4	3	.604
Female	2	1	4	
Age (years)	30.80	32.60	35.86	.680
Symptoms (ranged 0-4, lower is better)				
Nasal congestion	4.00	3.00	2.43	.157
Rhinorrhea	2.40	0.80	1.14	.155
Nasal itching	1.00	0.40	1.29	.480
Sneezing	1.60	0.80	0.86	.347
Loss of smell	2.60	2.60	1.29	.256
Ocular itching	1.40	2.60	0.43	.017*
Ocular redness	0.00	1.40	0.14	.065
Ocular watering	0.60	1.40	0.71	.704
Acoustic rhinometry				
Right minimum cross-sectional area	0.62	0.70	0.76	.770
Left minimum cross-sectional area	0.68	0.59	0.64	.933

[a]One-way ANOVA.
*P-value < .05.

smell at 30 U (P < .05). However, at 20 U, only nasal congestion and loss of smell improved (P < .05; Table 2).

Acoustic rhinometry was performed at weeks 0, 2, and 12. At 40 and 30 U, abobotulinum toxin A improved nasal patency at 2 weeks after treatment (P < .05). However, nasal patency had returned to baseline in all groups at week 12, indicating that the effects of the treatment had diminished (Table 3).

The mean total dosages of rescue therapy used over 3 months were 10.6, 7.6, and 11.9 tablets/person in the 40, 30, and 20 U group, respectively, with no statistical significance difference among groups (P = .88). Complications encountered in this study included minor epistaxis in one patient in the 40 U group and another in the 20 U group. There were two cases of nasal dryness in the 20 U group, and one in each of the other groups. There were no reactions related to the injection site.

TABLE 2 Patient symptoms

Week	0	1	2	4	8	12	Mean difference (95% CI)[a]	*P*-value[b]
Nasal congestion								
40 U	4.00	3.00	2.40	2.60	2.40	2.20	1.80 (0.76 to 2.84)	.018*
30 U	3.00	1.20	1.60	1.40	1.80	1.60	1.40 (−0.48 to 3.28)	.003*
20 U	2.43	1.57	2.00	1.83	1.67	1.83	0.60 (−1.29 to 2.62)	.022*
Rhinorrhea								
40 U	2.40	1.40	2.20	2.20	1.80	2.20	0.20 (−1.84 to 2.24)	.011*
30 U	0.80	0.40	0.60	0.00	0.20	0.60	0.20 (−1.84 to 2.24)	.098
20 U	1.14	1.00	0.86	0.17	0.33	0.17	0.97 (−0.15 to 2.15)	.101
Nasal itching								
40 U	1.00	0.80	0.40	0.40	0.60	0.80	0.20 (−1.16 to 1.56)	.208
30 U	0.40	0.40	0.40	0.20	0.20	0.20	0.20 (−0.83 to 1.24)	.137
20 U	1.29	0.43	0.29	0.50	0.33	0.83	0.46 (−0.60 to 1.60)	.054
Sneezing								
40 U	1.60	1.00	0.40	0.60	0.60	0.40	1.20 (−0.42 to 2.82)	.030*
30 U	0.80	0.60	0.40	0.60	0.80	1.00	−0.20 (−1.82 to 1.41)	.049*
20 U	0.86	0.43	0.57	0.33	0.17	0.17	0.69 (−0.19 to 1.52)	.076
Loss of smell								
40 U	2.20	2.40	2.20	1.40	1.80	1.80	0.40 (−1.68 to 2.48)	.046*
30 U	2.60	1.40	1.40	1.40	1.40	1.20	1.40 (−0.27 to 3.07)	.042*
20 U	1.29	1.71	1.71	1.17	1.17	1.17	0.12 (−1.17 to 1.40)	.040*
Ocular itching								
40 U	1.40	0.60	0.80	0.20	0.20	0.00	1.40 (−0.02 to 2.82)	.105
30 U	2.60	1.40	1.00	1.00	0.60	1.00	1.6 (−0.07 to 3.27)	.089
20 U	0.43	0.00	0.14	0.17	0.17	1.00	−0.57 (−1.95 to 0.95)	.069
Ocular redness								
40 U	0.00	0.20	0.00	0.00	0.00	0.00	0.00	.374
30 U	1.40	1.00	1.00	1.00	0.60	0.80	0.60 (−1.66 to 2.86)	.215
20 U	0.14	0.00	0.00	0.00	0.00	0.00	0.14 (−0.26 to 0.60)	.363
Ocular watering								
40 U	0.60	0.60	0.40	0.20	0.00	0.00	0.60 (−0.51 to 1.71)	.181
30 U	1.40	0.20	0.20	0.20	0.40	0.40	1.00 (−0.52 to 2.52)	.292
20 U	0.71	0.14	0.43	0.67	0.67	0.50	0.21 (−0.21 to 0.88)	.198

[a]Mean difference between baseline and week 12.
[b]Repeated measure ANOVA.
*P-value < .05.

TABLE 3 Acoustic rhinometry

Week	0	2	12	Mean difference (95% CI)[a]	*P*-value[b]
Right minimum cross-sectional area					
40 U	0.62	0.60	0.56	0.06 (−0.29 to 0.42)	.021*
30 U	0.70	0.85	0.46	0.24 (−0.23 to 0.81)	.011*
20 U	0.76	0.55	0.53	0.23 (−0.22 to 0.56)	.001*
Left minimum cross-sectional area					
40 U	0.68	0.85	0.39	0.29 (−0.03 to 0.62)	.004*
30 U	0.59	0.71	0.57	0.02 (−0.41 to 0.41)	.014*
20 U	0.64	0.48	0.46	0.18 (−0.36 to 0.52)	.002*

[a]Mean difference between baseline and week 12.
[b]Repeated measure ANOVA.
*P-value < .05.

The post-hoc power calculation was performed. This study yields up to 87.9% of power in the nasal congestion domain. Indicating this study has enough power to find a statistical difference in the outcomes.

4 | DISCUSSION

Allergic rhinitis is a common clinical entity, the symptoms of which include nasal congestion, rhinorrhea, sneezing, nasal itching, loss of smell, and eye itching, redness, and watering. Botulinum toxin is thought to reduce these symptoms via the following mechanisms: (a) suppression of acetylcholine release from the nerve ending in the nasal mucosa; (b) inhibition of acetylcholine release from the sphenopalatine ganglion; (c) initiation of apoptosis of the nasal submucosal glands; and (d) inhibiting the release of neuropeptides from the trigeminal and parasympathetic nerve ending.[9,12,24]

To date, there is no standard recommended dose of botulinum toxin for allergic rhinitis. Various dose strategies have been employed, ranging from 10 to 80 U of onabotulinum toxin A and 80 to 200 U of abobotulinum toxin A.[12]

Furthermore, there is no consensus regarding the lowest effective dose of botulinum toxin. To our knowledge, this is the first dose-escalation trial conducted to determine the lowest effective injection dose of abobotulinum toxin A for allergic rhinitis.

From a recent study, the authors injected the abobotulinum toxin A 80 U into both sides of the inferior turbinate. They found that botulinum toxin A can effectively reduce the sneezing, watery runny nose, and nasal obstruction ($P < .05$).[19]

We found that abobotulinum toxin A significantly improved nasal congestion, rhinorrhea, sneezing, and loss of smell at 40 U ($P < .05$) and nasal congestion, sneezing, and loss of smell at 30 U ($P < .05$). However, at a dose of 20 U, only nasal congestion and loss of smell improved ($P < .05$). We also found that nasal patency had significantly improved at 2 weeks after treatment at doses of 40 and 30 U ($P < .05$).

The duration of effect of botulinum toxin usually ranges between 8 and 12 weeks.[12] In this study, acoustic rhinometry indicated that the effects on nasal congestion diminished before 12 weeks, but that patients' symptoms were effectively managed during the 12-week period.

It is important that allergic rhinitis patients get an effective dose of botulinum toxin without significant side effects. In this study, epistaxis was found in one patient in the 40 U group and one in the 20 U group. Nasal dryness was found in two patients in the 20 U group and one in each of the other groups. This suggests that the side effects may not depend on the dosage. All patients considering botulinum toxin as their choice of treatment for allergic rhinitis should be informed of all possible side effects before initiating therapy.

The dose-escalating trial is usually exploratory and has a small sample size. The future trial with a larger sample size and power is needed to confirm this study results.

5 | CONCLUSIONS

Abobotulinum toxin A at a dose of at least 30 U effectively reduced most nasal symptoms.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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