Comparative Study of the Effectiveness Between letibotulinumtoxinA and onabotulinumtoxinA in the Treatment of Axillary Hyperhidrosis

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Abstract

Botulinum toxin (BTX) is a well-established, widely used, effective treatment for primary axillary hyperhidrosis (PAH). Recently, the off-label use of letibotulinumtoxinA (LetiBTX-A), including treating movement disorders and aesthetic purposes, has been dramatically increasing due to its good efficacy. The authors hypothesized that the effectiveness of LetiBTX-A for the treatment of PAH is non-inferior to that of onabotulinumtoxinA (OnaBTX-A) which is the only US Food and Drug Administration approved BTX for severe axillary hyperhidrosis. A prospective, double-blinded, split-sided, randomized controlled trial was conducted on 30 participants with moderate to severe PAH (≥2 hyperhidrosis disease severity scale (HDSS) score). Axillae of each participant was randomly assigned to receive LetiBTX-A 50 U or OnaBTX-A 50 U. Outcome was assessed 1 month after injection. All 30 participants with a mean (SD) age of 34.44 (7.82) completed the study. At 1 month after injection, the proportion of subjects who have ≥2-point improvement from baseline HDSS score in LetiBTX-A (93.33%) and OnaBTX-A (93.33%) group was no different. More than 50% reduction of hyperhidrosis area was observed at both LetiBTX-A and OnaBTX-A-treated axillae without statistically significant difference (LetiBTX-A, 68.13%; OnaBTX-A, 65.67%; P = 0.316). Additionally, participants were equally satisfied with both LetiBTX-A and OnaBTX-A-treated axillae. The mean (SD) onset of action was 1.700 (1.393) days for LetiBTX-A and 1.733 (1.388) days for OnaBTX-A (P = 0.317). Comparable procedure-related pain was observed between the 2 groups. No significant adverse events were reported. According to the findings, it can be implied that LetiBTX-A and OnaBTX-A have comparable effectiveness and safety for the treatment of PAH.

Keywords**:** *Botox, Hugel, Sweating*

1. Introduction

Primary axillary hyperhidrosis (PAH) is an idiopathic disease characterized by excessive sweating on axillae affecting approximately 1.4-5.75% of the general population (Fujimoto, Kawahara, & Yokozeki, 2013; Hashmonai et al., 2017; Hasimoto et al., 2018; Nawrocki & Cha, 2019a). Its symptoms can be devastating due to physical, functional, and psychosocial impairment. A study in the US population revealed that sweating was intolerable and interfered with daily activities in 32.4% of individuals with axillary hyperhidrosis (HH). The degree of limitation in daily activities including at work, in a public place, first time meeting people, developing personal relationships, intimate relationships, and in sports increased with the higher disease severity (Strutton et al., 2004). Regarding the psychological problem, feeling embarrassed was the most common issue experienced by patients diagnosed with primary HH, followed by shame and discomfort (Hasimoto et al., 2018).

HH, or excessive sweating, denotes sweat production is more abundant than a normal physiological need for thermoregulation. As previously mentioned, primary HH is an idiopathic disease that accounted for 93% of all patients diagnosed with HH. The symptom is usually focal, bilateral, and symmetrical (Nawrocki & Cha, 2019a). Although the etiology of primary HH remains unknown, there is growing evidence that supports 3 possible etiological factors i.e., genetic predisposing factor, histological change of sympathetic ganglia, and increased expression of acetylcholine and activin receptor in the sympathetic ganglia (Hashmonai et al., 2017).

Several treatment modalities are available for the management of HH. The treatment decision mainly depends on etiology (primary or secondary), localization, severity, safety, price, treatment availability, and

physician expertise. For PAH, topical antiperspirants are the first-line treatment. If symptoms continue to persist, the next treatment option is botulinum toxin (BTX) injections, followed by systemic oral therapy, energy-based devices, and local surgical procedures, respectively. Endoscopic sympathectomy is preserved to be the last treatment option (Nawrocki & Cha, 2019b).

BTX, a neurotoxin produced by *Clostridium botulinum*, has been used for several therapeutic and aesthetic purposes. Currently, there are 5 formulations approved by US Food and Drug Administration (FDA), however, a variety of formulations are commercially available and have been used off-label in several dermatological conditions (Mahant, Clouston, & Lorentz, 2000; Nawrocki & Cha, 2020; Padda & Tadi, 2020). OnabotulinumtoxinA (OnaBTX-A) is the only FDA-approved formulation for the treatment of severe axillary HH that is inadequately managed by topical agents in adult patients. Nevertheless, clinical studies showed favorable results with acceptable safety profiles of other formulations, including abobotulinumtoxinA (AboBTX-A) and rimabotulinumtoxinB (RimaBTX-B), for the treatment of PAH (An et al., 2015; Talarico-Filho et al., 2007; Wu et al., 2019).

LetibotulinumtoxinA (LetiBTX-A) is a new BTX-A formulation with FDA approval for blepharospasm. Because of its effectiveness, off-label uses of LetiBTX-A, including treating movement disorders and cosmetic purposes, have been increasing continuously (Chang et al., 2017; Do et al., 2017; Yoo et al., 2021). To the best of our knowledge, this is the first study to examine the effectiveness and safety of LetiBTX-A in the treatment of PAH.

2. Objectives

1) To compare the effectiveness of LetiBTX-A and OnaBTX-A in the treatment of PAH
2) To compare the onset of action of LetiBTX-A and OnaBTX-A in the treatment of PAH
3) To study adverse events of LetiBTX-A and OnaBTX-A in the treatment of PAH

3. Materials and Methods

Study design and participant

This was a prospective, double-blinded, split-sided, randomized controlled trial comparing the effectiveness and safety of LetiBTX-A and OnaBTX-A in the treatment of PAH. The study was approved by the Human Research Ethics Committee of Thammasat University (Medicine) (MTU-EC-OO-6-129/64) which is in full compliance with International Guidelines for Human Research Protection such as Helsinki Declaration of 1975, as revised in 1983. Informed consent were obtained from all participants.

Thirty healthy subjects diagnosed with moderate to severe PAH (≥2 hyperhidrosis disease severity scale (HDSS) score) were recruited. The exclusions were prior HH treatment within 12 months, neuromuscular diseases, active skin diseases, pregnancy or active breastfeeding, active skin diseases, and allergy to BTX or topical anesthesia. Participants were asked to discontinue deodorants for at least 1 week prior to and during the study.

Study protocol

Axillae of each participant was randomly assigned to receive LetiBTX-A 50 U (Botulax®; Hugel, Chuncheon, South Korea) in one axilla and OnaBTX-A 50 U (BOTOX®; Allergan, Inc., Irvine, CA) contralaterally, using computer-generated randomization. The encoding sequence was concealed in opaque and sealed envelopment. The assigned intervention was disclosed by a third person prior to the procedure. Participants and the treating dermatologists were not aware of the assigned intervention during the study.

After identifying the hyperhidrosis area of each axilla using the Minor iodine-starch test, 2.5% topical lidocaine was applied with an occlusive dressing for 45 minutes (Hexsel et al., 2010; Talarico-Filho et al., 2007). Thereafter, assigned BTX was injected intradermally by using a 30-gauge needle over the hyperhidrosis area of each axilla. The points of injection were evenly 1.5 cm apart (12-15 injections site per axilla). The outcomes were assessed by telephone call or office visit at 3 days, 1 week, and 1 month after injection.

Outcome assessment

The primary outcome was the number of subjects with at least 2-point improvement from baseline HDSS at 1 month. HDSS is a subject-rated 4-pointed scale used to indicate the tolerability and the interference of symptoms with daily activities. A higher score dictates a greater level of intolerance and interference of HH (Nawrocki & Cha, 2019a; Solish et al., 2007). Subjects with the baseline HDSS score of 2 required only 1-point improvement (Glaser et al., 2015; Lowe et al., 2007).

Secondary outcomes included the reduction of hyperhidrosis area using a percentage of area reduction from baseline, participant satisfaction score, and the onset of action. At baseline and month 1, the hyperhidrosis area was identified by the Minor iodine-starch test and photographed using a digital camera (EOS 50D, Cannon, Japan). The area was calculated by Image-J® software (National Institutes of Health, Bethesda, Maryland, USA) (Sun et al., 2015). Participants were asked to rate their satisfaction using a 10-cm visual analogue scale (VAS) (0 = completely unsatisfied to 10 = extremely satisfied) at month 1. At each visit, participants were asked about the onset of action or duration since injections to the time when participants noticed the very first improvement of their symptoms.

Pain perception was obtained immediately after injection using 10-cm VAS (0 = no pain to 10 = the worst pain imaginable). Adverse events were monitored at every visit.

Statistical analysis

The authors hypothesized that LetiBTX-A is non-inferior to OnaBTX-A in sweat reduction and the onset of action for the treatment of PAH. The sample size was calculated using the population proportion formula by assuming that the effectiveness of LetiBTX-A is not less than 25% of the effectiveness of OnaBTX-A for treating PAH. The values of variables substituted into the formula were:

α	(Significant level (one-sided))	=	0.05
β	(Power)	=	80
Δ_0	(Equivalence limit difference; $\pi_T - \pi_S$)	=	-0.25
Δ_1	(Expected difference)	=	0.00
η	(Proportion discordant)	=	$\pi 10 + \pi 01$

$$\frac{\eta(z\{1-\alpha/s\}+z\{1-\beta\})^2}{(\Delta_0-\Delta_1)^2}$$

Consequently, the sample size was 30 people.

Categorical data were described using frequency and percentage, while continuous data were presented as mean and standard deviation (standard deviation, SD) or median (interquartile range, IQR) depending on the distribution of data.

The number of subjects with at least 2-point improvement from baseline HDSS at 1 month was compared between groups using the McNemar test. Between-group comparisons of hyperhidrosis area reduction, participants' satisfaction, the onset of action, and pain perception were performed by using the paired t-test or Wilcoxon rank-sum test, depending on the distribution of data. P-values of <0.05 were considered statistically significant. Stata statistical software version 14.0 (StataCorp, College Station, TX) was used in all analyses.

4. Results and Discussion

4.1 Results

Thirty participants diagnosed with moderate to severe PAH (HDSS score of ≥2) were enrolled and completed the study. The baseline characteristics were demonstrated in Table 1.

Table 1 Table caption (no period ".")

Characteristics	n = 30
Male sex, n (%)	8 (26.67)
Age, year, mean (SD)	34.44 (7.82)
Age at onset, year, mean (SD)	20.47 (3.01)
Previous treatment, n (%)	
Antiperspirants and deodorants	23 (76.67)
Botulinum toxin injections	1 (3.33)
HDSS, n (%)	
2	7 (23.33)
3	17 (56.67)
4	6 (20.00)

The proportion of cases regarding HDSS score at baseline and month 1 was summarized by the interventions in Figure 1. Improvement in the HDSS score was observed for both groups. For primary effectiveness analysis, there were 28 subjects for the LetiBTX-A-treated group and 28 subjects for the OnaBTX-A-treated group who had at least 2-point HDSS improvement, which dictated no statistically significant difference (P = 1.000), see Table 2. The mean (SD) baseline hyperhidrosis area of LetiBTX-A-treated axillae was 20.127 (8.405) cm^2 and those of OnaBTX-A-treated axillae were 19.521 (7.83) cm^2. There was no statistically significant difference between the 2 groups (P = 0.347). At month 1, the hyperhidrotic area of both interventions reduced by more than 50% from baseline without a significant difference between LetiBTX-A- and OnaBTX-A-treated axillae (LetiBTX-A, 68.13%; OnaBTX-A, 65.67%; P = 0.316). Figure 2 demonstrated the comparison of the hyperhidrosis area identified by the Minor iodine-starch test at baseline and 1 month after injections between LetiBTX-A- and OnaBTX-A-treated axillae. Overall, participants were equally satisfied with both LetiBTX-A and OnaBTX-A-treated axillae.

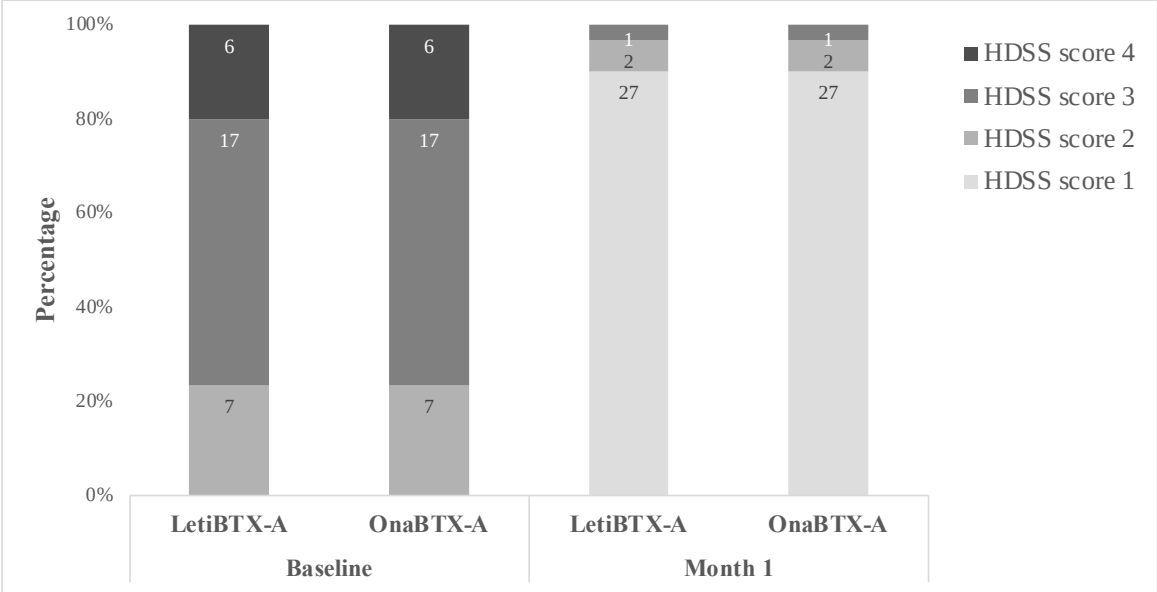

Figure 1 Proportion of cases regarding HDSS score at baseline and month 1
HDSS, hyperhidrosis disease severity scale; LetiBTX-A, LetibotulinumtoxinA; OnaBTX-A, OnabotulinumtoxinA

Table 2 Comparison of effectiveness, the onset of action, and pain perception between LetibotulinumtoxinA and OnabotulinumtoxinA

	LetibotulinumtoxinA (n = 30)	OnabotulinumtoxinA (n = 30)	P-value
Effectiveness			
≥2-point improvement of HDSS score, n (%)			
Month 1	28 (93.33)	28 (93.33)	1.000
Reduction of hyperhidrosis area, %, mean (SD)			
Month 1	68.13 (15.85)	65.67 (19.05)	0.316
Participant satisfaction score, mean (SD)			
Month 1	8.583 (1.463)	8.583 (1.463)	-[a]
Onset of action, day, median (IQR)	2(1)	2(1)	0.317
VAS pain score, mean (SD)	5.433 (2.431)	5.383 (2.406)	0.876

[*a] Outcome does not vary between groups.

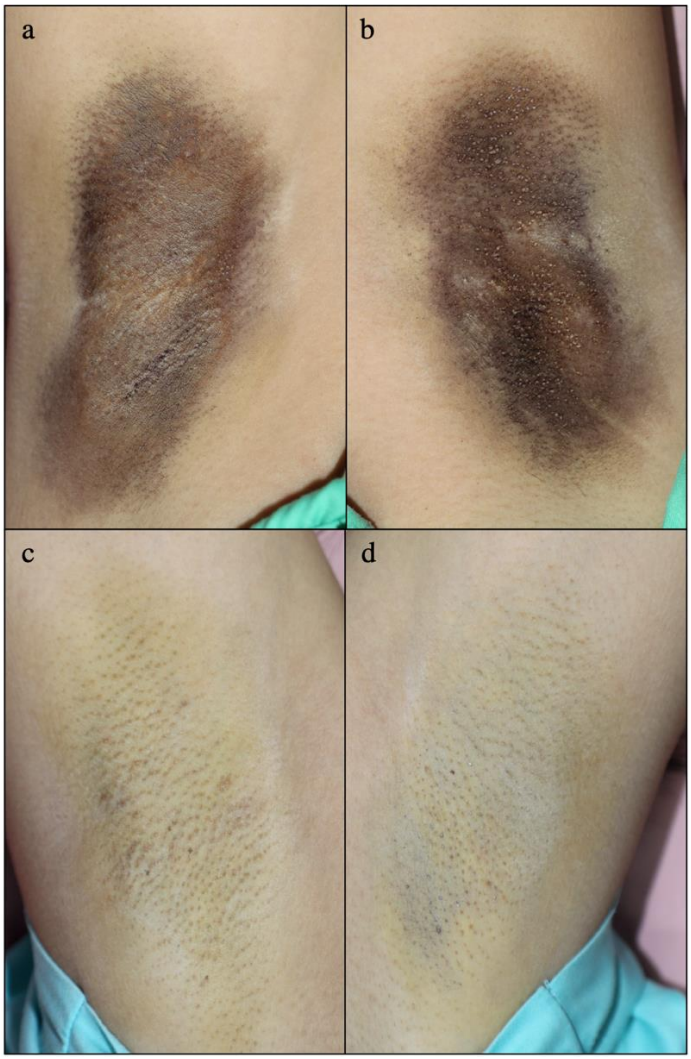

Figure 2 Hyperhidrotic area at baseline and 1 month after botulinum toxin injections

The comparison of hyperhidrosis area identified by the Minor iodine-starch test at baseline and 1 month after injections between LetiBTX-A- and OnaBTX-A-treated axilla was demonstrated (a, LetiBTX-A-treated axilla at baseline; b, OnaBTX-A-treated axilla at baseline; c, LetiBTX-A-treated axilla at month 1; d OnaBTX-A-treated axilla at month 1)

LetiBTX-A, LetibotulinumtoxinA; OnaBTX-A, OnabotulinumtoxinA

Regarding the onset of action, there was no significant difference between LetiBTX-A and OnaBTX-A-treated group (P = 0.317). The mean (SD) onset of action was 1.700 (1.393) days for LetiBTX-A (range, 0 to 7 days), which was slightly earlier than that of OnaBTX-A (mean (SD), 1.733 (1.388); range, 0 to 7 days). Only 1 participant reported 1-day earlier onset for the LetiBTX-A-treated side, while the others observed no difference. There were 5 participants who noticed the improvement of HH symptoms within 1 day after receiving BTX injections on both sides of the axillae. The longest onset of action was 7 days for both groups reported by 1 participant.

Participants experienced comparable pain between LetiBTX-A and OnaBTX-A treated sides (P = 0.876). One participant reported redness and pruritus at the LetiBTX-A injection site, which was spontaneously resolved within 1 day. Ecchymosis was observed in 2 participants at the injections of both axillae.

4.2 Discussion

Our study reported no difference between the therapeutic effect of LetiBTX-A and OnaBTX-A for PAH regarding effectiveness, the onset of action, and procedure-related pain, which can be interpreted that LetiBTX-A non-inferior to OnaBTX-A in sweat reduction and the onset of action for the treatment of PAH. In terms of adverse events, no significant motor or neurologic deficit was observed in both groups.

Considering the mechanism of action, BTX inhibits the release of acetylcholine resulting in the blockage of a glandular secretion at an exocrine gland (Dressler & Adib Saberi, 2005). Thus, BTX is effective for sweat reduction. Previous studies revealed the comparable antihidrotic effect of AboBTX-A and RimaBTX-B compared to OnaBTX-A (An et al., 2015; Talarico-Filho et al., 2007). Correspondingly, our study revealed that the antihidrotic effects of LetiBTX-A and OnaBTX-A are indistinguishable.

We reported that 93.33% of participants achieved at least 2-point improvement in HDSS score, hyperhidrosis area reduced by more than 50% from baseline, and participants were highly satisfied with both preparations of BTX-A 1 month after injection. These findings were consistent with the previously established effectiveness of BTX-A in the treatment of PAH (Flanagan, King, & Glaser, 2008) (An et al., 2015; Glaser et al., 2015; Naumann et al., 2003)

Kim et al. conducted a study on 272 participants with moderate-to-severe glabellar lines to demonstrate the non-inferiority of LetiBTX-A to OnaBTX-A for treating glabellar lines. Participants were randomized into 2 groups to receive 20 units of LetiBTX-A or OnaBTX-A. The study revealed comparable effectiveness between these 2 formulations in the treatment of glabellar lines which were evaluated by physicians' and subjects' assessment using a facial wrinkle scale at weeks 4, 8, 12, and 16. The incidence of adverse events were also comparable. Therefore, it can be inferred that the effectiveness and safety of LetiBTX-A in the treatment of glabellar lines are non-inferior to those of OnaBTX-A.

LetiBTX-A is a 900 kDA complexing protein consisting of the 150 kDA neurotoxin produced by *Clostridium botulinum* strain CBFC26, which is cloned by polymerase chain reactions. The CBFC26 strain has identical 16S RNA and toxin sequence to *Clostridium botulinum* producing strain of OnaBTX-A (ATCC 3502 Hall A strain). The additional manufacture process of LetiBTX-A is enzyme-free purification process aiming to remove nucleic acids which are expected to improve safety issues of products that may be caused by the use of animal enzymes and by remnant nucleic acids (Choudhury et al., 2021; Frevert et al., 2018; Hanna & Pon, 2020).

The present study suggested that the use of LetiBTX-A can achieve a similar level of effectiveness in the treatment of PAH to OnaBTX-A without differences in serious adverse events and procedure-related pain. Objective effectiveness assessment, i.e., hyperhidrosis area measurement was applied in our study to

provide reliable results. Confounding factors including baseline sweat production, temperature variations, physical and psychological alterations, and individual awareness level, were eliminated by comparing the effect of 2 BTX-A formulations in the same patient (split-sided trial). However, the study has certain limitations. The majority of enrolled patients were female and have a HDSS score of 3 which may compromise the generalizability of the results. In addition, our study lack of long-term follow-up, thus, long-term antihidrotic effects have not been investigated. A larger randomized controlled trial with a longer follow-up period is required.

5. Conclusion

The effectiveness of letibotulinumtoxinA and onabotulinumtoxinA for treating primary axillary hyperhidrosis were comparable at 1 month after injections. Both preparations were well tolerated.

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