Efficacy of topical botulinum toxin type A in liposome-based cream for treatment of primary axillary hyperhidrosis

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Introduction

Hyperhidrosis (excessive sweating) is a chronic and autonomic debilitating disorder that can lead to emotional and social embarrassment, as well as occupational, physical and psychological disability.1 Treatment of hyperhidrosis is directed towards the individual patient's needs despite unknown causes.2 Non-invasive treatments with varying degrees of efficacy include topical treatments, oral medications, and iontophoresis. Likewise, intradermal administration of botulinum toxin type A (BTX-A) has also proven efficacious for axillary hyperhidrosis with repeated treatment to avoid common compensatory hyperhidrosis.3 Meanwhile, the traditional needle-based botulinum toxin delivery is mainly associated with more pains and costs, as well as a number of adverse events following the injections such as flu-like symptoms, pains, redness at injection site, respiratory infection, and possible muscle weakness.4 In a recent study, application of topical BTX-A significantly showed the effectiveness in treatment of primary axillary hyperhidrosis (PAH) with a decreased risk of side effects, resulting in no systemic and very few local adverse events.5 Hence, our study aimed to evaluate the efficacy of low dose topical liposomal based BTX-A cream as a novel and cost-effective modality for treatment of PAH in Asian populations. Ultimately, this non-invasive topical method could yield treatment efficacy for PAH with minimally effective concentration of BTX-A. The objective of this work is to evaluate the efficacy of 10 units (U) compared with 20 U of topical BTX-A in liposomal based cream for treatment of primary axillary hyperhidrosis following the panel assessment of Iodine-starch test (IST) methods.

Methods

A prospective, randomized, double blinded, split site study was conducted in participants, aged > 18 years, having symmetrical sweating with hyperhidrosis severity scale (HDSS) 2-4. Exclusion criteria included pregnancy or lactation mother, previous botulinum toxin injection within 6 months prior to the day of screening, sweating 25% more than asymmetrical sweating between the two axilla, usage of concurrent medication within 30 days prior to the enrolment (any anticholinergic, aminoglycoside, or calcium channel blocker medications), history of myasthenia gravis, hyperthyroidism, pheochromocytoma, congestive heart failure, diabetic mellitus, treatment with hair removal laser within 3 months.

Topical Botulinum toxin in liposomal cream based preparation: BTX-A (Neuronox®, Medytox, Inc. Republic of Korea) was dissolved in 1.5 mL of 0.9% sterile, preservative-free saline, and mixed by inversion with multilamellar liposomal beaded capsule cream. Then, the 2 concentrations of 10 and 20 U BTX-A solutions were mixed with 3 mg of liposomal cream base, respectively.

Treatment: All participants were asked to shave axillary hair and avoid using antiperspirant and deodorant for 3 days prior to the study. After the completed questionnaire, HDSS was evaluated. The participants entered the temperature setting room (28-30 degree Celsius) for 5 minutes before performing the IST with digital
photography and being randomized into 2 treatment groups: one with 10 U and the other with 20 U of BTX-A cream. Both treatment regimens were double-blinded and applied once daily before bedtime with a total duration of seven days. The regimen products were labeled as number 1 and number 2 on the bottles. The participants received the instruction leaflet which precisely described how to use those regimen products. Each regimen product must be applied for 2 puffs per side of the axilla (using right hand for the left axilla and left hand for the right axilla), once daily before bedtime for 7 days, and kept in refrigerator after the use. In order to evaluate the compliance, all participants were instructed to bring both regimen products at every follow-up visit. For post-treatment care, the participants must avoid using antiperspirant, deodorant, hair removal laser, botulinum toxin injection, anticholinergic drug, sauna, streaming, warm-hot pool, and excessive exercise until the protocol completion.

**Efficacy measures:** The subjects were evaluated at 2, 6 and 8 weeks for post-treatment efficacies. Minor’s IST was done on both axillae to define the area of sweating before treatment and to quantify the change in area of sweating during the trial using digital photographs in the same fixed position to determine the area of sweating for each axilla. The expert panel assessment was performed for the improvement of sweating area from IST photography, using 5-point grading scale (0 = no improvement, 1 = minimally improve, 2 = moderately improve, 3 = markedly improved and 4 = almost completely improve). All panel experts were blinded from the data of each side’s treatment. HDSS and satisfaction score were also recorded in each visit.

**Safety measures:** Data on type, incidence, severity, and cause of all spontaneously reported adverse events throughout the trial were recorded. As well, all participants received the physical examination at screening and every visit until the end of the trial.

**Statistical analysis:** Results were reported as the clinical grading of improvement. The Mann-Whitney U test was used to compare continuous variables in the two groups; whereas, Friedman test was used to compare continuous variables in more than two related samples. P value < 0.05 was considered as statistically significant. The data of study was blinded to the statisticians.

**Results**

There were two male participants, aged 38 and 28 years, with HDSS 3 and the duration of hyperhidrosis for 18 and 11 years, respectively. The expert panel assessment by 3-blinded dermatologists significantly showed the improvement in both groups. The results maximized at 2 weeks after treatment and gradually decreased with the efficacy of sweat reduction until 6 weeks (Table 1 and Figure 1). The 10 U group showed the statistical improvement of score from 3.5 (2-4) to 2 (1-3) and 0 (0-1) at 2, 6 and 8 weeks, respectively (p=0.002). Whilst, the 20 U group statistically showed the score improvement from 3.5 (2-4) to 2 (1-3) and 0.5 (0-1) at 2, 6 and 8 weeks, respectively (p=0.006). However, there was no statistically different improvement between the two groups (p > 0.05) (Table 2). No eczematous reaction, dryness, itching, folliculitis, pain or serious adverse effect was observed in this study. The participants’ assessment of HDSS showed improvements from base line of 3 to 1-2 at 2-2 and 6 weeks, respectively, with maximum improvement of HDSS observed at week 2. Nevertheless, there was no significant statistical difference (Table 3).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Expert panel assessment of clinical grading of improvement of 10 and 20 units of BTX-A at 2, 6 and 8 weeks</th>
</tr>
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<tbody>
<tr>
<td>Dose of BTX-A (units)</td>
<td>W 2</td>
</tr>
<tr>
<td>Clinical grading of improvement, Median (range)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>20</td>
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Friedman Test, W = Week(s)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of expert panel assessment of clinical grading of improvement between 10 and 20 units of BTX-A at 2, 6 and 8 weeks</th>
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<tbody>
<tr>
<td>Dose of BTX-A (units)</td>
<td>W 2</td>
</tr>
<tr>
<td>Clinical grading of improvement, Median (range)</td>
<td>10</td>
</tr>
<tr>
<td>3.5 (2-4)</td>
<td>3.5 (2-4)</td>
</tr>
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Mann-Whitney U test
Table 3  Hyperhidrosis disease severity score (HDSS) of 10 and 20 units of BTX-A from baseline, week 0, 2, 6 and 8

<table>
<thead>
<tr>
<th>HDSS (range)</th>
<th>Dose of BTX-A (units)</th>
<th>W 0</th>
<th>W 2</th>
<th>W 6</th>
<th>W 8</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10</td>
<td>3-3</td>
<td>1-2</td>
<td>2-2</td>
<td>3-3</td>
<td>0.121</td>
</tr>
<tr>
<td>20</td>
<td>3-3</td>
<td>1-1</td>
<td>2-2</td>
<td>3-3</td>
<td></td>
<td>0.112</td>
</tr>
</tbody>
</table>

Friedman Test, W = Week(s)

Discussion

The US FDA has currently certified the use of botulinum toxin intradermal injection for treatment of axillary hyperhidrosis (2). Nonetheless, the treatment side effects are pains due to multiple injection points. This clinical trial was designed to investigate a topical formulation of BTX-A with multilamellar liposomal beaded capsule for the painless delivery of BTX-A through the skin, with the significant efficacy in PAH treatment.

A randomized controlled trial of subcutaneous injection of BTX-A 50 U per axillar in those with excessive axillary sweating showed the significant results of treatment with BTX-A. The statistically greater improvement was significantly exhibited in the physical component summary score at 16 weeks compared to the placebo-treated patients, which could be confirmed by gravimetry and minor’s iodine starch test.6 However, the pains and other complications, such as bruising are still the barriers to this injection of treatment modality.

![Figure 1 Minor's iodine starch test of 10 units (A, B) and 20 units (B, D baseline - top row) and Week 6 (bottom row) with significant improvement of sweating area](image)

This study aimed to demonstrate the delivery of BTX-A to targeted skin sites, and to evaluate the safety and effectiveness of this painless, topical application of BTX-A for treatment of primary axillary hyperhidrosis. When compared with the previous study of a randomized, double blinded, vehicle-controlled study of 200 U of BTX-A combined to transport peptide molecule to bind the toxin in a non-covalent manner for treatment of PAH, it was found that the topically applied BTX-A is effective in PAH treatment. The decreased severity of PAH was identified up to 4 weeks, and verified by minor’s IST with few local adverse events and no systemic events.5 Thus, this study confirmed the efficacy of pharmaceutical enhancing skin penetration of topical form of lower dose BTX-A. When compared with the previous study that applied one time of topical 200 U BTX-A with transport peptide molecule, this study could interestingly demonstrated that lower dose of BTX-A with more frequent application could significantly improve the treatment results of PAH. Nevertheless, there were some limitations to this study, such as the small sample size, short observation period, and lack of standardization of BTX-A concentration treatment dosage. Meanwhile, there are several variables that could affect sweat production; namely, the environment including temperature and humidity, seasonal conditions, and physiologic and psychological conditions of each patient. These variables could affect the testing for the assessment of patient sweating, like the starch-iodine test. Moreover, the amount of BTX-A concentration, the number of applying day, the amount of concentration in one day apply, the different mode of drug delivery, the treatment interval and number of treatment sessions, and longer duration of follow up were suggested to verify the efficacy of topical BTX-A formulation.
Conclusion

The results of low dose (10 and 20 U) of BTX-A inversion with multilamella liposomal beaded capsule cream could yield the effective treatment results of PAH, evaluated by the clinical grading of improvement of Minor’s IST. The clinical grading of improvement in both groups showed statistically significant improvement from baseline to 8 weeks ($P < 0.01$). Whereas, no statistical difference of efficacy was determined between 10 u and 20 u units of BTX-A in treatment of PAH ($p > 0.05$).

References