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Efficacy and Safety of Low-Doses of Botulinum Toxin Type-A in the Treatment of Primary Axillary Hyperhidrosis over 6 Months

Nisreen Darwish, MD, **Abdel Haleem Romieh,** MD, FRCS
and **Mahmoud Dalloul,** MD, FRCS

Department of Dermatology
Al-Assad University Hospital
Latakia, Syria
darwishnisreen@yahoo.com

Abstract. Primary axillary hyperhidrosis is a relatively common benign disease that has a negative impact on the patient's quality of life. Although primary axillary hyperhidrosis has readily been treated with standard doses of botulinum toxin type A, the efficacy of low-doses is not well established. The efficacy and safety of low-doses of botulinum toxin type A in the treatment of primary axillary hyperhidrosis over 6 months was evaluated. A randomized comparative side was performed-by side study in twenty-one patients treated with one course of botulinum toxin type A (Relife®), divided into 50 units injected in the right axilla and 25 units injected in the left axilla. Sweating was evaluated by minor iodine-starch test at weeks 1-4-16-24. The low-dose efficacy average was 100%, 90.48%, 80.95%, 71.43% at weeks 1-4-16-24, respectively; compared to standard-dose efficacy average of 100%, 95.24%, 90.48%, and 76.19% at weeks 1-4-16-24, respectively. Statistically, no significant differences in the efficacy of the two doses of botulinum toxin type A were found. Minor adverse effects were demonstrated in 33% of patients, thus, recovered completely with no need for medication. In conclusion, these results suggest that low dose of botulinum toxin type A is safe, effective and a well-tolerated treatment for axillary hyperhidrosis, and its benefits last for at 6 months.

Keywords: Axillary, Hyperhidrosis, Botulinum toxin.

Introduction

Hyperhidrosis is defined as the production of excess sweat, beyond the amount required to return elevated body temperature to normal, which is

Correspondence & reprint request to: Dr. Nisreen Darwish
Al-Assad University Hospital, 8 Azar Street, Latika, Syria
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slightly below 37°C[1]. This is a relatively common disease that affects approximately 2-3% of population. A large study in the United States of America revealed that 2.8% suffer from localized hyperhidrosis[2]. Hyperhidrosis can be classified to primary and secondary, or generalized and localized[1].

It has a deep impact on the patient's quality of life (QOL), and it provokes maceration and dermatological infection (*i.e.*, Tinea corporis, erythrasma…*etc.*)[3,4].

Axillary sweating is not a life-threatening disease, but nonetheless can have a substantial impact on the quality of the sufferer's life, both professionally and socially. Most patients with axillary hyperhidrosis have consulted many physicians in the past, most of the time without finding any substantial, long-lasting solution to their problem.

Primary or focal hyperhidrosis is caused by the over activity of normal sweat glands in response to mental stress, and not by glandular hypertrophy.

Hyperhidrosis is a chronic condition requiring a safe, long-lasting treatment. It is advisable that treatment should be approached in a stepwise manner. In patients who do not respond to topical treatments—such as aluminum salt solutions or (for palmoplantar hyperhidrosis) tap water iontophoresis—intradermal injections of Botox® can solve the problem in only a few minutes and on an outpatient basis. The negative side effects caused by aluminum metal salts applied to the affected axilla (irritation, contact dermatitis, coloration of the clothes...) made a way for botulinum toxin type A (BTX-A) to be the first line treatment for many patients. Botulinum toxin type A (BTX-A) is a neurological toxin produced by anaerobic bacterium clostridium botulinum, it blocks the autonomic innervations of sweat glands. High doses of BTX-A in the treatment of primary axillary hyperhidrosis (PAH) have well been studied[5]. But, the efficacy of low-doses has not been well established yet. However, no controlled study has proven that high doses of BTX-A are more effective than low-doses in the treatment of axillary hyperhidrosis[6].

The benefits of low-doses of BTX-A in the treatment of PAH are:

- Reduction of treatment cost
- Limitation of formation of anti-toxin antibodies

- Possibility of using one vial 100 unit of BTX-A for the treatment of axillary hyperhidrosis and other indications simultaneously.

Many products of BTX-A are available around the world. All preparations are measured by mouse unit; however, we should know that different preparations have different units and are not the same; each 1 unit of Botox® equals about 4 units of Dysport®[7].

This study was made to evaluate the efficacy and safety of low-doses of BTX-A in the treatment of PAH, compared with the efficacy of the standard doses of BTX-A in the same patient, and to study the possible side effects.

Materials and Methods

The patients were chosen from the out patients of Al Assad University Hospital in Lattakia, Syria from October 2009 till October 2010. The following criteria were used to select PAH patients: If the area of excess sweating is visibly focal and excessive for at least 6 months without any apparent cause and is associated with at least two of the following characteristics:

- Bilateral and relatively symmetric sweating
- Impairs daily activities
- Frequency of at least one episode per week
- Age of onset less than 25 years
- Positive family history
- Cessation of focal sweating during sleep.

Patients were evaluated to eliminate secondary axillary hyperhidrosis cases. Complete history and blood tests (including CBC, thyroid functions, liver and kidney functions, glucose...) were made. Patients with contraindication for BTX-A treatment (pregnant and nursing women) were eliminated. Every patient had the chance to get a complete explanation of the disease and the possible treatment, taking into account that most of them had moderate to severe hyperhidrosis, and had already used topical preparations of metal salts. Those patients stopped the treatment as they continued to suffer from hyperhidrosis or due to unbearable side effects.

Each patient had undergone minor iodine-starch test before the treatment session, and regularly at every follow up.

Each axilla was dried with gauze, iodine solution 10% was applied to each axilla, and starch powder was gently sprinkled on it. This test was performed to assess axillary hyperhidrosis objectively, and to outline the hyperhidrotic area. Photographs were taken, the treated area was remarked by a waterproof pen, and then, was cleaned with normal saline. Many products of BTX-A are available in Syria (Botox®, Neuroxin®, Neuronox®), thus, the present study used Relife® product. Each vial of Relife® 100 unit was dissolved in 3 cc of normal saline and used within 1 hour.

Each patient received 50 units in the right axilla, 25 units in the left axilla. About 20-25 injections were made in the right side and 10-15 injections in the left; however the dose at each injection point was about 2 units (Fig. 1).

After the treatment patients were told to go back to their normal life and activities, and inform us with any side effects.

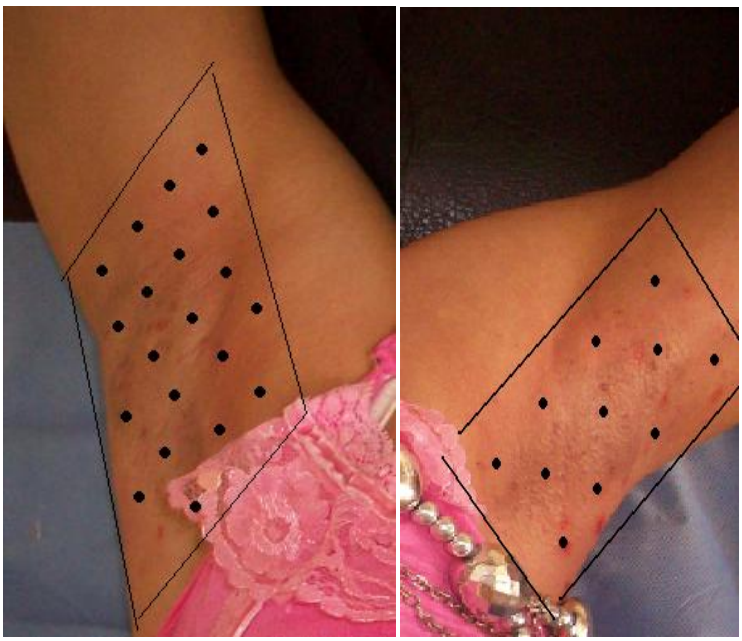

Fig. 1. Showing different injection points in each axillae.

Follow up was made regularly at weeks 1, 4, 16, 24. Sweat production was evaluated clinically by minor iodine–starch test. Patient's satisfaction was measured by a simple questionnaire. Two patients were

eliminated. One of them couldn't continue the study, because he didn't return to the clinic. The other showed a remarkable sweating at week 1, 4. This patient had received BTX-A treatment for glabella and forehead lines 10 months before; therefore, it was suggested that anti-toxin antibodies might have been developed, or simply the powder in the vial had lost its efficacy for some reason.

Results

Finally the study included 21 patients divided into 14 females and 7 males. Patients were of several ages, mainly from 15–25 years old.

Onset of the disease was after puberty in 66.67% of patients, family history for hyperhidrosis was positive in 13 patients (61.9%). Multifocal hyperhidrosis was registered in 11 patients (52%), and the most common hyperhidrotic area that accompanied axillary hyperhidrosis was palmoplantar (Table 1, Fig. 2). Patients were evaluated at weeks 1-4-16-24 after the treatment session by minor iodine-starch test, complete response to treatment was registered in Table 2 and shown in Fig. 3 and 4).

Table 1. Showing the number of multifocal hyperhidrosis patients.

Hyperhidrosis Areas	Patients Number
Only the axilla	10
Axilla + palmoplantar	7
Axilla + other	3
Axilla + palmoplantar + other	1
Total Number	21

Table 2. Patients complete response according to weeks.

	Complete Response in the Right Axilla		Complete Response in the Left Axilla	
Weeks	**Patients Number**	**Percent**	**Patients Number**	**Percent**
1	21	100%	21	100%
4	20	95.24%	19	90.48%
16	19	90.48%	17	80.95%
24	16	76.19%	15	71.43 %

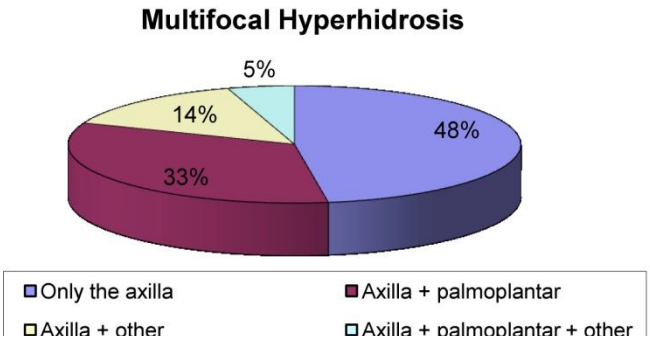

Fig. 2. Showing distribution of focal hyperhidrosis.

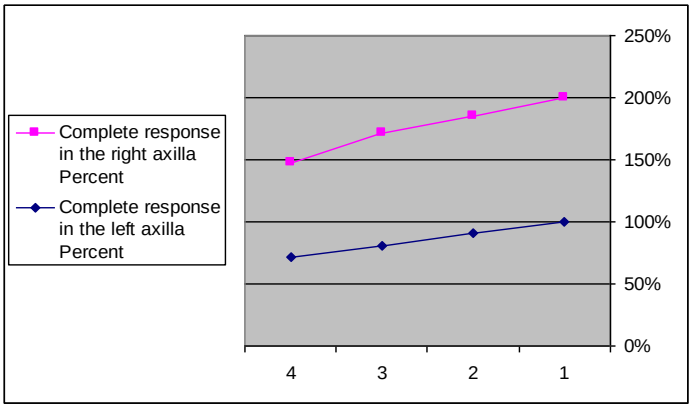

Fig. 3. Showing patients response according to weeks.

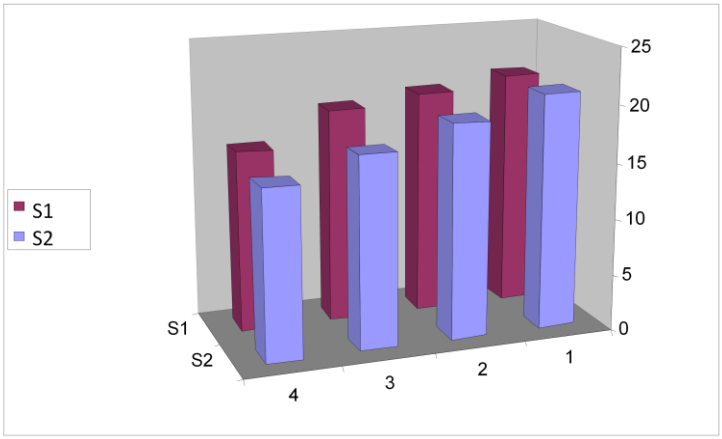

Fig. 4. Showing patient's response according to weeks.

Side effects on both sides were registered in 7 patients (33%) regardless of the dose. They included erythema, pruritus, edema, and small hematomas, but all of them were simple and bearable, plus spontaneously disappeared.

Statistically, IBM SPSS program version 19 was used to evaluate the efficacy of low doses of BTX-A (Relife®) in the left axilla compared with standard doses in the right axilla, and for studying the side effects that accompanied the treatment in both doses.

Statistically there were no significant differences in the efficacy of the two doses of BTX-A.

Patient's satisfaction was evaluated by simple questioners after 6 months. Seventy-one percent (71%) of patients preferred the low dose treatment (Table 3), and according to them they had approximately the same results over 6 months, but with less pain (Fig. 5).

Table 3. Patient's satisfaction at week 24.

Patient Satisfaction	Patient's Number
Weak	1
Good	5
Very good	8
Excellent	7

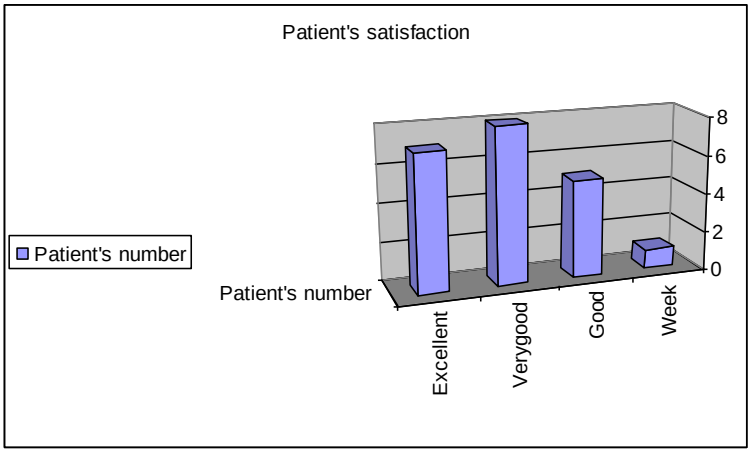

Fig. 5. Showing patient's satisfactions at week 24.

Discussion

This study can be criticized as it included few patients only which have a negative effect on the statistics accuracy. Nevertheless, on the other hand, similar studies were made at Al Ain Hospital, Dubai, UAE by Drs. Galadari, and Alkaabi, this study included only 15 patients and the results were similar to our study[8].

Most of the patients were females, although hyperhidrosis incidence is equal in both sexes, probably because females in our country seek medical help for such problems more than males. In addition to that, the study was not placebo controlled, as the efficacy of botulinum toxin A over placebo has already been established.

Although side effects percentage was 33%, they were not severe neither life-threatening. Further studies must be made for longer periods, and more patients should be included.

Finally, this study conclude that low doses of BTX-A are as safe and effective as standard doses in the treatment of PAH over 6 months.

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فعالية و أمان الجرعات المنخفضة من الذيفان البوتوليني نمط A في علاج فرط التعرق الإبطي الأساسي

نسرين درويش، وعبد الحليم رومية، ومحمود دلول

قسم الأمراض الجلدية والزهرية، مشفى الأسد الجامعي

اللاذقية – سوريا

المستخلص. فرط التعرق الإبطي الأساسي مرض سليم شائع نسبياً ذو تأثير سلبي على نوعية حياة المرضى. بالرغم من كون الجرعات القياسية من الذيفان البوتوليني نمط A أحد الخطوط الرئيسية في العلاج إلا أن فعالية الجرعات المنخفضة لم تحدد بدقة حتى الآن. هدف البحث هو تقييم فعالية و أمان الجرعات المنخفضة من الذيفان البوتوليني نمط A في علاج فرط التعرق الإبطي الأساسي خلال ستة أشهر. أجريت دراسة عشوائية شملت ٢١ مريض عولجوا بالذيفان البوتوليني نمط A (Relife®). تم حقن ٥٠ وحدة في الإبط الأيمن لكل مريض و٢٥ وحدة في إبطه الأيسر في نفس الجلسة. قيم التعرق لدى المرضى بواسطة اختبار اليود- النشاء في الأسابيع ١-٤-١٦-٢٤. كان معدل استجابة المرضى على الجرعات المنخفضة ٤٣،٧١٪، ٨٠،٩٥٪، ٩٠،٤٨٪، ١٠٠٪ في الأسابيع ٢٤-١٦-٤-١ على الترتيب، أما معدلات استجابة المرضى على الجرعات القياسية ١٠٠٪، ١٩،٧٦٪، ٤٨،٩٠٪، ٢٤،٩٥٪ في الأسابيع ٢٤-١٦-٤-١ على الترتيب. لم تسجل أية فروقات جوهرية إحصائياً في معدل استجابة المرضى و بالتالي فعالية العلاج بالجرعات المنخفضة مقارنة بالقياسية. سجلت آثار جانبية بسيطة لدى ٣٣٪ من المرضى تراجعت دون علاج. أثبتت الدراسة أن الذيفان

البوتوليني نمطA فعال و آمن بجرعاته المنخفضة في علاج فرط التعرق الإبطي الأساسي.