

**Original Article**

**BOTULINUM TOXIN TYPE A: AN EFFECTIVE, SAFE AND MINIMALLY INVASIVE TREATMENT OPTION OF AXILLARY AND PALMAR HYPERHIDROSIS**

**ESSA AJMI ALODEANI<sup>1\*</sup>**

College of Medicine, Aldawadmi, Shaqra University, Kingdom of Saudi, Arabia  
Email: m.arshad@su.edu.sa

*Received: 16 Mar 2016 Revised and Accepted: 17 May 2016*

**ABSTRACT**

**Objective:** The uncontrollable and excessive sweating is basically a disorder called Hyperhidrosis. Sweating is essential for thermal regulation but significantly impacts on the emotional and professional life of the people suffering from this. The aim of the present investigation was to observe the effectiveness of botulinum toxin type A in patients with hyperhidrosis, the incidence of the disease, duration of the results and possible adverse effects.

**Methods:** 27 patients with hyperhidrosis (axillary, palmar and axillary-palmar in combination) were treated with intradermal injection of botulinum toxin type A. Gender and racial compositions respectively was as follows; Male (n=17 or 63%); female (n=10 or 37%) and white (n=19 or 70%); black (n=8 or 30%). In the case of axillary hyperhidrosis, local infiltrative anesthesia with subcutaneous injections (Lidocaine 1% with adrenaline) dosed with 20-50 ml for 30-240 min duration was used while locoregional anesthesia (Lidocaine 1% without adrenaline) dosed with 2-5 ml was applied in the case of palmar hyperhidrosis. Diluted botulinum toxin was injected intradermally in an already anesthetized area. Each point was dosed with 2-4 U thus maximum total dose applied was 240 (60 x 4) for each anatomical region with hyperhidrosis (axillae and palm).

**Results:** Axillary-palmar clinical condition was found to be the most common incidence of the disease followed by alone axillary and isolated palmar hyperhidrosis. More than 50% drop in the quantity of the sweating was observed at the completion of one month. Relapse in 12 % cases was reported. 64% patients were found to be symptom-free for 9 mo. Only one patient showed side minor and easily manageable ecchymosis at a few points of intradermal injection and bilateral paresthesia hands and fingers.

**Conclusion:** Botulinum toxin treatment is an effective, safe, and minimally invasive therapeutic treatment option, although it is costly. It helps enhance the quality of life of the patients and bring them out of stress, anxiety and emotional stress.

**Keywords:** Axillary, Botulinum toxins, Anaesthesia, Hyperhidrosis

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**INTRODUCTION**

A disorder which leads to the uncontrollable and excessive sweating without any known triggering factor is termed as hyperhidrosis, which is manifested all across the gender at various ages [1]. Although sweating is essential for thermal regulation in the body especially during physical exercise, hyperhidrosis significantly impacts on the emotional and professional life of the people suffering from it, it is also observed that the symptoms stopped during sleep. Respondents with focal HH reported decreased participation in leisure activities and less time at work as a result of their perspiration. It is a genuinely serious condition that can lead to severe social impact such as isolation, social phobia, embarrassment, anxiety, physical discomfort, depression and other issues related with social life [2-4]. According to a national survey done in the USA revealed that hyperhidrosis is affecting 75 % of the population emotionally [5]. It is an equally common disorder as psoriasis [6], patients with diseases such as rheumatoid arthritis, multiple sclerosis and end-stage renal failure share almost the comparable quality of life with the patients suffering from hyperhidrosis [7-9].

However, patients who are suffering from this, seldom consult a physician as most of them are unaware that it is a clinically manageable illness. It is categorized as generalized (involvement of the whole body) and focal (involvement of a limited body area). Primary hyperhidrosis is the quotidian clinical form of hyperhidrosis constituting focal, an idiopathic, chronic, bilateral, and symmetrical variation in sweating process. A sympathetic autonomous nervous system that controls the eccrine sweat glands which produce sweat in response to change in body temperature and so the hyperactivity of the autonomic nervous system, triggers glandular hypertrophy and hypersecretions of the sweat gland leading to primary hyperhidrosis [10, 11]. There has been some evidence of genetic abnormality with primary hyperhidrosis as in 30% to 50% cases family history of the disorder has been noticed [12, 13]. Autonomic

neuronal dysfunction seems to be involved mainly in the areas sweat glands are a higher number such as the soles (plantar), palms (palmar) and axillae (axillary but less common on the scalp and facial region [14, 15]. Axillary hyperhidrosis is commonly bilateral pattern and may be triggered by mental stress, heat and is allied with complications such as contact dermatitis [16]. Various types of conservative treatment options for hyperhidrosis are there such as topical agents (aluminium salts), oral anticholinergic agents (methantheline, oxybutynin and) and adrenergic agonists (clonidine), iontophoresis, application of botulinum toxin as well as surgical treatment (Subdermal axillary liposuction, thoracic sympathectomy-video assisted, and retroperitoneoscopic lumbar sympathectomy-video-Assisted). The adverse effect of topical agents is skin irritation due to high salt concentration [17] and of oral agents is blurred vision, urinary hesitancy, marked tachycardia, dizziness and confusion while that of iontophoresis is dryness of mouth, dizziness, constipation, sedation and symptomatic drop in blood pressure [18]. The above-mentioned treatment modalities genuinely vary in the time duration of therapeutic effect, related adverse effects and treatment cost, and scientific evidence of their therapeutic efficacy. A neurotoxin (botulinum toxin) was considered as a deadly substance for several years. Clinical features of the botulism were explained in 19<sup>th</sup> century [19] but in the 1970's botulinum toxin was as significant research tool to investigate the spinal cord physiology. In 1980's evidence of therapeutic potential of botulinum toxin (BT) had emerged and over last 3 decades it has been observed to be immensely beneficial for the successful treatment of many conditions such as movement disorders, pain management, ophthalmic disorder, pelvic floor and gastrointestinal disorders and various cosmetic disorders [20] Botulinum toxin is a neurotransmitter, acetylcholine blocker, so it blocks synaptic transmission resulting in chemical denervation of the glands and temporary cessation of hyperhidrosis. Treatment of primary hyperhidrosis with botulinum toxin A is an easy treatment. Prior to

the administration, the botulinum toxin A the targeted region is anesthetized with either topical, locoregional anesthesia or even sedation. However, it has some disadvantage a temporary therapeutic action (7 mo), costly the uneasiness allied with multiple point injections [21, 22]. Primary hyperhidrosis affects people all over the world including Kingdom of Saudi Arabia with almost 2.8% of US population but the limited scientific investigation regarding the therapeutic efficacy, duration of its effect, adverse effect and satisfaction of the patients with this treatment option in Saudi Arabia has been carried out and so, the availability of research data is scarce to nonexistent [23-30]. The present investigation was aimed to evaluate the effectiveness, safety and adverse effects of botulinum toxin A and satisfaction of the patients with this therapeutic option in the population of Riyadh region of KSA with axillary and palmar hyperhidrosis.

## Patients and method

### Recruitment of patients

Patients suffering from primary hyperhidrosis were recruited from Riyadh region of the kingdom of Saudi Arabia following the ethical approval wide letter No. EA/CM/10/08/2014 Clinical history is taking and thorough examination of all the patients was carried out and well documented. Patients including all the genders (n=27) with primary axillary and palmar hyperhidrosis resistant to earlier treatment of topical agents were given conservative treatment after taking written consent from them using intradermal injections of botulinum toxin type-A. The age of all the patients ranged between 18 and 50 y with gender and racial compositions respectively was as follows; Male (n=17 or 63%): female (n=10 or 37%) and white (n=19 or 70%): black (n=8 or 30%). The study was accomplished between May 2011 and Jan 2016. All those patients exhibiting the amount of sweating higher or equal to 50 mg/minute measured by quantitative gravimetric analysis were included in the study.

### Exclusion criteria

Exclusion criteria involved in the present study was based on underlying severe systemic diseases, thyroid diseases, diabetes mellitus, neuromuscular alteration. Patients with the historical background of botulinum toxin sensitivity, usage of calcium channel blocker, aminoglycoside category of antibiotics, muscle relaxant, acetylsalicylic acid, and with recent surgery, infectious and inflammatory conditions in the skin or at the place of botulinum toxin application were also excluded from the study [31]. Pregnant and breastfeeding women, patients on systemic medications and with those with secondary hyperhidrosis were excluded too.

### Determination of intensity of hyperhidrosis

The intensity of the hyperhidrosis together with the most affected area was assessed using Minor's test (starch-iodine test) which was carried out by application of 10% povidone iodine over the axillary and palmar cutaneous surface followed by the application of a very thin layer maize starch for 5-10 min.

The dark violet color developed due to the reaction in the area of excessive sweating was evaluated to understand the intensity and affected location. Quantitative gravimetry was carried out before application, 15 d after, and every month over the period of one year. A filter paper was previously weighed on a very high-precision laboratory scale and the weight was recorded. The paper was then placed into the axillary cavity and on the cutaneous surface of palm for exactly 1 minute. The paper was taken back and weighed again to calculate the rate of sweat secretion per minute [37, 38].

### Reconstitution and storage of Botulinum Toxin-A

Due to the fragile nature of botulinum toxin, its reconstitution was handled carefully by introducing non-preserved normal saline (0.9% of sodium chloride as most preferred diluent) gently into the botulinum toxin-A vial in order to avoid foaming formation during reconstitution which could interfere with the results [32, 33]. The reconstituted botulinum toxin was stored in the refrigerator at 2-8 °C used within 3-4 h.

### Dose-dependent dilution of botulinum toxin

The content of each flask possesses 100 U of type A botulinum toxin, 0.5 mg of human albumin and 0.9 mg of sodium chloride in a sterilized, vacuum-dried form without a preservative [34]. Each vial was diluted with 4 cc of normal saline (0.9%) solution to achieve the final concentration of toxin 25 U/cc.

### Administration of the diluted botulinum toxin (25 U/cc)

Intradermal injection of type A botulinum toxin was performed under different anesthesia depending upon anatomical position of hyperhidrosis. In case of axillary hyperhidrosis local infiltrative anesthesia with subcutaneous injections (Lidocaine 1% with adrenaline) dosed with 20-50 ml for 30-240 min duration was used while locoregional (blocking of the median, radial, and ulnar nerves) anesthesia (Lidocaine 1% without adrenaline) dosed with 2-5 ml (habitual volume by each point of infiltration) was applied in case of palmar hyperhidrosis. Multiple-points marking (thirty-sixty points with a distance of 1-2 cm between them on each side of the axillary and palmar region) was carried out to ensure the equal distribution of the toxin so as to get an efficient result. Diluted botulinum toxin was injected intradermally in an already anesthetized area using 1 ml syringe (4 mm 30 G needle) at an angle of 30 ° to the skin surface and a mean depth of 4 mm. Each point was dosed with 2-4 U thus total maximum dose applied was 240 (60 x 4) for each anatomical region with hyperhidrosis (axillae and palm). The entire procedure took 30-60 min with an average of 45 per session and the session was repeated every seven months [34].

## RESULTS

Out of the total 27 only 25 patients successfully completed the one year of follow-up while 2(7.40%) patients (white female) failed to follow after third consultation owing to their personal reason. 2(8%) female and 5(20%) male patients were presenting isolated axillary hyperhidrosis while isolated palmar hyperhidrosis was observed in 2(8%) female and 4(16%) male patients. Axillary-palmar hyperhidrosis was observed in the case of four (16%) female and eight (32%) male patients which was the most common clinical conditions (fig. 1). Evaluation of sweat production of both the axillary and palmar area was measured by gravimetric assessment. Monthly percentage change in the quantity of sweat production determined for all the patients to observe the therapeutic effects of the botulinum toxin. 50% or more than 50% drop at one month in the production of sweat measured by gravimetric assessment was set as a criterion for the treatment given to be successful. After completion of the first month, almost all the patients were found to have successful treatment for isolated axillary and palmar as well as axillary-palmar hyperhidrosis as the sweat rate (mg/min.) was found to be significantly reduced by 98.1%. (in case of axillary hyperhidrosis), 97.4 % (in the case of palmar hyperhidrosis) and by 96.9% in case axillary-palmar hyperhidrosis. Evidence of sweat production in more than 50% (relapse) was found in only three patients (12%), 2 with axillary-palmar and 1 with axillary hyperhidrosis after three months of the commencement of the treatment who received small reinforcement botulinum toxin dose intradermally to treat the affected area. 11 patients had a family history of hyperhidrosis (4 axillary, 2 palmar and 5 axillary-palmar). Patients with longer prior-treatment duration of the disease (ranged 2-7 y) experienced the shorter post-treatment period of anhidrosis. A significant difference between both hands and both sides of axillae was not observed in any case (dominant versus non-dominant). The time duration of the therapeutic benefits of the toxin was observed to be ranged from 3-12 mo with the maximum number of patients benefited with prolonged time duration of a decrease in symptoms depending upon follow-up assessment and patients close observation was found to be 9 mo which has been detailed in fig. 2. Questionnaire based evaluation of results and tolerability was carried out to analyze the satisfaction level of the patients and possible side effects respectively. 88% of the patients were found to be very satisfied with the results, even though the temporary nature of the treatment. Compensatory sweating in 3 patients was recorded in the minor quantity not enough to disturb the quality of life. The Vascular deficit of hands and any neurological deficit were not evidenced. Self-limiting ecchymosis at a few points of intradermal

injection and bilateral paresthesia hands and fingers were observed in 4 patients. Only one male patient had a complaint of ecchymosis at a few points of intradermal injection and bilateral paresthesia hands and fingers with allied neuropathic pain and decrease in muscular force (oral ibuprofen and physiotherapy consultation was advised to him)

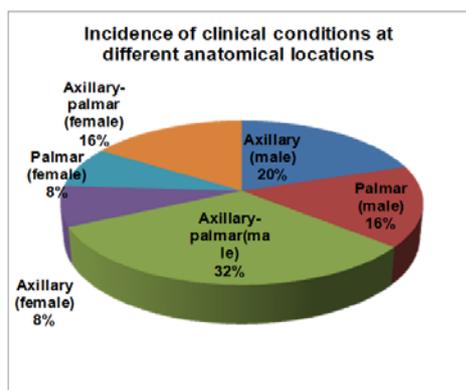


Fig. 1: Results evidencing the anatomical site impaired by hyperhidrosis

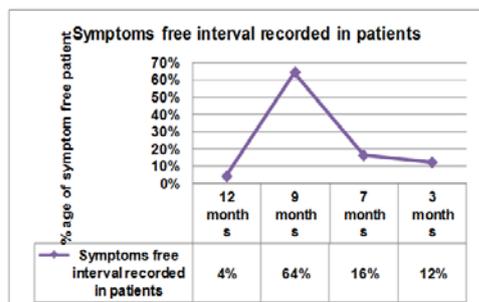


Fig. 2: Results exhibiting the therapeutic benefits of the botulinum toxin

## DISCUSSION

Keeping the risk associated, complications, limitations and adverse effects of different treatment options of hyperhidrosis, intradermal injection of type A botulinum toxin (conservative treatment) opted as therapeutic option in the present study as it has high satisfaction rate, minor complications and side effects [35, 36] while poor satisfaction rate, increased risks and permanent complications have been noticed with surgical options of treatment [37]. Use of botulinum toxin is preferable as synaptic transmission block is achieved to cause a drop in symptoms and perhaps it causes atrophy and involution of various eccrine sweat glands [38] 48% axillary-palmar, 24% isolated palmar and 28 isolated axillary cases were recorded during the consultation for hyperhidrosis. However, Grunfeld *et al.* [39] reported a high incidence of isolated axillary hyperhidrosis (51%), followed by isolated palmar (24%). The time duration of the therapeutic benefits of the toxin was observed to be ranged from 3-12 mo with the maximum number of patients benefited with prolonged time duration of a decrease in symptoms was found to be 9 mo. Benefit for up to 9 mo observed in 64% patients, for 7 mo in 16%, for 3 mo in 12% while 4% patients reported for one complete year which confirmed the efficacy of the botulinum toxin type in decreasing the hyperhidrosis (axillary, palmar and axillary-palmar). Solomon and Hayman [40] reported a significant reduction in recalcitrant palmar and digital hyperhidrosis using botulinum toxin type A dosed with 165 U/hand with anhidrosis lasting for 4-9 mo while reduced quantity of sweating remained in all the patients for 12 mo. In one study Lowe *et al.* [41] reported the use of Botox® versus placebo for the treatment of

palmar hyperhidrosis in 19 patients and concluded that patients experienced a significant improvement in palmar hyperhidrosis. Only one male patient had a complaint of ecchymosis at a few points of intradermal injection and bilateral paresthesia hands and fingers with allied neuropathic pain and decrease in muscular force which were possible related to a minor-trauma of nervous and vascular structures during the period of the anaesthetic block. Neuropathic pain was the part of reflex sympathetic dystrophy and causalgia (syndrome) caused by injury to the peripheral nerves during anesthetic drug infiltration. Baron and Zloty [42] reported a clinical case with complex regional pain syndrome during treatment of palmar hyperhidrosis; the syndrome diminished after clinical treatment and physiotherapy consultation [43].

## Limitations of the study

A variety of the studies has been done by the researcher targeting Hyperhidrosis: its diagnosis and treatment, botulinum toxin type A, as an effective treatment for hyperhidrosis. Still this disease is treated as a social stigma in the society so a lot to be done on this. On the other hand botulinum toxin type, A has some adverse effect, high cost and complicated method of application. So there is the need for further research and development to find out the novel agents to treat hyperhidrosis with low cost and easy route of application. The present investigation will prompt researchers as a platform for further research and development in this field.

## CONCLUSION

Application intradermal injection of type A botulinum toxin is a good therapeutic option for the treatment of isolated axillary, palmar and axillary-palmar hyperhidrosis as it has higher effectiveness, with greater safety and minimum invasiveness. It imparts a greater degree of satisfaction to the patients and makes them able to do a successful commencement of professional and social activities. Though treatment cost is high, it is precise and easily implementable techniques with temporary and infrequent adverse effects and associated complications. It helps enhances the quality of life of the patients and bring them out of stress, anxiety and emotional stress.

## ACKNOWLEDGEMENT

The author is highly thankful to Al-Kharj, Military hospital and Shaqra University, the kingdom of Saudi Arabia for accomplishing this study.

## CONFLICT OF INTERESTS

The author has no conflict of interest

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