Original article

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# Safety and prolonged efficacy of Botulin Toxin A in primary hyperhidrosis

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**Abstract**

*Background.* Hyperhidrosis is a condition characterized by generalized or localized hyperfunction of the eccrine sweat glands with a deep negative impact on patient's quality of life.

*Objectives.* To evaluate the efficacy and the safety of Botulin Toxin A (BTX-A) intradermal injection in the treatment of primary axillary and palmar hyperhidrosis, investigating symptoms-free period, and the subjective improving of quality life.

*Materials and Methods.* 50 consecutive patients with primary hyperhidrosis were evaluated detecting age, gender, hyperhidrosis onset period, disease duration and years of treatment with BTX-A, Minor's iodine test, Hyperhidrosis Disease Severity Scale (HDSS), Dermatology Life Quality Index (DLQI).

*Results.* The treatment is significantly effective both for axillae and palms: the majority of the patients improved their HDSS and Minor's scores from a value of 4 in the two tests, to values of 1 (HDSS) and 0 (Minor test). Patients reported a duration of symptoms relief from 4 to 12 months, with a mean of 5.68 months; specifically, we have observed that the axillary group experienced a longer symptoms-free period (mean RFS 7.2 months) than the palmar group (mean: RFS 4.27 months).

*Conclusions.* Authors suggest that BTX-A is a safe, easy, and fast procedure for the treatment of primary axillary and palmar hyperhidrosis. ***Clin Ter 2014; 165(6):e395-400. doi: 10.7417/CT.2014.1780***

**Key words:** *axillary hyperhidrosis, botulinum toxin, palmar hyperhidrosis*

## Introduction

Hyperhidrosis is a condition characterized by generalized or localized hyperfunction of the eccrine sweat glands; it can be considered as a primary disorder, otherwise secondary to endocrinological or neurological diseases (1).

Primary hyperhidrosis is an idiopathic and chronic illness without a recognizable cause exacerbated by emotional stimuli (2). The prevalence estimated is about 2.5% of the US population, probably undervalued owing to lack of consciousness (3); it may exert a deep negative impact on patient's quality of life, that means a significant decline of daily, occupational activities and social interactions (4).

The most commonly involved areas are axillae, palms of the hands, the soles of the feet and the face (axillary, palmar, plantar and facial hyperhidrosis) (5).

The therapeutic options currently available include topical aluminum salts, iontophoresis, systemic medications (including glycopyrrolate and clonidine). Surgical treatment such as liposuction, direct excision of the glands, or sympathectomy is a more invasive procedure that may lead to several complications (6).

Local injections of Botulinum toxin type A (BTXA) result in an effective and safe solution for primary hyperhidrosis (7). The principal target of BTX-A is the cholinergic nerve endings, with the action of blocking the release of acetylcholine from the presynaptic nerve terminal, obtaining a temporary and reversible local chemodenervation (8-12).

The aim of the study is to evaluate the efficacy and the safety of BTXA intradermal injection in the treatment of primary axillary and palmar hyperhidrosis, investigating symptoms-free period, and the subjective improving of quality life.

## Materials and Methods

50 consecutive patients with primary hyperhidrosis (24 axillary and 26 palmar involvement) were included in this study.

For each patient we detected age, gender, hyperhidrosis onset period, disease duration and years of treatment with BTX-A, Minor's iodine test, Hyperhidrosis Disease Severity Scale (HDSS), Dermatology Life Quality Index (DLQI).

The HDSS is a disease-specific scale for hyperhidrosis based on how the disease affects patient's daily activities. A score of 3 or 4 indicates severe sweating, while a score of 1 or 2 indicates a mild or moderate hyperhidrosis. According to the Canadian Hyperhidrosis Advisory Committee, a successful treatment consists in an improvement from a score

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*Table 1. Extension of hyperhidrotic area identified by Minor's test.*

| Sweating area's rate in the target zone | Minor's Score |
|---|---|
| **No involvement** | 0 |
| **<25%** | 1 |
| **25-50%** | 2 |
| **>50%** | 3 |

of 4 or 3 to a score of 2 or 1, whereas a disease relapse is a two-point worsening from the obtained score.

The DLQI is a validated questionnaire, useful to evaluate both the disability caused by the cutaneous symptoms and the improvement related to the treatment. It is calculated by summing the score of each question ranging from a minimum of 0 to a maximum of 30.

The Minor's test is an effective technique that provides a visualization of the extension of hyperhidrotic area: it's performed by spreading a 2% of iodine solution on the skin, then a mais starch powder is applied. After 15 minutes, the presence of sweating is shown by the onset of a dark-blue color. According to the extension rate of sweating within the target zone (palm or axilla), a score is assigned (Table 1).

The inclusion criteria were age >18, positivity to Minor's iodine test, a HDSS) score of 3 or 4, and the lack of response to conventional topical and physical treatments (e.g., local anti-perspirants containing aluminium salts, acids or aldehydes, iontophoresis). Patients were excluded if they: 1. were pregnant or breast-feeding women; had secondary hyperhidrosis, infections, neuromuscular diseases; were taking systemic medications that could interfere with neuromuscular activity. Moreover, all subjects underwent routine laboratory tests.

A written informed consent was obtained before treatment.

The identified hyperhidrotic areas - both on the hands and the axillae - were marked using a dermographic pen and each area was then subdivided into 2.25 cm² squares. Lyophilized botulinum toxin type A (Botox®; Allergan, Irvine, CA, USA) 100 mouse units (MU) was dissolved into 5 mL sterile 0,9% saline solution. A dose of 0.10 mL (2 MU) was injected intracutaneously into each square using a single injection with a 27x0.40x0.4 gauge needle. Hence all patients received a fixed dose of 2 MU per 2.25 cm² - both at palmar and at axillary level - as recommended by the Canadian Hyperhidrosis Advisory Committee. No local anesthesia was needed for axillary injections, whilst ice anaesthesia was used for the palms.

The clinical assessment included a baseline examination of hyperhidrotic patients, and post-treatment evaluation 1, 6, and 12 months after BTX-A injection. A new treatment was performed when first inclusion criteria (Minor test positivity and 3 or 4 score of HDSS) were met.

### Statistical analysis

In order to statistically analyze the data, we firstly verified that the sample's features were independent from the hyperhidrosis localization (palms or axillae). For the gender we used the Chi square test applied to the crossed frequencies tables (Table 2), while for age, disease and treatment duration we used the *t* Test statistic (Table 3). For both the tests, we verified their correspondent *p*-values, by considering that these have to be ≤0.05 in order to guarantee the low incidence of randomness inside our samples.

*Table 2. Frequencies distribution of all the patients by gender and location of the treatment (plus the chi square used to test the independency of the part treated to the gender).*

| Gender | All patients | Axillae | Palms | Value of the Chi-square test (and p-value) for gender and location (axillae or palms) |
|---|---|---|---|---|
| Males | 19 | 9 | 10 | 0.005 (0.944) |
| Females | 31 | 15 | 16 | |
| Total | 50 | 24 | 26 | |

*Table 3. Mean values of age, disease and treatment durations for all patients, patients with axillary hyperidrosis, and patients with palmar disease (and value of the T Test to verify the independency of the means to the location).*

| | All patients (n = 50) | Axillae (n = 24) | Palms (n = 26) | t Test (p-value) for the mean and the location of the treatment |
|---|---|---|---|---|
| Age (years) | 34.9 | 36.5 | 33.4 | 1.11 (0.27) |
| **Disease duration (years)** | 18.3 | 17.3 | 19.3 | 0.69 (0.49) |
| **Treatment duration (years)** | 3 | 3.5 | 2.6 | 1.10 (0.27) |

*Table 4. Transition tables of HDSS pre and post treatment, for all the patients and for the specific localization of the treatment.*

| HDSS | | | Post | | | Total | Chi square (p-value) |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3-4 | | |
| General | Pre | 3 | 9 (53%) | 6 (35%) | 2 (12%) | 17 | 3.91 (0.142) |
| | | 4 | 22 (67%) | 4 (12%) | 7 (21%) | 33 | |
| | | Total | 31 (62%) | 10 (20%) | 9 (18%) | 50 | |
| Axillae | Pre | 3 | 4 (57%) | 3 (43%) | 0 | 7 | 2.91 (0.088) |
| | | 4 | 15 (88%) | 2 (12%) | 0 | 17 | |
| | | Total | 19 (79%) | 5 (21%) | 0 | 24 | |
| Palms | Pre | 3 | 5 (50%) | 3 (30%) | 2 (20%) | 10 | 2.03 (0.36) |
| | | 4 | 7 (44%) | 2 (12%) | 7 (44) | 16 | |
| | | Total | 12 (46%) | 5 (19%) | 9 (35%) | 36 | |

*Table 5. Transition tables of the Minor test pre and post treatment, for all the patients and for the specific localization of the treatment.*

| Minor Test | | | Post | | | | | Chi square (p-value) |
|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | 2 | 3 | Total | |
| General | Pre | 3 | 14 (82%) | 2 (12%) | 1 (6%) | 0 | 17 | 1.31 (0.73) |
| | | 4 | 23 (70%) | 7 (21%) | 2 (6%) | 1 (3%) | 33 | |
| | | Total | 37 (74%) | 9 (18%) | 3 (6%) | 1 (2%) | 50 | |
| Axillae | Pre | 3 | 7 (88%) | 1 (12%) | 0 | 0 | 8 | 0 (1) |
| | | 4 | 14 (88%) | 2 (12%) | 0 | 0 | 16 | |
| | | Total | 21 (88% | 3 (12%) | 0 | 0 | 24 | |
| Palms | Pre | 3 | 7 (78%) | 1 (11%) | 1 (11%) | 0 | 9 | 1.98 (0.58) |
| | | 4 | 9 (53%) | 5 (29%) | 2 (12%) | 1 (6%) | 17 | |
| | | Total | 16 (62%) | 6 (23%) | 3 (12%) | 1 (3%) | 26 | |

To verify the efficacy of the treatment, we firstly evaluated the Pearson linear correlation between all the continuous variables. In the second step we built the transition matrices (before vs after the treatment) for the HDSS and for the Minor's test scores (Tables 4 and 5), considering three groups: the total of the patients, patients with axillary hyperhidrosis and those with palmar disease. For each matrix we also evaluated the Chi square test and its associated p-value.

Furthermore, we used *t*-Test and Chi square to evaluate the existence of significant differences of the treatment efficacy according to the area.

## Results

Sixty-two percent of patients were females and the mean age was 35 years old. Most of patients had severe hyperhidrosis (the mean HDSS score was 3.66 and the mean DLQI was 21.34) with a mean illness duration of 18 years. Patients referred a mean treatment period lasting 3 years.

The *p*-value of the statistical tests confirmed the independency between the baseline features (gender, age, disease duration and years of treatment) and the disease localization ($p > 0.05$) (Tables 2 and 3). Furthermore, *p*-values referring to Minor's test, HDSS and DLQI pre-treatment demonstrate the homogeneity of our sample (Tables 6 and 7).

As evidenced in Tables 4, 5 and 6, the treatment is significantly effective both for axillae and palms: the majority of the patients improved their HDSS and Minor's scores from a value of 4 in the two tests, to values of 1 (HDSS) and 0 (Minor test). Concerning the HDSS observed for the axillae, the Chi square is slightly significant (less than 0.08); this could derive from a high concentration of patients switching from a value of 4 to 1 (88%). The other Chi square indexes are not statistically significant (Table 4).

Tables 7 and 8 show a negative significant correlation (overall and for the axillae) between DLQI after the treatment and the Relapse Free Survival (RFS). This analysis affirms that if the RFS is longer, the DLQI is associated to lower values; we could observe, that this is not so significant for the palms (the correlation is equal to 0.56), showing that the treatment of this area provides variable results.

Patients reported a duration of symptoms relief from 4 to 12 months, with a mean of 5.68 months; specifically, we have observed that the axillary group experienced a longer symptoms-free period (mean RFS 7.2 months) than the palmar group (mean RFS 4.27 months). In all repeated treatments, we did not observe any lack of efficacy or reduction of the duration of symptom relief.

As to side effects, in the palmar group, 23% of patients had temporary handgrip weakness, whereas 20% of all subjects had mild pain during the injections, most of them belonging to palmar group.

*Table 6. Distribution of frequencies for all the patients and according to the body's area (absolute and percentages), plus the value of the Chi square tests (for each variable and localization).*

| | **All patients (*n* = 50)** | **Axillae (*n* = 24)** | **Palms (*n* = 26)** | **Chi square (p-value)** |
|---|---|---|---|---|
| Minor test pre-treatment (%) | | | | |
| **2** | 17 (34%) | 8 (33,3%) | 9 (34,6%) | 0.009 (0.924) |
| **3** | 33 (66%) | 16 (66.6%) | 17 (65.4%) | |
| Minor test post-treatment (%) | | | | |
| **0** | 37 (74%) | 21 (87.5%) | 16 (61.5%) | 5.60 (0.133) |
| **1**<br>**2**<br>**3** | 9 (18%)<br>3 (6%)<br>1 (2%) | 3 (12.5%) | 6 (23.2%)<br>3 (11.5%)<br>1 (3.8%) | |
| HDSS pre-treatment (%) | | | | |
| **3** | 17 (34%) | 7 (29.2%) | 10 (38.4%) | 0.48 (0.488) |
| 4 | 33 (66%) | 17 (70.8%) | 16 (61.6%) | |
| HDSS post-treatment (%) | | | | |
| **1** | 31 (62%) | 19 (80%) | 12 (46%) | 10.52 (0.005) |
| **2** | 10 (20%) | 5 (20%) | 5 (19%) | |
| **3-4** | 9 (18%) | 0 | 9 (34.6%) | |
| **Pain (%)** | 20 | 4 | 34 | |
| **Weakness (%)** | / | / | 23 | |

*Table 7. Mean values for Relapse free survival, DLQI pre and post treatment (and of their difference) for all patients and according to body's area.*

| | **All patients (*n* = 50)** | **Axillae (*n* = 24)** | **Palms (*n* = 26)** | **p-value** |
|---|---|---|---|---|
| Relapse Free Survival (months) | 5.68 | 7.20 | 4.27 | 3.80 (<0.05) |
| DLQI pre-treatment | 21.34 | 21.8 | 20.90 | 0.49 (0.62) |
| DLQI post-treatment | 4.50 | 1.80 | 7 | 2.80 (0.007) |
| Diff DLQI (post-pre) | -16.84 | -20 | -13.90 | 2.70 (0.009) |

*Table 8. Value of the linear correlation between DLQI evaluated post the treatment and the relapse free survival (with the correspondent p values).*

| General | Axillae | Palms |
|---|---|---|
| 0.716 (<0.05) | 0.72 (<0.05) | 0.56 (<0.05) |

## Discussion

Focal idiopathic hyperhidrosis (FIH) is a chronic functional disorder whose aetiopathogenesis still remains controversial (1).

Eccrine glands are distributed around the body with high concentrations in areas such as palms, soles, and forehead. These glands are innervated by the cholinergic fibers of the sympathetic nervous system. Patients with hyperhidrosis do not demonstrate any histopathologic findings in the sweat glands or changes in their numbers. A complex dysfunction in the sympathetic system likely contributes to the pathogenesis.

FIH is a condition affecting functional impairment and quality of life, satisfaction and limitations at work.

There are a wide array of modalities available to treat focal hyperhidrosis. These include nonsurgical (i.e., topical, systemic) and surgical treatments that vary in their therapeutic efficacy, side effects, cost, and duration of effect (6).

The administration of BTX-A in the treatment of FIH significantly modified the assessment of patients non-responding to topical medications (8-12).

BTX-A represents the most innovative clinical acquisition in this field so that the prognosis of non-responders suffering from FIH mostly depends on the duration of euhidrosis induced by BTX-A.

It is a neuromodulator that works by blocking presynaptic acetylcholine release.

BTX-A injections are less invasive than surgical procedures and provide longer-lasting results than topical therapies. The effects of BTX-A last for 4–9 months on average in axillary use (13-17) and are associated with a very high satisfaction rate among patients. A small study of pediatric patients with palmar hyperhidrosis treated with BTX-A demonstrated improvement lasting a mean of 7 months, which is longer than the duration of improvement reported in other studies (17-19). Recent studies demonstrate an increase in duration of efficacy of BTX-A with repetitive injections in patients with primary axillary hyperhidrosis (20), contrasting with previous studies that showed the symptom-free interval does not change significantly after multiple treatments (15).

Patient tolerability of the procedure is variable, and injections tend to be less tolerable on the palms and soles because of the increased sensitivity and thickness of acral skin.

In this study, authors evaluated the efficacy and the safety of BTX-A intradermal injection in the treatment of primary axillary and palmar hyperhidrosis, investigating the symptoms-free period, and the subjective improving of quality of life.

We therefore analysed the following factors: gender, age, history of disease duration, localization (palms or axillae), DLQI, HDSS and rate of extension of sweating area using Minor test.

We found a complete responder rate, with a good grade of global satisfaction: all hyperhidrotic patients experienced a great reduction of disease severity with a significant improvement of DLQI and reduction of the extension of sweating area. Furthermore, all patients returned for repeating treatment.

Botox injection is efficacious both for axillae and palms even if our study shows a greater effectiveness of the axillary treatment compared to the palmar one.

Authors also demonstrate that RFS was shorter in patients with palmar hyperhidrosis than in the axillary group who experienced a longer symptoms-free period. In all repeated treatments, we did not observe any lack of efficacy or reduction of the duration of symptom relief.

Our data confirm some clinical reported evidences according to which for the same dosage per cm2 , the therapeutic response to BTX-A in patients suffering from palmar hyperhidrosis is shorter than in patients suffering from axillary hyperhidrosis.

Naumann et al. first reported that the length of BTX-A action in axillary hyperhidrosis was 4–12 months, whereas in patients suffering from palmar hyperhidrosis it was mainly 4–6months (21, 24).

Glogau et al. (22) reported that the average length of RFS is shorter in patients suffering from palmar hyperhidrosis and that this effect does not seem to be so long as it is in axillary hyperhidrosis.

Lowe et al. also showed a long-term efficacy of BTX-A in therapy of axillary hyperhidrosis and the mean duration of the effect was 6 months (21, 24).

Referring quality of life our data are in agreement with literature (4).

Campanati et al. in a cohort of 79 patients suffering from axillary and palmar hyperhidrosis showed that HDSS decreased from a pretreatment value of 4 to a post-treatment value of 0. They demonstrated that relapse-free survival was shorter in patients suffering from palmar hyperhidrosis (24).

We reported the effectiveness of BTX-A injections for the treatment of axillary and palmar hyperhidrosis, showing statistically significant differences between the two groups, in terms of RFS, HDSS, DLQI ($p < 0.05$).

In conclusion, based on our findings, we suggest that the BTX-A local therapy for the axillary and palmar hyperhidrosis, along the period of 12 months, is an effective, easy and fast procedure, especially useful for non-responder patients to other conventional treatments. Further investigations are needed in case of a more prolonged treatment.

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