

Efficacy and Safety of Botulinum Toxin Type A in the Treatment of Palmar Hyperhidrosis: A Double-Blind, Randomized, Placebo-Controlled Study

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BACKGROUND. Recent studies demonstrate that botulinum toxin type A (BTX-A) decreases palmar hyperhidrosis.

OBJECTIVE. To evaluate the efficacy and safety of BTX-A for palmar hyperhidrosis.

METHODS. Patients ($n = 19$) received injections of placebo (normal saline) in one hand and BTX-A in the other. Assessments included gravimetric measurement of sweat production and physician's and patient's rating of severity. Safety evaluations included measuring grip strength. Preliminary 28-day results are reported.

RESULTS. The mean percentage decrease in gravimetric measurement at day 28 was significantly greater with BTX-A versus placebo. One hundred percent of 17 patients rated the treatment as successful, while only 12% (2/17) rated placebo injection successful. Grip and hand strength were unchanged with either treatment. Only 21% (4/19) reported mild adverse events.

CONCLUSION. BTX-A injections produce significant improvements in palmar hyperhidrosis without a concomitant decrease in grip or dexterity, or the occurrence of serious adverse events.

N. J. LOWE, MD HAS RECEIVED RESEARCH GRANTS AND CONSULTANT PAYMENTS, AND OWNS STOCK IN ALLERGAN, INC.

HYPERHIDROSIS IS excessive secretions by the eccrine sweat glands resulting in profuse sweating. Focal hyperhidrosis usually occurs in the axillae, palms, and soles. In severe cases, sweat literally drips from the axillae, hands, and feet, soaking clothing and impeding grip. This condition handicaps patients both professionally and socially, and can lead to secondary infections due to skin maceration.

Conservative treatments for hyperhidrosis include topical applications of aluminum chloride preparations and tap water iontophoresis.^{1,2} Oral anticholinergic agents may also alleviate hyperhidrosis, but the dosage required usually results in unacceptable side effects.² In cases where conservative treatments have proved ineffective, sympathectomy has successfully decreased focal hyperhidrosis.³ However, in addition to the possible adverse events associated with the surgery, sympathectomy results in compensatory hyperhidrosis in up to 70% of patients.³⁻⁷ In clinical studies where the level of severity of compensatory hyperhidrosis was assessed, this side effect was considered major or disabling in approximately 26% of patients.⁸

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Recent studies have demonstrated that botulinum toxin type A (BTX-A) can effectively decrease axillary and palmar hyperhidrosis.⁹⁻¹⁷ BTX-A acts by blocking the release of the neurotransmitter acetylcholine, which normally activates the eccrine sweat glands. Some concern has been expressed that BTX-A injection, particularly in the palm, may also impede the release of acetylcholine at neuromuscular junctions, thus decreasing the motor function of the hand. The current study was designed to investigate the efficacy of BTX-A treatment for palmar hyperhidrosis and to evaluate the safety of BTX-A injection using an objective measure for grip strength. This article reports the results of the first 28 days of the study. Long-term crossover studies are being completed.

Patients and Methods

The study was designed as a single-center, prospective, double-blind, randomized, placebo-controlled, within-patient comparison that enrolled 19 patients between the ages of 18 and 80 years of age with bilateral, symmetrical palmar hyperhidrosis, including the fingers. Key inclusion criteria included a gravimetric measurement of sweat production of at least 40 mg/min, as well as an unsatisfactory response to previous treatment by local and/or systemic drug therapy. Sub-

jects also had to understand the requirements of the study and sign an informed consent form. Key exclusion criteria included a history of palmar hyperhidrosis for less than 6 months; current or planned pregnancy; lactation; or any concomitant disease (eg, myasthenia gravis, amyotrophic lateral sclerosis) or medication (eg, aminoglycoside antibiotics) that interferes with neuroglandular transmission; profound atrophy or weakness of palmar muscles; infection, either locally at the site of injection or systemically; allergy or sensitivity to any study medication; and current or previous botulinum toxin therapy. In addition, patients could not have participated in another investigational drug study within 30 days of the baseline visit.

This study complied with the Declaration of Helsinki recommendations regarding biomedical research involving human patients, and approval was obtained by the governing institutional review board (IRB). Before study enrollment, the study design, purpose, and possible risks of participation were discussed with each patient and written informed consent was obtained.

Randomization/Blinding

The computer-generated randomization code randomly allocated the left and right palms of each subject to BTX-A 100 U or placebo. The injector physician was unaware of whether the patient received BTX-A or placebo.

Study Medications

Each vial of study medication contained BTX-A 100 U and was reconstituted with 1.5 ml of 0.9% sterile saline without preservatives. Placebo injections consisted of 0.9% sterile saline without preservatives.

Injections

On day 0, injections of BTX-A and placebo were assigned randomly to each palm. One hour before injection, lidocaine/prilocaine cream was applied to each palm under plastic glove occlusion followed by ice packs for 10 minutes. Fifteen 0.1 ml injections (BTX-A 6.67 U at each site for a total dose of 100 U) using a 30-gauge, 0.5 inch needle were administered to each hand, 10 injections into the palm and 1 injection into each digit (Figure 1). Injections were intradermal, with a wheal at each injection site. All treatment vials were identical and marked only with patient numbers. The number and volume of injections were identical for both treatments. At a screening visit, patients provided written, informed consent. Medical (including hyperhidrosis) and medication histories were taken. Each patient underwent a physical examination, and female patients were tested for pregnancy. For every study visit, patients were instructed to bathe/shower on the morning of the visit and to not apply any antiperspirant to the palms for the duration of the study.

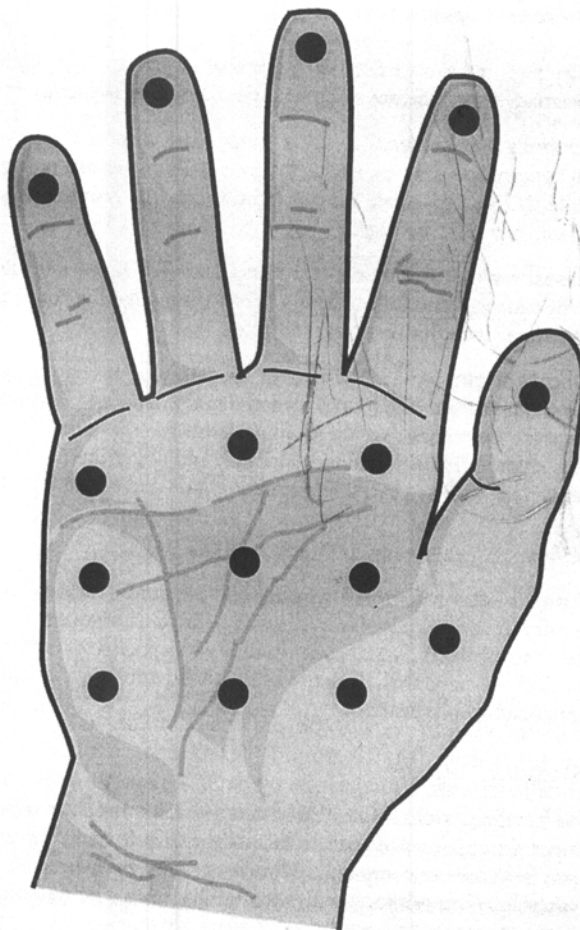


Figure 1. Fifteen injections were administered to each hand, 10 in the palm and 1 in each digit.

Follow-Up

Patients returned for study visits at 7, 14, and 28 days after injection. At each study visit, all efficacy measures were obtained.

Efficacy Measures

Gravimetric Measurement. At each visit, the patient applied a powder-free vinyl glove containing 1 preweighed Wattman 80 mm filter paper to each hand. After 5 minutes, the gloves were removed and the filter paper reweighed. The difference in the filter paper weights was used as the gravimetric measurement of sweat production.

Minor Iodine Starch Test. At each visit, an iodine solution (2 g iodine in 10 ml of castor oil and alcohol to 100 ml) was painted over the palms, then upon drying, was followed by application of potato starch powder. The mixture turns dark blue when exposed to sweat, and this color change was recorded using a standardized camera system.

Physician's Assessment. The clinical severity of hyperhidrosis was assessed at each visit by the investigator using a scale of 1 to 5 (1 = no sweating, 2 = minimal sweating, 3 = mild sweating, 4 = moderate sweating, and 5 = severe sweating).

Patient's Assessment. Patients graded the clinical severity of hyperhidrosis at each visit using a 10 cm visual analog scale (VAS). This scale ranged from 0 cm (no sweating) to 10 cm (severe sweating).

Assessment of Treatment Success. Patients completed the hyperhidrosis impact questionnaires to measure the impact of palmar hyperhidrosis on their lives.

Grip Strength. At each visit, grip strength was measured using a Jamar hydraulic hand dynamometer. The test was repeated three times and the average score for the three trials was recorded. Intrinsic muscle strength and finger/thumb dexterity were assessed by patient questionnaire and examination.

Safety

Patients were monitored throughout the study for adverse events. A serious adverse event was defined as an event that resulted in death, significant disability/incapacity, or a congenital anomaly/birth defect; was life threatening; or required inpatient hospitalization.

Statistical Analysis

At baseline, a chi-squared test was used to compare treatment groups for categorical variables and a Student's *t*-test was selected to compare treatment groups for continuous variables. The primary analyses were based on the outcome of the gravimetric measurement of sweat production. The mean difference in the gravimetric measurement between baseline and day 28 assessments of the hands receiving BTX-A 100 U was compared to the hands receiving placebo (paired comparison). The secondary analyses compared the investigator's evaluation of clinical severity, the patient's evaluation of clinical severity, and grip strength over 28 days. Discrete variables were compared between treatments using the Fisher's exact test, while the Student's *t*-test (paired) was used to compare continuous variables. The Fisher's exact test was used to analyze the percentage of patients who were successfully treated after 28 days based on the investigator's assessment of the gravimetric measurement of sweat production.

There were four unplanned interim analyses performed. Since multiple analyses may alter the true significance level of a test by introducing a type I error (false-positive finding), the Bonferroni adjustment was applied to adjust the significance level from 0.05 to 0.013.

Results

Of the 19 patients enrolled in the study, 16 completed day 28, and 3 exited the study due to protocol violations (did not reach day 28). The mean age of the pa-

Table 1. Patient Demographics

No. of patients	19
Age, years (mean \pm SD)	31 \pm 8.6
Sex	
Male	10 (52.6)
Female	9 (47.4)
Weight, kg (mean \pm SD)	75.5 \pm 15.5
Race	
Caucasian	10 (52.6)
Black	4 (21.1)
Asian	3 (15.8)
Hispanic	1 (5.3)
Other	1 (5.3)

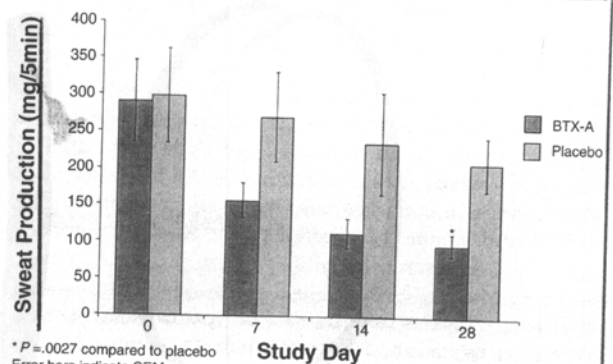
Values are number (percentage) unless otherwise indicated.

tients was 31 years and the mean weight was 75.5 kg (Table 1). The patients were predominantly male (53%) and Caucasian (53%).

Efficacy

Gravimetric Measurement of Sweat Production. Mean sweat production declined steadily during the 28 days following BTX-A treatment (Figure 2). The mean percentage change from baseline was significantly greater in the BTX-A-treated palms than in the placebo-treated palms at day 28 ($P = .0037$). However, there was a modest reduction in sweating in the placebo-injected palms.

Minor Iodine Starch Test. Results of the iodine starch test paralleled those of the gravimetric sweat test and permitted visualization of the improvement in the treated hands (Figure 3). Clear differences can be seen between the day 0 and day 28 BTX-A-treated palms. Improvement in most patients was visible by day 7.



* $P = .0027$ compared to placebo
Error bars indicate SEM.

Figure 2. Gravimetric measurement of sweat production. Sweat production is determined over 5 minutes by absorption onto a filter paper. Error bars indicate SEM. $P = .0027$ versus placebo.

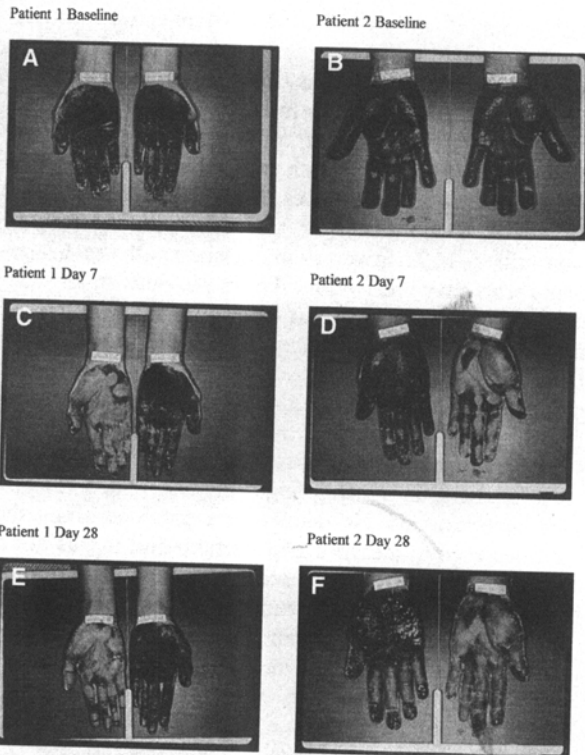
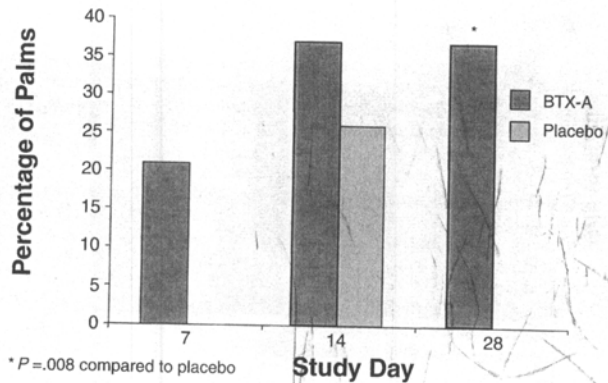


Figure 3. Iodine starch test photographs of the results in two patients at baseline, and on days 7 and 28 after injection. Patient 1: A) Severe bilateral palmar hyperhidrosis with uniform severe palmar sweating. B) Results of iodine starch test 7 days after injection of BTX-A or placebo. C) Further improvement is apparent on the palm of the treated hand 28 days after injection. Patient 2: D) Severe bilateral palmar hyperhidrosis with uniform severe palmar sweating. E) Results of iodine starch test 7 days after injection of BTX-A or placebo. F) Note that some decrease in sweating is seen on the fingers of the placebo-treated hand on days 7 and 28. However, the response with placebo is appreciably less than that of the BTX-A-treated hand.

Physician's Assessment. At each follow-up visit, more BTX-A-injected palms had improved by two or more points on the physician's assessment scale than had the placebo-injected palms (Figure 4). The difference was statistically significant on day 28 ($P = .008$).

Patient's Assessment. Patients rated sweat production on the BTX-A-treated palms as significantly less severe than on the placebo-treated palms at every follow-up visit ($P \leq .0062$) (Figure 5). The mean improvement from baseline at day 28 was significantly greater for the BTX-A-treated palms compared to the placebo-treated palms ($P < .0001$).

Patient Satisfaction. No patient assessment was available for two patients. Among the 17 patients available for assessment, 100% (17/17) rated the treatment as suc-



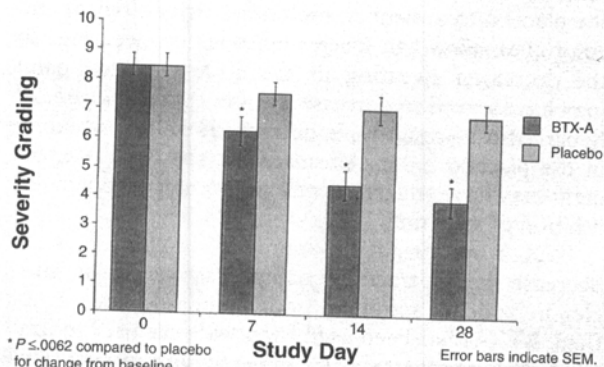
* $P = .008$ compared to placebo

Figure 4. Physician's assessment of clinical severity: BTX-A-treated palms improving by at least 2 points from baseline versus placebo-treated palms using a scale of 1 to 5 (1 = no sweating to 5 = severe sweating). * $P = .088$ versus placebo.

cessful in the BTX-A-treated palm compared with 12% (2/17) in the placebo-treated palm ($P < .0001$).

Safety

No significant difference was seen in grip strength between the palms receiving BTX-A or placebo at any point during the study (Figure 6). All patients were specifically asked if they experienced any problems with hand dexterity or strength. Only one patient reported minor thumb and finger weakness, which resolved within 2 weeks. Only four patients reported any adverse events during the 28-day follow-up period: one patient with tingling and slight numbness in the fingers of the hand receiving BTX-A, one patient with weakness in the hand receiving placebo, one patient with pain in both hands, and one patient with osteoarthritis (judged to be unrelated to the study treatment).



* $P \leq .0062$ compared to placebo for change from baseline.

Figure 5. The patient's assessment of clinical severity, based on the 10 cm visual analog scale (0 = no sweating and 10 = severe sweating). Error bars indicate SEM. * $P = .0062$ compared to placebo for change from baseline.

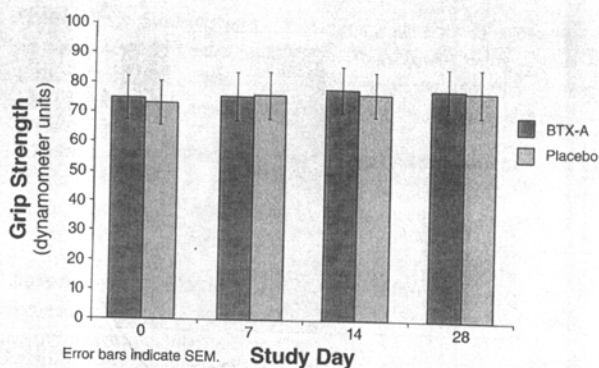


Figure 6. Grip strength measured using a Jamar hydraulic hand dynamometer. Error bars indicate SEM.

All treatment-related adverse events were rated as mild and resolved successfully. No patient withdrew from the study due to adverse events.

Discussion

In this study, patients experienced a significant improvement in palmar hyperhidrosis without a concomitant decrease in grip strength, significant finger dexterity, or the occurrence of serious adverse events. These results support data from prior studies demonstrating the efficacy of BTX-A injections for palmar hyperhidrosis.⁸⁻¹⁴ The change in the gravimetric measurement of sweat production in this study was greater for the palms receiving BTX-A than for those receiving placebo. However, this difference only reached statistical significance on day 28. This was most likely due to study methodology. The standard deviation for the gravimetric measurement was very high, even at baseline. All of the assessed patients rated the BTX-A treatment as successful, while only two patients classified the placebo treatment as successful. Psychological and emotional stress can trigger episodes of sweating, so the decreased sweating in the BTX-A-treated palm may have served to decrease the anxiety component of hyperhidrosis, resulting in decreased levels of sweating in the placebo palm. Alternatively, the BTX-A treatment may have triggered some autonomic feedback inhibition of sweating.

BTX-A was originally approved for clinical use to decrease the contractions of hyperactive ocular muscles in patients suffering from blepharospasm. Since then, BTX-A has been used for a wide range of indications that involve relaxing hyperactive muscles. This raised the concern that intradermal treatment of hyperactive palmar sweat glands with BTX-A would also induce a concomitant decrease in muscle tone in the hand. A previous study by Saadia et al.¹⁸ demonstrated

that either 50 or 100 U of BTX-A injected intradermally in each palm decreased sweating in patients with primary hyperhidrosis for at least 2 months in all patients and 6 months for most patients. The authors observed that handgrip strength was not affected by either dose, but finger pinch strength was decreased in some patients at both doses that gradually improved. However, 6 months after treatment, pinch strength was still 7-11% lower than baseline. Of the 67 patients who have received BTX-A in previous small studies and case reports, 24 patients subjectively described mild, transient weakness, usually of the thumb, after BTX-A injections.⁸⁻¹⁴ Most of the studies were not randomized or controlled, and the one placebo-controlled trial¹² did not objectively measure grip strength. One previous study¹⁰ reported no change in handgrip force in the four patients (eight palms) treated for palmar hyperhidrosis. No details were provided about the methods used to measure grip strength and it was not a controlled trial. In the present double-blind, randomized, placebo-controlled study, well-documented, objective measurement of grip strength in the palm receiving BTX-A 28 days after injection did not differ significantly from baseline levels or from the palm receiving placebo.

This study reported preliminary results after 28 days of follow-up. Data are being analyzed on the duration of benefit from BTX-A injections. Previous studies^{9,10,12-14} have found that the duration of clinical benefit varied widely, but was at least 4 months in patients with good responses, and some patients remained anhidrotic for 12 months. Re-treatment for relapse appears to be effective.¹⁰

In conclusion, this bilateral, placebo-controlled study demonstrates that BTX-A injections can provide significant relief from palmar hyperhidrosis without a concomitant loss of grip strength or any notable adverse effects.

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