Botulinum toxin type A in primary palmar hyperhidrosis

Randomized, single-blind, two-dose study

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Article abstract—*Background:* Primary palmar hyperhidrosis is characterized by excessive sweating due to increased sympathetic cholinergic sudomotor nerve traffic to the palmar surface of the hands. Clinical studies suggest that intradermal injections of botulinum toxin are effective in the treatment of palmar hyperhidrosis. *Objectives:* To establish the effectiveness of intradermal botulinum toxin in reducing hyperhidrosis, to determine the most effective dose of toxin, and to examine its effect on muscle strength. *Methods:* In a prospective, single blind, randomized trial, 24 patients with severe palmar hyperhidrosis received either a low (50 U) or a high dose (100 U) of botulinum toxin type A (Botox, Allergan) injected intradermally in 20 sites in each palm. *Results:* Following injection with either dose, iodine starch test revealed a significant decrease in sweating within the first month. Six months after injection, the anhidrotic effect was still evident in two thirds of the patients in both groups. Handgrip strength was not affected with either dose but finger pinch strength, 2 weeks after the injection, decreased 23 ± 27% with 50 U ($p < 0.05$) and 40 ± 21% with 100 U ($p < 0.001$). Pinch strength improved gradually but 6 months after treatment it was still 7–11% lower than at baseline. *Conclusions:* Both 50 and 100 U of botulinum toxin type A, injected intradermally in each hand, decreased sweating in patients with primary hyperhidrosis for at least 2 months in all the patients, and 6 months in most patients. Weakness in the intrinsic muscles of the hand was observed.

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Primary hyperhidrosis is a disorder of unknown etiology characterized by excessive uncontrollable sweating most often in the palmar surface of the hands, armpits, groin, and feet due to increased firing of sympathetic cholinergic sudomotor nerves. Patients sweat excessively in response to thermal and emotional stimuli but also spontaneously for no apparent reason.[1] Primary hyperhidrosis is mainly socially embarrassing but it may be very disabling, not only because of skin maceration and secondary microbial infections[2] but also because it may prevent patients from performing many activities with the hands, such as writing. The disorder frequently starts in early childhood and affects 0.6 to 1% of the population.[3]

Available medical treatments, including systemic anticholinergics and beta-blockers, and topical agents, such as aluminum antiperspirants and tap water iontophoresis, are largely ineffective or of little value.[2] Surgical sympathectomy significantly reduces sweating but has frequent side effects including pneumothorax, Horner's syndrome, and compensatory sweating in other areas of the body.[4,5] Recently, intradermal injections of botulinum toxin type A (Botox, Allergan Inc., Irvine, CA), which blocks the release of acetylcholine during nerve stimulation, have been reported to reduce excessive sweating in patients with primary palmar hyperhidrosis.[6-12] Whereas therapy with botulinum toxin is now widely used for palmar hyperhidrosis, its effectiveness, appropriate dose, and side effects are poorly documented. Furthermore, although muscle weakness has been reported in some uncontrolled studies, the effect of intradermal botulinum toxin on muscle strength has not been analyzed. Accordingly, we conducted a prospective, single-blind, parallel group trial comparing the anhidrotic effect of a high and low dose of botulinum toxin type A (Botox) injected intradermally in the hands of patients with severe palmar hyperhidrosis. We examined the duration and pattern of the anhidrotic effect, patient satisfaction, and the impact on muscle strength.

Methods. The first five patients were assigned to receive the low dose of botulinum toxin (i.e., 50 U per hand). Once treatment safety was established, the following seven patients were assigned to receive the high dose of the toxin (i.e., 100 U per hand). Information from these patients was used to determine the necessary sample size. Based on Altman's nomogram,[13] we estimated that controlling the probability of type I error at $\alpha = 0.05$, a sample of 11 subjects in each group would provide 75% power to detect a 20% difference between the treatment groups in the sweating area of the palmar side of the hand. Thus, 12 additional patients were subsequently recruited into the

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study and, following the initial evaluation, assigned to either the low or the high dose group by a computer running a random number generating algorithm.

The study included 24 patients (13 male, 11 female) with severe palmar hyperhidrosis (age 30 ± 7 years, mean ± SD). The selection criteria consisted of a history of excessive sweating of the hands for more than 3 years, confirmed by clinical observation and an iodine-starch test.[14] Exclusion criteria included secondary hyperhidrosis (e.g., hyperthyroidism), neuromuscular disease, and satisfactory therapeutic response to oral anticholinergics or beta-blockers. Patients taking medications that could affect autonomic function were also excluded from the study. The Mount Sinai School of Medicine Institutional Review Board approved the project, and all patients signed an informed consent.

The study lasted 6 months from the day of botulinum toxin injections. The sponsor of the study, Allergan, supplied botulinum toxin but did not design the study, collect, analyze, or interpret the data and did not write any part of this report. Patients were evaluated every 2 weeks during the first month, and then every month until the end of the study. Patients received either 50 (low dose) or 100 (high dose) U of botulinum toxin type A (Botox) in each palm, divided equally in 20 injection sites following a predefined grid drawn in the hand. Patients were blinded to the dose received. Botulinum toxin was diluted in 0.9% saline solution to achieve a concentration of 2.5 U per 0.15 mL in the low dose (50 U) group and 5 U per 0.15 mL in the high dose (100 U) group. The solutions had similar appearance. After applying ice cold packs for 15 minutes or spraying liquid ethyl chloride (Gebauer Company, Cleveland, OH) for 10 seconds to "numb" the palmar surface of the hands to decrease pain during injection, 0.15 mL of Botox was injected intradermally in 20 sites in each palm approximately 2 cm apart, using a 28-G insulin syringe, in a single treatment session. Dilution preparations and injections were performed by D.S. and H.K., who were aware of the patients' group assignment but did not participate in data collection or statistical analysis. A.V., who conducted image and statistical analyses, and the technicians who took the pictures and evaluated strength and treatment satisfaction were blinded to the dose received by each patient.

Sweating assessment. To assess baseline sweating and the effect of botulinum toxin injections, an iodine starch test was performed and the sympathetic skin responses (SSR) were recorded prior to and on each scheduled visit following botulinum toxin injections. The iodine-starch test[14] was performed by dusting the entire surface of the palmar side of the hands, including fingers, with iodinated starch powder, which, in contact with sweat, turned dark purple. A digital photograph (Epson [Long Beach, CA] digital camera PhotoPC 750Z, 1600 × 1200 pixels resolution) of both hands taken 5 minutes after application of the powder was used to determine the size of the area that turned purple (i.e., sweating area), which was expressed as the percentage of the total surface of the hands. Image analysis was performed using SigmaScan Pro software (SPSS, Inc., Chicago, IL).

SSR was recorded bilaterally with standard EMG apparatus (TECA Synergy, Oxford Instruments, Pleasantville, NY), using surface EMG disc electrodes applied to the palmar and dorsal surfaces of the hand, as active and reference electrodes, respectively.[15] Electric stimuli (square wave pulses) of 12.5–50 mA intensity and 0.2 msec duration were applied 5 to 10 times to the median nerve at the wrist, at irregular intervals to avoid adaptation of the response. The amplitude of the response was measured as the absolute value from baseline to the largest peak.

To assess patient satisfaction with treatment, on each visit, participants were asked to compare their current sweating with sweating before the botulinum toxin injections. On the first two visits (2 and 4 weeks after the procedure), a three-point scale was used: 1—no improvement, 2—some improvement, 3—excellent improvement, with improvement defined as reduction in sweating. On all successive visits, another three-point scale was used: 1—no sweating, 2—some sweating, 3—sweating as much as before treatment.

Evaluation of muscle strength. Handgrip and thumb-index pinch strength were evaluated with a hydraulic dynamometer (Sammons Preston, Inc., Bolingbrook, IL). Subjects were asked to apply maximal force for 15 seconds in three successive attempts, and the average value was recorded. Patients were also questioned about presence and duration of muscle weakness experienced after the injection.

Statistical analysis. The analysis compared the extent of the anhidrotic effect and the length of time the effect persisted according to the dose of botulinum toxin received. The primary variables were the area of the palmar side of the hand sweating, the change in SSR amplitude, the patients' satisfaction with the anhidrotic effect, and the muscle strength. Of the 24 patients initially enrolled, four were unable to return and did not complete the study. These patients moved out of New York and, despite being offered reimbursement of travel expenses, were unable to return for follow-up. Of these four, one person was lost to follow-up at 30 days, two at 90 days, and one at 150 days after the injections. Using intention-to-treat analysis, these patients were considered nonresponders; thus, for each of the missed follow-up observations through the rest of the study we recorded their results at their respective baseline levels (i.e., before treatment). However, when applied to measurements of muscle strength, reverting data to baseline greatly biased the results in the direction of more transient muscle weakness. To address this concern while still complying with the intention-to-treat method, we analyzed muscle strength data using a carry-over principle; i.e., assigning to the missing visits the values recorded on the last available visit. This method, of course, biased the results in the direction of a more persistent muscle weakness.

Sweating palm area and muscle strength data were averaged for both hands in each patient. Independent-measures t-tests and χ^2 tests were used to compare baseline demographic data of the two dose groups. χ^2 tests were also used to evaluate patients' subjective ratings of treatment effectiveness and side effects. The area of the palmar side of the hand sweating, expressed as percentage of the total palmar area of the hand, measurements of grip and thumb-index pinch strength, and the SSR amplitudes were evaluated by two-way analyses of variance (dose × time), with repeated measures on the time factor, followed, when significant, by multiple comparison tests with Bonferroni correction. The relationship between the SSR am-

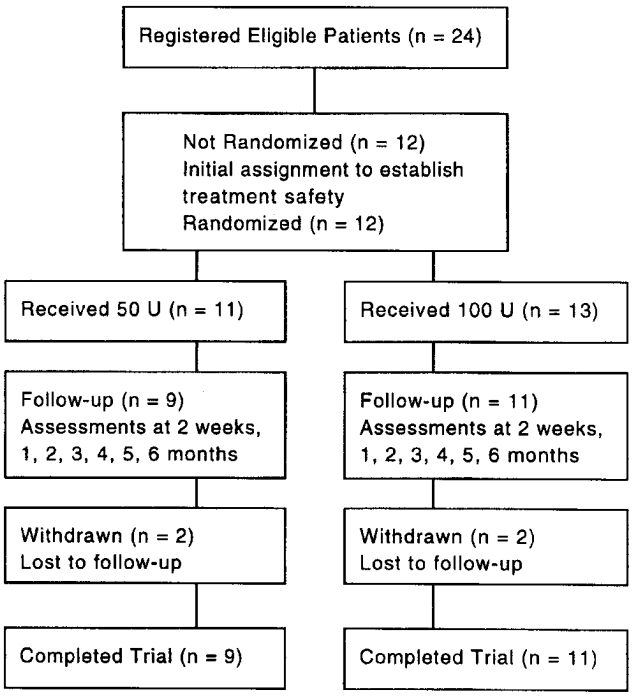

Figure 1. Flow diagram shows number of patients enrolled in the trial, the number in each group, duration and schedule of follow-up, and the number that completed the study.

plitude and the palmar area sweating was examined using Pearson linear correlation. Test results with probability values < 0.05 were considered significant.

Results. Nine patients who received 50 U (low dose) and 11 who received 100 U (high dose) of botulinum toxin in each hand completed the study (figure 1). Both groups were of similar age (30 ± 7 and 29 ± 7 years, for the 50 and 100 U doses) and sex distribution (5:6 and 8:5 M:F). At baseline, the size of the area of excessive sweating in the hands was similar in patients receiving 50 and 100 U of botulinum toxin (76 ± 19% in the 50 U group and 59 ± 34% in the 100 U group). Within 1 month after botulinum toxin injection, the size of the area of excessive sweating decreased dramatically in both groups: to 22 ± 29% in the 50 U patients and to 11 ± 14% in the 100 U patients (figure 2). Most of the surface still sweating corresponded to the fingertips, which were not injected. Some degree of sweating reappeared at variable times, but the anhidrotic effect was still significant 6 months after injections in the 50 U (low dose) group and 5 months after injections in the 100 U (high dose) group. Analysis of variance revealed a significant time effect ($p < 0.00001$), but no dose effect ($p = 0.14$) of injections on the sweating area.

At baseline, SSR was present in all patients. In both dose groups, the SSR amplitude had reached its lowest levels 4 weeks after botulinum toxin injections, decreasing from 3224 ± 1543 μV to 768 ± 874 μV ($p < 0.001$) in the 50 U patients and from 1764 ± 1265 μV to 436 ± 450 μV ($p < 0.01$) in the 100 U patients. From that time on, SSR amplitude in both dose groups was significantly lower than baseline levels. There was a correlation between SSR amplitude and the size of the area of sweating in the 50 U

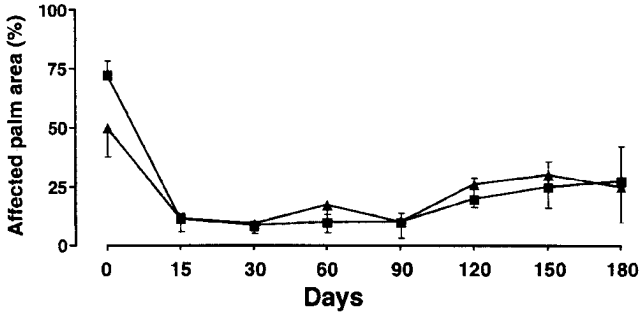

Figure 2. Percentage of palmar area sweating excessively as determined by iodine-starch test, before (baseline) and after injections of 50 (■) and 100 U (▲) of botulinum toxin. Values are averaged for both hands. All post-injection values were significantly lower than baseline in both dose groups; n = 11 and 13, for the 50 and 100 U group, respectively. Data = mean ± SE.

(low dose) group ($r = 0.92$, $p < 0.01$) and in the 100 U (high dose) group ($r = 0.73$, $p < 0.05$) (figure 3).

Ten of 13 patients (77%) who had received 100 U and 5 of 11 patients (45%) receiving 50 U of botulinum toxin reported hand and finger weakness (50 versus 100 U, ns). In all cases, weakness was rated as mild. It was noticed 1 to 3 days after injections, and subjectively lasted approximately 10 days, except in one subject who reported hand weakness lasting 22 days.

Objective assessment of grip strength showed no significant weakness in patients of either dose group (figure 4A). In contrast, thumb-index pinch strength decreased noticeably within 2 weeks after injections: by 23 ± 27% in patients receiving 50 U ($p < 0.05$), and by 40 ± 21% in patients receiving 100 U ($p < 0.0001$) (figure 4B). Thereafter, there was a steady improvement in pinch strength in both groups. However, at the end of the 6-month follow-up period, when compared to baseline, a small yet significant weakness was still demonstrated by the dynamometer in both groups, although the patients were not aware of it. The persistence of muscle strength slightly below baseline may be explained by the intention-to-treat analysis, as the four drop-out subjects were analyzed as if their muscle weakness had persisted unabated following their early

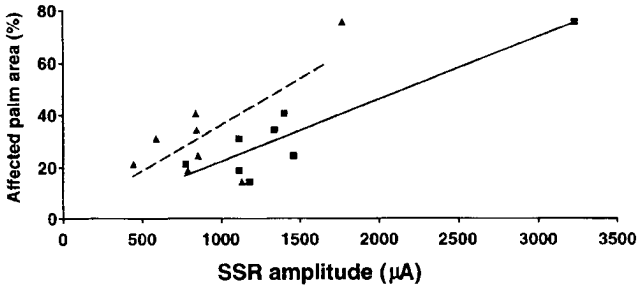

Figure 3. Relationship between the amplitude of sympathetic skin response (SSR) and the percentage of palmar area sweating in patients injected with 50 (■) and 100 U (▲) of botulinum toxin. Points represent group means at each follow-up visit. Trend lines represent linear regression in the 50 U (solid line, r = 0.92, p < 0.01) and 100 U group (dashed line, r = 0.73, p < 0.05).

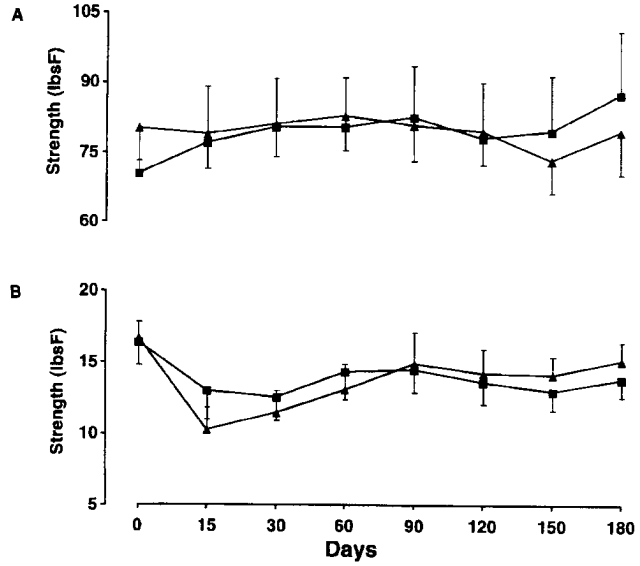

Figure 4. Strength of handgrip (A) and pinch between the thumb and index fingers (B) before (baseline) and after injections of 50 (■) and 100 U (▲) of botulinum toxin. Values are averaged for both hands, n = 11 and 13, for the 50 and 100 U group, respectively. Data = mean ± SE.

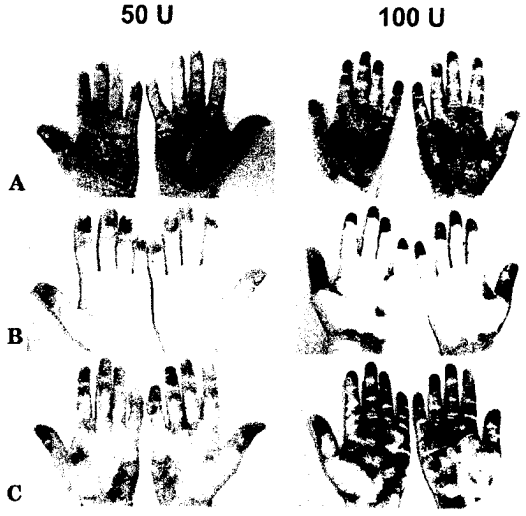

Figure 5. Iodine starch test before (A) and after 2 weeks (B) and 6 months (C) of botulinum toxin type A injections.

withdrawal from the study. Of course, physiologically, this persistent muscle weakness is unlikely to have occurred. Indeed, when we "corrected" muscle strength data of the drop-out subjects based on the response of the 20 patients for whom full data were available and to whom the four "drop-outs" were almost identical in their initial decrease in muscle strength, muscle strength at the end of 6 months was not statistically different from the baseline in either dose group (data not shown).

During 24 weeks of follow-up, no significant adverse events were associated with treatment. Temporary adverse effects were pain during injections and soreness during the first 1 or 2 days after the procedure in all patients. One month after injections, 7 of 11 patients (64%) who had received 50 U (low dose) per hand and 12 of 13 patients (92%) who had received 100 U (high dose) per hand of botulinum toxin reported excellent improvement of symptoms (50 versus 100 U, ns). After 6 months, 3 of 11 patients (27%) in the 50 U and 5 of 13 patients (38%) in the 100 U groups were still sweating less than before treatment (50 versus 100 U, ns).

Discussion. Our study confirms the effectiveness of local intradermal injections of botulinum toxin to decrease palmar sweating in patients with primary hyperhidrosis. This was ascertained by image analysis of the iodine starch test, by the reduction in amplitude or disappearance of the SSR, a neurophysiological marker of sweat production, and by the patient's evaluation of sweating, most of whom rated the anhidrotic effectiveness of treatment as excellent.

Dosages of botulinum toxin type A used for the treatment of palmar hyperhidrosis have ranged from 30 to 100 U per hand.[6,9-11] In our study, total dosages of 50 or 100 U of botulinum toxin per hand divided in 20 injection sites (i.e., 2.5 or 5 U per site) were similarly effective in reducing sweating. There was, however, a trend toward higher patient satisfaction in the 100 U dose group. Both 2.5 and 5 U of botulinum toxin injected intradermally produced a similar circular area of anhidrosis of approximately 1.7 to 2 cm in diameter (figure 5), suggesting that the toxin had limited local spread, binding to sympathetic sudomotor nerve terminals only within a small area close to the injection site. In some cases, sweating persisted in thin strips of skin borderline between injection sites. Therefore, although we injected 20 sites in all subjects, adjusting the number of injections according to hand size may be more appropriate. As seen in figure 5, we did not inject the fingertips.

In addition to anhidrosis, 77% of patients who had received 100 U and 45% of those receiving 50 U of botulinum toxin reported hand weakness. Objective strength measurements with a dynamometer showed no effect on handgrip strength but a weakened pinch between the thumb and index fingers. We postulate that these findings indicate that spread of botulinum toxin around the injection sites impaired neuromuscular transmission in the intrinsic muscles of the hand, necessary to pinch the thumb and index finger (e.g., superficial muscles, such as opponens pollicis and flexor pollicis brevis) but did not affect proximal forearm muscles used for handgrip movements (e.g., flexor pollicis longus and flexor digitorum profundus). All patients rated the weakness as mild, noticed it 1 to 3 days after injections, and felt it, generally, for around 10 days.

Similar to previous reports,[7-11] some degree of palmar anhidrosis lasted in most patients 6 months following botulinum toxin injection. In the neuromuscular junction, recovery of function following botulinum toxin injections occurs by resprouting of the axons and formation of new acetylcholine receptors in about 3 months.[16-18] It is likely that sudomotor recovery also occurs by resprouting of sympathetic axons

and formation of new acetylcholine receptors in the sweat gland surface.

Our study shows that a 2.5 U dose of botulinum toxin injected intradermally drastically reduced sweating in patients with hyperhidrosis. Thus, we recommend using low dosages of botulinum toxin per injection site, and determining the number of sites to inject according to hand size. It is likely that low dosages may also reduce side effects because there was a trend toward milder finger weakness in patients receiving the low dose (50 U per hand) of botulinum toxin. Both groups—i.e., 50 and 100 U per hand—had similar reduction in sweating 6 months after treatment, as determined by iodine-starch test, SSR, and subjective evaluation, further supporting the use of low dosages of botulinum toxin. The main drawback of botulinum toxin treatment was pain during the injection, which can be avoided by local median and ulnar nerve blockade.[19]

Finally, the effectiveness of botulinum toxin in halting sweating in patients with primary hyperhidrosis confirms the neurogenic origin of the disorder. Sympathetic cholinergic nerves activate both thermoregulatory and emotional sweating but these stimuli produce sweating in different distribution in the body and are controlled by different neurons in the CNS. Primary hyperhidrosis may be due to abnormal central control of emotional sweating because it affects the same body areas (hands and feet, as well as axillae) as emotional sweating.

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