

Side-controlled intradermal injection of botulinum toxin A in recalcitrant axillary hyperhidrosis

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Background: Although topical application of aluminium chloride is the most common measure against axillary sweating, severely affected patients often undergo surgical procedures that are expensive and may have considerable side effects. Recently botulinum toxin A (BT-A) has been reported as a potentially effective antihyperhidrotic agent.

Objective: Our purpose was to determine the therapeutic strength, safety, and mode of application of BT-A in severe axillary hyperhidrosis.

Methods: Intradermal injection of BT-A (Dysport) was given in an open left-versus-right side trial with each patient being his own control for initial efficacy, followed by treatment of the contralateral side.

Results: Seven days after initial treatment sweat production fell to below 10% of the untreated contralateral axilla as determined by gravimetry. Satisfaction was rated unanimously as "very good," the highest of 5 rankings. No side effects such as skin irritation or muscle weakness were noted in any patient.

Conclusion: Intradermal injection of BT-A is a potent and well-accepted therapeutic option in patients with recalcitrant axillary hyperhidrosis. (*J Am Acad Dermatol* 1999;41:987-90.)

Hyperhidrosis is characterized by excessive and uncontrollable sweating induced by sympathetic hyperactivity.^{1,2} It occurs typically in young adults affecting primarily the palmo-plantar and/or axillary areas where eccrine sweat glands are most dense.³ Although the line between normal and hyperhidrotic persons may be debatable at times, axillary hyperhidrosis may reduce the quality of life in severely affected patients who typically suffer from soaked clothes and embarrassing sweat stains despite frequent washing and changing of garments.

Treatment of axillary hyperhidrosis requires choosing between multiple therapeutic options considering feasibility, prospective success, and possible side effects for each individual patient. The majority

of cases may be sufficiently controlled by applying 10% to 30% aluminum chloride preparations topically to the affected areas.^{4,5} The higher the salt concentration, the higher its efficacy but also its potential for skin irritation, which is the major limiting factor. Alternatively, anticholinergic drugs may be prescribed,³ but they may cause nausea, dizziness, drowsiness, and visual problems among other unwelcome side effects.

Consequently, patients inadequately controlled by conservative approaches are offered surgical procedures including removal of axillary sweat glands by liposuction^{6,7} or excision.¹ Persistence of sweating may occur if the hyperhidrotic area exceeds the excised area compatible with primary wound closure. Eventually sympathectomy of the involved ganglia may be advocated.^{8,9} This procedure, however, bears the risk of pneumothorax and Horner's syndrome. In addition, compensatory sweating in other areas occurs in 65% to 90% of patients and is the most frequent cause of postoperative dissatisfaction.¹⁰

Because sympathetic activity in sweat glands is transmitted only by acetylcholine, whereas all other sympathetic responses are transmitted by epinephrine or norepinephrine, it can be blocked selectively by botulinum toxin A (BT-A), a potent inhibitor of

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Supported by a grant from an investigator-initiated study from the Departments of Dermatology and Neurology.

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Fig 1. Intradermal injections of botulinum toxin A. **A**, Delineation of the hypersecretory area within the axilla by the iodine-starch test. Note that only the central part of the axilla displays hyperhidrotic activity. **B**, Prospective injection points were marked, assuring an even distribution within the hyperhidrotic area. Botulinum toxin A is injected strictly intradermally using a 30-gauge needle to infiltrate the drug around each spot.

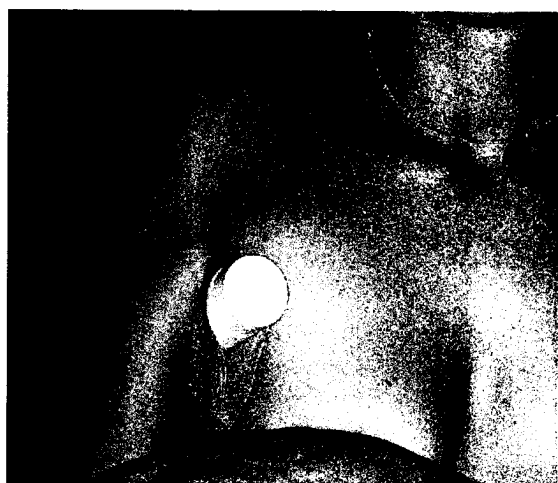


Fig 2. Performance of gravimetry using standardized layers of filter paper, which is held in the axilla with direct skin contact for exactly 1 minute.

synaptic acetylcholine release.¹¹ First clinical evidence came from the observation that anhidrosis could be induced in neurologic patients treated with BT-A as well as in normal volunteers.¹² Subsequently, suppression of hyperhidrosis was reported in individual cases of Frey's syndrome,¹³ axillary hyperhidrosis,^{14,15} palmoplantar hyperhidrosis,¹⁶⁻¹⁸ and compensatory sweating after sympathectomy.¹⁹ BT-A has been widely used by neurologists to treat spastic disorders and by dermatologists to diminish mimic wrinkling.²⁰ We report a series of 12 patients treated for severe axillary hyperhidrosis in an open clinical trial to investigate success rate, likelihood of unwanted side effects, and feasibility of using BT-A.

PATIENTS AND METHODS

Patients

Written informed consent was obtained from all patients. Only patients suffering from severe hyperhidrosis defined as sweat secretion above 100 mg per axilla per minute as assessed by gravimetry were entered into the trial. Sex, age, and duration of symptoms are detailed in Table I.

Gravimetry

Quantitative gravimetry of sweat secretion was conducted with standardized filter paper (Melitta GmbH, Minden, Germany), which was weighed on a high-precision laboratory scale (Sartorius, Hamburg, Germany, precision + 0.5 mg). The paper was then inserted in the armpit for exactly 1 minute and weighed again, yielding the rate of sweat secretion in milligrams per minute. Sweat secretion was also documented by the iodine-starch method and by photography of sweat stains, which typically exceeded 15 cm in diameter.

Application of BT-A

Immediately before injection one vial of lyophilized BT-A (Dysport) was dissolved in 2 mL of sterile saline, yielding a final concentration of 250 U/mL. The hyperhidrotic area in each axilla was identified by the iodine-starch test and outlined with a waterproof skin marker (Fig 1). Within this area 8 to 10 injection points were marked in an evenly distributed fashion no more than 2.5 cm apart from each other. The axilla was then cleansed and disinfected, followed by strictly intradermal injections without placing the needle tip within ink marks (Fig 1). Each injection site received at least 0.1 mL, causing a slightly visible wheal. The total dose per axilla was consistently 250 U Dysport. Initially only one axilla was treated in each patient to allow for direct left-versus-right comparison. Gravimetry was repeated at days 3, 7, and 14, after which the contralateral side was treated in the same fashion. Further follow-up by gravimetry was carried out quarterly thereafter.

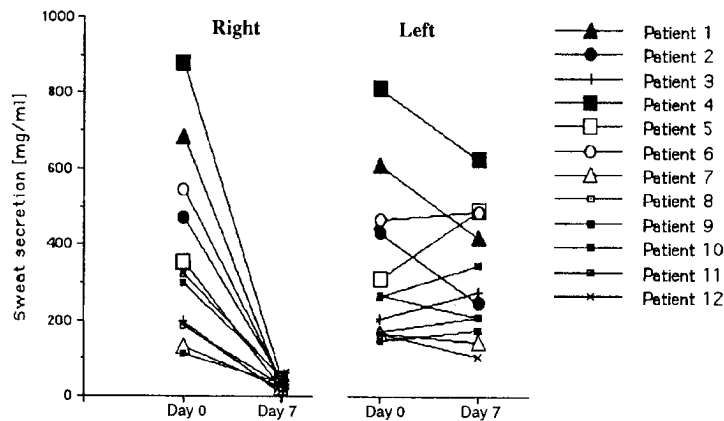


Fig 3. Results of gravimetric measurements of sweat secretion before and 7 days after unilateral BT-A treatment as described under "Methods."

RESULTS

All patients reported a substantial reduction of axillary sweating within 48 to 72 hours after BT-A injections, which was readily noticeable by the lack of sweat stains on the treated side. This was confirmed by the iodine-starch test revealing sweat secretion only on the contralateral side but no longer on the treated side. This test, however, can only delineate the area of sweat secretion but not assess the actual sweat rate. Therefore quantification was carried out by gravimetry (Fig 2). Sweat rates ranged from 150 to 890 mg/min, revealing considerable interindividual variations before treatment. Seven days after treatment, however, sweat rates had dropped to below 50 mg/min consistently in each patient. At the same time measurements on the contralateral side displayed the natural range of sweat rates variations (Fig 3). After evaluation of treatment at day 14, each patient wanted subsequent treatment of the contralateral side, which responded in the same fashion as assessed by gravimetry (Fig 3).

Of 4 ratings ("completely satisfied," "almost completely satisfied," "partly satisfied," "not satisfied"), 10 patients chose "completely satisfied," whereas patients 7 and 9 chose "almost completely satisfied."

None of the patients noticed muscular weakness or any other neurologic deficit. Four patients felt a temporary stinging during the first day after treatment, however, which subsided without further intervention. Other side effects such as nausea, dizziness, or skin irritation, which were explicitly requested during follow-ups, did not occur.

The longest symptom-free interval recorded up to the present was 12 months (patients 2, 3, 5-9) and 9 months (patients 10-12). The two patients with the highest initial sweat rates (patients 1 and 4) reported

Table I. Patients

Patient No.	Age (y)	Sex	Duration of symptoms (y)
1	34	M	8
2	21	M	2
3	23	F	9
4	31	F	17
5	39	F	22
6	42	M	16
7	33	M	12
8	27	F	10
9	21	F	7
10	22	M	9
11	27	F	15
12	38	F	24

recurrence of sweating between 3 and 6 months after BT-A injection. Their sweat rates did not exceed 200 mg/min as compared with more than 600 mg/min before treatment. Both patients chose a second injection of BT-A and were then free of symptoms during 6 months' follow-up.

DISCUSSION

Prompt relief from sweat staining and the lack of any visible hyperhidrotic residuals strongly underscore the efficacy of BT-A as an antihyperhidrotic agent. This effect could be objectively quantified by gravimetry comparing not only *before* and *after* treatment, but also left-versus-right sides, which appears to be more appropriate to eliminate the impact of body and ambient temperature as well as physical and psychologic conditions that may affect sweating variably at different time points (Fig 1).

Because the extent of sweat reduction (up to 10-fold) was far beyond the range that could be expected of a placebo effect, a blinded study of BT-A at this point was not deemed necessary. Moreover, no evidence for a placebo effect of BT-A was found in a recent double-blind study investigating BT-A in palmo-plantar hyperhidrosis by Schnider et al.²¹ Although we agree with the conclusion of their study about the antihyperhidrotic potential of BT-A, we find its benefits even more convincing in patients with axillary compared with *palmoplantar* hyperhidrosis for the following reasons: axillary injections can be easier applied (softer skin) and are less painful.^{15,22} Even more important, muscular side effects such as disturbance of digital fine movement after palmar injection did not occur (and are extremely improbable) in the shoulder girdle after axillary injections. This allowed us to use a rather large dose and produce lasting sympathetic blockage. It is noteworthy that the two major commercially available preparations of BT-A, Dysport (Speywood, Wrexham, UK) and Botox (Allergan, Irvine, Calif) are not identical regarding their activity in units^{23,24} and therefore should not be interchanged without adjusting dosage appropriately. About 3 to 5 units of Dysport are equivalent to 1 unit of Botox.^{23,24} Although smaller doses were reported to be effective in milder cases in which sweating did not exceed 200 mg/min,^{14,25} the rationale for the dosage in our series was (1) higher sweat rates in our patients compared with other reports, (2) absence of potential muscular side effects, and (3) full usage of one vial per patient because freezing and storing after initial dissolving of BT-A is not recommended by the suppliers (applicable for both, Botox and Dysport).

In conclusion, we found intradermal injections of BT-A a fast, safe, effective, and well-accepted approach to cope with severe hyperhidrosis, which may prove a valid alternative to surgical intervention. Presently a multicenter trial is being conducted to provide further information on how to optimally use this therapeutic tool.

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