Current and Emerging Therapeutic Modalities for Hyperhidrosis, Part 2: Moderately Invasive and Invasive Procedures

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Hyperhidrosis (HH) hinders patient quality of life and causes the secondary effect of excess cutaneous sweat. Treatment modalities include conservative and noninvasive therapies such as topical agents and iontophoresis. This article reviews moderately invasive and invasive procedures, such as botulinum toxin, curettage, and endoscopic thoracic sympathectomy (ETS), and compares their advantages and disadvantages in safety and efficacy.

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This article is the second article in a 2-part series providing a comprehensive review of hyperhidrosis. In this article, we will analyze moderately invasive and invasive treatments for hyperhidrosis, including botulinum toxin injections, surgical subcutaneous curettage, sympathectomy, and sympathicolysis.

MODERATELY INVASIVE PROCEDURES

Botulinum Toxins

Botulinum toxin (BTX) is produced from the spore-forming bacillus *Clostridium botulinum* and acts as an irreversible inhibitor to the presynaptic release of the neurotransmitter acetylcholine.[1] Because eccrine glands are innervated by cholinergic sympathetic fibers, they are effective targets for BTX. The pathophysiology of hyperhidrosis (HH) suggests that hypersecretion mostly is the result of overstimulated eccrine glands rather than hypertrophic or hyperplastic glands[2]; therefore, a neuromediated approach to reducing the stimulation of sweat glands is an ideal method to directly treat HH.

The use of BTX for the treatment of HH began in the early 1990s and it is being used with increasing frequency in Europe and Canada.[3,4] Several major clinical studies in the past decade have safely and effectively used 50 to 250 U of BTX type A (BTX-A), the most potent of BTX serotypes,[5] to treat the palms, soles, axillae, forehead, and labia, as well as to treat gustatory HH (Frey syndrome)[6] (Table). Although the side effects and pathology of BTX are clearly established,[29] a thorough review of the literature suggests that a cautious and well-informed physician can safely and effectively administer this agent as therapy for HH.

BTX Type A—BTX-A is the most potent agent of the BTX serotypes.[5] BTX-A successfully has been used to treat facial spastic conditions such as blepharospasm, strabismus, focal dystonia, spasmodic dysphonia, and achalasia.[1,30] Yamauchi and Lowe[30] demonstrated that 1 U of Botox® was approximately equivalent in potency to 4 U of Dysport® (not available in the United States) for the treatment of hyperfunctional upper facial expression lines.

BTX Type B—BTX type B (BTX-B) is another potent neurotoxin that has been used to treat spastic conditions. It is approved by the US Food and

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Summary of Botulinum Toxin Therapy for Hyperhidrosis*

Source	N	Location	Type	Dose	Results†	Adverse Effects	Notes
Naumann et al[7]	174	Axilla	BTX-A‡	50 U	Excellent	Minimal (pain, burn)	Decreased HH >50% after 4 wk in 83%−96% of subjects
Heckmann et al[8]	145	Axilla	BTX-A‡	200 U	Excellent	Minimal (irritation, burn, headache, muscle soreness)	Subjects previously unresponsive to $AlCl_3$
Wollina et al[9]	47	Axilla	BTX-A‡	200 U	Excellent	Moderate (burn, pain)	Anhidrosis >19 mo; high dose had longer effect
Kreyden et al[10]	1	LUH forearm	BTX-A‡	NA	Excellent	Minimal	Recommended as first-line treatment of LUH
Naumann and Lowe[11]	307	Axilla	BTX-A‡	50 U/axilla	Excellent	Minimal	Decreased HH >50% after 4 wk in 94% of subjects
Maillard et al[12]	10	Axilla, palm	BTX-A§	100−250 U	Excellent	Pain, headache	2−9 mo
Lowe et al[13]	12	Axilla	BTX-A‡	50 U	Excellent	Minimal	Average remission lasted 7 mo
Dressler et al[14]	19	Axilla	BTX-A‡ and BTX-B	100 MU of BTX-A; 2000 and 4000 MU of BTX-B	Excellent	Dry mouth	BTX-A lasted longer; 20:1 conversion factor between BTX-B and BTX-A for axillary HH
Sevim et al[15]	32	Palm, sole	BTX-A‡	45−65 U	Good	Thenar atrophy	None
Dressler and Benecke[16]	6	Axilla	BTX-B	4−10,000 U	Very bad	Decreased accommodation (ocular)	Systemic spread BTX-A vs BTX-B; BTX-B more diffusible
Wollina and Karamfilov[17]	10	Anal fissure/fold	BTX-A‡	30−50 U	Good	None	Effective combined therapy for spasticity and HH
Naumann et al[18]	320	Axilla	BTX-A‡	50 U	Excellent	Minimal (burn, pain)	QOL, HHIQ surveys reflected positive changes

Source	N	Location	Type	Dose	Results†	Adverse Effects	Notes
Lowe et al[19]	19	Palm	BTX-A‡	50 U/palm	Excellent	Minimal	None
Odderson[20]	18	Axilla	BTX-A‡	50 U/axilla	Excellent	Minimal	Still effective at 5 mo
Wollina and Karamfilov[17]	10	Palm (recalcitrant)	BTX-A‡	200 U/hand	Excellent	Injection burn/pain	None
Swartling et al[21]	37	Palm	BTX-A	NA	Good	None	Authors discourage doses >8 U/cm^2
Filosto et al[22]	1	Axilla (severe)	BTX-A§	200 U/axilla	Excellent	None	None
Glogau[23]	NA	Palm	BTX-A; BTX-B	NA	Good	None	Alternative to more invasive surgical procedures
De Almeida et al[24]	NA	Palm	BTX-A	NA	Good	None	None
Boger et al[25]	12	Cranium and face	BTX-A§	2.5–4.0 ng	Excellent	Frown weakness	Most subjects were anhidrotic for 29 mo
Braune et al[26]	10	Focal frontal HH	BTX-A‡	86 MU	Good	Frown weakness	No accommodation problems
Saadia et al[27]	24	Palm	BTX-A‡	50 or 100 U	Excellent	Hand muscle weakness	20 sites on each palm
Vadoud-Seyedi et al[28]	23	Palm (recalcitrant)	BTX-A	NA	Good	None	Nerve block was effective

*BTX-A indicates botulinum toxin type A; HH, hyperhidrosis; $AlCl_3$, aluminum chloride; LUH, local unilateral hyperhidrosis; NA, not available; BTX-B, botulinum toxin type B; MU, mouse units; QOL, quality of life; HHIQ, Hyperhidrosis Health Impact Questionnaire.

†Excellent=most subjects extremely satisfied with results; good=most subjects satisfied with results; very bad=most subjects unsatisfied.

‡Botox®.

§Dysport®.

Drug Administration for the treatment of patients with cervical dystonia.[30]

BTX-A and Axillary HH—Numerous clinical studies have compared the treatment of axillary HH with BTX-A versus placebo. Naumann et al[7] conducted a multicenter, randomized, controlled trial of 207 subjects with HH (174 subjects completed the study) given a single treatment of BTX-A 50 U in each axilla. A comparison of a set of parameters evaluating quality of life (ie, confidence, general happiness, embarrassment, sexual behavior, changes in leisure activities or attendance at social events) was conducted intermittently from pretreatment until 16 weeks posttreatment. Results indicated that improvements were reported by subjects in the experimental versus the control group in all parameters considering quality of life. Of note, these subjects reported a substantially improved outlook including overall satisfaction and ability to perform work activities. Subjects with a sweat reduction of at least 50% from documented baseline levels, termed *responders*, comprised more than 90% of the experimental treatment arm. These subjects responded to therapy within the first 4 weeks of treatment, and the response persisted at 16 weeks for at least 80% of subjects compared with the placebo treatment group (36% at 4 weeks; 21% at 16 weeks). Adverse effects were considered minor and included temporary pain and a mild burning sensation.[7]

In another study, conducted by Heckmann et al,[8] subjects with axillary HH showed similar results when treated with BTX-A. In this study, 145 subjects with baseline sweating rates greater than 50 mg/min who were unresponsive to aluminum chloride ($AlCl_3$) treatment were given BTX-A 200 U in one axilla versus placebo in the other axilla. After 2 weeks, BTX-A 100 U was injected into the axilla previously treated with placebo. Changes in the rates of sweat production were calculated. The sweating rate of the axilla treated with BTX-A 200 U substantially decreased from 192 mg/min to 24 mg/min compared with the control axilla, which showed a slight decrease from 192 mg/min to 144 mg/min ($P<.001$); 6-month follow-up revealed 65 mg/min and 67 mg/min rates in the BTX-A and placebo groups, respectively. Adverse effects were reported to be mild to moderate and included irritation, burning, headache, and muscle soreness.[8]

Wollina et al[9] experimented with high-dose (200 U) BTX-A in 47 subjects in Germany and evaluated the antihidrotic effect compared with the safety index. The study reported a longer period of anhidrosis (up to 29 months in one patient) compared with lower doses of BTX-A. Nearly half of the subjects (22/47) were free from relapse for at least 12 months; of those subjects who did relapse, a second or third injection generally resulted in remission. Compared with previous studies of lower doses of BTX-A, a statistically significant ($P<.05$) higher number of subjects responded with a longer disease-free interval using the high-dose therapy.[9]

BTX and Palmoplantar HH—Double-blinded placebo-controlled studies have been conducted to evaluate the effects of BTX-A compared with placebo. The authors of a study comparison reported that BTX-A doses ranging from 50 to 200 U have been successfully used in Europe.[30] Prior to that study, those same authors conducted a study of 19 subjects with palmar HH treated with BTX-A 50 U/palm.[19] Subject results were reported to be successful by day 28, at which time they showed an approximate 50% decrease from baseline compared with a 12% placebo effect. One objective of that study was to determine if other common adverse effects of injections, such as muscle weakness, could be prevented if attention was paid to BTX-A administration technique. The study found that injections meticulously placed high into the dermis prevented deep penetration of BTX-A, where it affects muscular function, because most subjects did not experience the previously noted side effects. Therefore, complications reported in other studies,[3,12,17] such as grip weakness in the hands and fingers, were avoided using this technique.[19]

Pain on injection may be mitigated by administering a nerve block[24,28] or by cryoanalgesia using dichlorotetrafluoroethane.[12] When administering a nerve block to the soles, the sural and posterior tibial nerves should be targeted to reduce pain; in the palms, the ulnar, radial, and/or medial nerves should be blocked, depending on which region the injections will be given. Although considered safe, nerve blocking does include complications such as nerve damage and/or paresthesia. When the decision has been made to perform a nerve block, the physician should include the adverse events in the patient informed consent process.[31]

A clinical study by Schnider et al[32] reported that an injection of BTX-A 120 mouse units (MU) in each palm showed a 26% decrease in hand sweating that persisted for more than 3 months ($P<.001$) compared with placebo. The adverse effects included weakness of intrinsic hand muscles and finger grip where BTX-A was administered.[32] As with axillary HH, palmar HH may be graded in its dose response to BTX-A injections. Higher doses of BTX-A have been demonstrated to have a longer-lasting effect and a bigger reduction in diaphoresis from baseline levels without resulting in more pronounced or extreme side effects.[27]

BTX-A Versus BTX-B—Dressler et al[14] compared the effect of BTX-A versus BTX-B for the treatment of axillary HH. In this study, 9 subjects received BTX-A 100 MU unilaterally and BTX-B 4000 MU contralaterally; an additional 10 subjects received BTX-A 100 MU unilaterally and BTX-B 2000 MU contralaterally. There was no difference in the duration of improvement between BTX-A and both doses of BTX-B. The average duration of improvement was approximately 16 to 17 weeks for all cohorts. More subjects reported a faster onset of action with both doses of BTX-B compared with BTX-A. Additionally, BTX-B was associated with more discomfort compared with BTX-A. The authors concluded that the autonomic nervous system may be relatively more sensitive to BTX-B compared with BTX-A.[14]

In another study, the diffusion characteristics of BTX-B appeared to show potentially advantageous clinical profiles in the treatment of HH compared with BTX-A.[12] Other studies have shown that although BTX-A and BTX-B appeared to have equal efficacy in the treatment of axillary HH, intradermal injections of BTX-B appeared to be more painful than BTX-A.[14,30] There is a general consensus among these authors that a 20:1 conversion factor between BTX-B and BTX-A seems sufficient to treat axillary HH.[12,14,30]

BTX-A Summary—As a therapeutic option for axillary or palmoplantar HH, BTX-A is a favorable choice for patients unresponsive to topical medications or other conservative measures.[14,30] The adverse effects are minimal and tolerable by most patients, and evidence of circulating neutralizing antibodies has not been noted.[14,30] Furthermore, with proper and attentive injection technique, muscular infiltration may be avoided.

BTX-B Summary—Because clinical data on BTX-B as a treatment for HH are sparse compared with BTX-A, a general statement about its efficacy, dosage, or adverse effects would be premature. Serotype B BTX has been associated with more systemic side effects compared with BTX-A.[33,34] However, BTX-B also has demonstrated similar safety and efficacy.[14,30] Some differences to consider are the mode of therapy and dosage used in each study. Therefore, more studies are needed to yield an accurate understanding of the utility of BTX-B as a candidate for therapy for HH.

INVASIVE PROCEDURES

Local Surgical Curettage

Local surgical procedures or combinations of procedures such as curettage and/or liposuction of axillary adipose tissue have been performed to excise a large number of sweat glands in the axilla. One study compared the personal reports of 113 patients, noting their experiences and results to therapy with local sugery compared with BTX injections.[35] Ninety patients who underwent local surgery recommended local surgery, whereas 23 patients who received injections recommended injections. A major difference between the patients' responses was the duration of sweat reduction. At the end of follow-up, the local curettage treatment group showed a median of 28 months of sweat reduction, whereas the BTX arm of the study reported a mean of nearly 8 months of sweat reduction.[35]

A benefit of curettage as a choice of therapy not only is the long-term reduction of sweating but also the avoidance of the risk of compensatory sweating associated with more invasive surgeries such as endoscopic thoracic sympathectomy (ETS).[36] However, disadvantages of this treatment modality include the complications associated with other cutaneous surgical procedures—namely necrosis, infection, scarring, and restriction of arm movement. Thus, BTX injections are favored because of their combined safety and efficacy.[36]

Endoscopic Thoracic Sympathectomy

ETS is considered to be the most invasive surgical procedure performed to treat HH. This process involves the removal of thoracic sympathetic chains, which are considered to be the upstream nervous system centers responsible for the hyperstimulation to the cholinergic nerve fibers downstream adjacent to the sweat glands. This treatment option is the only absolute and long-term cure for HH because it eliminates the insulting agents from the nervous connection.[37,38]

ETS generally is an outpatient procedure and includes an extensive workup by the surgeon to rule out thyroid, metabolic, cardiorespiratory, and nervous bases for HH.[36] After blood study results and other indices are gathered, patient consent is obtained and, after a couple of hours of surgery under general anesthesia, the procedure is completed and the patient is discharged. The advent of thoracoscopic technology has enabled surgeons to perform this procedure with minimal scarring (two 1-in scars are left deep within each axilla). On identifying the T2 level of the thoracic sympathetic nervous chain, the surgeon cauterizes between the subsequent level (T3) with endoscopic bipolar forceps.[36,38-41]

Possible complications with ETS include infection; compensatory HH, the most common complication of ETS; pneumothorax, which occurs if the pleura is not adequately closed after the incision is made; and/or Horner syndrome (ptosis, anhidrosis, miosis).[36] Because of these potential difficulties, most patients are advised to consider more

conservative treatment options; however, ETS would be suggested for patients with recalcitrant HH.[36]

Percutaneous Thoracic Phenol Sympathicolysis

Percutaneous thoracic phenol sympathicolysis (PTPS) involves the introduction of small volumes (total, 0.8 mL) of phenol (75%–90%) into multiple sites on every side of the T2 to T4 sympathetic trunks and ganglia.[42] This procedure is guided by C-arm fluoroscopy and performed under local anesthesia (sometimes also with intravenous general anesthesia). Wang et al[42] performed a clinical study using PTPS for 50 subjects with palmar HH or axillary bromidrosis. Of the subjects undergoing PTPS, 80% (40/50) noted satisfactory results as measured by the termination of HH. Interestingly, subjects who described their therapy as successful also demonstrated an elevated thumb temperature, from 5.3°C to 5.4°C (an increase of 0.1°C), whereas those who did not respond to therapy showed no change in skin temperature at the site of the thumb. The authors noted that this may be a useful clinical marker for successful PTPS therapy for future patients.[42]

PTPS is not widely used in practice nor cited frequently in the literature. As mentioned with ETS, the complications of surgery should be thoroughly considered and explained to the patient. Nevertheless, PTPS may prove to be a promising treatment modality as more clinical data are obtained.

COMMENT

HH may present in several forms and distributions throughout the body; additionally, it may be idiopathic or secondary to systemic disease. The multiple therapeutic modalities that have been developed and established for this disease adequately reflect the range and severity of the disease. While some patients find topical $AlCl_3$ application and/or antiperspirant to be helpful, others must undergo highly invasive procedures such as curettage or ETS to mitigate or rectify their disease.

BTX-A has the highest patient satisfaction to side effects index that has been reported in most studies published worldwide.[1,4,5,7-9,12,17,19,24,41,43] BTX-A shows a promising duration of action (6–29 months, which is longer than standard conservative measures), and patients incur minimal side effects. Although some patients relapse shortly after their course of treatment, most studies report that a second set of injections often will successfully remit these patients for similar amounts of time as their nonrelapsing counterparts. BTX-A has been approved by the US Food and Drug Administration for HH because the clinical data from double-blind and placebo-controlled studies have indicated it has a high safety and efficacy profile.

Surgical procedures may be suggested for some patients who prefer an aggressive approach to eradicate diaphoresis or substantially reduce it long-term. Modifications in ETS will be developed as successful treatments support such advancement. Local curettage and removal of glands also show promise as less invasive methods compared with ETS because their long-acting results are of interest to many patients. PTPS also may be considered for refractory cases of HH; however, it should not precede less invasive options because there is a lack of clinical data to support this use. Also, some patients do not tolerate the complications and side effects of this surgical treatment. The compensatory HH seen with ETS is a common phenomenon that usually is not seen with BTX injections or local surgical procedures.

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