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Treatment of Hyperhidrosis With Botulinum Toxin

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Abstract

Botulinum toxin type A is a safe and effective method for treating focal hyperhidrosis, providing longer-lasting results than topical treatments without the necessity of invasive surgical procedures. Although more useful for axillary hyperhidrosis, botulinum toxin injections can also be effective in treating palmar and plantar disease. The effects of botulinum toxin last for six to nine months on average, and treatment is associated with a high satisfaction rate among patients. In this article, the authors discuss their preferred methods for treating axillary, palmar, and plantar hyperhidrosis. This article serves as guide for pretreatment evaluation, injection techniques, and posttreatment care.

Keywords

Botox, cosmetic medicine, hyperhidrosis

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Hyperhidrosis is defined as sweating in excess of what is required to regulate body temperature. As many as 1.3 million Americans are diagnosed with severe hyperhidrosis.[1] Affected patients are hampered in occupational and social situations, leading to diminished physical and emotional well-being, difficulty in personal relationships, and social stigmatization.[2-6]

Primary hyperhidrosis can be treated both surgically and nonsurgically. First-line nonsurgical therapies involving topical antiperspirants such as aluminum chloride are often short-acting and require frequent reapplication, are ineffective in reducing sweat production, and are intolerable secondary to irritant dermatitis.[7,8] Surgical procedures include endoscopic transthoracic sympathectomy (ETS), arthroscopic shaving of the glands, and excision of sweat glands. These treatments are invasive, may be associated with serious complications and high recurrence rates, and require operative fees, time to recuperate, and anesthesia.[9-13] Therefore, the ideal treatment would be safer and less invasive than surgery, as well as longer-lasting and more tolerable than topical agents, and it would result in high patient satisfaction rates.

With these criteria in mind, botulinum toxin type A has emerged as an important treatment option for patients plagued with focal hyperhidrosis. The toxin temporarily inhibits the release of acetylcholine, preventing the hyperstimulation of eccrine sweat glands that leads to excessive sweating.[14] Researchers originally proposed that injection of the toxin could be beneficial to patients with hyperhidrosis after noticing its inhibitory effects on sweat production in healthy patients.[15] Several randomized studies have shown that botulinum toxin type A is a safe, effective, and durable method of treating patients with primary hyperhidrosis.[2,3,7,16-22]

Research demonstrates that when patients who have been unresponsive to topical antiperspirants are injected with botulinum toxin, they experience a 75% reduction in sweating,[20] an improvement in emotional and physical

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well-being,[18] and a decrease in activity limitations[22] without any serious adverse events. In our practice, we have witnessed a reduction in symptoms within two weeks of treatment, an asymptomatic period lasting an average of six to nine months, and a high patient satisfaction rate.[23]

PREOPERATIVE EVALUATION

Primary hyperhidrosis is defined as idiopathic, excessive sweating lasting for six months or more and has at least two of the following features: impairment of daily activities, bilateral symmetric sweating, frequency greater than once a week, positive family history, onset before age 25, and cessation of focal sweating while asleep.[6] Focal hyperhidrosis is commonly localized to the axillae, palms, and soles and does not involve a more widespread autonomic dysfunction. Although emotional triggers enhance symptoms, hyperhidrosis is not considered a psychiatric disorder. Hyperhidrosis can also be triggered by heat and spicy food (gustatory hyperhidrosis). The etiology is unclear, but it is believed to result from a nonthermoregulatory sympathetic hyperstimulation of eccrine sweat glands.[24] Family history analyses indicate that hyperhidrosis can be inherited in an autosomal dominant manner.[25]

Clinically, the diagnosis of primary hyperhidrosis is determined by the severity of daily impairment secondary to the sweating disorder. As with all disease, the first step is to obtain the patient's history. Most patients describe having had excessive sweating since childhood or adolescence. Although the majority of patients suffer from idiopathic hyperhidrosis, all patients must be evaluated for possible causes of secondary hyperhidrosis, such as those triggered by malignancy, medication, infection, and endocrine and neurological disorders.[26] Several rare forms of focal hyperhidrosis occur with specific syndromes, including Ross syndrome, Frey syndrome, and localized unilateral hyperhidrosis (LUH).

Several objective and subjective measurements have been developed to assess the degree of patient impairment and severity of excessive sweat production. The objective measurements for focal sweating disorders are gravimetry and the Minor's starch iodine test. In the Minor's test, the skin is cleaned, shaved, and dried. A 3.5% iodine in alcohol solution is applied to the skin of the affected area, and starch flour (purchased at the supermarket) is sprinkled on top. The color changes to a dark violet as sweat contacts the iodine-starch mixture. This indicates a positive sweat test and yields a diagram of the distribution of active eccrine glands.[27] The gold standard of objective measurement is gravimetry, most commonly used to assess axillary hyperhidrosis. Filter paper is weighed before and after exposure to axillary skin for a defined time period (60 seconds or five minutes). The weight difference quantifies the amount of sweat produced over a period of time. Axillary hyperhidrosis is defined as >50 mg/min.[28]

There are two common questionnaires for subjectively assessing quality-of-life impairment from hyperhidrosis. The Dermatology Life Quality Index (DLQI) is a validated measure that consists of 10 questions, each with four possible answers, focused on defining the impact of a skin disease on quality of life.[29] The Hyperhidrosis Disease Severity Scale (HDSS) is another measure designed to evaluate the effects of hyperhidrosis on the patient's life by quantifying the patient's symptoms on a one to four scale.[30]

Table 1. Hyperhidrosis Disease Severity Scale

Score	Patient Response
1	My underarm sweating is never noticeable and never interferes with my daily activities.
2	My underarm sweating is tolerable but sometimes interferes with my daily activities.
3	My underarm sweating is barely tolerable and frequently interferes with my daily activities.
4	My underarm sweating is intolerable and always interferes with my daily activities.

Adapted from the Hyperhidrosis Disease Severity Scale study[30]

Given that effective treatment is a function of the patient's perceived impairment and quality of life, we find that subjective measurements are more valuable and simpler to administer in the office setting. Our preference is the HDSS, a validated four-point scale for assessing the severity of hyperhidrosis, for which patients rate their tolerability of symptoms and its degree of interference with daily life (Table 1). The HDSS was designed for axillary hyperhidrosis, but the gradation scale can be extrapolated for both palmar and plantar symptoms. A higher HDSS score indicates a greater interference with daily activities and increased intolerability.[30]

Patients are often plagued by the psychosocial sequelae of hyperhidrosis, leading to decreased socialization, anxiety, and difficulty in personal and occupational situations.[2-6] As a result, patients self-refer to the plastic surgeon's office or are referred to us by their primary care physicians. In our practice, we have treated patients who are older than age 14 years and have persistent primary (idiopathic) hyperhidrosis. Prior to injecting with botulinum toxin, patients must demonstrate failure of nonsurgical treatment options such as topical antiperspirants for the axillary, plantar, and palmar regions as well as tap water iontophoresis for the palmar and plantar regions. Tap water iontophoresis reversibly disrupts ion channels by passing a direct current through an electrolyte solution in contact with moisturized pedals placed on the skin. This remains an acceptable nonsurgical method for treating palmoplantar hyperhidrosis.[31] Two weeks of treatment with topical agents is usually sufficient to test efficacy. We grade the patient's symptoms based on the HDSS. Treatment is offered to patients who score a three or four on the HDSS scale, indicating that the patient's symptoms are barely tolerable and interfering with daily activities. All patients undergo standard pretreatment counseling regarding the risks, benefits, and alternative treatment options.

CONTRAINDICATIONS

Botulinum toxin injections are not offered to patients who suffer from hyperhidrosis secondary to an underlying disease, who have undergone previous surgical debulking of sweat glands, or who have severe blood-clotting disorders. Patients who have a concurrent infection at the injection site or systemic infection are asked to return to the office after the infection has cleared. We avoid treating patients who have an existing medical condition that may interfere with neuromuscular function, such as myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis. Female patients who are pregnant or breastfeeding are excluded from treatment as well.

TECHNIQUE

Botulinum Toxin Solution

Botulinum toxin type A is a neurotoxin derived from *Clostridium botulinum*, an anaerobic bacterium. Botulinum toxin (BTX) temporarily chemodenervates the eccrine glands involved in hyperhidrosis by binding to the receptor located on the presynaptic membrane, blocking the release of acetylcholine from skeletal and autonomic cholinergic nerve terminals. Of the seven known serotypes of botulinum toxin (A, B, C, D, E, F, and G), only serotypes A, B, E, and F are poisonous to humans. Types A and B are found in terrestrial environments; Type E occurs in marine environments. Each serotype is antigenically-distinct, but all share a common subunit and have similar molecular weights.[32] International studies of serotype A (BTX-A) in the form of Botox (Allergan, Inc., Irvine, California) or Dysport (Ipsen, Brisbane, California)[33] have demonstrated its safety and efficacy for numerous indications. Both products are based on the BTX-A serotype but have different dosing regimens and thus cannot be used interchangeably at the same dose. Currently, onabotulinumtoxinA (BoNT-ONA; Botox) is the only US Food and Drug Administration (FDA)–approved BTX-A formulation for treatment of hyperhidrosis. BTX-B, available as Neurobloc (Elan Pharmaceuticals, Dublin, Ireland), may be useful in patients who do not respond to BTX-A therapy.[34] We administer BoNT-ONA diluted in a sterile saline solution. Typically, 1 mL of saline is mixed for every 25 U of BoNT-ONA (Table 2). Some authors also add lidocaine to the solution to reduce the pain associated with injection.[35] Typically, 50 U of BoNT-ONA is injected for each axilla, 100 U for each palm, and 150 U for each sole. In our practice, we have injected up to 200 U of BoNT-ONA in one treatment session. FDA recommendations state that the cumulative dose should not exceed 360 U in a three-month period.

Axillary Treatment

Some authors administer the Minor's starch iodine test to determine the location of the sweat glands in the axilla, which provides a template for treatment. In our practice, we rarely apply the starch iodine test; instead, we define the hyperhidrotic area of each axilla according to the hair-bearing area, which is delineated with a marking pen (Figure 1) prior to administering a betadine prep (Figure 2).

We inject botulinum toxin in the axillary area with a 26- or 30-gauge needle on a TB syringe (Figure 3). In most patients, 40 evenly-distributed injection sites are placed subdermally in each axilla (20 injections per milliliter of injection solution), with the injection sites approximately 8 mm apart. The needle is inserted at a 45-degree angle, approximately 2 mm

Table 2. Botulinum Toxin Type A Reconstitution

Parameter	Recommendation
Diluent	0.9% saline solution
Concentration	25 U botulinum toxin to 1 mL 0.9% saline solution
Axillary dilution	50 U botulinum toxin in 2 mL saline per axilla (3 mL for larger axillae); 40 injections per milliliter of injection solution
Palmar dilution	100 U botulinum toxin in 3-4 mL saline per palm
Plantar dilution	150-250 U botulinum toxin in 6-8 mL saline per sole

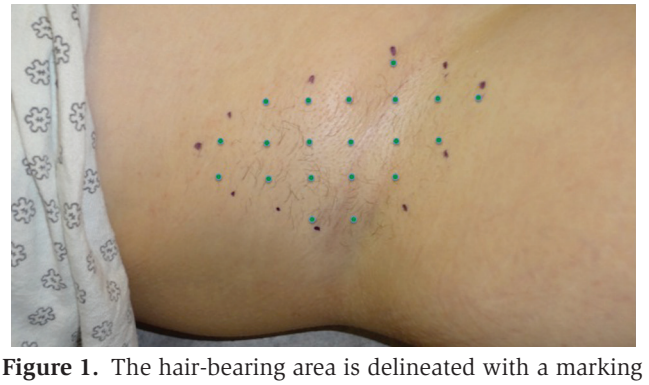

Figure 1. The hair-bearing area is delineated with a marking pen (purple dots at periphery). These markings can be imagined as a grid of injection sites (green dots).

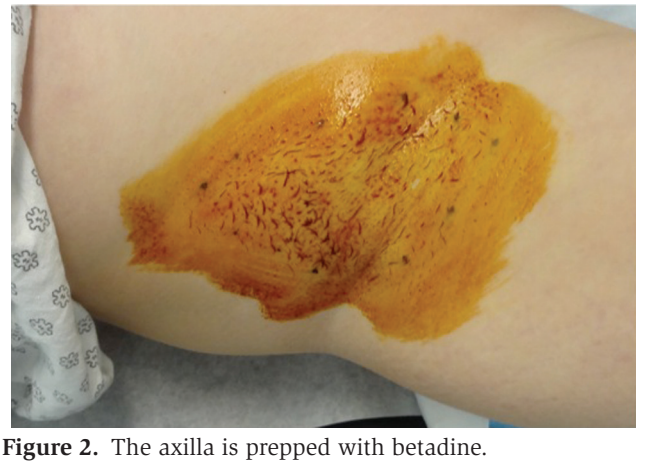

Figure 2. The axilla is prepped with betadine.

Figure 3. A 26- or 30-gauge needle on a TB syringe is used for injections.

into the dermis, bevel side up (Figure 4). Once inserted, the syringe is slowly depressed to deposit approximately 0.05 mL of the solution subdermally, after which it is withdrawn. The injection should be performed in one smooth motion to reduce trauma to the area.

The total injection volume per axilla is 50 U of reconstituted BoNT-A, which was found to be the minimal dose necessary to cause anhidrosis in healthy volunteers.[15] In most patients, these 50 U is diluted in 2 mL of normal saline, but in patients with larger axillae, up to 3 mL is occasionally used to reconstitute 50 U.

Palmar and Plantar Treatment

The pain associated with BoNT-ONA injections for palmar and plantar hyperhidrosis can deter patients from undergoing the procedure. Due to the rich nerve endings in the palms and soles, pain can be significant with the numerous injections needed to achieve the desired effect. In an effort to reduce discomfort from the injection, several anesthetic methods have been reported, including oral and intravenous sedation, Dermojet (AKRA, Pau, France), topical lidocaine cream, nerve blocks, Bier's block, and cryoanalgesia (ice block).[36] Radial and ulnar nerve blocks, when administered properly, are very effective in minimizing pain and are commonly utilized prior to injection. However, not all physicians can reliably perform the procedure, and there is the added risk that the block can temporarily or permanently damage the nerve. Also, many patients dislike the sensation of a temporarily disabled hand. Dermojet is a device that dispenses needle-free anesthesia by utilizing air pressure to inject 2% lidocaine. However, this device requires numerous injections since the injector must stop after treatment of four or five sites to ensure that botulinum toxin is administered only in the limited area pretreated with Dermojet.[37]

Of the numerous methods available to minimize pain while treating palmoplantar hyperhidrosis, we favor the cryoanalgesia due to its convenience, effectiveness, low risk, and minimal cost. Ice packs are placed on the area for 15 minutes prior to injection to cool it. For patients who are more sensitive to pain or are wary of the pain

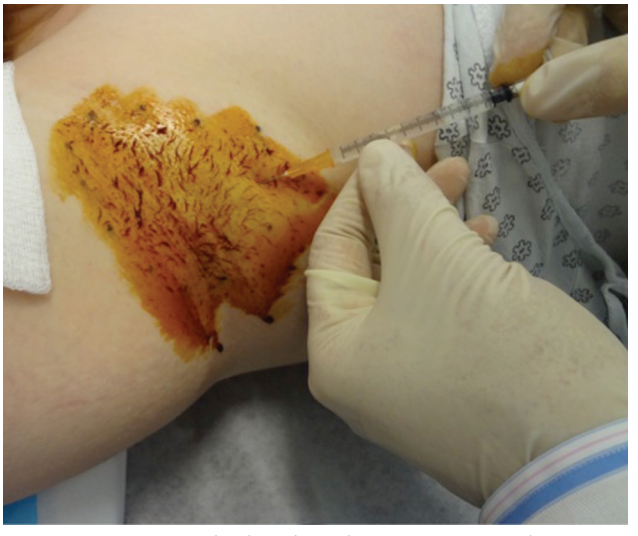

Figure 4. Forty evenly-distributed sites are injected subdermally in each axilla, with injection sites approximately 8 mm apart. During injection, the needle is inserted at a 45-degree angle approximately 2 mm into the dermis, bevel side up. Once inserted, the syringe is slowly depressed to deposit approximately 0.05 mL of the botulinum toxin solution subdermally before it is withdrawn.

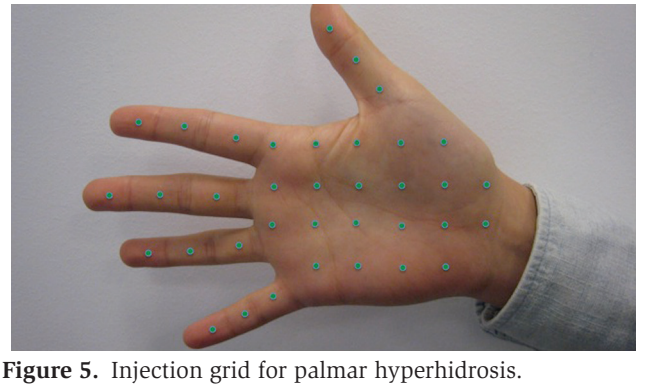

Figure 5. Injection grid for palmar hyperhidrosis.

associated with the injection, topical 2.5% lidocaine cream is applied 30 to 60 minutes prior to the procedure. Some physicians use vibration in conjunction with ice packs to reduce pain sensation. It is believed that the stimulation of vibration receptors inhibits the interneurons that transmit the pain signal.[38] Vibration can be administered with a handheld massager or other similar device.

Similar to our treatment protocol for the axilla, we do not routinely use Minor's iodine test in the palmar region for several reasons, including that patients dislike the iodine dying their hands. We define our injection field as a grid on the palm and sole (Figures 5 and 6). Once the field of injection is defined, a total of 100 U per palm of BoNT-ONA is injected with a 26- or 30- gauge needle and a TB syringe. The BoNT-ONA is diluted in 3 to 4 mL of normal saline and then subdermally injected into each 1-cm square area of the palm and three sites in each digit.

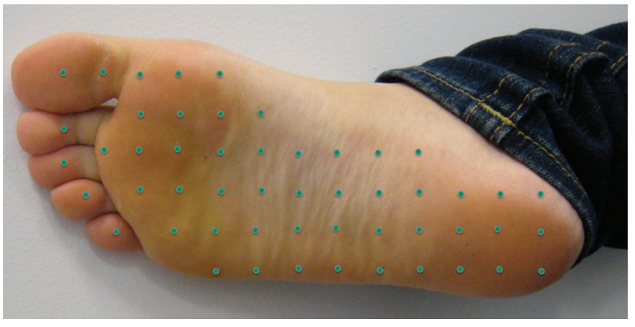

Figure 6. Injection grid for plantar hyperhidrosis.

After the procedure, ice packs are applied while the patient waits in the exam room for 15 minutes to confirm no immediate reaction to the toxin.

Curiously, a greater reduction in sweat production often occurs in the nondominant hand after injection.[39] Muscle weakness is the most commonly published adverse complication. Weakness is noted usually on maximal opposition and is often transient, lasting a few weeks after injection.[40]

Plantar hyperhidrosis presents the same difficulties as palmar. Both regions are particularly sensitive and have a thick epidermis, making topical agents less effective. Given the larger surface area of the soles as compared to the axilla and palmar regions, 150 U of BoNT-ONA is injected through a 26- or 30-gauge needle with a TB syringe following a grid of injection sites (Figure 6). The BoNT-ONA is diluted in 6 to 8 mL of normal saline. Due to the high sensitivity of the area, it is iced before and after the procedure. In particularly sensitive patients, topical lidocaine is applied 30 to 60 minutes prior to the procedure.

A video of the authors' injection technique is available at www.aestheticsurgeryjournal.com. You may also use any smartphone to scan the code on the first page of this article to be taken directly to the video on www.youtube.com.

Posttreatment Care

Patients are monitored in the office for signs and symptoms of adverse events (AE) and encouraged to report any AE that occur following treatments and between follow-up visits. We routinely call patients within two weeks of treatment to confirm that they have noted a decrease in symptoms. Patients are advised to self-refer for repeat treatment once their symptoms begin to return.

EXPECTED OUTCOMES

Efficacy and Duration of Symptom Relief

Most patients report an improvement in symptoms within the first week after treatment. Following the above treatment regimen, reinjection with toxin due to initial treatment failure is rarely required. Our data and data published by others have demonstrated that botulinum toxin treatment for hyperhidrosis has an average of six to nine months of efficacy duration.[23,39]

As the neurotoxin reduces all transmission of acetylcholine to the eccrine glands, both moderate and severe cases are resolved equally, in our experience. Although several patients have been referred to us who have previously experienced failed treatments, we have had very few in our own practice. Patients often state that other physicians have injected the toxin perpendicularly through a grid of perforations, possibly leading to injections that are deep within the tissue, below the presynaptic membranes of the cholinergic nerves. In our technique, the botulinum toxin is injected at a 45-degree angle into the dermis, leading to successful chemodenervation of the eccrine gland.

Natural History of the Disease

In our experience, we have not seen patients "grow out of" the condition. In our previous study, we presented patients who were treated with up to nine injections over the course of 5.6 years, indicating that in severe cases, patients are committed to a prolonged course of treatments.[23] Interestingly, in our experience and in reviewing the work of others, we noted that some patients only present for one treatment. We hypothesize that this may be due to the expense of treatments and the discomfort associated with injections.[23]

Patient Satisfaction

Patients who have undergone BTX-A injections claim a significant decrease in excess sweat production and improvement in quality of life.[3] Our patients have reported decreases in occupational and emotional impairment, time managing their hyperhidrosis, and difficulty in social and occupational situations.[23] In randomized placebo-controlled trials with botulinum toxin, patient satisfaction markedly increased after treatment with botulinum toxin compared to placebo (93% vs 30%).[41] Patients also report an increased satisfaction with botulinum toxin treatment over nonsurgical options for hyperhidrosis, such as topical agents.[2,21] When reviewing the data for axillary hyperhidrosis treatment, patient satisfaction with the procedure ranged from 66% to 100%, indicating that patients were very happy overall with this treatment.[23]

DISADVANTAGES

The primary disadvantage to treating hyperhidrosis with botulinum toxin is its impermanence. Although there may be an attenuation effect, anhidrosis typically lasts six to nine months, and thus repeated injections are required. Our data demonstrate that patients who have had more than four treatments tend to return more frequently for subsequent injections. We speculate that this occurs because patients are less tolerant of symptoms once they become accustomed to the anhidrosis. However, research suggests that some patients may develop antibodies to the toxin, leading to reduced treatment efficacy.[42] Botulinum

toxin injections are ideal for patients who seek excellent results through a noninvasive procedure if they have moderate-to-severe hyperhidrosis, seasonal disease, or focal hyperhidrosis as well as a severe comorbidity that would make surgical intervention high-risk.

CONCLUSIONS

Botulinum toxin type A injections are a safe, rapid, relatively durable, and effective way to treat symptomatic hyperhidrosis in the axillary, palmar, and plantar regions. Across the literature, patients report a high satisfaction rate, increased emotional and physical well-being, reduced limitation of activity, and more comfort in social and occupational situations.

Disclosures

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