Botulinum Toxin for Hyperhidrosis of Areas Other than the Axillae and Palms/Soles

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KEYWORDS

• Inguinal • Submammary • Facial • Compensatory • Amputee hyperhidrosis • Botulinum toxin

KEY POINTS

- Hyperhidrosis can affect many different areas of the body. Identifying and localizing the specific hyperhidrotic area with starch-iodine testing is important.
- Botulinum neurotoxin-A is an effective and safe treatment option for hyperhidrotic areas of the body.
- Patients should be counseled about their expectations with treatment.
- Injections should be placed at the dermal-subcutaneous junction.
- The dosing and the duration of effect of botulinum toxin are variable, and depend on the location and size of the involved area.

INTRODUCTION

Primary hyperhidrosis (HH) commonly affects the axillae, palms, and soles, but may occur on many body sites including the scalp, face, submammary regions, and groin (**Table 1**).[1,2] There are limited treatment options available for HH of areas other than the axillae and palms/soles. Although topical treatments are usually considered the first-line therapy, botulinum neurotoxin-A (BoNT-A) is an effective and safe treatment option for most hyperhidrotic areas of the body. This article focuses on BoNT-A treatment of hyperhidrosis of areas other than the axillae and palms/soles. Areas that are commonly affected, such as the face and groin, and less common areas like the submammary region and gluteal cleft, are discussed. Frey syndrome, compensatory sweating, and postamputation stump hyperhidrosis are also discussed.

PATIENT EVALUATION OVERVIEW

A thorough HH history and review of symptoms should be obtained from the patient, including age of onset of HH, location and symmetry of sweating, aggravating/alleviating factors, prior treatments for HH, family history of HH, and current medications that may exacerbate the condition. A physical examination should also be performed to help rule out a possible secondary cause of HH and to localize the affected area. A starch-iodine test is then performed to identify the dimensions of the involved area for treatment.

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Table 1
Most common body sites of hyperhidrosis in a North American population

Body Site	Percentage of Patients
Axilla	73.0
Palms	45.9
Soles	41.1
Face or scalp	22.8
Groin	9.3
Other[a]	9.6

[a] Other includes sites such as the chest, back, abdomen, arms, or legs.

Data from Lear W, Kessler E, Solish N, et al. An epidemiological study of hyperhidrosis. Dermatol Surg 2007;33(s1): S69–75.

The Minor starch-iodine test is an inexpensive and simple procedure commonly used to localize focal areas of sweating. The starch-iodine test does not correspond with the severity of disease, and it may not be possible to illicit a response at every visit. Before performing this test, every patient should be asked about allergies to iodine. To perform the Minor starch-iodine test, the affected area is first thoroughly dried, then a solution of iodine in castor oil is brushed onto the skin and allowed to dry. In addition, corn starch powder is sprinkled on top, and the area is observed for a few minutes. A modified starch-iodine test is more commonly used in clinical practice and generally a povidone-iodine–based surgical preparation, such as Betadine, is used instead of the iodine-castor oil solution. Purple-black dots develop when sweat interacts with the starch and iodine (**Fig. 1**). The treating practitioner can then use a marking pen to create evenly spaced injection markings as a template for BoNT-A injections.

MANAGEMENT GOALS AND BOTULINUM TOXIN PREPARATION

The goals of BoNT-A therapy are to provide a long-lasting reduction in excess sweating, with the smallest effective amount of BoNT-A, and with minimal side effects. It is important to manage patient expectations so that there is an understanding that the goal is improvement in excess sweating, but that complete anhidrosis is rarely achieved. Risks of the procedure should be reviewed and an informed consent obtained. The authors have patients, or their representatives, review and sign a consent form before each treatment session. Most patients undergo repeated treatments over the years, and an untoward effect could occur with any injection session.

The only BoNT-A approved by the US Food and Drug Administration for axillary hyperhidrosis is onabotulinumtoxin-A (ona-BoNT-A; Botox [Allergan, Irvine, CA]), and it is the most common BoNT-A used off-label for hyperhidrosis of all involved areas. Abobotulinumtoxin-A (abo-BoNT-A; Dysport [Ipsen Ltd, Slough, Berkshire, UK]) has also been used effectively for hyperhidrosis. Ona-BoNT-A and abo-BoNT-A are not bioequivalent, and there is no consensus on the ideal conversion factor between these two preparations. The ratio of efficacy in axillary and palmar hyperhidrosis ranges from 1:1.5 to 1:3 for ona-BoNT-A/abo-BoNT-A,[3–5] and is unknown for other forms of hyperhidrosis. Incobotulinumtoxin-A (Xeomin, Merz Pharmaceuticals, Frankfurt, Germany) is a newer BoNT-A that has been shown to be effective in axillary and palmar hyperhidrosis in several studies,[6] and has been shown to be of equal efficacy to ona-BoNT-A for palmar hyperhidrosis in a single study.[7] We have the most experience with ona-BoNT-A for hyperhidrosis, and typically use it to treat patients with hyperhidrosis.

For axillary HH, the recommended reconstitution of ona-BoNT-A is with 4.0 mL of 0.9% nonpreserved saline, although we prefer to use preserved saline, which does not affect ona-BoNT-A efficacy.[2] The dilution volume of 4.0 mL allows for 2.5 units of ona-BoNT-A to be injected in a volume of 0.1 mL. Other volumes of diluent can be used for toxin reconstitution. In general, the more dilute the solution, the more diffusion of the drug that occurs, and this should be taken into consideration.[8] Injections are usually performed with a 1-mL Luer-Lock syringe and 30-gauge 12.5-mm needle. The drug should be placed at the dermal-subcutaneous junction, which is where the sweat glands reside, and this injection depth also minimizes the risk of diffusion to deeper muscles. In general, the needle is inserted into the skin at an oblique angle to maintain the superficial placement of the drug, and to minimize any loss of the botulinum solution. A small amount of blanching may be seen when BoNT-A is injected properly into the dermis.[2]

CRANIOFACIAL HYPERHIDROSIS

Primary hyperhidrosis of the scalp most commonly displays one of 4 patterns: the forehead; a band-like distribution around the scalp, known as the ophiasis pattern; a combination of the forehead and ophiasis scalp; or the entire scalp and forehead.[2] Less commonly involved areas include the upper lip, cheeks, nose, and chin. Several areas can be involved simultaneously.[2] With the exception of Frey syndrome, primary HH is not

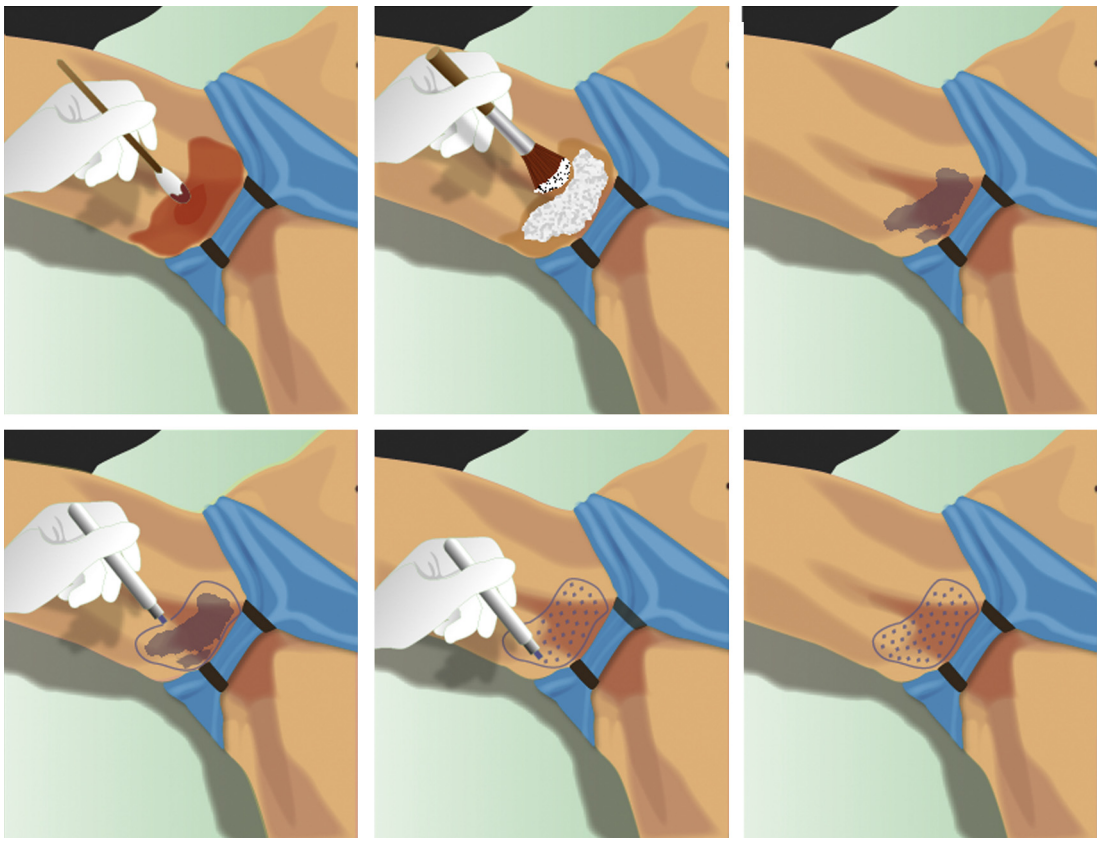

Fig. 1. Proper sequence for the Minor starch-iodine test, and marking the area for injection. First, the hyperhidrotic area is dried and an iodine solution is painted on and allowed to dry. Corn starch is then sprinkled on the area and allowed to sit for several minutes. Purple-black dots develop when sweat interacts with the starch and iodine. The treating practitioner can then use a marking pen to create evenly spaced injection markings as a template for BoNT-A injections. (*Courtesy of* Albert Ganss, International Hyperhidrosis Society, Quakertown, PA; with permission.)

usually unilateral, and patients presenting with unilateral involvement should be worked up for possible neurologic disease.[2] The Minor starch-iodine test helps to identify the specific distribution of sweating on the forehead and other areas of the face (**Fig. 2**) but is not practical for scalp involvement, unless the patient is bald. The importance of performing a starch-iodine test is highlighted in **Fig. 2**C, which shows involvement of the nasal ala, an uncommonly involved area of the nose.

BoNT-A treatment of facial HH should be carefully performed, because of the numerous muscles in the treatment areas. Even with properly placed injections, there is a possibility of having muscle weakness around the injection site, which may cause temporary functional and/or cosmetic irregularity.[2] The total amount of ona-BoNT-A, and the number of intradermal injection sites, varies with the location and pattern of sweating. Treatment of facial HH with abo-BoNT-A is also effective, although abo-BoNT-A has a greater area of diffusion compared with ona-BoNT-A,[9] and there may be a greater potential of adverse events within this area.[9] With the exception of the forehead, there is a paucity of published literature on BoNT-A treatment of facial and scalp hyperhidrosis.

The average total dose of Botox for the forehead is approximately 40 units, with a range of 33 to 100 units.[2] For the forehead, 2 to 3 units of Botox per injection site, spaced at regular 1-cm to 2-cm intervals should be delivered to the dermal-subcutaneous junction. This dose ensures confluence of the medication, and minimizes diffusion into the muscles.[2] Avoiding the 1-cm to 2-cm area above the eyebrows may be needed to avoid brow ptosis, which is especially important in individuals with preexisting brow ptosis. Some patients may need to have the most inferior portion of their forehead treated to provide maximum improvement of their sweating, but they need to be warned of potential eyebrow and eyelid ptosis,

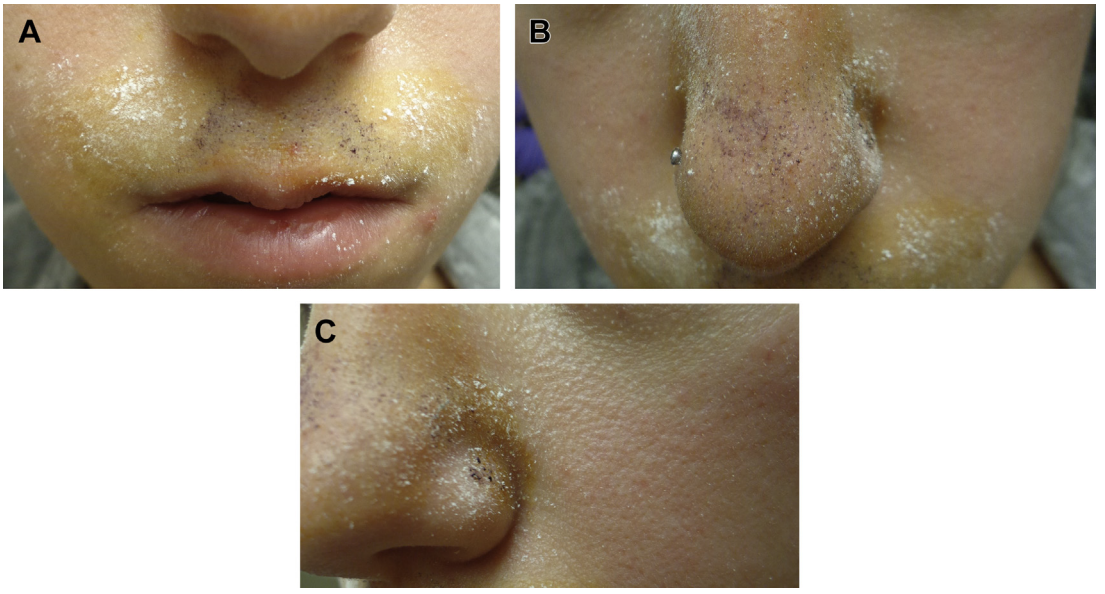

Fig. 2. A positive starch-iodine test of the upper lip (*A*), and the nose (*B*), including the nasal ala (*C*).

both of which are temporary and self-limited.[2] In most patients, treating the area above and into the hairline is required.[2] It is the authors' experience that injections into the frontal hairline provide superior outcomes for patients. We usually carry the injections approximately 2 to 4 cm into the hair-bearing scalp or based on the starch-iodine test if the patient is bald. **Fig. 3** shows an example of the proper injection technique for the forehead. Most commonly it is our practice to use 100 units of ona-BoNT-A for this area.

When treating the ophiasis pattern of scalp hyperhidrosis, we commonly inject 100 units of ona-BoNT-A. Approximately 2.5 units are injected at 2-cm intervals. When the entire scalp is treated (excluding the forehead), ~2.5 units of ona-BoNT-A are injected at 2-cm intervals, for a total of 200 units.[10] In our experience, 300 units are necessary to treat the forehead and entire scalp.

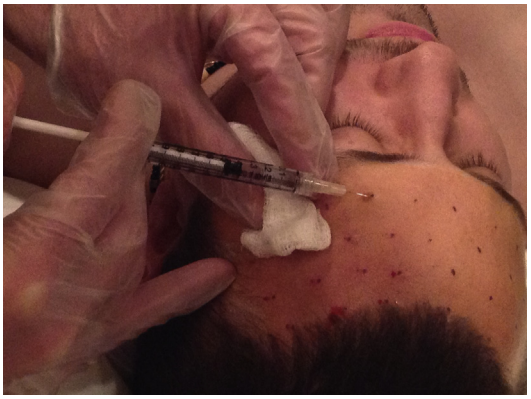

Fig. 3. Botulinum toxin injection technique into the forehead. (*Courtesy of* Albert Ganss, International Hyperhidrosis Society, Quakertown, PA; with permission.)

Some patients may not be able to identify where the sweating originates, because it can quickly spread over the scalp. It is important to try to get the patient to pinpoint the location to help reduce the numbers of units needed. If a subunit of the scalp is not treated and the patient discovers that it is affected, the physician can treat the missed area at a future appointment. It is difficult to perform a starch-iodine test in the hair-bearing scalp. We sometimes ask patients to do some light exercise or walking in the office to try to elicit a sweat response such that we can determine the areas that need to be treated and estimate the amount of botulinum toxin needed.

Botulinum toxin-A can be safely and effectively administered for nasal HH. A dose of 1 to 2 units per injection spaced every 0.5 to 1.0 cm, for a total dose of 10 to 20 units of ona-BoNT-A, is usually required.[11,12] Take care to avoid the lacrimal system and the nasal muscles when injecting at the lateral nasal wall, keeping injections as medial as possible. Very small aliquots should be injected superficially to help avoid muscle effects. Patients should be warned of a drooping of the upper lip and an inability to flare the nostrils. The latter can decrease air intake through the nostrils with heavy exercise.

Upper lip hyperhidrosis can been treated effectively with ~1 unit of ona-BoNT-A per injection, spaced at 0.5-cm intervals,[13] or with 2 units per injection, spaced at 1 cm.[11] Even with proper

injection technique, patients may experience a dropped lip, decrease pursing of the lips, a change in speech, or oral incompetence.[11] Chin hyperhidrosis is treated effectively with 2 units per injection.[11] Patients can have oral incompetence, dropped chin, or an asymmetric smile. The typical doses of BoNT-A required per facial locale are summarized in **Table 2**. Overall, side effects are uncommon with good injection technique and when small doses are used. Side effects are typically minimal, and depend on the area of injection (**Table 3**).[2,14] The duration of benefit may be shorter when treating facial hyperhidrosis and patients should plan on treatments 2 to 3 times per year.

FREY SYNDROME (GUSTATORY SWEATING)

Frey syndrome, known as gustatory sweating, presents with sweating and/or flushing of the preauricular and mandibular areas from injury to the parotid gland. Parotid injury is most commonly unilateral, and is seen after surgical procedures such as parotidectomy and face lift surgery, or less commonly from neuropathy associated with diabetes. In a recent population-based study, 3% of patients after parotidectomy developed Frey syndrome that required treatment after a mean of 9.6 months.[15] Frey syndrome is thought to be caused by aberrant regeneration of the parasympathetic nerves innervating the sweat glands.[16,17] The abnormal sweating on the face can appear when the person eats, sees, or even thinks about certain foods that produce strong salivation. Frey syndrome has been well studied, and there is consensus regarding the safety and efficacy of BoNT-A therapy.[16]

Eliciting a history of gustatory sweating in a patient several months after parotidectomy, or surgical face lift, is sufficient to diagnose most patients. A starch-iodine test can be performed to confirm the problem (**Fig. 4**) and to identify the area of involvement.[16] After the skin is prepped with iodine and corn starch powder, the patient can be asked to eat food known to provoke sweating in that patient, such as sweet or tart foods, or chewing gum.[17]

Compared with the other areas of facial sweating, there is more substantial literature supporting the efficacy of both abo-BoNT-A and ona-BoNT-A. Abo-BoNT-A, at 10 to 20 units per 1 cm^2 of affected skin, can effectively reduce gustatory sweating for 8 to 16.5 months.[16,18] Likewise, 1.5 units of ona-BoNT-A per 1 cm^2, for a total average dose of 38 units, can effectively reduce gustatory sweating for an average of 15 months.[17] However, there is great variability in the duration of effectiveness reported in the literature, and it seems to be independent of age, sex, or extent of parotidectomy.[16,17] In our experience, it is common for patients to achieve remission for 1 to 3 years and doses can range from 15 to 100 units of ona-BoNT-A. The affected area is treated with 2.5 to 3 units injected every 1 to 1.5 cm. There are few side effects with BoNT-A treatment. Dry mouth and a potential to cause temporary weakness with mastication have been reported.[17] Smile asymmetry is also possible.

SUBMAMMARY HYPERHIDROSIS

There is a lack of published data regarding the prevalence and treatment of submammary hyperhidrosis. Patients frequently have difficulty pinpointing the area of sweating because the sweat solution spreads along the chest wall, and even down to the abdomen. Starch-iodine testing is helpful for localizing the affected areas for treatment. In our experience, ona-BoNT-A at 2.5 units per injection, spaced evenly at 1.5 to 2 cm per injection, is effective for this region. There are times when a positive starch-iodine test cannot be elicited, in which case we treat an area 2 to 4 cm inferior and superior to the submammary crease, from the midline of the inferior chest/upper abdomen to the lateral edge of the breast or sometimes to the

Table 2
Craniofacial hyperhidrosis: typical doses of ona-BoNT-A

Facial Area	Units Per Injection	Spacing of Injections (cm)	Average Total Dose (units)	Average Duration of Effectiveness (mo)
Forehead and anterior scalp	2–3	2	100	4–6
Ophiasis scalp	2.5	2	100	4–6
Scalp and forehead	2–2.5	2	300	4–6
Nose	1–2	0.5–1	10–20	3–6
Upper lip	2	0.5–1	10	3–6
Chin	2	0.5–1	10	3–6

Table 3
Side effects of botulinum toxin injection of the face/scalp

Common Adverse Events	Uncommon Adverse Events
Injection site pain	Brow or eyelid ptosis
Bruising/erythema	Malaise
Swelling	Ectropion
Headache	Xerophthalmia
Local paresthesia	Blepharoptosis
Asymmetry	Oral incompetence
	Diplopia

Data from Glaser DA, Hebert AA, Pariser DM, et al. Facial hyperhidrosis: best practice recommendations and special considerations. Cutis 2007;79(Suppl 5):29–32; and Dorizas A, Krueger N, Sadick NS. Aesthetic uses of the botulinum toxin. Dermatol Clin 2014;32(1):23–36.

midaxillary line. Because of the variations in size of the thorax and submammary region, a total of 50 to 150 units of ona-BoNT-A may be required per affected side.

HYPERHIDROSIS OF THE GROIN

There are few published reports regarding hyperhidrosis of the groin. The inguinal folds, perineum, gluteal cleft, anal fold, and buttocks can be affected. Patients complain of and present with sweating in the groin area. Patients may complain of wet underwear and clothing, as well as leaving wet marks on surfaces after sitting. Patients can have noticeably wet areas on their clothes at presentation. The starch-iodine test helps to localize the area of sweating in these locations, but can be challenging to perform in areas such as the gluteal cleft/anal fold.[19] An example of a positive starch-iodine test of the inguinal fold, and marking the area for injection, is given in **Fig. 5**. A positive starch-iodine test of the anal fold is shown in **Fig. 6**.

The ideal dose of botulinum toxin for these regions has not been established. Several case reports have found that 2 to 3 units of ona-BoNT-A injected 1 to 2 cm apart, for a total of 50 units per inguinal fold, is effective for inguinal hyperhidrosis.[20–22] If a starch-iodine test is negative, we inject ~2 cm medial and 2 cm lateral to the inguinal crease, making sure to avoid injection of the labia minor. The effects of treatment typically last 3 to 6 months.[20,21] The few reported side effects are related to the injections, and include temporary edema and small hematoma formation.[20]

A prospective trial of 11 patients[19] showed effective ona-BoNT-A treatment of anal fold hyperhidrosis. One unit of ona-BoNT-A was injected at 1-cm intervals, for a total dose range of 30 to 54 units, depending on the size of the involved area. With the exception of pain with injections, no other side effects of treatment were noted, even with the proximity to the anal sphincter. When injecting this area, the authors try to stay 1 to 2 cm lateral to the anal verge to prevent diffusion of BoNT-A into the anal sphincter. We have not seen anal incompetence after injecting the gluteal cleft/anal fold, although it is important to review the possible risk of temporary fecal incontinence with each patient.

HYPERHIDROSIS OF AMPUTATED LIMBS

Hyperhidrosis is reported in 23% to 56% of limb amputees, and has a significant impact on their

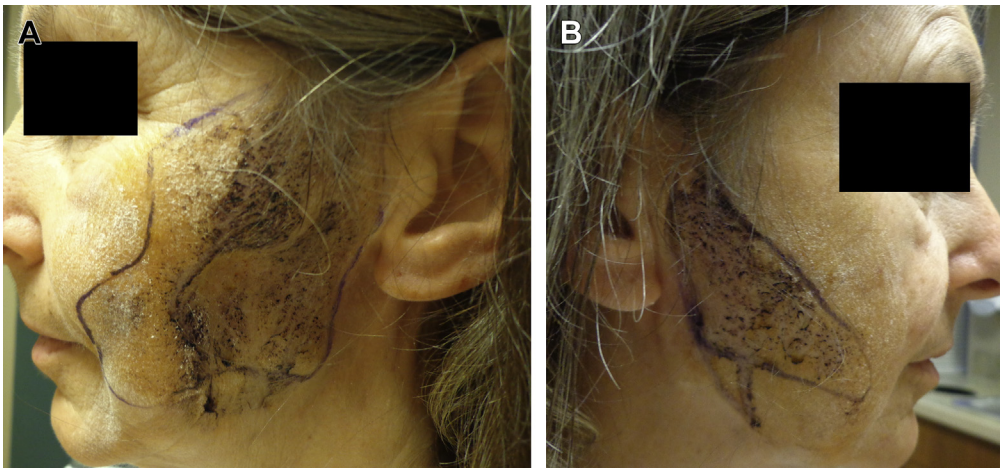

Fig. 4. A patient with bilateral Frey syndrome showing the variation in the affected surface area on each side (*A* and *B*), which highlights the importance of performing a starch-iodine test.

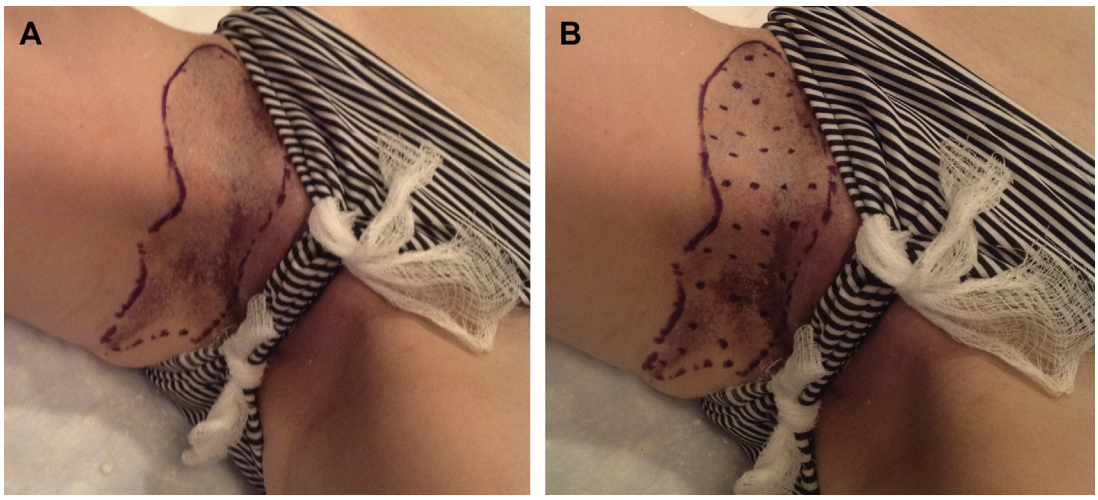

Fig. 5. A positive starch-iodine test of the inguinal fold (*A*), and an example of how to properly mark the inguinal fold for botulinum toxin injection (*B*). (*Courtesy of* Albert Ganss, International Hyperhidrosis Society, Quakertown, PA; with permission.)

quality of life.[23] The excess sweating can interfere with the prosthesis fitting comfortably and properly. The exact pathophysiology is unknown, and is likely multifactorial. It is possible that the remaining sweat glands in the surgical area compensate for the decreased amount of secretory tissue.[24] The use of nonpermeable suction stockings and silicone liners within the prosthesis exacerbates the problem.[23,25]

Patients report that perspiration depends on friction and physical exertion, rather than temperature.[23,26] A starch-iodine test pinpoints the areas of excess sweating, and allows more precise treatment. In this patient cohort, the iodine and starch are applied as usual, but the patient may need to apply the prosthesis for several minutes in order to produce the most accurate results.[26]

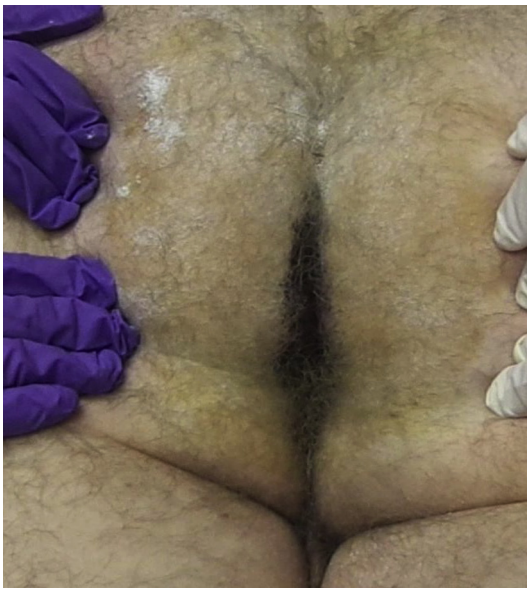

Fig. 6. A positive starch-iodine test of the anal fold.

Ona-BoNT-A, at 2 to 3 units per injection, is injected circumferentially at 1-cm to 2-cm intervals within the identified area of the amputee's socket.[25,26] The total amount of ona-BoNT-A varies depending on the affected limb, but can be as high as 300 to 500 units per treatment.[25] Treatment effectiveness and duration vary, but can last from 4 to 12 months.[26,27] Kern and colleagues[23] found that a total of 1750 units of botulinum neurotoxin-B (BoNT-B), injected into 20 spots, spaced at 2-cm to 4-cm intervals, was effective at controlling limb hyperhidrosis for 3 months (end of study visit).[23] The investigators concluded that BoNT-B seems to be as effective as BoNT-A but has a wider area of diffusion, which may be beneficial for the large areas involved in amputated limbs.

Because low doses of BoNT-B are required for treatment of hyperhidrosis, in contrast with doses of 5000 units or greater for cervical dystonia, the autonomic side effects were few and minimal.[23] Reported autonomic side effects of BoNT-B included dry mouth, blurry vision, and dry nasal mucosa.[23] Side effects of ona-BoNT-A treatment are minimal, and include small hematomas at the sites of injection and injection pain.[26] A botulinum toxin type A is preferred by the authors to minimize the risks of systemic side effects.

COMPENSATORY HYPERHIDROSIS

Compensatory hyperhidrosis (CHH) is seen in 60% to 90% of patients after treatment of severe axillary and/or palmar HH with thoracic sympathectomy.[28,29] Approximately 40% of patients have CHH, for which treatment is sought.[28] The mechanism for CHH is unclear, and there is no accurate way to predict which patient may have this entity after sympathectomy. CHH most commonly affects the back (**Fig. 7**), abdomen, and chest, but the groin and thighs are common areas as well. CHH can be more debilitating and intolerable than the primary hyperhidrosis, and it is thought to be irreversible.[30] CHH may be irreversible, even in cases after surgical clip removal, which has been seen in 2 prospective clinical trials.[24,31]

The patient can help identify the most troubling regions of CHH, and a starch-iodine test should be used to define the size of the areas to be treated. Ona-BoNT-A is an effective therapy that can last an average of 4 months per treatment.[30] Patient outcomes tend to be less satisfying for CHH than for other body areas already discussed, probably from under dosing because the surface areas tend to be so large. Injections are spaced 1 to 2 cm apart using 2.5 units per injection site. The total amount of ona-BoNT-A can vary from 100 to 500 units, depending on the surface area involved.[30,32] Doses of ona-BoNT-A are generally limited to 300 to 400 units per session to minimize the risk of side effects. Concurrent therapy with topical antiperspirants and/or oral anticholinergics may be necessary. Minor injection site pain is the most common side effect.

Fig. 7. CHH commonly presents on the back and can affect a large surface area, making treatment challenging.

SUMMARY

Botulinum toxin-A therapy is an effective treatment option for patients with primary or secondary focal hyperhidrosis. The amount of BoNT-A required per treatment, and the duration of effectiveness, vary with the area of hyperhidrosis. Accurate identification of the area of excess sweating with a starch-iodine test can help maximize outcomes. Injections placed at the dermal-subcutaneous junction ensure the best efficacy, minimize muscular uptake, and reduce the risks of local muscle weakness. Repeat treatments are necessary and botulinum toxin injections can be combined with other hyperhidrosis therapy.

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