Botulinum Neurotoxin Treatment of Palmar and Plantar Hyperhidrosis

Tessa Weinberg[a], Nowell Solish, MD, FRCPC[b,*], Christian Murray, MD, FRCPC[b]

KEYWORDS

• Botulinum neurotoxin • Palmar plantar hyperhidrosis • Nerve blocks • Hypehidrosis

KEY POINTS

- Palmar and plantar hyperhidrosis is relatively common and can have severe psychological and medical consequences for those afflicted.
- A multitude of treatments exist but are often inadequate especially for those with significant disease; in these cases BoNT, in its various formulations, provides a reliable method for reducing the symptoms and improving QOL.
- Although the actual administration is relatively straightforward pain management is a crucial component that requires a mastery of several techniques.
- Patients have a high degree of satisfaction with BoNT treatment and are motivated to come back for repeat treatments, usually every 6 months.

INTRODUCTION AND OVERVIEW

Hyperhidrosis (HH) is an excessive sweating disorder that affects approximately 2.8% of the population in the United States,[1] likely with similar incidences in other countries.[2] It is commonly defined as sweating beyond what is expected for environmental conditions and thermoregulation with duration of more than 6 months.[3] Some have added specific diagnostic criteria, which are discussed later[4] and do apply to the palms and soles. A quantitative definition of HH as the production of more than 50 mg of sweat in one palm per minute has also been suggested for use in studies and when examining therapeutic intervention[5]; however, this fails to account for surface area. Clinically, sweating is considered excessive if it significantly interferes with daily life.

HH can be classified as primary or secondary and further as general or focal. Focal is further subclassified by anatomic area. Eccrine glands cover most of the body and have a density of approximately 60/cm^2, except on the palms and soles where their density is at approximately 600/cm^2.[6] It is thus not surprising that patients experience HH in areas of high eccrine density, such as the soles (30%) and palms (24%).[7] It should be noted that in primary focal HH, neither the number, density, nor size of eccrine glands are abnormal; rather, there is overactivity of the postganglionic sympathetic cholinergic fibers (sudomotor) innervating them.[8] This explains the effectiveness of botulinum neurotoxin (BoNT).

In clinical practice significantly more patients present with axillary than palmar HH and more with palmar than plantar HH.[9] In many cases individuals suffer with more than one site involved. Most patients who present with palmar HH have had the condition since childhood or early

[a] School of Medicine, Royal College of Surgeons of Ireland, 123 Street Stephen's Green, Dublin 2, Ireland; [b] Division of Dermatology, Women's College Hospital, University of Toronto, 76 Grenville Street, Room 5142, Toronto, Ontario M5S 1B2, Canada
* Corresponding author. Division of Dermatology, Women's College Hospital, University of Toronto, 76 Grenville Street, Toronto, Ontario M5S 1B2, Canada.
E-mail address: n.solish@utoronto.ca

Dermatol Clin 32 (2014) 505–515
http://dx.doi.org/10.1016/j.det.2014.06.012
0733-8635/14/$ – see front matter

adolescence with no known cause and report "sweaty palms" that cause them social embarrassment. The effects later in life are physical and emotional. Physically, the wetness may be bothersome enough that patients go to great lengths to avoid shaking peoples hands and frequently hide their hands in their pockets. Plantar HH may cause patients to frequently change their socks and slip in their shoes. HH is a well-established risk factor for cutaneous infection and eczematous dermatitis. Psychologically HH causes anxiety, emotional distress, embarrassment, and a markedly diminished quality of life (QOL).[3,4] Interestingly, a study by Lear and colleagues[7] suggested that spontaneous regression might occur over time because there is a low prevalence of the disorder in the elderly population.

Multiple modalities are available for treatment of primary focal HH, including topical medications, such as aluminum chloride[10]; oral medications, such as clonidine[3,11]; physical treatments, such iontophoresis[3,11]; injectable treatments, such as BoNT; and even surgical sympathectomy.[2,12]

In this article, the role of BoNT in the treatment of primary focal HH of the palms and soles is discussed.

PATIENT EVALUATION

A careful clinical history and focused physical are imperative. The first fact to establish is whether the patient has primary or secondary HH. There are many causes of secondary HH that have been well documented previously[13] and include febrile illness (ie, chronic infections), endocrine disorders (thyroid dysfunction), medication use (ie, antidepressants), and cancer (ie, pheochromcytoma). Secondary is more likely if the sweating is associated with other constitutional symptoms and is generalized in nature. If secondary HH is suspected the work-up should at minimum include a complete blood count, fasting glucose level, and thyroid function tests. Any suspected offending medications should be discontinued and if necessary appropriately substituted. Further investigations should be guided by elements of the history and the examination.

The generally accepted diagnostic criteria for HH in general and palmar-plantar specifically is excessive sweating that lasts at least 6 months without any obvious cause and has at least two of the following features: impairs daily activities, a bilateral and relatively symmetric pattern of sweating occurring at least once per week, an age of onset younger than 25 years, cessation of focal sweating during sleep, or positive family history.[4] Bilaterality is not a diagnostic criteria and it should be noted that palmar HH can present unilaterally in 6% of cases.[4]

It is important to quantify the impact of HH on the patient's QOL.[14] This not only helps to decide on the need for and success of treatment but may also aide in obtaining insurance approval for treatment. The HH Disease Severity Scale (HDSS) is an easy tool for this (**Table 1**).

It is important to take a family history because there is evidence that primary HH is an autosomal-dominant trait with variable penetrance.[15,16]

MANAGEMENT GOALS AND STRATEGY

The goal of management is to improve the quality of the patient's life with acceptable risks. QOL studies have in general shown a significant improvement in the QOL after treatment of axillary,[17] for palmar and planter HH.[18]

Several methods have been used to measure the amount of palmar and plantar sweating before and after treatment. These include the evaporimeter,[19] persprint paper,[20] patient reports of the number of days of dryness,[21] digitized ninhydrine test,[22] gravimetry sweat production test,[23] the Minor iodine starch test,[24] and the HDSS. We clinically prefer the HDSS because it is easy and quick to administer and has been found[25] to be

Table 1
Hyperhidrosis Disease Severity Scale

"How Would You Rate the Severity of Your Hyperhidrosis?" Patient Response		Score	Clinical Interpretation
1	My sweating is never noticeable and never interferes with my daily activities	1	Mild
2	My sweating is tolerable but sometimes interferes with my daily activities	2	Moderate
3	My sweating is barely tolerable and frequently interferes with my daily activities	3	Severe
4	My sweating is intolerable and always interferes with my daily activities	4	Very severe

a reliable diagnostic tool. It can also be used to monitor the effectiveness of treatment. Success may be considered a reduction in HDSS of 1 or more. Although a subjective test, it accurately reflects patient QOL, which is most relevant to patients.

The Canadian Hyperhidrosis Advisory Committee has made several treatment recommendations.[26] In review, the committee recommends topical aluminum chloride as a first-line option, in a concentration of 20% to 50% for treating mild focal or multifocal HH. For patients with moderate to severe HH, the committee recommends starting treatment with topical aluminum chloride and, if ineffective, trying iontophoresis or onabotulinumtoxinA (A/Ona) injections. Surgery should be reserved for patients who do not respond to less invasive interventions. Of note, endoscopic thoracic sympathectomy although established may have significant complications and deleterious side effects including compensatory HH. Surgery should be reserved for patients in whom less invasive treatments have proved ineffective and who understand the risks and benefits of the surgery.[2,12]

BoNT

There are four types of BoNTs approved by the Food and Drug Administration for clinical use in the United States: A/Ona (Botox; Allergan, Irvine, CA), A/Inco (Xeomin; Merz Pharmaceuticals, Greenboro, NC), abobotulinumtoxinA (A/Abo; Dysport; Medicis, Scottsdale, AZ), and rimabotulinumtoxinB (B/Rima, Myobloc; Solstice Neurosciences, Louisville, KY).

BoNTs block the release of acetylcholine and several other neurotransmitters from presynaptic vesicles by deactivating SNARE proteins. These toxins use different presynaptic proteins for their site of action. For instance, for A/Ona the protein is synaptin 25.

There are several important facts that must be considered before instituting therapy with BoNT. First, all four types of commercially available BoNT are considered pregnancy category C drugs and one should avoid injection in actively nursing women. Second, treatment of the palms and soles for primary focal HH is considered an off-label use of BoNT. Third, one must always screen for previous allergic reaction to BoNT. Fourth, one must be aware of the patient's current medication list because certain medications can theoretically alter the metabolism of neurotoxin, such as aminoglycoside antibacterials, cholinesterase inhibitors, and calcium channel antagonists. Finally, the use of BoNT can exacerbate some neuromuscular disorders, such as myasthenia gravis.

EVALUATION OF TREATMENT AND RECOMMENDATIONS

There are many different types of studies for BoNT treatment of palmar and plantar HH. The placebo-controlled evidence for palmar HH is reviewed in **Table 2**. There is one single-agent study each for A/Abo,[22] A/Ona,[23] and B/Rima.[25] These studies are small and of short duration; however, they do confirm the effectiveness of these products. This allows the conclusion that the evidence supports a Level B recommendation for BoNT-A and a Level C recommendation for BoNT-B for the treatment of palmar HH.[3,27] On further examination of the evidence one can conclude that there are insufficient data for the individual formulations, so each receives a Level U recommendation. The side effects were in the order of what is expected and are covered in more detail in the complications section.

The comparative effectiveness studies are interesting (see **Table 2**). In one study BoNT A/Ona and A/Abo at mean doses of 69 U and 284 U per palm, respectively, were compared.[24] The difference in doses is explained because the dose for A/Abo is usually relatively higher by a factor of 2.5 to 4. In a second the study 50 U of A/Ona and 100 U of A/Ona were compared,[28] and in a third study A/Ona and A/Inco were compared.[29] The Simonetta Moreau and coworkers[24] study showed no statistically significant difference at 1 month post-injection in the reduction in sweating between the A/Abo- and A/Ona-treated palms, although there was a tendency for greater efficacy of A/Abo. At 3 months, the reduced sweating persisted for the A/Abo- but not A/Ona-treated palms. The duration of effect ranged from 8 to 32 weeks with both agents (mean, 17 weeks for A/Abo and 18 weeks for A/Ona). In the study of two different doses of A/Ona, both doses reduced sweating in all patients at 2 months, with an evident anhidrotic effect at 6 months in one-third of both dose groups.[28] In the Campanati and coworkers study,[29] there were no differences in efficacy or side effects for the A/Ona and the A/Inco groups.

One can also see from **Table 2** that in a recent double-blind randomized study the effects of concentrations of A/Ona, A/Inca, A/About, and B/Rima were studied using the starch iodine test.[30] The optimal dose was 25 IU/mL for A/Ona and A/Inca, 100 U/mL for A/Abo, and 50 U/mL for B/Rima. They concluded that concentration is a critical factor when considering HH treatment.

In other studies efficacies of 80% to 90%, similar to that seen in axillary HH, have been described with the use of BoNT-A in the treatment of palmar HH[11] and this corresponds to our clinical

Table 2
Palmar hyperhidrosis: significant single agent and comparative studies

Reference	AAN Class	Design	N	Follow-Up	Agent	Dose	Results	Adverse Events
Placebo-Controled Studies								
Schnider et al,[22] 1997	II	R, DB, PC Within-group comparison	11	13 wk	A/Abo	120 MU/palm PCO contralateral palm	Sweat production dropped: 26%, 26%, and 31% at wk 3, 8, 13 (P<.001) and improvement in VAS 38%, 40% and 35% at wk 3, 8, 13, respectively (P = .002)	Minor, reversible weakness of handgrip lasting 2 and 5 wk In three patients.
Lowe et al,[23] 2002	II	R, DB, PC	19	28 d	A/Ona	100 U/palm, PCO in contralateral palm	Percentage change from baseline was greater A/On-treated palms at day 28 (P = .0037). Minor test confirmed results.	Finger tingling and numbness in one A/Ona patient. One patient bilateral hand pain.
Baumann et al,[25] 2005	II	R, DB, PC	20	120 d or event-driven until return of sweating	B/Rima	5000 U/palm or PCO	Patient assessed efficacy significant difference B/Rima through day 120. Physician assessment no difference at day 30. Mean duration of effect; 3.8 mo.	Transient dry mouth in 18. Transient muscle weakness in 12.
Comparative Studies								
Simonetta Moreau et al,[24] 2003	II	R, DB, active	8	6 mo	A/Ona or A/Abo	A/Ona, 69 U/palm, or A/Abo, 284 U	Decrease in mean PSA; 76.8% A/Abo (P = .002) vs 56.6% A/Ona (P = .003) at 1 mo. At 3 mo decrease in PSA was 69.4%, A/Abo (P = .008) and 48.8%. A/Ona (NS). Mean duration of benefit 17 wk A/Abo; 18 wk A/Ona.	Pinch weakness, two times more frequent in A/Abo than A/Inco.

Saadia et al,[28] 2001	II	R, SB, comparison of two doses, intraindividual comparison	24	6 mo	A/Ona	50 U or 100 U/palm	Significant decrease in sweating within 1 mo. At 6 mo anhidrotic effect evident in both dose groups. Both doses effective at 1 mo and lasted 6 mo in low-dose, 5 mo in high-dose groups.	No difference in hand grip strength. Finger pinch strength decreased.
Campanati et al,[29] 2014	II	R, DB	25	6 mo	A/Ona and A/Inco	A/Ona, 100–150 U/palm, and A/Inco, 100–150 U in other palm	A/Ona and A/Inco equivalent short- and long-term effects.	No difference in muscle strength between A/Ona and A/Inco.
Rystedt et al,[30] 2013	II	R, DB	20	3 mo	A/Ona, A/Inco B/Rima, A/Abo	Varying doses	Optimal doses of A/Ona, A/Abdo, A/Inco, and B/Rima: 25 U/mL, 40 U/mL, 25 U/mL.	N/A

Abbreviations: A/Abo, abobotulinumtoxinA; AAN, American Academy of Neurology; A/Inco, incobotulinumA; A/Ona, onabotulinumtoxinA; B/Rima, rimabotulinumtoxinB; DB, double blind; MU, mouse unit; PC, placebo controlled; PCO, placebo; PSA, palm sweating area; R, randomized; SB, single blind; VAS, visual analog scale.

Adapted from Naumann M, Dressler D, Hallett M, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of secretory disorders. Toxicon 2013;67:147; and Lakraj AA, Moghimi N, Jabari B. Hyperhidrosis: anatomy, patho physiology and treatment with emphasis on the role of botulinum toxins. Toxins (Basel) 2013;5:821–40.

experiences. However, response to therapy varies more than that seen in axillary HH.

There are no placebo-controlled studies for plantar HH. There are several small studies that show benefit of BoNT-A.[18,31–33] These studies show that BoNT is efficacious and well tolerated if appropriate pain management strategies are instituted.

BoNT has been used in combination with several agents, specifically aluminum chloride, for treatment of palmar and plantar HH.[10] However, this as in other combination studies is small and does not allow conclusions to be drawn. In our practice we find an efficacy of approximately 50%.

TREATMENT COMPLICATIONS

The most common side effects from injection of BoNT into the palms and soles are bruising and discomfort during and immediately after treatment. Significant bleeding is not usually an issue but it should be noted that reactive hyperemia might follow regional nerve blockade to the wrists, with increased oozing at each injection site. Frank hematomas are very uncommon. BoNT injections in the palm in general and those specifically can lead to weakness of the muscles of the hand and over time may lead to atrophy (see **Table 2**, multiples studies). Weakness is quite common (see **Table 2**), more frequent with higher doses of the agent,[28] and at least in one study more frequent with BoNT A/abo than A/Ona. Although the weakness is usually of short duration, in one study it lasted 6 months.[28] Of note, one study showed the HH increased after treatment of the palms with BoNT injections[32]; however, this has not been our experience.

Palmar injections can be complicated by adverse events related to regional nerve blocks, such as inadvertent vascular puncture, impaired hand dexterity, and neuropathy from repeated nerve injuries, as reported by several authors.[34]

PROCEDURE FOR ADMINISTRATION OF BONT

BoNT Dilution

Dilution is an issue that one must contend with because there are many potential dilutions for BoNT. There is no consensus on the amount of dilution to use. One author has suggested that the optimal dilution of A/Ona is 25 U/mL.[30] We find that for palmar and plantar injections, reconstitution of one vial of Botox (100 units) with 3 mL of bacteriostatic preserved saline results in a manageable dilution (33 U/mL) for injection. With the 3-mL dilution, each 0.1 mL results in 3.3 IU of Botox. To prevent toxin wastage in the vial and to avoid blunting the needle we recommend removing the bottle stopper. To avoid toxin wastage in the syringe we always use hubless syringes. It is important also not to let the needle touch the bottom of the vial because it blunts the needle. If using A/Abo Dysport for HH (300 units per vial) we recommend diluting with 3 mL of bacteriostatic preserved saline, which gives a final dilution of 10 U per 0.1 mL.

Multiple Needles for Injection

Given that palmar and plantar skin is very thick, needles dull quickly after serial injection. We therefore draw up the A/Ona Botox 100 U into six 0.5-mL syringes (B&D Ultra-Fine II 30-gauge hubless insulin needle syringes; Becton-Dickinson, Franklin Lakes, NJ). This ensures the needles are changed regularly and makes it easier to inject the fluid in the thick dermis.

Iodine Starch Test

The Minor iodine-starch test (**Figs. 1** and **2**) can be used to estimate the surface area of involvement that requires treatment. We have found this test of limited value initially, in that it tends to show involvement of the entire palm or sole and that it poorly estimates the amount of sweating. It is of significant value in follow-up to help delineate any missed areas (see **Fig. 2**). For most patients, we advocate marking both the hands and feet in a gridlike pattern with a pen.

Injection Pain Reduction

Injection pain is a very significant factor in the treatment of patients with palmar or plantar HH and pain is likely a significant factor in compliance. Many techniques have been proposed to reduce the pain. These include needle-free anesthesia[35]; ice[36]; skin cooling devices, such as those made by Zimmer; vibration analgesia[37];

Fig. 1. Starch iodine test of a palm before treatment.

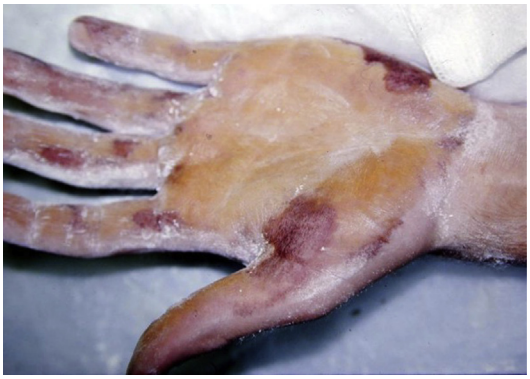

Fig. 2. Starch iodine test of a palm after treatment.

pocketed microneedles[38]; modified Bier blocks[39]; and nerve blocks.[40] These methods can be used in combination routinely or when a nerve block is incomplete. In our practice, we advise the use of either ice, a high-intensity vibration device (eg, AcuVibe, Poway, CA), or nerve blocks alone or in combination adjacent to each injection site to overstimulate nerve fibers.

Ice alone is used frequently in our HH clinic. Ice cubes held with gauze (or frozen with gauze on the outside) must be held on the skin for approximately 10 seconds before injection.[36] The ice is then moved to the next location while the injection is taking place. Ice is preferred over freezer packs because ice maintains a constant temperature. An absorbent pad under the hand is recommended to help with the melting ice. When using a cooling device for pain control on the palms, be careful to avoid freezing the BoNT solution in the needle when injecting.

Nerve Blocks

Nerve blocks are also used frequently by us and others[40] with success. Nerve blocks do have several disadvantages. These include the issues that there is a steep learning curve, that they are very user dependent, that nerve injury is a significant risk, that the patients spend a long time in the office, and that the patients generally cannot drive themselves home.

For the palms, median and ulnar nerve blocks are required (**Fig. 3**). It is imperative to know the relevant anatomy (**Fig. 4**). To perform a median nerve block, locate the palmaris longus tendon and the flexor carpi radialis tendon just proximal to the proximal wrist crease. The best way to accentuate these tendons is to ask the patient to make a fist and then to ask them to resist you pushing the wrist into extension. We then insert the needle just proximal to the proximal wrist crease between the palmaris longus and flexor carpi radialis tendons. We usually inject 2 mL of 1% lidocaine. We inject 0.3 mL above the fascia to get the palmar cutaneous nerve and 1.7 mL below the fascia for the main nerve. It is imperative to warn the patient that if they feel any unusual pain, numbness, tingling, and "shocks" during the injection that they should tell you immediately because this may signify intraneural injection.

For the ulnar nerve block, we identify the flexor carpi ulnaris tendon at the proximal wrist crease. To find the flexor carpi ulnaris tendon, we ask the patient to make a fist, then ulnarly deviate the wrist, and finally resist you pushing the wrist into extension.

We usually inject 2 mL of 1% lidocaine just radial to flexor carpi ulnaris at the proximal wrist crease. Once again we inject 0.3 mL above the fascia to get the dorsal sensory branch of the ulnar nerve and 1.7 mL below the fascia to get the main nerve. It is important to watch for symptoms of intraneural injection. In each case one should always withdraw to ensure that the needle tip is not intravascular.

For plantar injections, sural nerve and posterior tibial nerve blocks are needed.[13] A sural nerve block anesthetizes the fifth toe and lateral side of the sole. It requires injection of 3 to 5 mL of 1% lidocaine between the lateral malleolus and the Achilles tendon. A posterior tibial nerve block anesthetizes the heel and middle of the sole of the foot. For this nerve block, palpate the posterior tibial artery near the medial malleolus. The nerve is lateral to the artery. Inject 5 mL of 1% lidocaine in the groove between the medial malleolus and the Achilles tendon. Wait 15 minutes for regional nerve blocks to take full effect. Regional nerve blocks may be incomplete despite several attempts. In these cases we add ice or the AcuVibe.

Treatment Area

The hands and feet are marked in a gridlike pattern (**Figs. 5** and **6**). Each injection point is spaced 1- to 1.5-cm apart because it is likely less diffusion occurs on the palms and soles compared with other body sites. With experience, the grid pattern becomes second nature to the injector and the sterile pen markings are not required.

The BoNT should ideally be placed at the junction of the dermis and the subcutaneous tissue because this corresponds to the location of the eccrine glands. However, given the likelihood of significant muscle weakness (see **Table 2**) with a subcutaneous injection our preference is to place the injections intradermal, which thus limits

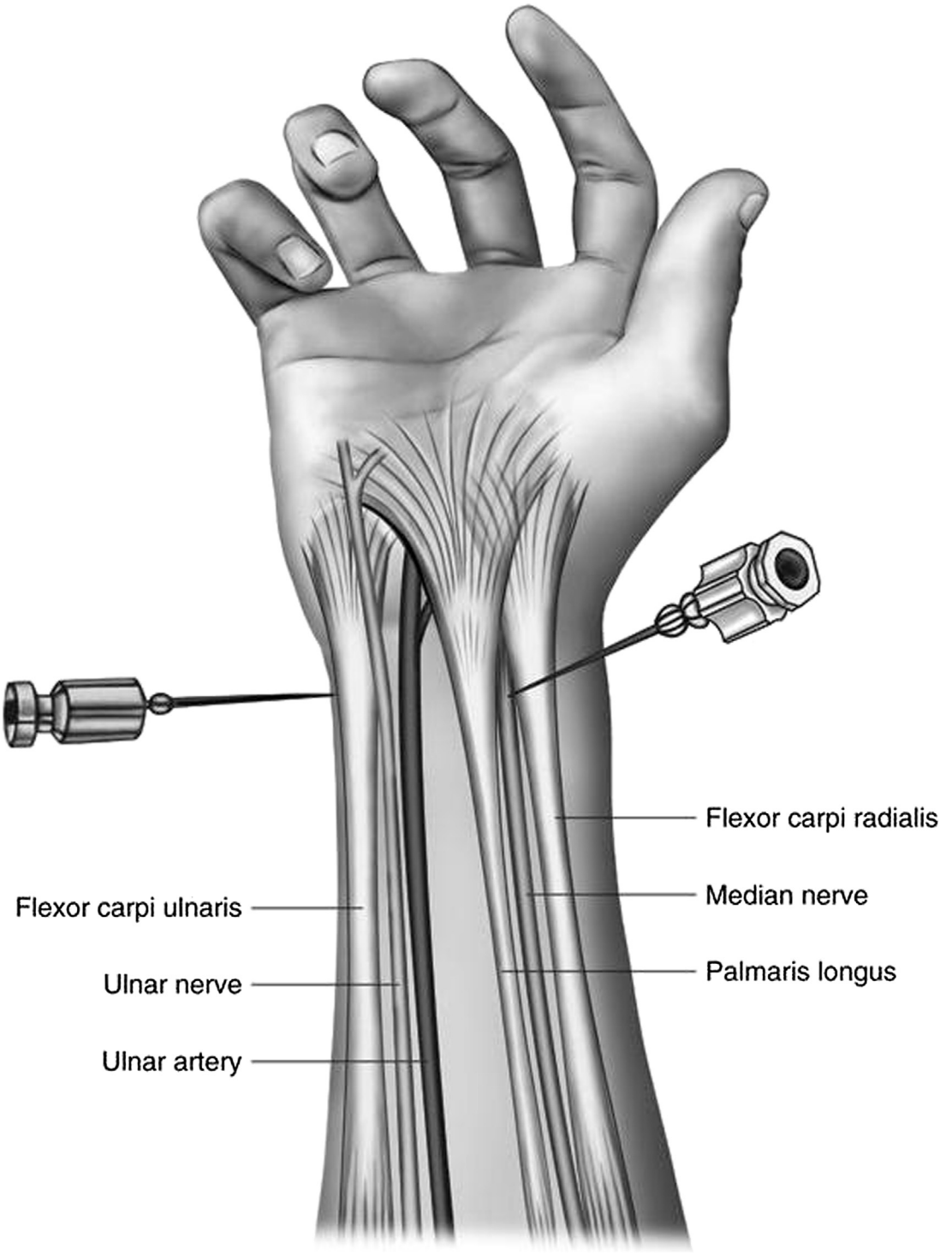

Fig. 3. Schematic showing the typical injection sites for median and ulnar nerve blocks.

diffusion of the product into the muscles. This is more important in the hands than the feet because there is less subcutaneous tissue in the hands and weakness in the hands would be more noticeable.

Weakness usually presents with complaints, such as difficulty using a key or activities that require grip strength. One should note that it is common to see a small zone of blanching and uncommon

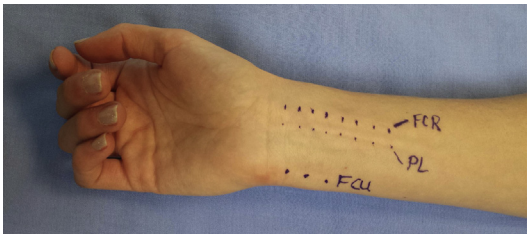

Fig. 4. Forearm surface anatomy showing the tendons of flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), and palmaris longus (PL).

to see a wheel around each injection point on the palms and soles.

Injection Dose

The optimal dosing for palms and feet is uncertain because of a paucity of studies. Some authors recommend a range from 50 to 100 U for A/Ona and 100 to 240 U of Abo/A BoNT per hand (see **Table 2**). The size of the hand helps to determine the final dose. Two to thee units should be used for each injection site. Muscle weakness in the hand is an issue and may be dose dependent so we recommend starting with 50 U A/Ona Botox per hand then reassessing the first-time patient at 1 month. Injections have been shown to last about 6 months[13,32] and are thus typically repeated every 6 months.

Injection Technique

The intradermal injection technique required in the palms and soles tends to result in backflow, which can manifest as leaking out of the injection site. There are several injection techniques to minimize this. They include injecting with the bevel down, maximal acute angling of the needle to the skin surface, injecting slowly over 1 to 2 seconds to allow time for normalization of pressure, pausing for 1 second after injection is complete before withdrawing the needle, and making sure there are no air bubbles in the syringe.[34,41]

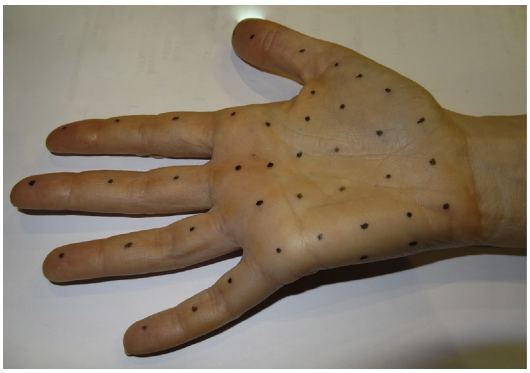

Fig. 5. Typical injection grid for the palm.

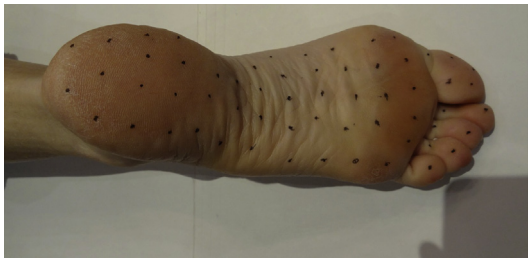

Fig. 6. Typical injection grid for the foot.

Patient Monitoring and Followup

Patients are monitored in the office for signs and symptoms of adverse events and encouraged to report any that occur following treatments and between follow-up visits. We counsel patients that they will begin to notice a difference in 7 to 10 days. We recommend follow-up every 5 months in treatment-naive patients and every 6 to 7 months in patients treated on a regular basis. We routinely call patients within 2 weeks of treatment to confirm that they have noted a decrease in symptoms.

For patients who are in professions that require fine hand movement and strength, we recommend first treating the nondominant hand and then the dominant hand at a later visit after further discussion with the patient.

SUMMARY

Palmar and plantar HH is relatively common and can have severe psychological and medical consequences for those afflicted. A multitude of treatments exist but are often inadequate especially for those with significant disease. In these cases BoNT, in its various formulations, provides a reliable method for reducing the symptoms and improving the QOL. Most of the studies have been done for Botox A/Ona and show significant efficacy. Although the actual administration is relatively straightforward, pain management is a crucial component that requires a mastery of several techniques. Patients have a high degree of satisfaction with BoNT treatment and are motivated to come back for repeat treatments, usually every 6 months.

REFERENCES

1. Strutton DR, Kowalski JW, Glaser DA, et al. US prevalence of hyperhidrosis and impact on

individuals with axillary hyperhidrosis: results from a national survey. J Am Acad Dermatol 2004; 51(2):241–8.
2. Lin TS, Fang HY. Transthoracic endoscopic sympathectomy in the treatment of palmar hyperhidrosis—with emphasis on perioperative management (1360 case analyses). Surg Neurol 1999;52:453–7.
3. Lakraj AA, Moghimi N, Jabari B. Hyperhidrosis: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins (Basel) 2013;5:821–40.
4. Hornberger J, Grimes K, Naumann M. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 2004;51:274–8.
5. Naumann MK, Hamm J, Lowe NJ. Effect of botulinum toxin type A on quality of life measures in patients with excessive maxillary sweating: a randomized controlled trial. Br J Dermatol 2002;147: 1218–26.
6. Sato K. The physiology, pharmacology and biochemistry of the eccrine sweat gland. Rev Physiol Biochem Pharmacol 1997;79:51–131.
7. Lear W, Kessler E, Solish N. An epidemiological study of hyperhidrosis. Dermatol Surg 2007;33:S69–75.
8. Manca D, Valls-Sole J, Callejas MA. Excitability recovery curve of the sympathetic skin response in healthy volunteers and patients with palmar hyperhidrosis. Clin Neurophysiol 2000;111:1767–70.
9. Glaser DA, Herbert AA, Pariser DM, et al. Palmar and plantar hyperhidrosis: best practice recommendations and special considerations. Cutis 2007;79(5):18–28.
10. Wooley-Loyd H, Valins W. Aluminum chloride hexahydrate in a salicylic acid gel base: a case series of combination therapy with botulinum toxin type A for moderate to severe hyperhidrosis. Cutis 2011; 88:43–5.
11. Walling HW, Swick BL. Treatment options for hyperhidrosis. Am J Clin Dermatol 2011;12(5):285–95.
12. Lewis DR, Irvine CD, Smith FC, et al. Sympathetic skin response and patient satisfaction on long-term follow-up after thoracoscopic sympathectomy for hyperhidrosis. Eur J Endo Vasc Surg 1998;15(3): 239–43.
13. Grunfeld A, Murray CA, Solish N. Botulinum toxin for hyperhidrosis: a review. Am J Clin Dermatol 2009; 10(2):87–102.
14. Hamm H, Naumann M, Kowalski JW, et al. Primary focal hyperhidrosis: disease characteristics and functional impairment. Dermatology 2006;212:343–53.
15. Haider A, Solish N. Focal hyperhidrosis: diagnosis and management. CMAJ 2005;172(1):69–75.
16. Kaufmann H, Saadia D, Polin C. Primary hyperhidrosis: evidence for autosomal dominant inheritance. Clin Auton Res 2003;13(2):96–8.
17. Solish N, Benohanian A, Kowalski JW, Canadian Dermatology Study Group on Health-Related Quality of Life in Primary Axillary Hyperhidrosis. Prospective open-label study of botulinum toxin type A in patients with axillary hyperhidrosis: effects on functional impairment and quality of life. Dermatol Surg 2005;31:405–13.
18. Campanati A, Bernardino ML, Gesuita R, et al. Plantar focal idiopathic hyperhidrosis and botulinum toxin: a pilot study. Eur J Dermatol 2007;17(1):52–4.
19. Goh CL. Aluminum chloride hexahydrate versus palmar hyperhidrosis. Evaporimeter assessment. Int J Dermatol 1990;29(5):368–70.
20. Akins DL, Meisenheimer JL, Dobson RL. Efficacy of the drionic unit in the treatment of hyperhidrosis. J Am Acad Dermatol 1987;16(4):828–32.
21. Dolianitis C, Scarff CE, Kelly J, et al. Iontophoresis with glycopyrrolate for the treatment of palmoplantar hyperhidrosis. Australas J Dermatol 2004;45(4):208–12.
22. Schnider P, Binder M, Auff E, et al. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. Br J Dermatol 1997; 136:548–52.
23. Lowe NJ, Yamauchi PS, Lask GP, et al. Efficacy and safety of botulinum toxin type a in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. Dermatol Surg 2002;28: 822–7.
24. Simonetta Moreau M, Cauhepe C, Magues JP, et al. A double-blind, randomized, comparative study of dysport vs botox in primary palmar hyperhidrosis. Br J Dermatol 2003;149:1041–5.
25. Baumann L, Slezinger A, Halem M, et al. A double-blind, randomized, placebo-controlled pilot study of the safety and efficacy of myobloc (botulinum toxin type B) for the treatment of palmar hyperhidrosis. Dermatol Surg 2005;31:263–70.
26. Solish N, Bertucci V, Dansereau A. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. Dermatol Surg 2007;33(8):908–23.
27. Naumann M, Dressler D, Hallett M, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of secretory disorders. Toxicon 2013;67:141–52.
28. Saadia D, Voustianiouk A, Wang AK, et al. Botulinum toxin type A in primary palmar hyperhidrosis: randomized, single-blind, two-dose study. Neurology 2001;57:2095–9.
29. Campanati A, Giuliodori K, Martina E, et al. Onabotulinumtoxin type A (Botox) versus incobotulinumtoxin type A (Xeomin) in the treatment of focal idiopathic palmar hyperhidrosis: results of a comparative double-blind clinical trial. J Neural Transm 2014; 121(1):21–6.
30. Rystedt A, Karlqvist M, Bertilson M, et al. Effect botulinum toxin concentration on reduction of sweating: a randomised, double blind study. Acta Derm Venereol 2013;93:674–8.

31. Benohanian A. Treatment of recalcitrant plantar hyperhidrosis with type-A botulinum toxin injections and aluminum chloride in salicylic acid gel. Dermatol Online J 2008;14(2):5.
32. Gregoriou S, Rigopoulos D, Makris M, et al. Effects of botulinum toxin therapy for palmar hyperhidrosis in plantar sweat production. Dermatol Surg 2010; 36:496–8.
33. Tracey C, Vlahovic TC, Dunn SP, et al. Injectable botulinum toxin as a treatment for plantar hyperhidrosis. A case study. J Am Podiatr Med Assoc 2008;98(2): 156–9.
34. Fujita M, Mann T, Mann O, et al. Surgical pearl: use of nerve blocks for botulinum toxin treatment of palmar-plantar hyperhidrosis. J Am Acad Dermatol 2001;45:587–9.
35. Benohanian A. Needle-free anaesthesia prior to botulinum toxin type A injection treatment of palmar and plantar hyperhidrosis. Br J Dermatol 2007;156(3): 593–6.
36. Smith K. Ice minimizes discomfort associated with injection of botulinum toxin type A for the treatment of palmar and plantar hyperhidrosis. Dermatol Surg 2007;33:S88–91.
37. Moraru E, Auff E. Hyperhidrosis of the palms and soles. Curr Probl Dermatol 2002;30:156–69.
38. Torrisi BM, Zarnitsyn V, Prausnitz MR, et al. Pocketed microneedles for rapid delivery of a liquid-state botulinum toxin A formulation into human skin. J Control Release 2013;165:146–52.
39. Solomon P. Modified bier block anesthetic technique is safe for office use for botulinum a toxin treatment of palmar hyperhidrosis. Dermatol Online J 2007; 13(3):6.
40. Hayton MJ, Stanley JK, Lowe NJ. A review of peripheral nerve blockade as local anaesthesia in the treatment of palmar hyperhidrosis. Br J Dermatol 2003; 149:447–51.
41. Murray CA, Cohen JL, Solish N. Treatment of focal hyperhidrosis. J Cutan Med Surg 2007;11:67–77.