Botulinum Toxin for Hyperhidrosis in Palmoplantar Area

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Abstract

Hyperhidrosis is a skin condition that leads to excessive production of sweat more than required for normal thermoregulation, affecting both men and women from childhood or adolescence. It is estimated that hyperhidrosis affects 3% of the US population. Areas such as the palms and soles are frequently affected, and it may exert deep negative impact on patient's

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personal and professional life. Treatment is difficult, and various therapeutic methods are available with limited effectiveness. Botulinum toxin has been used for 20 years safely and effectively. We will discuss the literature and bring clinical experience with this treatment.

Keywords
Sweat · Hyperhidrosis · Botulinum toxin

Introduction

Sweat is secreted by eccrine sweat glands that are stimulated by cholinergic fibers of the sympathetic nervous system. Its main function is to regulate body temperature, and it is produced in heat situations and emotional disorders such as anxiety. Excessive production of sweat, which goes beyond the physiological stimuli, is called hyperhidrosis (Fig. 1). It affects nearly 3% of the population and may represent a significant negative impact on quality of life, both social and professional (Campanati et al. 2003).

The sites of greatest concentration of these glands are the palms of the hands, soles of the feet, and underarms that are also the most commonly involved areas.

Peculiar forms of hyperhidrosis are described as gustatory sweating (Frey syndrome), front focal hyperhidrosis, inguinal, and perianal, among others.

Fig. 1 Excessive sweat in palms (palmar hyperhidrosis)

In addition to the social impact and significant impairment in quality of life, hyperhidrosis has been linked to diseases such as bromidrose, eczema, chronic infections, and pitted keratolysis (Ayres 2015).

There are reports of botulinum toxin treatment in hyperhidrosis since 1996, but it was approved by the FDA for the treatment of axillary hyperhidrosis in 2004 and, since then, is routinely used off label for hyperhidrosis in other areas.

Classification

Hyperhidrosis can be classified as primary or secondary and also as focal or generalized types. Focal hyperhidrosis is restricted to parts of the body and can be caused by local heat or food or represent a primary idiopathic type. Generalized hyperidrosis affects all skin, and its etiology is usually secondary, varying from exposure to heat, use of drugs, and metabolic and febrile diseases, among others.

- Primary or idiopathic: does not have a well-established cause, although studies have shown that family history is positive in 30–50% of cases, (Chia et al. 2012) suggesting genetic involvement. There is also much evidence for abnormalities in autonomic nervous system function. It is usually induced by emotional stress and affects underarm (51%), plants (30%), palm (24%), and face (10%) (Chia et al. 2012). It affects both sexes (Ayres and Sandoval 2016) and usually appears in childhood and adolescence. The diagnostic criteria include hyperhidrosis at least in the past 6 months without secondary cause, and it has at least two of the following: impairment of daily activities, bilateral and relatively symmetric sweating, episodes at least once a week, beginning before age 25, ceases during sleep, and family history (International Hyperidrosis Society 2016).
- Secondary: can be localized or generalized and may be due to underlying conditions such as menopause, infections, malignancy, drugs, genetic syndromes, and neurologic, endocrine and vasomotor disorders, among others.

Diagnosis

The diagnosis is essentially clinical, with complete personal history to exclude the possibility of secondary causes for the frame. It is based on the level of impact on the patient's quality of life, which can be measured by the Quality of Life Questionnaire in Dermatology (DLQI) and Severity Scale Hyperhidrosis Disease (HDSS), and also in the amount of sweat that may be reviewed by gravimetric testing and Minor's test.

To perform gravimetry, a filter paper is placed in contact with the area to be evaluated, where it stays for 1–5 min. In palmar hyperhidrosis, the weight difference of the paper before and after contact with the skin should be more than 100 mg of sweating in 5 min for both sexes, according to a retrospective analysis published by Thorlacius et al. (2015).

The starch iodine test or Minor's test is the most practical and used in everyday clinic. It helps to quantify the sweating, to limit the affected area, and also helps the evaluation of response to treatments performed. At first 3–5% iodine in alcoholic solution is applied in the area, and then cornstarch is applied above it. The sweat becomes purple after the interaction with iodine and starch, delimiting the area of increased production of sweat (Fig. 2).

Fig. 2 Iodine-starch test or Minor's test showing area of palmar hyperhidrosis

Treatment

There are several ways of treating hyperhidrosis, since clinical therapies to surgical approaches, but all have limitations and possible complications. The dermatologist's challenge is to find the optimal therapeutic intervention for each patient, based on the location and intensity, also considering the DLQI and the HDSS (Brown et al. 2014). We will discuss the options in primary hyperhidrosis, with emphasis on toxins for palmoplantar hyperhidrosis.

Topical

Topical medications are the first choice in the treatment of palmoplantar hyperhidrosis because they are easy to access and handling, for having low cost and relatively satisfactory results. However, it requires continuous application by its short half-life and often requires high concentrations of products for a better response, which can cause dryness, itching, and eczematization. The mechanism of action of antiperspirants is a mechanical obstruction of the sweat glands, with decreased sweat production.

The aluminum chlorohydrate at a concentration of 20–50% in ethanol or salicylic acid gel is the most effective and most used drug. It should be applied to dry palms and soles at night to increase the absorption and can be removed only in the morning, about 6–8 h later. This process should be repeated every night until there is a reduction in sweating, when the frequency of applications will be decreased to 1 time every 1–3 weeks. It can also be associated with other procedure such as iontophoresis and botulinum toxin, especially in more severe cases or in case of partial response of these treatments.

Iontophoresis

It is a second-line therapy for the control of moderate hyperhidrosis and first line in severe cases, with or without topical agents. It is a simple, well tolerated, safe, and effective in some cases, but

required serial treatments to reduce perspiration and maintenance therapy, which lowers the adherence. The mechanism of action is still not well established.

The technique is the introduction of ionized substances through intact skin by electric current. It can be made with water, solutions containing anticholinergics in more severe cases, and botulinum toxin has also been described. Glycopyrrolate has been reported in some papers with superior response to water iontophoresis, in spite of the higher risk of possible side effects by systemic absorption of the drug. The use of iontophoresis and botulinum toxin is not routine, but the most recently published work on this approach supports the idea of a longer anhidrosis than in relation to water iontophoresis (Davarian et al. 2008).

Solish et al. (2007) recommend 20–30-minute sessions, 3–4 times a week, using a device that sends a current of 15–20 mA. The sweat control usually occurs between the sixth and 15th day after the session begins when the maintenance every 1–4 weeks may be started. The duration of the treatment varies from 2 to 14 months after the last session.

Kacar et al. (2014) present iontophoresis as an effective therapeutic modality in children with palmar hyperhidrosis in a retrospective study published in 2014, but protocols must be better established as the ideal interval between sessions.

Adverse events are infrequent and well tolerated as xerosis, scaling, and erythema; however, there may be systemic absorption of anticholinergic drugs when they are used, which can cause dry mouth, visual disturbances, and urinary retention, among others.

Contraindications to the procedure are pregnancy, arrhythmia, pacemaker, intrauterine contraceptive devices, or metal prostheses.

Systemic

Anticholinergic drugs are systemic drugs commonly used to treat hyperhidrosis, since the eccrine sweat glands are cholinergic fibers stimulated by the sympathetic nervous system. They act as competitive inhibitors of acetylcholine in the synapse junction. Therapeutic options are considered isolated or adjuvants in the treatment of severe palmar hyperhidrosis when there is failure in response to aluminum chlorohydrate and/or iontophoresis or botulinum toxin, according to Solish et al. because of the potential risk of adverse events such as dry mouth, constipation, urinary retention, palpitations, mydriasis, hyperthermia, and convulsions. Even so many studies have shown the effectiveness of some drugs of this class and with relative safety, taking this treatment modality to the second choice in the control of palmar and axillary hyperhidrosis.

Oxybutynin has been increasingly used and has shown a promising drug including in children, according to Wolosker et al. (2014), with clinical improvement of symptoms and DLQI in more than 80% of patients. Dry mouth was the main side effect and only one child had drowsiness. In the experience of the authors, this drug is a new and cost-effective therapeutic option, with safety and effectiveness. They suggest starting with 2.5 mg once a day, and the dose is gradually increased up to 5 mg two times a day within a 12-week interval.

Glycopyrrolate is another potential emerging drug as second-line treatment. There is an improvement in about 70% of patients at a dose of 2–6 mg. In a retrospective analysis of 2012, Paller et al. (2012) showed a cost-effective use of medication in the pediatric population, effectively in more than 70% of cases and dose-dependent side effects, particularly dry mouth and dry eye. In Kumar et al. (2014) reinforce the same findings and the importance of glycopyrrolate as a therapeutic option in children.

Surgical Treatment

Endoscopic thoracic sympathectomy should be considered when there is refractory to all medical therapies because it is an invasive procedure with considerable risks of complication. Compensatory hyperhidrosis is the main one and can occur in over 60% of cases.

The results are effective and permanent, and the technique is safe. The most recent studies have

shown satisfactory results in palmar hyperhidrosis with significantly reduced rates of compensatory hyperhidrosis, by using the technique of unilateral endoscopic thoracic sympathectomy, instead of the usual bilateral mode.

Devices

Energy-based devices, such as radiofrequency, have recently been described for the treatment of primary axillary hyperhidrosis, suggesting they are effective in reducing the amount of sweating. However, very limited published data of successful treatment is available, and studies in palmoplantar hyperhidrosis are lacking.

Botulinum Toxin

Botulinum toxin inhibits the release of acetylcholine from the presynaptic nerve terminal, obtaining a temporary and reversible chemodenervation in eccrine sweat glands, reducing the production of sweat (Grunfeld et al. 2009).

It is a therapy of first choice in the treatment of severe hyperhidrosis and second line in moderate cases. It is considered a revolutionary therapeutic modality to control sweating for its efficiency and high levels of satisfaction in improving the DLQI and HDSS in most cases, even in children as shown by Santos et al. (2009), Kouris et al. (2015) and Gordon and Hill (2013). However, its limited effect a few months, the high cost, and the pain caused by various application points, especially on the palms and plants that are richly innervated, make an additional challenge procedure in the treatment of these areas (Benohanian 2009; DÉpiro et al. 2014; Doft et al. 2012).

Managing Pain

Although considered to be a safe treatment technique, it is considered to be very painful for some patients. Pain can be a limiting factor to the performance of the procedure, and therefore analgesia is essential. Several methods are available; however, there is not an ideal gold standard method. Each case should be assessed individually, respecting the experience of the professional. The techniques described are the use of topical anesthetics, dipping the hands into ice water, vibratory anesthesia, crioanalgesia, dichlorotetrafluoroethane spray, ice packs immediately before punctures, needleless injection systems such as Med-Jet®, medial nerve blockade and ulnar Bier block anesthesia or modified by Solomon method, and more recently the use of nitrous oxide as inhalational analgesia (Almeida et al. 2001).

The authors recommend the use of topical anesthetic under occlusion for 30 min followed by applying ice directly to the skin immediately before each puncture (Fig. 3).

For palmoplantar hyperhidrosis, when the patient does not tolerate the pain with the described analgesia and does not present contraindications, anesthetic block can be performed. The palmar sensory innervation is mainly due to the median nerve, responsible for much of the palmar innervation, the ulnar nerve, and the radial nerve responsible for innervating the side of the palm and thumb (Fig. 4). The median nerve is located between the tendons of the palmar and radial flexor carpi that can be viewed in the central part of the wrist in flexion. The median nerve can be blocked injecting 3–5 ml of lidocaine or anesthetic solution between tendons 1 cm apart the wrist line. The ulnar nerve can be blocked by

Fig. 3 Ice application immediately before each puncture to minimize pain during botulinum toxin injection for palmar hyperhidrosis

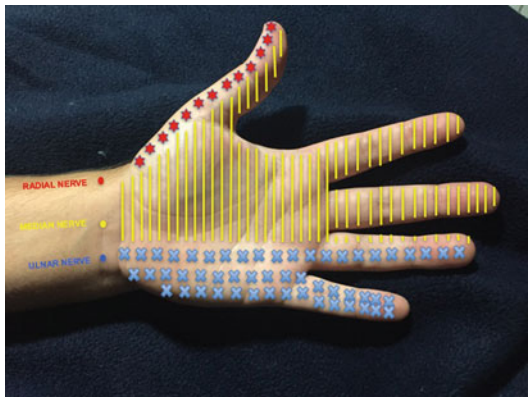

Fig. 4 Areas of sensitive innervation in palms

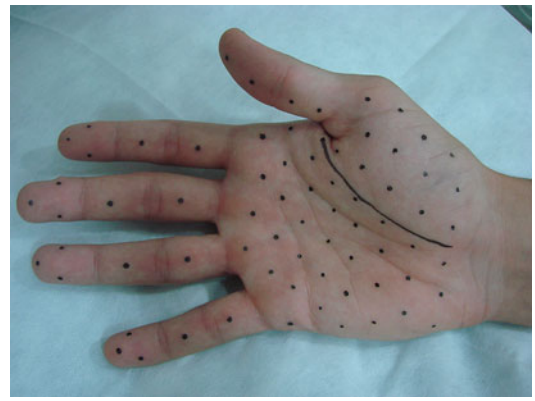

Fig. 5 Applications points for botulinum toxin injections

injecting the same amount of anesthetic between the ulnar artery and the tendon of the flexor carpi ulnaris, guiding the needle into the ulnar styloid process, 1 cm apart the wrist line. When the radial nerve blockade is required, it can be done by injecting the anesthetic in the lateral surface of the wrist line with reference to the radial artery, as they are side by side, always with care to avoid intravascular injection.

Application Technique

Before application, the area to be treated should be limited to Minor's test and photographed for later comparison. Generally the whole palm and sole are affected including the region of the fingertips. Although usually there is an extensive area affected, often some parts have a higher intensity of sweating and can be prioritized.

The dilution of botulinum toxin may be in 2–4 ml of 0.9% saline with or without preservative, for each vial of 100 U of onabotulinumtoxinA or the equivalent of other toxins (El Kahky et al. 2013). The application must be in intradermal level injecting 1–3 U of onabotulinumtoxinA per point with 1–2 cm distance between them (Fig. 5).

In the treatment of palmoplantar hyperhidrosis, the recommended total dose is between 100 and 200 U of onabotulinumtoxinA. Hypohydrosis starts 2 days after injection, and a new Minor's test should be performed after 2 weeks, when results can be seen (Fig. 6) and a new application can be carried out if excessive sweat is remaining.

According to Tamura et al. (2004) experience for treating plantar hyperidrosis, diluting 100 U vial of onabotulinumtoxinA in 4 or 5 ml of saline is suggested. A foot shoeing a shoe size 35 can benefit from 50 U by foot if hyperhidrosis is mild to moderate.

The treatment lasts lower than in axillary hyperhidrosis, about 6 months, ranging from 4 to 12 months.

Contraindications

Contraindications to botulinum toxin are pregnancy; lactation; allergy to albumin; patients with neuromuscular disorders, such as myasthenia gravis and Lambert-Eaton disease; and peripheral motor neuropathy (amyotrophic lateral sclerosis).

Side Effects

Side effects of the procedure include local pain, bruising, and formation of antibodies after repeated treatments, which appears to be related to high doses and short breaks between sessions. The temporary muscle weakness especially of hands and fingers occurs in 5–77% of patients. It is self-limiting in 10–42 days, dose related and application in the subcutaneous tissue. The authors suggest superficial intradermal injections

Fig. 6 Iodine-starch test before and 2 weeks after botulinum toxin injections for palmar hyperhidrosis

and small doses, no higher than 1 U onabotulinumtoxinA per square centimeter, in thenar and hypothenar areas.

Although botulinum toxin is a safe and effective treatment for palmoplantar hyperhidrosis, some patients do not tolerate needle injections, and pain is a limiting factor for others. Therefore, new methods of application have been described such as iontophoresis and more recently topical botulinum toxin, whose studies are in phase 3 of research and expected to be in the near future commercially available. Recent studies from Issa et al. have shown the fractional laser-assisted botulinum toxin delivery as a new possibility for hyperhidrosis treatment.

Fractional Laser-Assisted Botulinum Toxin Delivery for Hyperidrosis

The skin is almost impermeable for most hydrophilic and charged molecules, and a molecular weight (MW) of 500 Da is generally accepted as the upper limit for passive diffusion of lipophilic molecule. Therefore, there is strong interest in developing dermal penetration enhancement techniques (Haak et al. 2012).

Recently, the use of ablative fractional RF or CO_2 laser associated with high-pressure ultrasound (US) has been described as a successful method for drug delivery in alba-type stretch marks (Issa et al. 2012), hyperthrophic scar treatment (Issa et al. 2013), and areata alopecia (Issa et al. 2015).

BTXA injections are highly effective in treating hyperhidrosis; however, pain associated with injection is the major limitation (Benohanian 2009). Fractional laser-assisted drug delivery for palmar hyperhidrosis treatment was suggested by Letada et al. (2010) in a study using aminolevulinic acid on the palmar area. The authors had evaluated this new modality of treatment (fractional laser-assisted BTXA) for hyperidrosis in some cases.

Protocol Used by Authors

Before each session, the area to be treated was cleaned with alcoholic clorexedine and then with physiologic solution. Any anesthesia was necessary, but an air cooling device was applied during the procedure.

The treatment procedure comprised three steps: (1) ablative fractional CO_2 laser for skin perforation, (2) topical application of BTXA, and (3) acoustic pressure wave US to enhance BTXA penetration into the skin (Fig. 7).

The fractional CO_2 laser device used in this protocol has a roller tip which slides on the skin surface, producing micro-channels (pixels). It triggers a short-duration pulse of fractioned light via special beam splitter lens with fixed gaps between each 7×1 pixels. Laser parameters: CO_2 roller tip with 60 W, 50 mJ/pixel, spacing 1 mm. It produces microscopic holes having depth of 150–300 μm and diameter of 125–150 μm. The acoustic pressure module (US) is composed of a

Fig. 7 TED procedure with fractional ablative CO_2. First step, applying the CO_2 roller tip; second step, botulinum toxin (BTXA) on the perforated skin; third step, applying the acoustic pressure US on the palmar area

transducer, a sonotrode, and a distal hollow. The mode of operation is based on mechanical pressure and torques by propagation of US wave (27 kHZ), creating a hammering-like effect on the thin layer between the topical BTXA, the skin, and the sonotrode. US parameters: 50 Hz (frequency of shocks) with 50% of impact intensity for 5 s in each 2 × 2 cm grid.

The 100 units of 900 kD botulinum toxin (Botox®) was diluted in 2 ml of physiologic solution 0.9% and dropped (2 U/2 cm^2) on the skin pretreated with laser.

With aim to compare this new modality of treatment to the standard protocol of botulinum injections, we used only 50 U of BTXA after the laser, and the other 50 U was injected on the contralateral hand.

After the procedure patients were advised to wear latex gloves for 4 h before cleaning the hands.

Fig. 8 Iodine-starch test before, 30 days and 3 months after TED procedure (CO_2 laser + BTXA + US) on palmar area

Clinical Effects

A 2-point improvement in hyperhidrosis disease severity scale (HDSS) score (80% reduction in sweat production) could be observed after 1 and 3 months in most cases, and it was sustained for 6 months (some cases) in both hands (injected and laser assisted) (Fig. 8). Curiously, iodine-starch test showed a homogenous reduction of sweat on the side treated with TED comparing to the side

treated with injection where a halo of BTX diffusion was noticed.

Side Effects

Side efffects included discrete erythema and a low intensity pain (burning sensation) during the procedure and for the following 4 h.

Discussion

This new method can be a good option for patients who cannot sustain the pain or tolerate needle injections. More studies are necessary to determine the best parameters and to define the protocol.

Take Home Messages

- Although the exact pathophysiology of primary hyperhidrosis is not completely known, there is much evidence for abnormalities in autonomic nervous system function and may be genetically determined.
- Treatment options available to patients with primary hyperhidrosis can be categorized as nonsurgical (topical antiperspirants, iontophoresis, systemic medication) or surgical (endoscopic thoracic sympathectomy, excision of axillary tissue).
- The use of botulinum toxin A has become an important option in the treatment of palmoplantar hyperhidrosis especially in patients who do not respond to conservative therapies.
- To avoid muscle weakness, be careful to inject intradermally and superficially and small doses, no higher than 1 U onabotulinum toxin A per square centimeter, especially in thenar and hypothenar areas.
- Patients with fear of needle and sensitive to pain can benefit from other methods of application of botulinum toxin such as iontophoresis or fractional laser-assisted botulinum toxin delivery.
- Fractional laser-assisted BTXA for hyperhidrosis is a very new possibility, and more studies are necessary to establish the protocol.

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