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Variety of therapeutic approaches to primary hyperhidrosis(HH) and botulinum toxin priority over other treatment options in this condition - a review

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Abstract

Introduction and purpose

Hyperhidrosis(HH) is a medical conditions that affects more and more people every year. It is characterized by undue sweating without any temperature changes and significantly above the body's thermoregulation needs. Primary hyperhidrosis is associated with genetic and psychological factors, as the etiology is not yet found. Treatment is aimed at the symptoms. Secondary

hyperhidrosis happens as an adverse event of drugs taken by patient or is a part of neurological, endocrine or oncological diseases. Teratment should be focused on the main underlying disease. The quality of life of these patients is reduced and it affects their psychological health.
This study inevstigates currently available methods of treatment.

State of knowledge

Various treatment options for hyperhidrosis range from topical aluminum salts for mild cases to oral anti-cholinergic agents for more severe conditions. Additional methods include iontophoresis, lasers like Nd:Yag, and botulinum toxin injections, known for their effectiveness. Surgical procedures such as Endoscopic Thoracic Sympathectomy, local skin excision, liposuction-curettage are also available for severe cases. Consultation with a healthcare provider is crucial to determine the most suitable treatment based on individual needs and preferences.

Conclusions

Literature provides valuable insights into hyperhidrosis and its treatments, emphasizing the importance of patient expectations and safety. Starting with topical aluminum salts for mild cases, treatments need to be reapplied regularly. Surgical options are considered if conservative treatments fail, but they come with potential risks. Botulinum toxin injections stand out for their efficacy, quick procedure, and the convenience of one or two annual sessions, making them a popular choice in many aesthetic clinics. Consulting with healthcare professionals is key to selecting the most suitable treatment approach for individual needs.

Keywords: hyperhidrosis; primary hyperhidrosis; botulinum toxin; treatment; quality of life; iontophoresis; sympathectomy.

Introduction and purpose

Hyperhidrosis(HH) is a condition of excessive uncontrollable sweating that happens to a patient at any time without temperature changes or abnormal physical activity. The sweating is much over the need to keep homeostatic temperature regulation of the body. [1,3] Studies show that there is no abnormality found in the glands' morphological structure; the reason for overstimulation of the eccrine glands lays in the abnormal reaction of the hypothalamus, the centre of the body

thermoregulation. It is believed to be caused by over-activation of sympathetic nervous system and overstimulation of eccrine sweat glands. [2]There are two types of sweat glands: eccrine and apoeccrine. Primary Hyperhidrosis is associated with eccrine glands located mostly in the area of the face, palms, axillae, soles and these ares are the most common body sites affected by this condition.

Hyperhidrosis can be classified as primary and secondary. While the etiology of primary hyperhidrosis remains unknown and is mostly contributed with genetic and psychological factors, the secondary hyperhidrosis may be due to adverse effect of specific drugs like antipsychotic, selective serotonin reuptake inhibitors or be a part of systemic disorders: neurological, endocrine or oncological. Diagnostic and therapeutic pathways differ in each type. [3]

In secondary hyperhidrosis we should focus not only on the symptoms alone but the underlaying disorder should be treated.

Diagnostic criteria for primary hyperhidrosis:

1. Hyperhidrosis for 6 or more months
2. Sweating involves axillae, palms, soles and/or face
3. Bilateral and symmetric sweating
4. Decreased or no sweating at night
5. Sweating episodes last at least 7 days
6. The person is 25 years old or younger
7. There is family history of over-sweating
8. Sweating affects daily life activities negatively. [1,3]

Hyperhidrosis affects patients' everyday life negatively and reduce quality of life. From shaking hands with others to seeing wet stains on the clothes, it causes embarrassment and leads to social limitations. While this condition is not life threatening, correct treatment can change one's life and reduce risks of psychological disorders.[4] It usually begins in childhood or during puberty. [5]

Nowadays, there is variety of treatment options available. From conservative like topical agents to advanced surgical procedures. The best treatment should be least invasive and cause minimal or zero adverse events. Choosing the best treatment pathway should be followed by evaluation of the patient's history, previous therapeutic approaches and results. In this review we describe methods of treatment, their effectiveness and safety with emphasis on treatment with botulinum toxin as it seems to be the most effective and least invasive method in this condition. [4,7]

Methodology

The following review was based on articles from the PubMed and Google Scholar databases. Key search terms included hyperhidrosis; primary hyperhidrosis; botulinum toxin; treatment; quality of life; iontophoresis; sympathectomy.

The state of knowledge

Diagnostic tests for hyperhidrosis

There are a few methods to asses a severity of hyperhidrosis. Gravimetric analysis, skin conductance, dynamic sudorometry or Minor's test. The most common and probably the easiest to carry out is Minor's test.

Minor's test is conducted with iodine solution which is applied to the skin and after it dryes off the starch powder is put on top of it. After a couple of minutes when those substances react with sweat, the are changes its color to violet. The violet colour indicates the area with the biggest glands reactivity.[3]

The gravimetric analysis is also an easy test but in opposite to Minor's test it does not indicate the area with the biggest glands reactivity. In this method the filter paper has to be weighted and then inserted in the area of hyperhidrosis. After 60 seconds or 5 minutes it is taken and weighted again. The difference between the initial weight and the weight after shows the amount of sweat in mg per minute. [7]

Axillary hyperhidrosis is defines when the amount of released sweat is over 50 mg per minute; on the hand's palm it is 20 mg per minute.[2]

Canadian Advisory Hyperhidrosis Committee introduced a Hyperhidrosis Disease Severity Scale(HDSS) in which patients characterize the intensity of their condition from 1 to 4. The scale is useful in comparing the severity before and after treatment. One-point improvement means approximately 50% reduction of sweating, while two-point improvement about 80% reduction.[6,7]

Treatment methods

There is a vast of treating options for patients with primary hyperhidrosis as topical treatments, oral and iontophoretic treatments, botulinum toxin injections and surgical procedures.

Non-surgical methods

Topical treatments play a role only if the hyperhidrosis is mild. First of these are aluminum salts.

Their work of action is associated with keratin in the sweat ducts. Commonly used antiperspirant contains salts in concentration from 1% to 2%. Medications contain concentration of 15% to 20%. By binding with keratin in the sweats ducts they promote its closing and then atrophy. The effects is time limited ands to be reused 3 times a week. The only side effect is skin irritation and numbing feeling. The use of topical formaldehyde or glutaldehyde is limited as they cause allergic reactions. [8,9,10]

Another conservative treatment option is iontophoresis. It is mostly used in hyperhidrosis of the palms and soles. This method uses continuous direct current and water. The mechanism of action is not precisely known. Some studies suggest glands obstruction, dysregulation of electrical gradient of sweat or increasing the threshold for stimuli in the sympathetic nervous system. While this method delivers good results in patients, it is problematic. It has to be carried out two/three times a week until the effect is achieved. After achieving therapeutic effect, it has to be repeated every two/ three weeks. It remains a good option but is very time consuming. [9,10,11]

Laser technology may also be used as a treatment option. 1,440 nm and 1,064 nm Nd:Yag lasers show a significant role in hyperhidrosis. Studies show, there is no change in histological structure of the sweat gland before and after treatment but both objective and subjective improvements are noted. Laser treatment is performed once a month and the effect lasts up to one year post-treatment but further studies should be conducted.[7,12]
When it comes to 800 nm diode laser, studies showed no significant changes in sweating.[7]

There is also a microwave-based FDA-approved device designed to treat HH. It is designed by Miramar Labs and is. This technology uses microwaves to heat the dermis and glandular tissue what results in cellular thermolysis.[10] The results are promising: over 90% of patients experience a decrease in sweating. The side effects are localized and include redness, swelling, discomfort.[7] There was a case of post-treatment median and ulnar neuropathy but it resolved after one year. Hong et al treated 31 axillary HH patients with microwave-based device. During the follow at month 1, 3, 6 and 12, 94% of the patients reported one-point drop at the HDSS and 55% two-point drop at the HDSS.[13]

Oral drugs can be considered when other options fail to work or hyperhidrosis is more generalized[8]. Oxybutynin is well known anti-cholinergic medication. It has been often used for

overreactive bladder symptoms. In trials with placebo, over 90% of patients treated with oxybutynin report satisfactory results. The most common reasons why patients stop this treatment are side effects. Taken orally, Oxybutynin as an anti-cholinergic agent reacts with receptors throughout the body, not only in the are affected with HH, thus it may cause headaches, mouth dryness, urinary retention, constipation.[7] For patients who find it difficult during the long-run therapy, other options should be considered. Wolosker et al conducted a study to evaluate the long-term effect of oxybutynin. From 431 patients with axillary hyperhidrosis only 181 met the criteria of taking the drug for 6 months. 34 patients failed to improve and were referred for VATS, 26 patients reported improvement but did not want to stay with oral medications for a long time, they were also referred to VATS, 6 patients refused the forward intake due to side effects of oxybutynin. 93,4% of 181 patients reported improvement at the sixth week and after twenty fourth week 82,9% patients maintained this state. Comparing the results from the week 6 to the median time of 17 months 57,4% patients maintained the initial improvement, 23,3% reported even more improvement, while 19,4% reported deterioration of alleviated symptoms. [14]

Surgical methods

One of the most common surgery procedure for HH is sympathectomy. This treatment focus on ablating the second, third and fourth thoracic ganglia.[15] The positive outcomes are documented for axillary, craniofacial and palmar HH. Patients should be educated about possible adverse events after the surgery. Like every surgical procedure, there is possibility of adverse during the surgery but also many patients report problem with excessive sweating in areas that were not affected before.[16] Patients find it very difficult and often regret undergoing the procedure. Bell et al conducted a study to evaluate the efficacy and adverse events occurrence in 210 patients that underwent Endoscopic Thoracic Sympathectomy due to axillary, palmar or craniofacial hyperhidrosis. A significant improvement has been seen in all the groups: 97% in palmar HH, 71% in palmar HH and 93% in craniofacial HH. Unfortunately, 75 % of patients developed CH, condition of excessive sweating after sympathectomy. [17]

Another option is sympathotomy. This surgery does not cause neural injury as the ganglions are not cut. Furthermore, most studies show that sympathotomy is as effective as sympathectomy but does not cause compensatory over-sweating in another body site. Atkinson et al evaluated 155 patients who underwent endoscopic thoracic limited sympathotomy. After 3 months post-surgery 96,6% of patients reported desirable effect on palmar HH, 69,2% on axillary sweating and 39,8% improved

on plantar HH. Five patients had a recurrence of palmar sweating and severe compensatory hyperhidrosis was only reported in two patients.[18]

Surgical excision of sweat glands may be conducted in two different ways: radical skin excision and excision without skin removal. Results are good and comparing to sympathectomy/sympathotomy this method needs only local anesthesia. Patient does not have to stay at the hospital but still drains are required and the site of excision is prone to infections, hematomas, necrosis or seromas.[7,10]

Liposuction-curettage is performed with cannulas to destroy the axillary glandular tissue between dermis and subcutaneous tissue.[10] Differently to skin excision the curettage needs only 2 excision so there is no danger for scars. The procedure is carried out with local anesthesia. In one study Tronstad et al compared isolated currettage with liposuction-curretage in 22 patients. Each received liposuction-currettage to one axillae and isolated curettage to the opposite one. 17 patients were examined at the follow-up at 3, 6 and 12 months after the operation. All of them reported more significant alleviation of HH symptoms in axillae treated with liposcution-currettage. Liposuction-currettage not only breaks down the glandular tissue what is done in the isolated curettage but also resects it. Resection prevents from glandular tissue recovery. [19]

Botulinum toxin injections

Botulinum toxin(BTX) is a toxin produced by Clostridium botulinum bacterium. In form of a drug it can be used to reduce facial wrinkles like glabellar lines, horizontal forehead lines or crown's feet, strabismus, blepharospasm, cervical dystonia and hyperhidrosis. There are 7 serotypes of toxin produced by Clostridium botulinum.[20] While the type A(BTX-A) is widely used in aesthetic medicine, ophthalmology and neurology, type B(BTX-B) needs further studies. What has been known until now is that type B has similar results in palmar hyperhidrosis and comparing to type A, the autonomic nervous system is more sensitive to type B than the motor system.[21] The mechanism of action is associated with inhibiting the release of acetylcholine from sympathetic neurons at the neuromuscular junctions. BTX-A target is SNAP-25 SNARE protein while BTX-B target is VAMP SNARE protein. Without SNARE proteins the vesicles with acetylcholine cannot bind and release its content into the synapse.[21,22] In hyperhidrosis the target is not located in the skeletal muscles but in eccrine glands which are also innervated by the sympathetic nervous system. By inhibiting the release of acetylcholine from the presynaptic vesicles botulinum toxin blocks the cholinergic transmission to sweat glands and in this way reduce the perspiration.[23]

BTX-A(BOTOX; Allergan, Irvine, CA, USA) has been approved by the FDA for the treatment of axillary hyperhidrosis but has also great efficacy in palmar and plantar HH.[23]This treatment is a good option for patients when the topical agents and other non-surgical procedures failed to work. It is quick and the effect lasts for 6 or more months. Some studies shows the slow release of the symptoms up to 24 months.[24] Adverse events may occur but are temporary and include pain during injections and muscle weakness(palms). Pain may be controlled with the use of liposomal lidocaine. When it comes to muscle weakness BTX-B can be considered as it does not have such a significant effect on muscle strength as BTX-A.

Before starting the procedure the Minor's iodine-starch test should be done to asses the exact target zone with the greatest sweating. Target zone should be marked with pen and divided into even 1,5 x 1,5 cm squares. These squares are the injections spots; it is indicated to administer 2 MU of BTX-A(BOTOX; Allergan, Irvine, CA, USA) intradermally per square. Mostly, 50 MU of BTX-A are administered in one axilla. In palms and soles 100 MU per one.[23]

Studies prove that patients treated with BTX-A have a high and rapid(in one week) alleviation of the uncomfortable symptoms(up to 95%) comparing to patients treated with placebo (up to 37,2%) [25]. In another study Nauman and Lowe demonstrate 320 patients suffering from axillary hyperhidrosis and who were treated with BTX-A. They indicate a great improvement in emotional, daily, social and work life.[25] Ibrahim et al compared BTX-A injections to Liposuction-currettage in 20 patients with axillary hyperhidrosis. Each patients was given BTX-A injections in one axillae and lipuscution-currettage was performed in the opposite one. At the follow-ups at 3,6 and 12 months no significant differences in results were noted for both treated areas. Moreover, at month 3 and 6 patients reported a greater satisfaction with the area treated with BTX-A comparing to the side treated with liposuction-curretage.[26] Castiglione et al involved 81 patients with axillary hyperhidrosis treated with BTX-A at their hospital over a year. All patients reported a great improvement in symptoms. HDSS scores were reduced form 3.4 to 1.5. They saw that the more severe the initial sweating is the better improvement is reported.[27]

Glaser et al conducted a study to prove the efficacy and safety of use botulinum toxin in adolescents with primary axillary hyperhidrosis. The results of this study showed no difference from other studies on adult patients. Botulinum toxin are beneficial to this group of patients.[28]

Introducing botulinum toxin as a remedium for hyperhidrosis change the approach of many practitioners to this condition.[29] Earlier in the days it was believed to be triggered only by emotions, while nowadays we know that this is the separate disease to be adressed.[30]

There is a concern that repetitive injections of Botulinum toxin may lead to immunoresistance as the body produces neutralizing antibodies to it. Studies show that it is likely to occur mostly when periods between treatment are short and doses are high.

Conclussions

This literature provides an actual knowledge about hyperhidrosis treatments, the ones investigated before and others that require further studies, research and confirmation of their efficacy in this condition. Topical medications are still the first-line treatments for hyperhidrosis. Aluminium salts in concentration of 15-20% in medications play a great role in HH treatment but the lasting effect is only up to 48h. Another side effect may be skin irritation and stains on the clothes. Oral agents like Oxybutynin might be a good option for patients who tolerate side effects of anti-cholinergic medications. The long-term use may be difficult due to constipation, mouth-dryness, difficult urination and headaches. Iontophoresis, even though it has a proven action in hyperhidrosis is not as commonly used in the clinics as other treatment options. Not only, is it not available but has to be repeated to sustain the decrease of symptoms. Researches about laser technology like 1,440 nm and 1,064 nm Nd:Yag report very good long-term results after series of treatment once a month. Comparing to other non-surgical methods, this treatment should be examined meticulously as probably it will change the approach to treating HH. While laser treatment seems to be affordable, its downside is that it also has to be repeated to provide the effectiveness. The micro-wave technology is not a popular option amongst clinicians. Not only does it not have wide-range of studies showing its efficacy but also adverse events like ulnar neuropathy may occur during treatment. Surgical methods should be considered in patients when other treatment options failed to work. The most commonly performed surgery is Endoscopic Thoracic Sympathectomy. While the alleviation of symptom after this operation is great, the adverse event of compensatory hyperhidrosis is very often and patients regret undergoing ETS. Endoscopic Thoracic Sympathotomy is upgraded version of sympathectomy in which neural ganglions are not cut. This method seems to have a better overall outcome as reductions of symptoms is comparable to sympathectomy and the adverse events are rare. Liposuction-currettagge and local skin excision are not performed very often nowadays. When comparing this two methods, liposuction-currettagge has less adverse events in form of necrosis, infections and hematomas than skin excision but still, both treatment has to be performed with high-quality equipment by well-trained practitioners. Botulinum toxin is one of the best studied and most available treatment for hyperhidrosis nowadays. With the only side effect of painful injections it has a great efficacy in decreasing the symptoms.

Pain during the injections may be alleviated by using topical anesthetic agents or by mixing the solutions with lignocaine. While the BTX-A treatment is not a cheap procedure it has to be repeated once or twice a year. Considering the minimal side effects, availability and great results in reducing the symptoms botulinum toxin injections seems to be most prominent treatment for hyperhidrosis nowadays.

Disclosure

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