Daily oscillations of sweating in hyperhidrotic individuals before and after treatment with botulinum toxin A

Abstract

BACKGROUND: Primary focal hyperhidrosis is caused by excessive secretion by eccrine sweat glands, usually at axillae, palms and soles. The underlying mechanism is unclear. Botulinum toxin A is a highly efficient treatment for this condition. A subjective self-assessment scale has been shown to be a useful tool in assessing the variation in sweat levels before treatment. It has also been shown that treatment of hyperhidrosis with botulinum toxin A increases the patients’ quality of life. OBJECTIVES: To study the daily variations of sweating in hyperhidrotic individuals and how this affects quality of life (QOL) before and after treatment with botulinum toxin A, using a subjective self-assessment scale. METHODS: 18 patients with a history of hyperhidrosis (7 axillary, 5 palmar and 6 general) were studied. Each participant self-assessed rates of sweating for 7 days on an hourly basis using a subjective evaluation scale (SES) ranging from 0 to 10 before, one, three and six months after treatment with botulinum toxin A. The patients also recorded one VAS (Visual Analogue Scale) -QOL value before and after treatment. RESULTS: Following treatment, VAS-QOL increased in all patients (Median value before and after 5 and 9, respectively, p< 0.01), and there was also a reduction in sweating after one and three months in all patients (SES_{before} = 4.2, SES_{1 month} = 0.8, SES_{3 months} = 0.9, p < 0.0001). After six months, the difference was not significant, but the values had not reached the pre-treatment level. Different patterns of sweating were observed before treatment, and most patients also showed the same pattern after treatment, but the values were lower. CONCLUSIONS: Successful treatment of hyperhidrosis with botulinum toxin A gives a significant increase in VAS-QOL and significantly decreases the sweat levels after one and three months.

1.0 Objectives

To study the daily variations of sweating in hyperhidrotic individuals and how this affects quality of life before and after treatment with botulinum toxin A, using a subjective self-assessment scale.

2.0 Background

2.1 Introduction to hyperhidrosis

Hyperhidrosis is excessive sweating beyond what is required to return elevated body-temperature to normal.¹ Physiologically, sweating can occur as emotional, gustatory and thermoregulatory. In palms, soles and axillae, the thermoregulatory component
of the sweating is minimal. The condition may be primary (essential) or secondary, localized to certain skin areas or generalized.

A number of diseases may induce secondary sweating as a result of indirect dysregulation of sweat gland function in localized skin area or the whole body skin. Some of these conditions are mentioned below:

**Generalized:**
- drugs (Propranolol, physostigmine, pilocarpine, TCAs)
- cardiovascular disease (Increased sympathetic activity)
- respiratory insufficiency
- infections (Due to fever)
- malignant diseases (especially at sleep, mechanisms poorly understood)
- endocrine metabolic disease (f.ex. acromegaly, thyreotoxicosis, hypoglycemia, Parkinson disease)

**Regional:**
- stroke
- peripheral nerve damage
- central or peripheral nerve lesion giving localized anhidrosis with compensatory sweating (f.ex. spinal cord injury, Ross syndrome)

**Focal:**
- Frey’s syndrome (Can sometimes occur after parotidectomy. The cause is that the nerves responsible for saliva secretion grow into the cut autonomic nerves of the skin. This leads to redness of the skin and sweat secretion on the cheek and temporal region (on the operated side) when eating.)
- gustatory sweating
- tumour
- eccrine tumours

Primary focal hyperhidrosis is a disorder characterized by excessive, symmetrical sweating in the palms, soles and/or axillae or groin, head or face, of no known reason. Armpits are affected in about 50 % of the patients, feet in 29 %, palms in 25
% and the face in 20%. The excessive sweating must be of at least 6 months duration, and two or more of the following criteria need to be present:

- bilateral and symmetrical sweating (Although axillary sweating relatively often occurs not to be symmetrical).
- sweating interferes with daily activities
- episodes with severe raised sweating at least once a week
- presentation before 25 years of age
- heredity (About 50-70% of the patients)
- no sweat during sleep

There is a clear hereditary component, and in one study, 67% of the patient reported that one of their near relatives had the same condition. Hyperhidrotic individuals do not have an increased number of sweat glands, and the glands are also structurally normal and of normal size. Hyperhidrosis may develop in early childhood (especially palmar, solar sweating), but the presentation of symptoms mostly occurs in puberty or early twenties. Mean onset for palmar hyperhidrosis is about 13 years and for axillary about 19 years. The disorder seems to be equally distributed between the sexes, and has a prevalence of about 1% in the general population. The disorder may have a heavy impact on quality of life and may cause marked psychosocial problems. Many patients find that the disorder is keeping them from having a normal social life, regarding both spare-time activities and work.

2.2 Sweat gland morphology

Birgitte Berntsen and Ritika Gupta 2006
There are three different types of sweat glands: eccrine, apocrine and apoecrine. The apocrine glands are mainly located to the axillae and urogenital regions and are not involved in the pathophysiology of hyperhidrosis. They are important in producing body odour in humans, and this activity is stimulated by androgens and circulating adrenalin. In addition, the ducts are supplied by an adrenergic sympathetic nerve.

![Histology of apocrine sweat gland from nipple](image)

The development of eccrine sweat glands are visible in human fetuses at around 3 months of gestation. They are considered mature by 32 weeks, but do not carry out their function before birth. The process starts in the skin of the palmar fingers and continues in the soles, axillae and other body areas. In fetal life, the density of the sweat gland anlagen is about 3000/cm² in the 24th gestational week, at birth it is about half and at 18 months it has been reduced by another two thirds. The adult density of about 120/cm² is not changed further throughout life.

The main function of eccrine sweat glands is to allow body cooling by evaporation and to moisten the skin, especially on palms and soles. Eccrine sweat glands are localized all over the skin surface, but not on mucous membranes. The numbers vary greatly with site, and the highest numbers are found in palms, soles and axillae. The glands consist of a secretory coil in the junction between dermis and the subcutis and a duct portion which deliver the sweat directly to the skin surface.
2.3 Sweat production

The secretory coil produces a fluid; the precursor secrete. The main constituents of the precursor secrete is Na, Cl, K, urea and lactate. The concentration of the constituents is similar to that of plasma, but it does not contain plasma proteins. The precursor secretion is modified while flowing through the duct portion of the gland. This modification involves reabsorption of ions, mostly Na and Cl, which creates a hypotonic, water-like fluid. The extent of reabsorption depends on the sweat rate:

**Low sweat production:** This is the sweat rate at rest and cool temperatures. In this situation the precursor fluid passes the duct slowly. This gives time for maximum reabsorption of Na$^+$ and Cl$^-$ ions. In addition, water is reabsorbed osmotically because of the reduced osmotic pressure in the fluid. This leads to a small amount of sweat reaching the surface of the skin. The finished product consists of a lower concentration of Na$^+$ and Cl$^-$ and a higher concentration of K$^+$, urea and lactate than in the precursor secretion.

**High sweat production:** This is the sweat rate at exercise and hot temperatures. In this situation, large amounts of precursor secretion are produced, and passes the duct rapidly. This gives little time for reabsorption of Na$^+$ and Cl$^-$ and the amount of...
water reabsorbed osmotically is therefore also reduced. Larger amounts of sweat reach the surface of the skin, containing Na\(^+\) and Cl\(^-\) concentrations about one half of the plasma concentration. Concentrations of the other constituents are also elevated; K\(^-\) :20 % higher, urea: 50% higher, lactate: about four times higher than plasma levels.

All the cells of the secretory coil are attached to the basement membrane, and outside this, there are myoepithelial cells that contract when exposed to acetylcholine. The eccrine sweat glands are innervated by sympathetic nerve fibres, and the presynaptic pathway arises from the intermediolateral cell nucleus within the spinal cord. These fibres synapse in the sympathetic ganglion of the sympathetic trunk, and the postsynaptic fibres, which are non-myelinated C-fibres, terminate as periglandular nerve endings around the sweat glands. Transmission of a nerve impulse through this pathway results in the release of acetylcholine at the nerve ending, resulting in activation of the sweat glands. Achetylcholine is the main transmitter of the periglandular nerves, but in addition, several other substances have been detected by immunohistochemistry. Examples are S-100 protein, substance P, vasoactive intestinal polypeptide (VIP) and calcitonine gene-related peptide (CGRP).
3.0 Treatment options

3.1. Topical treatment
This is the least invasive method and it involves application of aluminium salts on the affected area. The effect is due to obstruction of the glands, and possibly atrophy of the secretory cells\(^1\). The effect of the treatment is approximately 48 hours, and repeated applications are necessary. The most common side-effects are irritation of the skin, localized burning and stinging.

3.2. Oral treatments
These are anticholinergic drugs, e.g. oxybutynin (Ditropan). They are antagonists to muscarinic acetylcholine receptors in sweat glands, and thereby also the sweat gland function. The most common side-effects are orthostatic hypotension, nausea, bladder muscular disturbances, inhibition of ejaculation, decreased secretion of saliva and disturbances in accommodation.

3.3. Iontophoresis\(^6\)
This method may be used for treatment of palmar and/or plantar hyperhidrosis. It is non-invasive, cheap, well tolerated and efficient. In this method, electric current helps the transport of ions through the skin. In the direct current method of tap water iontophoresis, an average current of 15 mA at a voltage of 20-40 V is most frequently used. This gives burning and tingling and it is therefore possible to use lower current, e.g. a fixed voltage of 16 V, to avoid this.

Method: The device consists of two electrode plates lowered in a bowl of tap water. The patient removes all metal items, and bathes hands and/or feet in the bowl. Amperage is slowly being increased, until the patient’s threshold for discomfort is reached. Amperage maintains just below this. The treatment should be repeated initially 3-5 times per week, for about 20 -30 minutes. Effect is seen after approximately 10-15 treatments. When sweating is sufficiently reduced, the treatment must be maintained after an individual schedule.

Most common side-effects are dysaesthesia and burning, erythema and urticaria, electrical stings by abrupt change in voltage.
Contraindications are pregnancy, pacemakers and metal implants.
3.4. Liposuction/curette\textsuperscript{7,8} 
This is used for treatment of axillary hyperhidrosis. The major advantage of this procedure, over excisional surgery, is that it gives much less scarring. The procedure is done in tumescent anaesthesia. The patient’s arm (s) are abducted approximately 90°, the vaults are painted with iodine and dry sprinkled with starch powder. The powder turns black from the sweat and gives the surgeon an idea of the area to be treated. Two or three incisions sites are made at the anterior and posterior axilla border. A cannula is inserted through the incision sites. The other end of the cannula is connected to a suction device which collects the aspirate, so it can be sent for histological identification. The suction holes in the cannula have sharp edges which gives the opportunity for creation of criss-crossed tunnels. In this way, deep dermis and upper subcutaneous fat, including eccrine and appocrine glands, can synchronously be removed without damaging the underlying tissue. Post-operative a compressive dressing is applied to the axilla for 24 hours, and the patient is given prophylactic oral antibiotics and analgetics. After 24 hours the patient gets compressive garment for 2 weeks and return to their daily activities within a week. Possible complications are recurrence of sweating, bleeding, infection, pain and haematoma.

3.5. Sympathectomy \textsuperscript{9} 
The sympathectomy is performed at different levels, depending on the localization of the hyperhidrosis:

- T2 for face/scalp
- T3 for palmar
- T4 for axillary

Operative technique: Both sides are never operated at the same time, and all procedures are performed under general anaesthesia. Three thoracoscopic ports are used, and CO\textsubscript{2} is insufflated to aid in exposure of the sympathetic chain. The correct level is identified with the help from the relation between the ribs, and ablated with the cautery. The patients are usually discharged home within the day. Most patients return to pre-operative activity level in approximately 3 days.
Possible complications:  
- compensatory sweating is reported in as many as 85% of the patients in some materials  
- pneumothorax (rare)  
- bleeding (rare)  
- Horner syndrome  
- Arrhythmias (especially bradycardia)

3.6. *Botulinum toxin A*  

Botulinum toxin in general:  
The toxin is produced by Clostridium botulinum, an anaerobe, gram positive, spore-forming bacteria. There are 7 different types of botulinum toxins; A, B, C, D, E, F and G. A, B, E, and F cause illness in humans. C. botulinum organisms are categorized as groups I-IV, depending on which toxin(s) they produce. The toxin is elaborated in foods, wounds and infant gut. It is neurotoxic, and amongst the most poisonous toxins known (low LD50). The spores are very heat-resistant, but the toxin itself is heat-labile, and can be destroyed by heating at a temperature of 80-100°C for 5-10 minutes.

Botulinum toxin acts in the cell cytosol on selected proteins, but the toxin must enter the nerve endings to exert its effect. The toxin is internalized inside endocytic vesicles. They are large zinc metalloproteins of ~150000 Da, composed of two parts: A 50000 Da piece which is the catalytic subunit, and a 100000 Da piece, containing an N-terminal translocation domain (makes it possible for the light chain to cross the endosomal membrane) and a C-terminal binding domain (binds the light chain to the vesicle membrane). The light chain and the heavy chain are linked with a disulfide bridge. If this bridge is broken before the toxin is inside the cell, the light chain cannot enter, and it loses its toxicity.

Target proteins of botulinum toxins are the SNARE proteins (soluble n-ethylmaleimide-sensitive fusion protein accessory protein receptor). They form a heterotrimeric coiled-coil SNARE- complex that induces the docking of the neurotransmitter-containing vesicle to the cytosolic face of the presynaptic membrane and give fusion between the vesicle and membrane.
There are two types of SNARE proteins: v-SNAREs and t-SNAREs. Vesicles that bud off from a membrane carry v-SNAREs. The target membrane contains t-SNAREs. In order for the vesicle to dock on the target membrane, the v-SNAREs must bind to the t-SNAREs.

After docking, a complex of membrane-fusion proteins assembles at the docking site and catalyses the fusion with the target membrane. When the SNARE proteins are cleaved by botulinum toxin, the SNAREs cannot mediate fusion of the vesicle and the target membrane. By all the above mentioned mechanisms, botulinum toxin leads to the inhibition of the release of acetylcholine at the presynaptic membrane of cholinergic nerve terminal. Hence, the nerve impulses cannot be transmitted.

For types B, D, F and G, the target is VAMP/synaptobrevin. VAMP forms a family of vesicular SNAREs, and different isoforms (especially VAMP 1 and 2) are located on cell vesicles and contribute to guide each vesicle to their target membranes for fusion; neuroexocytosis. Types A and E cleave a protein associated with the presynaptic membrane; SNAP25 (25 kD synaptosome-associated protein). There are few isoforms of SNAP25. They bind to the target membrane via fatty acids, which are linked to cysteine residues in the polypeptide chain of the SNAP protein. Botulinum toxin C cleaves SNAP25 and syntaxin, another protein involved in
neuroexocytosis. Syntaxin binds to the target membranes via a hydrophobic tail. The isoforms mainly involved in neuroexocytosis are 1A, 1B and 2.

Botulinum toxin A in the treatment of hyperhidrosis\(^{17,18,19}\):
This method is mainly used for the treatment of axillary and palmar hyperhidrosis. The procedure is described below (Material and methods). The advantages of this method is that it is minimally invasive, extremely efficient without the induction of side-effects, which is reported in many studies. The patients report improvement in several daily –life activities: Improvement in state of mind, emotional status, social situations, work productivity, engage in sex and athletic activities. In one study\(^{26}\) it was shown that the quality of life was significantly increased after treatment with botulinum toxin A, especially regarding social activities such as being in public places and meeting people for the first time. After treatment, the negative consequences on the emotional status because of hyperhidrosis, was also reduced. When comparing quality of life for patients with hyperhidrosis and patients with other skin diseases, such as acne vulgaris and psoriasis, the hyperhidrotic patients have a lower quality of life than these groups of patients. This is shown to be improved after treatment with botulinum toxin A.\(^{30,31}\) One study also reported reduction in depression, anxiety and social phobia.\(^{31}\) It is also a safe treatment that can be repeated without the problem with formation of neutralizing antibodies against the toxin.

Very few side-effects are reported; such as pain during the procedure and dryness of the palmar skin requiring moisturiser at times. Slight reduction in power of the thumb-index finger grip is seen in one study (Swartling et.al)\(^{20}\), and is most pronounced 3 weeks after the injections. This is most often seen in median innervated muscles, but also in muscles with ulnar nerve supply. The methods used to measure effects of botulinum toxin in muscles were repetitive nerve stimulation, single fibre EMG, measurements of muscle power and compound muscle action potential (CMAP). The muscle strength returns to normal after some weeks. In this study 76 % of the patients experienced muscle weakness, but 91% still wanted the same dose of Botox when having a new treatment, telling us that the effect of Botox treatment is more beneficial to the patient than the disadvantage of slightly reduced grip function. In another study (Lowe et. al)\(^{21}\), reduction in grip strength was not seen. In contrast to the sympathectomy, compensatory sweating does not prevail after the botulinum toxin treatment\(^{16}\). There are some disadvantages with botulinum toxin treatment: It is
expensive (2000 NOK for 100 E Botox) and must be repeated. The duration of the
treatment lasts approximately 4-12 months.

Precautions: Adrenaline, prednisolone and antihistamine should be available in case
of severe reactions to the drug. Effective and safe use of botulinum toxin is
accomplished by proper storage (2-8°C refrigeration), correct dose and proper
administration techniques.33

Drug interactions: One must pay extra attention to drugs that may cause increased
muscle weakness (aminoglycosides, cyclosporine) or antagonize the onset of
paralysis from botulinum toxin (aminooquinolines, d-penicillamine, tubocurarine,
succinylcholine) by either:

1) Action on the cell membrane by inhibiting the binding of the toxin or preventing
transport into the cell.

2) Action in the cell interior which inhibits the lysosomal processing of the toxin.33

Contraindications are infection at the injection sites, neuromuscular disorders (such
as myasthenia gravis), peripheral motor neuropathic diseases (such as amyotrofic
lateral sclerosis), pregnancy and lactation, organic causes of hyperhidrosis and
medications that may interfere with neuromuscular transmission3,33.

4.0 Material and methods
In this study we included 18 patients; 3 men and 15 women. The patients were
divided into three groups: - axillary (total: 7 patients; 1 man, 6 women)
- palmar (total: 5 patients; 1 man, 4 women)
- general (total: 6 patients; 1 man, 5 women)

The median age in our material was 26.5 (range 14-62). The median age of the
women was 26 years, and 35 years for the men. Figure 1 below shows the
distribution within the groups, considering sex, age and type of hyperhidrosis.
Figure 1  Distribution of age, sex and type of hyperhidrosis

For the 18 patients as a total, the median age of presentation was 13.5 years. (range 1-58). However, this variable varies between the groups. Median age of symptom appearance for the axillary group (women + man) was 16 years (range 6-30). For the palmar group 13 years (range 1-13) and for the general group 14.5 years (range 1-58).

It is a well-known phenomenon that hyperhidrosis has a clear hereditary component. In our study, 6/7 of the patients in the axillary group, 4/5 in the palmar group and 3/6 in the general group had one or more relatives with similar problems.

In our material, all patients were either working (office/sitting job: 6 patients, job requiring physical activity: 6 patients) or students (6 patients).

2 of the axillary patients, 3 in the palmar group and 4 with general hyperhidrosis reported that they have and/or have had additional diseases. These are: Endometriosis, hypothyreosis, chronic urinary tract infections, contact dermatitis, psoriasis, rheumatoid arthritis, osteoporosis, erythromelalgia, depression, asthma and atopic eczema.

3/18 of the patients were smokers, and 5/18 of the patients reported that they have had allergic reactions when exposed to certain allergens.

The patients were referred for treatment to the regional centre, where the diagnosis was confirmed by one dermatologist. The diagnosis criteria was confirmed upon
clinical findings, iodine-starch test (in axillary patients) and the interview containing the relevant questions regarding the condition connected to:

Pattern of sweating (which areas are involved?)
- daily variations?
- duration
- symmetrical sweating?
- are there any trigger factors?
- age of presentation
- does the sweating interfere with daily activities / quality of life?
- heredity
- check for symptoms that indicate secondary hyperhidrosis

The patients were asked to assess their sweating on a premade diary schedule on an hourly basis from 8 am to 12 pm for 7 following days before the treatment. The sweating (SES –subjective evaluation sweating score) was evaluated, using a scale from 0 to 10, where 0 means “no sweating” and 10 means “the most intense sweating the patient can imagine”. They are also encouraged to make free-text comments, regarding e.g. physical activity, stress, etc. for each SES to explain the variations in levels of sweating during the day and give information about underlying causes that give increased sweating. SES has been demonstrated to be useful when studying variations in sweating, and also in the diagnostic process. The patients were also asked to fill in a questionnaire regarding several aspects of hyperhidrosis (including age at presentation, heredity, smoking and allergy). The questionnaire also contained a VAS scale of subjective judgement of quality of life (QOL). The patients were asked to assess their quality of life on a scale ranging from 0 -10. In addition they were asked to fill in and diaries and assess quality of life 1,3 and 6 months after the treatment. The treatment is accomplished by the following procedure, and differed between the types of hyperhidrosis:

Palmar: The median and ulnar nerves are anaesthetized, using lidocaine $10 \text{ mg/ml}^{-1}$, 5 ml for each nerve. Botulinum toxin A (Botox®, Allergan) 100 U is dissolved in 1 ml saline. The injection sites, which are 1,5 cm apart, are marked with ink before giving Botox. Each finger is injected in 7 sites, 2 in proximal and middle phalangs and 3 in distal phalangs,
using a 30-µL syringe with a 30 G x 8-mm needle. Each hand is given approximately 75-80 injections. The duration of the treatment is approximately 90 minutes for both hands.
Injection of Botox in the palm

The area to be treated is outlined using the iodine-starch test. No anaesthesia is given. 50 U of Botox diluted in 4 ml saline was injected intracutaneously (30 G needle) with approximately 15-20 in each axilla. The duration of the treatment is 5-10 minutes for each axilla.

Treated palm (left) and untreated palm (right)

Axillary: The area to be treated is outlined using the iodine-starch test. No anaesthesia is given. 50 U of Botox diluted in 4 ml saline was injected intracutaneously (30 G needle) with approximately 15-20 in each axilla. The duration of the treatment is 5-10 minutes for each axilla.
Iodine-starch test

Iodine-starch test completed. The black colour outlines the area to be treated

The axilla marked with ink dots\textsuperscript{23}
**General:** These patients were treated with an anticholinergic drug; oxybutynin (Dridase). The dose used was 5mg x 2.

### 4.1 Statistical analysis
Analysis of total scores of VAS-QOL and SES-values was performed by a non-parametric Mann-Whitney-Wilcoxon test for paired samples. When comparing the SES-values before and after treatment in the axillary and palmar group only, we used Friedman's test for related samples, since we had several values for each patient. A Wilcoxon test was used to compare the two groups when significant calculations were achieved with Friedman's test. Statistical significance was considered at p< 0.05. Non-parametric statistics were used, as a normal distribution could not be assumed in the limited number of data sets.

### 5.0 Results
30 patients were included in the present study. During the post treatment period 12 dropped out and further analyses are based on 18 patients.

### 5.1. Quality of life
We have data regarding VAS-QOL from 6 patients in the axillary group, 4 in the palmar group and 5 in the group with general hyperhidrosis. We only used the information from the patients with registration both before and after treatment. If the patients provided information about VAS-QOL at several follow-ups, we used the highest value recorded. Irrespective of sweat localization or treatment modality all three groups of patients showed an increase of VAS-QOL after the treatment. (Fig. 2abc below).
Fig. 2 Median VAS-QOL before and after treatment of the patients with a) axillary sweating (n=6), b) palmary sweating (n=4) and c) general sweating (n=5). The after treatment value represent the single highest reported VAS-QOL value for each patient in the follow up period.
Median value summarized from the three groups of patients before treatment was 5 (median, range 0-10). After the treatment, the value increased to 9 (range 5-10, p<0.01, n=15). Fig. 3 below.

![Box plot showing QOL scores before and after treatment](image)

**Figure 3** Median VAS-QOL, 95% confidence interval and range before and after treatment in all patients (p=0.002, n=15). The after treatment value represent the single highest reported VAS-QOL value for each patient in the follow up period.

**5.2 SES-values before and after treatment**

In the whole group of patients we found a clear significant decrease from baseline one and three months after the treatment with respectively botulinum toxin and peroral medication. (SES = 4.2, n=15 before treatment. One month after treatment SES=0.8, n=17, and three months after treatment SES=0.9, n=12. p<0.0001). (Fig. 4abc).
Figure 4 Variations in SES-values during the week before and after treatment. Coloured lines indicate treatment status, see explanatory text in figure; a) Whole group, n=18  b) axillary group, n=7  c) palmar group, n=5
Mean SES-values before the botulinum toxin treatment was 5.5, n=11. A statistical significant reduction was found between baseline SES-values and the values recorded 1 (SES=0.21, n=12, p=0.006) and 3 months (SES=0.17, n=9, p=0.000) after treatment. Six months after treatment, the SES- value was still reduced near to a significant level (p=0.069, n=7). The SES was quite stable over the week in all groups of patients both before and after the treatment. (Fig.5 below)

Figure. 5  Mean SES-values in the axillary and palmar group of patients. The measurements at 2 weeks after treatment was only performed by the palmar patients. **p<0.01, ***p<0.001
5.3. Hourly oscillations in SES-values

We have in detail observed the hourly variation of oscillations in sweating before and after the treatment. (See fig. 6 a-k)

Axillary group (patients 1-7):
Patient 6, after 3 months

Patient 7, before

Patient 7, after 1 month

Patient 7, after 3 months

Palmar group (patients 8-11):

Patient 8, before

Patient 8, after 1 month

Patient 8, after 3 months
Figure 6 a-k  Patients’ hourly registrations of sweating during one week.
6.0. Discussion

We found a statistically significant increase in VAS-QOL after the treatment in all patients. Because of the drop outs it was not possible to make statistical calculations on each group separately. However, the results show that regardless of the type of hyperhidrosis, a reduced sweat level gives an increase in VAS-QOL. We may assume that the hyperhidrosis itself is the cause of the reduced VAS-QOL in these patients. It would, however, be interesting to compare the before levels of VAS-QOL before treatment with a similar assessment in a group of healthy controls to be certain that the increase in VAS-QOL is due to the decreased levels of sweating.

The increase in VAS-QOL is in well accordance with previous studies.\textsuperscript{26,30} The advantage with this instrument is that it is a very simple method in contrast to the more complicated questionnaires such as DLQI(Dermatology Life Quality Index), HHIQ(Hyperhidrosis Impact Questionnaire and SF-12 (Medical Outcomes Trust Short Form-12 Health Survey).

After treatment we found a significant reduction in sweating after 1 and 3 months in all patients. After 6 months, the difference was not significant, but the values had not reached the pretreatment level. This is in accordance with previous findings.

Reduction of sweat after the botulinum toxin treatment last for 3 to 18 months. In most studies a medium of 6 month duration has been documented.\textsuperscript{19,21,32} Patients with axillary hyperhidrosis follow the same pattern however, their sweat level at 6 months is still considerably reduced although it did not reach statistical significance. In the palmar group, the level at 6 months is higher than the level before treatment. This is interesting, because there is no evidence that treatment with botulinum toxin further increases the sweating when the treatment effect is diminished. One possible explanation may be that psychological factors play an important role: When the sweating returns after a period of minimal sweating problems, it might seem more excessive than before treatment, since the patients have adapted to a life without the manifestations of hyperhidrosis and therefore exaggerate the symptoms when they return.

In the group of general hyperhidrosis too few patients finished the study and therefore it is not possible to make conclusions about the efficacy of the peroral treatment. The few patients who finished the whole study had a good effect of the medication and an increase in VAS-QOL as patients treated with botulinum toxin.
The patients were instructed to fill in a SES-value in the diary every hour from 8 a.m. to midnight, but not all hours were filled in. We interpreted the hours without registration as SES-value= 0.

Two patterns could be distinguished in the axillary group before treatment: Some showed large variations in SES-values during the day, while others demonstrated a stable pattern of high values. One and 3 months after treatment, the patients who had great variations prior to treatment also have variations after treatment, but the values are lower. The patients that showed a stabile pattern before treatment, also show this 1 and 3 months after treatment.

For the palmar patients, we recognize three patterns: Before treatment, some show great variation, some have a more stable pattern in the middle of the SES-scale, while others have very low values most of the time, but with occasional spikes. After one month, SES-values for most patients have fallen to almost zero. After 3 months, some of the patients still have full effect of the treatment, and some have regained their sweating, but at lower values compared to levels before treatment. The patients that had low values before treatment reported that they had assessed the SES-values during the summer during the vacation, and therefore these values did not demonstrate their every day values during the year.

We also have to take into consideration, that it is every patient’s own experience of sweat intensity and level that makes up the base of our material. Their assessments varies with physical activity, stress, etc and other every day factors. We have not recorded this type of information. However, it is probable that the patients keep on with the same type of activity, work and exposure to stressful events during the whole study period. The subjective experience of, what is “high” level and what is “low “in this group of patient varies between the patients. The patients judge the sweating in a personal manner. However, the judgements seem to be relatively consistent from day to day in each subject although a large hourly variation was obtained in many patients. SES diary seems to constitute a good way of assessing this dynamic and fluctuating symptom in lack of objective methods to continuously measure the sweating in the every day life of the patient.  SES is shown to be sufficiently sensitive to give accurate information about the sweat levels in each patient, and is also a unique tool to demonstrate the daily variations of sweating, both before and after treatment. In addition, it is helpful in the diagnostic process and provides useful information about the efficacy of treatment.
Originally, we included 30 patients in this study. During follow-ups only 18 completed the diaries. This might be due to the fact that the patients improved. SES-levels near to zero might be boring to register and it is possible that they in such cases considered the information less interesting and irrelevant. It is also a possibility that some of the patients did not experience desired effect of the treatment and therefore lost the interest for further participation. Some of the patients probably felt that the SES-registration was too demanding and took too much time. This explanation seems most probable since we have checked the hospital records, and found that several of the drop out patients were satisfied, and have returned for further treatment.

7.0. Conclusion
In this study, we have shown that the patients have a significant increase in VAS-QOL after treatment for hyperhidrosis. We can also conclude, that treatment of hyperhidrosis with botulinum toxin A gives a significant reduction in sweating 1 and 3 months after treatment.
References


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