Evaluation of treatment of axillary and palmar hyperhidrosis with botox injections

Degree Project in Medicine

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Abstract

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Key words: Axillary hyperhidrosis, palmar hyperhidrosis, botulinum toxin, evaluation of treatment.

Introduction: Hyperhidrosis is a skin condition were patients sweat excessively. It affects 3% of the population and has a major impact on quality of life. Primary hyperhidrosis has a mostly unknown pathogenesis, but sympathetic overstimulation of sweat glands is a main cause. Sahlgrenska’s dermatology department started offering botulinum toxin (botox) injections in September 2013 after a Health Technology Assessment concluded that there was scientific evidence to support palmar and axillary treatment. Since then 179 unique patients have received injections but this far no evaluation has been made.

Aim: To evaluate the hyperhidrosis treatment with botox in the clinic by examining life quality in the patients, duration of treatment effect, effectiveness of treatment and side-effects.

Methods: The treatment form data was assembled in Microsoft Excel. Melior was used to search for any missing data. Analysis was performed with the help of the department statistician, who used the R-project statistics program.

Results: Pre-treatment dermatology life quality index (DLQI) showed significant improvement ($p < 0.0001$) over time for all age groups and for both palmar and axillary treatment. Duration only increased significantly ($p < 0.05$) between treatment 1 and 2 for
palmar patients < 20 and 20-30 years. Effectiveness of treatment was significantly higher for axillary treatment (mean 8.6) compared to palmar (mean 8.1). Pain from treatment was best reduced with nerve block, though this caused most pain by administration. Ice did not significantly differ from being without anesthetics in terms of treatment pain reduction. Side-effects were mostly unreported: 3 % of the appointments reported muscle weakness, 1 % fainting and 0.4 % increased general sweating.

**Conclusion:** Treatment with botox injections improves quality of life in hyperhidrosis patients over time, and not only when treatment is in effect.
Introduction

Sweat glands

Sweat glands are apocrine, eccrine and apoeccrine. The eccrine glands are mainly responsible for normal sweating and help with thermoregulation and improving the grip on the palms and soles. Eccrine glands exist all over the skin, excluding lips, external ear canal, clitoris and labia minora. The amount and size of the glands vary between people and the region of the body, causing each person to sweat an individual amount, and different regions to have their own sweat rate. The eccrine glands are made of a secretory coil in dermis and subcutaneous tissue and a duct leading up to the epidermis, opening to the surface of the skin. Cell types in the secretory coil are (seen in a light microscope): dark cells, secretory cells (of tubular epithelium) and myoepithelial cells whose function is to support the gland and help with secreting the sweat. The duct has luminal cells and basal duct cells, the basal cells can pump sodium and take part in reabsorbing salts from the ductal lumen [1, 2].

Composition of sweat

The main components of sweat are NaCl (sodium chloride), K (potassium), H$_2$CO$_3$ (bicarbonate), ammonia, lactate and urea. The sweat is isotonic when excreted from the gland cells, but after passing through the duct it becomes hypotonic due to reabsorption from the ductal cells (reabsorption cannot keep up with increased sweat rate). Depending on the rate of sweating the concentration of Na can increase up to 10 times. Some diseases such as cystic fibrosis (saltier sweat), Addisons (saltier sweat) and badly regulated diabetes (glucose in the sweat) can change the composition of sweat [1, 2]. Membrane protein pumps for water has also been found in both the secretory coil and in the duct, helping in transportation of water during the sweat production [3].
**Eccrine gland control**

The glands respond to signals from sympathetic nerves of non-myelinated c class type and the main transmitter signal is cholinergic. Triggers of the signal can be thermal, osmotic, mental, emotional or gustatory factors or a cyclic spontaneous type of sweating [4]. Mental stimuli cause sweating especially on the soles and the palms. The myoepithelial cells are mostly controlled by cholinergic signals from sympathetic nerves [1].

**Hyperhidrosis**

Hyperhidrosis is a skin disorder that causes excessive sweating in relation to thermoregulation, activated by heat, stress and physical effort. It can be primary or secondary, general or focal. General affects most of the sweat producing areas of skin and focal means that smaller regions such as the axillae, the palms or the soles are affected [1, 5]. The primary disease is of mostly unknown pathogenesis, though overstimulation of the sympathetic nervous system is one main cause. Secondary hyperhidrosis needs to be ruled out when making the diagnosis as it can be caused by a number of serious illnesses such as infectious (e.g. tuberculosis, malaria, endocarditis), metabolic (e.g. diabetes, hyperthyroidism, phaeochromocytoma), neurological, drugs (e.g. fluoxetine), menopause and congestive heart failure [1].

The hyperhidrotic sweat gland, its duct and secretory coil have the same morphological picture as a normal sweat gland, but are much more active and can be several times larger due to over-activity [6].

Patients’ onset of disease depends on the affected area, axillary often starting during puberty and palmar starting before 18 years [7].
**Prevalence**

The prevalence of hyperhidrosis is around 3% with males and females affected equally. An American survey from 2004 [8] found that approximately 2.9 % (2.9 % for males, 2.8 % for females) of the American population suffers from hyperhidrosis, and further that 50.8 % (1.4 % of the population) of them has axillary hyperhidrosis.

The survey wanted to find the number of affected individuals independently of whether they had gone to a doctor for a diagnosis. Only 38 % of the responders had brought up their problem of sweating to a health care professional (47.5 % of the females, 28.6 % of the males) suggesting that the need is much bigger than the patients who ask for help. About one third (32.4 %) in the same survey said that sweating was ‘barely tolerable or intolerable’ and that it interferes ‘frequently or always’ (representing 3 or 4 on HDSS) and 91.6 % said it interferes on some level in their life [8].

**Genetic transmission**

Primary hyperhidrosis is inherited in a likely autosomal dominant manner, though with incomplete disease penetrance [9]. In a study of 49 patients 65 % had a family history, compared to 0 % in the control group. The prevalence of the disease allele was said to be 5 % in the population and that 1 or 2 copies are enough to give someone hyperhidrosis 25 % of the time. Healthy alleles only cause hyperhidrosis 1% of the time [10]. Another study found that 37 % of hyperhidrosis patients had a family history compared to 9 % in the control group and that 40 % of axillary patients reported family history and 28 % of palmar patients [5].

**Diagnosis**

When a patient asks for help with excessive sweating it is important to make sure it is not due to secondary hyperhidrosis, and most often an interview and a clinical examination are enough. The general questions should focus on: pattern of sweating, age of onset, impact on
daily life, family history and symptoms that point to a secondary cause. The clinical examination should focus on finding evidence of excessive sweating and any symptoms pointing to secondary cause.

Primary focal hyperhidrosis should have affected the patient for at least 6 months at the point of diagnosis. It should have at least 2 out of 6 symptoms: ≥ 1 episode per week, symmetrical and or bilateral sweating, stopping during sleep, starting before 25 years, impairment on daily life and a family history of the disease [11].

**Impact on daily life**

Hyperhidrosis can have a large impact on many aspects in patients’ lives, making them suffer socially and professionally and holding themselves back from doing what they want [5, 8].

Feeling self-conscious or hesitant when shaking hands, feeling limited when being with family or friends or in intimate situations, selecting clothes that will not show sweat stains, spending a lot of time on hygiene, or damaging papers from sweaty hands are just the beginning of a long list of situations that patients say they are limited in due to their hyperhidrosis [8]. Some patients even avoid certain jobs or feel that they can’t do their job properly, which can have an even greater negative impact in the long run [5].

Symptoms and limitations make that mental health is worse in hyperhidrosis patients compared to the normal population. Depression and anxiety is more common than in control groups [8]. One study showed that 63 % felt unhappy or depressed and that axillary patients reported this more often than palmar patients [5].

**Hyperhidrosis disease severity scale (HDSS)**

The HDSS is a quick and easy tool to use for measuring the disease impact on a patient’s life (attachment 1). It has 4 score levels: score 1-2 represent mild or moderate hyperhidrosis, score
3-4 severe hyperhidrosis. The score is determined by asking the patient which statement out of 4 that fits their disease at the time. Statement 1 represents score 1 on HDSS: ‘my sweating is never noticeable and never interferes in my daily activities’. The same pattern returns in statement 2, 3 and 4, though the intensity increases. Statement 2: ‘… tolerable but sometimes interferes …’ Statement 3: ‘… barely tolerable and frequently interferes…’ Statement 4: ‘… intolerable and always interferes…’

Each level correlates to the sweat production and a 1 point improvement has been shown as a 50 % reduction of sweat and 2 points a 80 % reduction [12].

**Dermatology Life Quality Index (DLQI)**

This instrument of measurement of life quality in dermatology patients was created in 1993 (Appendix A). To form the questionnaire 120 dermatology patients were asked to write down how their skin disease and the treatment of it affected them in their daily life. The answers became the basis for the DLQI’s 10 questions, such as how embarrassed/self-conscious the patient has felt during the last week because of their skin disorder, or if it has disturbed working, studying or leisure time etcetera. Each question can be answered with ‘very much’ (valued to 3 points), ‘a lot’ (2 points), ‘a little’ (1 point) and ‘not at all’ (0 points). Some questions also have a ‘not relevant’ option (0 points). In total the score can reach maximum 30 and minimum 0 points, the higher the score the greater the negative impact in the patient’s life [13]. The test showed high reliability and is now a common tool in dermatology studies and clinical work for evaluating treatments and it has been translated into 55 languages and used in 32 countries [5, 14].
Treatment

The first step of treatment, after proper diagnosing and informing the patient about the condition, is assessment of the area needed to be treated. In case of large or multiple areas a combination of treatments may be necessary [15, 16].

Aluminum chloride is usually the first step and can be applied to any part of the skin. It can be bought over the counter in pharmacies, and comes in different strengths. It should be applied to clean dry skin and in the case of the strongest type, used before bedtime and washed off in the morning. It can be reapplied on a weekly basis or daily if needed. Eczema and dry skin are common side-effects that are treated with a mild cortisone cream [12, 15-18].

Systemic treatment with oral anticholinergic is more useful in the case where large areas need treatment. In Sweden oxybutynin (an anticholinergic also known as Ditropan) is the most commonly used and treatment is started if aluminum chloride does not give satisfactory effect. The treatment unfortunately often causes side-effect to the extent that patients find it unbearable. Side-effects are dry mouth, constipation, urinary retention, and tachycardia [15-18]. In a study with 19 patients 79 % (15 people) taking glycopyrrolate (an anticholinergic) had an effect on sweating, but 79 % also developed side-effects. One third had to stop because of their adverse effects and 21 % stopped the treatment when it was ineffective [19].

Iontophoresis is a method of sending an electrical current through a water bath, where hands or feet are placed. The current inhibits the sweat secretion and sometimes an anticholinergic agent is added to the water to increase this effect. The treatment takes about half an hour per use and needs to be repeated 4 times weekly [17, 18]. Side-effects are dry, irritated skin and pain. Because it is so time-consuming the treatment is not popular and not every clinic offers it, but the device can be purchased online [15, 16].
Local surgery with removal of the sweat glands is in Sweden only used for axillary hyperhidrosis [15]. This can be done with e.g. suction curettage and excision. Excision has more complications such as excessive scarring and infection [17, 18]. Suction curettage has the risk of bleeding, hematoma, seratoma, infection, pain and scarring [20].

**Botox**

The botulinum toxin (BT) consists of a heavy amino acid chain and a light amino acid chain, combined with a disulfide bridge, which is what makes it biologically active. Injected BT binds to glycoproteins in the cholinergic nerve ending; the light chain is taken up by said nerve ending and starts cleaving the proteins that help transporting acetylcholine vesicles to the synaptic cleft. This hinders the synapse to signal and temporary sprouting of new synapses takes place until the synapse can regenerate. Because of regeneration the BT effect is not permanent, but dose and injection site can lead to different duration of effect.

The molecule can travel along the nerve, but does not have any effect on the central nervous system due to the blood brain barrier and the slow speed (becomes inactive before reaching the central nervous system), side effects can instead come from systemic spread in the blood and local spreading of the botox to other nerve endings close to the injections sites that control muscles.

The most common types of botulinum toxin used in health care are Botox, Dysport, Myobloc/Neurobloc and Xeomin [21]. Because of proteins in the preparation antibodies can be formed either against the BT or against the inactive complexing protein, possibly causing treatment failure if against the active toxin [21, 22].

Botox injections have in several studies proved to improve quality of life in palmar and axillary hyperhidrosis and for both adults and children [23-26]. Solish et al. looked at the
impact in life and quality of life after botox injections. They found that after treatment patients reported being more satisfied and being less limited at work and in personal relationships, feelings of being emotionally damaged lessened and patients needed less time for managing their hyperhidrosis. Life quality measured by Dermatology Life Quality Index also improved [7].

With botox being more common as a treatment, the length of time to study its effects has increased and some studies point towards that duration of treatment effect seems to have the potential of increasing over time with continuous treatments [27-29].

Botox has in the treatment of hyperhidrosis shown to have mild to moderate side-effects [22, 30] that resolves within weeks or a few months. Common side-effects are weakness in hands, or other muscle weakness, and pain or irritation in injection sites [30, 31].

Health Technology Assessment

At Sahlgrenska Dermatology Clinic a health technology assessment (HTA), led by Kristina Maltese, MD, and Madeleine Ryndel, MD, was published in March 2012. Its purpose was to assess the need of offering patients botox injections as treatment for axillary, palmar and compensatory hyperhidrosis (caused by sympathectomy). The search included botox type A and B and comparing its effects on quality of life, duration of treatment, sweat production, to aluminum chloride, oral anticholinergic treatment, sweat gland curettage and placebo/no treatment.

The assessment found that botox has better effect in axillary hyperhidrosis than placebo and aluminum chloride at improving quality of life and sweat production. Botox was also better than placebo in terms of duration of treatment effect. Botox was not found better than subcutaneous curettage at improving quality of life and duration of treatment effect (curettage
is considered a permanent solution) in axillary hyperhidrosis. Palmar treatment was found to have more increase in quality of life and more effect on the sweating with Botox compared to placebo.

Most side effects were considered mild or moderate, with some patients with axillary hyperhidrosis getting compensatory sweating and almost half of patients with palmar hyperhidrosis getting passing muscle weakness after injections.

The yearly cost of treatment for one patient was estimated to 8200 SEK [32].

**Aim**

The aim was to evaluate the hyperhidrosis botox treatment at Sahlgrenska Dermatology Department, by examining DLQI, effectiveness, duration of treatment effect and side-effects. Also evaluation of the treatment form as a tool for gathering the patients’ information.

**Project plan research questions**

- How long is the duration of treatment effect, comparing axillary and palmar treatment or the combination of the two?
- How big of an effect do the patients experience after the treatments?
- How are the patients according to the Dermatology Life Quality Index (DLQI) score, after treatments, comparing axillary, palmar and the combined treatment?
- How many patients have answered the DLQI-form?
- Are the results in accord with current research on hyperhidrosis botox treatment?
- How well does the clinic use the treatment form to follow their patients?
- Is there a need for the clinic to improve its follow up and assessment of their patients who get botox injections?
Method

A few months after the treatments started a form was constructed in Microsoft Excel (Microsoft Corporation, Washington, USA) to follow the patients’ response. This treatment form was the base of information for this evaluation.

A list of patients who had visited the clinic was taken from the booking system ELVIS (Elektroniskt VårdInformationsSystem, Region of Västra Götaland, Sweden), an electronic patient booking system, and compared it to the treatment forms to make sure no patient was excluded in case a form was missing.

The first patient to visit the clinic came at 3rd of September 2013 and all patients who received botox injections and had information about the treatment in the treatment form or in Melior (Siemens, München, Germany) until 2nd of September 2016 were included.

The form included 13 points of interest:

- The doctor or nurse who performed the treatment.
- Date of treatment.
- Hyperhidrosis Disease Severity Scale (1-4, 4 being the worst), at the time of treatment.
- Treated area (either axillary, palmar, combined (both areas at same appointment) or mixed (both areas at separate appointments)).
- Dose and type of botulinum toxin (Dysport or Botox).
- Amount of dilution.
- Choice of anesthetics: ice (ice in a plastic bag held against injection sites for 15 minutes before injections), nerve block (injected), Coolsense (a pen-like applicator with a frozen core), Emla (a lidocaine and prilocaine cream) or no anesthetics (often called ‘none’ in graphs and tables to save space).
- Pain caused by anesthetics on VAS (0-10, 10 being the worst).
- Pain during treatment, answered on VAS (0-10, 10 being the worst).
- Effectiveness of treatment (0-10, 10 being the best), estimated by patient at following appointment.
- Duration of treatment effect (answered in weeks or months), estimated by patient at following appointment.
- Side-effects (none or description of side-effect as experienced by patient), answered at following appointment.
- Dermatology life quality index (DLQI), questionnaire answered at the same day as treatment (when no effect has set in, called pre-treatment) and 3 weeks post-treatment (when full effect has been reached).

Melior was used to complement missing or lacking information. If Melior had information that did not correspond with the forms then the information in the forms was used and a comment was made in a commentary field in Excel. All data was collected in Excel.

**Ethics**

Permission to gather patient information from the treatment forms and Melior and to visit the clinic to observe the treatments was received from the head of the dermatology clinic Helena Gustafsson.

**Statistical methods**

The R Project for Statistical Computing version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) was used. I had the help of the statistician Martin Gillstedt in the department of dermatology for calculations and analysis.

**Pain:**

- Kruskal-Wallis test was used for comparing the different anesthetic options’ treatment pain and administration pain (separate test for axillary and palmar treatment).
- Where significant change was found Pairwise Wilcoxon’s rank-sum test (also called Wilcoxon’s signed-rank test) was used to further look into each anesthetic compared to the other.

**Effectiveness:**

- Wilcoxon’s rank-sum test was used to compare genders in the axillary and palmar treatment and also used to compare axillary with palmar treatment.

Duration of treatment effect:
- Wilcoxon’s rank-sum test was used on axillary and palmar treatment separately on whether the duration changed with more treatments.

- Pairwise Wilcoxon’s rank-sum was used on each age group between treatment appointment 1 and treatment 2.

**DLQI**

- Spearman correlation compared each age group, treatment area and gender with number of treatments to see if change happened over time.

- Kruskal-Wallis was performed at first appointment for the treatment areas to find any difference in DLQI-score.

**Kruskal-Wallis:**

- Non parametric test to compare the samples in two groups. A significant test means that at least one sample differs from another. It does not tell which sample, but just compares the groups.

**Spearman correlation:**

- Non parametric test to assess the relationship between x and y, who do not have to have a linear relationship for Spearman to give significance.

**Wilcoxon’s rank-sum:**

- Non parametric test that compares a related sample or one sample with many measurements.

- Wilcoxon’s signed-rank test: similar but comparing a sample’s value over time with other similar samples, it is a test meant for paired data.
Results

The patients

Since the start (3/9 2013 - 2/9 2016) 179 unique patients have received treatment. Of these 60 % were women and 40 % men, with similar ages at 1st appointment. Females had the mean age 26.6 years and males the mean 28 years. The oldest person at their first appointment was 72 years and the youngest 14 years. Most patients were between 20-30 years (45 %). The patient groups < 20 years (28 %) and > 30 years (27 %) were of similar size, though the older had a much wider age span.

Treatment area

About half of the patients (48 %) received only axillary treatment and 37 % only palmar. Fewest were the 5 % in the combined treatment group and the mixed group at 10 %.

Hyperhidrosis disease severity scale (HDSS)

The HDSS had most data from the patients’ first appointment with 77 % answered. Appointment 4-8 only had 1 HDSS-entry. There were too few data to see any significant lowering of the mean, but appointment 2 - 3 seems to be going in the right direction (table 1).

Men and women have at the 1st appointment similar means; females 3.57 (95 % CI 3.45-3.69) and males 3.64 (95 % CI 3.50-3.78).

<table>
<thead>
<tr>
<th>Table 1 – HDSS scores for all hyperhidrosis patients at appointments 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appointment no. 1</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Appointment no. 2</td>
</tr>
<tr>
<td>Appointment no. 3</td>
</tr>
</tbody>
</table>

Appointment numbers (no.) 4-8 only had 1 reply out of the total 102 appointments and therefore excluded. There was too few HDSS data to calculate significance in score changes.
The treatment

Treatment appointments

The number of visits the patients did to the clinic was minimum 1 and maximum 8 times.

Most patients returned only maximum 2 times (table 2): median 2 and mean 2.77 (95 % CI 2.51-3.02).

<table>
<thead>
<tr>
<th>No. of unique patients</th>
<th>1 Appoint.</th>
<th>2 Appoint.</th>
<th>3 Appoint.</th>
<th>4 Appoint.</th>
<th>5 Appoint.</th>
<th>6 Appoint.</th>
<th>7 Appoint.</th>
<th>8 Appoint.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>30%</td>
<td>21%</td>
<td>21%</td>
<td>14%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

51% of patients came only for 2 treatment appointments. Only 3 patients came back 8 times for treatment.

Pain from treatments

In the beginning the clinic offered 4 types of anesthetics; Coolsense, Emla, ice and nerve block, but ice and nerve block were the most commonly offered and used (table 3).

<table>
<thead>
<tr>
<th></th>
<th>Palmar patients</th>
<th>Axillary patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coolsense</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Emla</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>No anesthetic</td>
<td>17</td>
<td>202</td>
</tr>
<tr>
<td>Ice</td>
<td>145</td>
<td>10</td>
</tr>
<tr>
<td>Nerve block</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>226</td>
<td>229</td>
</tr>
</tbody>
</table>

Axillary treatment pain

All axillary treatments were included in these calculations, including patients with the combined and mixed treatments.
There was no significant difference between the three choices (Kruskal-Wallis \( p = 0.21 \)) (figure 1A).

Emla-cream was not common (7 \%) and had the VAS score mean of 4.03 (95 \% CI 2.55-5.52). Ice was also uncommon (4 \%) with the mean 5.40 (95 \% CI 4.22-6.58). Most common was not using anesthetics (88 \%) with the mean 5.06 (95 \% CI 4.76 – 5.36).

**Figure 1- Pain measured on VAS caused by botox injections after administration of patients’ choice of anesthetics**
**Palmar treatment pain**

All palmar treatments were included in these calculations, including patients in the combined and mixed treatments.

There was no significant difference (Pair wise Wilcoxon’s rank-sum test $p > 0.05$) between Coolsense, Emla and ice compared to no anesthetics (figure 1B).

Coolsense was uncommon (2 %) with the mean 5.8 (95 % CI 3.11-8.49). Emla, also uncommon (2 %), had the mean 7.67 (95 % CI 6.23-9.10). Ice was used the most (64 %) and had the mean 5.96 (95 % CI 5.64-6.29).

Nerve block (used 24 %) had the significantly lowest score compared to ice, no anesthetics and Emla. Nerve block had the mean 3.33 (95 % CI 2.52-4.14) (figure 1B).

Not using any pain relief had the mean 6.35 (95 % CI 5.29-7.40).

**Pain caused by administering anesthetics**

For the axillary treatment there was no significant difference between ice and Emla (Kruskal-Wallis $p = 1.00$). Emla and ice both had the mean 0.

For palmar treatment nerve block was significantly more painful than all other choices using
Pairwise Wilcoxon’s rank-sum test: ice ($p=0.0001$), Emla ($p=0.018$), Coolsense ($p=0.001$) (figure 2). Ice had the mean $0.3$ (95% CI 0.1-0.6) and nerve block had the mean 5.1 (95% CI 4.4-5.8). Emla and Coolsense both had the mean 0.

**Duration of treatment effect**

**Treatment areas**

Axillary had longer duration than palmar. Palmar had the mean 112.2 days (95% CI 102.9-121.6) and axillary the mean 126 days (95% CI 117.3-135.0).

Neither palmar nor axillary had an increase in duration correlating to more treatments (figures 3A and 3B). Palmar treatments 3-7 had few patients and as seen wide confidence intervals.

![Graph A](image1.png)  
**Spearman correlation between treatment appointments and duration of treatment effect (days) showed no significance ($p = 0.8$). There was no data for appointments 7 and 8.**

![Graph B](image2.png)  
**Spearman correlation between treatment appointments and duration of treatment effect (days) showed no significance ($p = 0.7$). There was no data for appointment 8.**

**A - Axillary treatment**

**B - Palmar treatment**

**Figure 3 – Duration of botox treatment effect for each treatment appointment**
1\textsuperscript{st} and 2\textsuperscript{nd} appointment

There is a visible increase in duration between appointment 1 and 2 (figure 3B).

Pairwise Wilcoxon’s rank-sum test found significant increase for the palmar patients < 20 years old \( (p = 0.026) \) and 20-30 years old \( (p = 0.014) \) (figure 4). For the palmar patients > 30 years old no significant change could be found.

None of the axillary patients in either age group had an increase in duration (figure 4).

![Graph showing duration of botox treatment effect after 1\textsuperscript{st} and 2\textsuperscript{nd} treatment appointment.]

\textit{Only palmar patients < 20 years old (p = 0.026) and 20-30 years old (p = 0.014) had a significant increase in duration of treatment effect between their 1\textsuperscript{st} and 2\textsuperscript{nd} appointment using the Pairwise Wilcoxon’s rank-sum test.}

\textbf{Figure 4 – Duration of botox treatment effect after 1\textsuperscript{st} and 2\textsuperscript{nd} treatment appointment}
Effectiveness of treatment

The estimated effectiveness of the injections was higher in the axillary group than palmar

![Figure 5 - Effectiveness of botox treatment measured on VAS for axillary and palmar patients](image)

(Wilcoxon’s rank-sum $p = 0.006$). Axillary patients had the mean 8.6 (95 % CI 8.2-8.9) and palmar patients the mean 8.1 (95 % CI 7.7-8.5) (figure 5).

The axillary patients > 30 years had significantly higher score than 20-30 years (Pairwise Wilcoxon’s $p = 0.003$). 20-30 years had the mean 7.9 (95 % CI 7.3 - 8.6) and > 30 years had the mean 9.3 (95 % CI 8.9 - 9.7).

The palmar age groups had no significant difference (Kruskal-Wallis $p = 0.75$).

Patients with only one area of treatment had no significant difference to those with the combined treatment (Kruskal-Wallis test $p > 0.05$).
Dermatology Life Quality Index (DLQI)

Patients had an increased life quality with more treatments; they were less limited in their daily life by their condition, and this even when they had the least effect from the treatment.

At the 1<sup>st</sup> appointment some patients had never been treated with botulinum toxin before, while others might have had the disease for years and gotten treatments at other clinics.

DLQI pre-treatment for all patients had a significant decrease with more treatments (Spearman correlation: \( p < 0.0001 \)).

At 1<sup>st</sup> appointment the mean was 12.8 (95 % CI 11.2- 14.4). The 8<sup>th</sup> appointment had the mean 2 (CI not available because of lack of data) (figure 6A).

All age groups, axillary and palmar patients had a significant decrease of pre-treatment DLQI with more treatments when using the Spearman correlation \( p < 0.005 \).

There was no significant difference in DLQI between the different treatment areas (Kruskal-

![Figure 6 – DLQI for hyperhidrosis patients at treatment appointments 1-8](image)

Figure 6 – DLQI for hyperhidrosis patients at treatment appointments 1-8
Wallis $p = 0.75$).

There was no significant difference in the post-treatment DLQI with more appointments (Spearman correlation: $p = 0.27$). Patients reached the same level of life quality post-treatment after several appointments.

DLQI for all patients after 1st appointment (post-treatment) had the mean 3.3 (95 % CI 2.2-4.4). Appointment 8 had the mean 2, but this was based on only 1 reply (figure 6B).

**Side-effects**

Pain was an anticipated occurrence during treatment and was not accounted for here. Of the 495 treatment appointments few reported side-effects but also only 24 actual reports of no side-effects (4.8 % of the treatment appointments) and most treatment forms were blank in this section.

The most common side-effect was muscle weakness, reported 15 times (3.0 %): 14 (2.8 %) included weakness in the thumb and index-finger grip, 3 (0.6 %) had general weakness in the hands and 1 (0.2 %) had weakness in the distal part of the arms, hands and fingers. The weakness always receded within weeks; the longest period was 6 weeks.

Irritation around the injections sites such as pain, itching and or bruising was reported 6 times (1.2 %).

5 patients (1.0 %) fainted during or shortly after the injections, most assumed to be a reaction to the pain of the treatment. 4 of these 5 were < 20 years old and 1 was 23 years. 4 of the 5 had used ice as pain relief, 1 had no reported use of pain relief.

2 patients (0.4 %) reported increased general sweating.
Missing data

Throughout the treatment form there were many boxes left empty. HDSS was missing 68 %: 1st appointment had 77 %, 4th-8th only 1 entry in total. DLQI pre-treatment was missing 54 % and post-treatment missed 55 %. Effectiveness was missing 45 % and duration was missing 40 %. Side-effects lacked most data: 88.3 % were empty boxes.
Discussion

Life quality

The quality of life pre-treatment improved over time. That it was measured before the renewal dose means that patients feel better even at their worst, which is a good sign. That fact that the mean post-treatment DLQI does not reach 0 point shows that there still is a lingering disturbance from the hyperhidrosis even with treatment at full effect, and also that patients are never problem free.

The HDSS was not answered in enough extent to see significant change over time, and makes it hard to compare to other studies. The median and mean did lower from appointment 1 to 2 and 3, which hints that it was going in the right direction. Improvement on the HDSS can be translated to reduction of sweat [12] and as patients have rated their treatments > 8 on 10 for effectiveness they likely would have rated lower on HDSS too if asked, since it has done so in other studies [12, 33].

Perhaps if the treatment is given enough time it will improve patients to that degree that they are no longer aware of their condition, both physically and mentally. In a study from Stockholm where 84 patients were treated with Xeomin and Neurobloc, axillary patients went from mean DLQI score of 12.0 pre-treatment to 1.7 3 weeks post-treatment and the palmar patients from 10.3 to 1.2. 45 % of axillary patients and 43 % of palmar patients had reached 0 on DLQI [25], so it is possible to be completely without problems from the disease with the right treatment. There was no information on the level of problem these patients had before the treatment.
Duration of treatment effect

The duration did not increase except for the younger patients in the palmar group between appointment 1 and 2. Treatments 3 -8 for axillary and palmar patients did not have enough patients or data to make proper conclusions. In two studies by Lecouflet et al. with palmar and axillary patients during 11 years the duration increased by 3 months for axillary patients and 2.5 for palmar [27, 28]. The current duration 112 days (3.7 months) for palmar and 126 days (4.2 months) for axillary is similar to what others have reported [30]. Perhaps the change the clinic made from Botox to Dysport during the 3 years also is preventing a visible increase in duration (though one study did not find significant difference in duration between Botox and Dysport [34]). Or is it as simple as needing more time to see an increase in duration. The duration increase in Lecouflet’s study had 11 years to build and also treated only with Dysport so maybe in a few years we will see the difference, but more data would be beneficial for analysis as well.

Pain

The treatment is quite painful and even the anesthetic administration is (though clearly nerve block stands out). It is interesting to see that ice remains the most popular, though patients with multiple appointments should have noticed that it is not of much help. Is ice useful as more than being a pain relief? Could it be that the stress of needles and a painful procedure is helped by feeling that they are doing something?

What is also interesting is that other clinics seem to have a varied approach to the pain. Axillary studies mostly offer nothing for the pain [25, 31], sometimes Emla [25], and one study reporting only mild pain with no anethetics [35]. Palmar vary between ice from 5-10 seconds [33] to 15 min [36] , to nerve block, one study complementing nerve block in case of incomplete effect with ice [37], to inhalation of a mixture of oxygen and nitrogen, or
hypoanalgesia (not specified) [28]. A study of 46 palmar patients mentioned the difference in perceived pain if nerve block did not take fully. The partial block happened to 17 % of whom 75 % felt mild pain and 25 % moderate pain, compared to no pain for the patients who had successful pain nerve block [37]. Though the patients in this evaluation estimated their pain on VAS and thus not straight away translatable to mild or moderate, the mean 3.3 (95 % 2.52-4.14) at least points out that most patients did not reach complete pain relief. Could this be because of clinicians’ technique of injection?

Nerve block makes a significant difference in pain, but it is also very painful. Are a few minutes of VAS 5 when getting nerve block injections worth 10-15 minutes of VAS 3 during the treatment? Who are the patients who choose either anesthetic?

Perhaps patients get better at handling the treatments over time and therefore notice the pain less? Recently there has been an improvement in how the ice is administrated at the clinic and patients have responded positively. In the beginning ice was administered with an ice block that did not cover the palm very well, now ice in a bag that better fits the hands is used instead. Future evaluation will tell if this has given a change in the treatment pain.

**Patients and appointments**

According to the American survey [8] there is little difference in female to male ratio, but big difference in how they ask for help. More females than males have received the treatment and this is the case in several other studies too[33]. Skin conditions cause a lot of emotional pressure on patients. Perhaps patients more prone to acknowledging their emotions and emotional disturbances will look for treatment and help more often that those who perhaps because of society’s expectations and norms are less in tune with their own emotions. The treatment has been offered for over 3 years, with up to 2 axillary and 3 palmar treatments offered yearly per patient. For some reason 51 % of patients have not shown up for more than
1-2 treatments, which is surprising as most also have a HDSS of median 4 and mean 3.6 at 1st appointment and should have reason to keep at the treatment.

Why do patient not ask for help and why do patients drop out? Are they not informed enough to understand their disease and their options? Hyperhidrosis is not a well-known disease and if more patients were reached with proper information maybe they would understand their condition and how the treatment works better, making them participants instead of passive receivers of the treatment. If it is the pain that makes them quit, making sure patients understand that nerve block is the best option, or perhaps combining anesthetic options for best result, could it be a solution? Asking, perhaps by a follow-up phone call, why patients drop out would be one way to get necessary information on how to improve the treatment of hyperhidrosis.

**Side-effects**

No side effects were serious, but 16 times (3 % of all appointments) muscle weakness was reported, though it was only 5 % that actually had a reported side effect. While I was registering the data it was unfortunately not possible to tell if an empty box was left empty on purpose or if it was forgotten, as many boxes were empty in many fields and columns. Other reports have also mentioned muscle weakness and thumb-finger grip weakening, some with a higher frequency of side effects and some with less [26, 31, 32]. Technique of injection might be an important factor in this.

**Treatment forms**

There are a lot of different types of answers, and a lot of empty boxes. This makes it hard to compare results and draw conclusions as so much is missing. DLQI, duration of treatment effect and pain had enough to find significant differences, but side-effects and HDSS who are
both important to patients’ satisfaction with the treatment did not have enough data for comparisons. With limited time during appointments it is understandable that quick fixes sometimes are made. A new form might make the data gathering easier and quicker. A form in the computer system with shared access for clinicians, with clearer instructions (e.g. how to show in the form that no data was gathered) and less options (such as in the pain relief box; instead of 4 options where not all are used, maybe only 2 options) or quick answers, like a check box, would maybe help the efficiency of the filling out the form. If one just needs to check the boxes then perhaps even patients could be allowed to fill out some answers themselves, saving time for the clinicians and keeping the patients in the loop of how they are affected by the treatment.

Conclusion

This evaluation showed that treatment with botox injections improves quality of life in the clinic’s hyperhidrosis patients over time, and not only when treatment is in effect. Contrary to previous studies the duration of treatment effect did not increase for unknown reasons. Pain was best suppressed with nerve block, but it caused the most pain in its administration. It would be interesting to ask patients why they drop out or end the botox treatment, this could give important information that the clinic could use to improve the treatment of hyperhidrosis patients.
Populärvetenskaplig sammanfattning

Behandling av överdrivna svettningar i armhålor och händer med botoxinjektioner

Hyperhidros är en hudsjukdom där man har överdrivna svettningar. Hyperhidros drabbar ca 3 % av befolkningen. Sjukdomen kan ha sociala och professionella konsekvenser eftersom svetfläckar och rinnande svett kan påverka hur omgivningen bemöter de drabbade.

Botox är förkortning för nervgiftet botulinum toxin som när det injicerats i huden förstör nervändarna till svettkörtlarna, vilket minskar de aktiverande signalerna och får patienter att svettas mindre. Nervändarna förnyas dock efter ett tag varför patienter måste få injektioner regelbundet.

Sedan hösten 2013 har Sahlgrenska ebjudit patienter med hyperhidros botoxinjektioner. Denna utvärdering är den första sedan starten och görs med hjälp av att sammanställa datan från 179 unika patienters behandlingsformulär och patientjournaler. Målet är att utvärdera resultatet av behandlingen och hur bra formuläret är på att samla patientinformation.

Dermatology Life Quality Index (DLQI) är ett frågeformulär som mäter livskvalitet hos hudpatienter. Vid varje förnyad behandling och 3 veckor efter behandlingen fick patienterna fylla i DLQI. Klinikens patienter fick bättre livskvalitet efter några behandlingar även innan de fick en påfyllnadsbehandling, alltså kunde patienterna leva mer ostört från hyperhidrosen.

Injektionerna gör ont och patienterna fick skatta smärtan på en skala från 0-10 (10 var värst). Händerna gjorde mest ont på medelvärdet 6 medan armhålor skattades med medelvärde 5. Armhålorna fick oftast ingen bedövning men handpatienterna fick välja mellan nervblockad och is. Is gav inte någon skillnad jämfört med att vara utan bedövning, men nervblockad hade bra effekt (smärtan hade medelvärde 3). Problemet med nervblockad är att det också gör ont
att injicera (medelvärde 5) och patienterna inte kan använda sina händer när de är bortdomnade under några timmar.

Hur länge effekten sitter i av botoxinjektionerna har i några studier visat sig öka med upprepade behandlingar. Hudklinikens patienter hade inte någon ökad duration av behandlingseffekten, förutom mellan 1:a och 2:a behandlingen för de med handhyperhidros som var under 30 år.

Patienterna tycker att effekten av botoxinjektioner är hög. De fick skatta den på en skala från 0-10 (10 var bäst) och tyckte att handbehandlingen var 8.1 och armhålebehandlingen var lite bättre på 8.6.

Den vanligaste biverkan, som rapporterades vid 3% av alla besök, var muskelsvaghet. Muskelsvaghet kan ske om botoxet sprider sig till nervändarna som går till muskler i injektionsområdet. Särskilt handpatienterna kan ha det besvärligt, oftast med att greppa mellan tumme och pekfinger, men alla klinikens patienter blev bättre inom några veckor.

Sammanfattningsvis får patienterna bättre livskvalitet efter upprepade botoxbehandlingar och de tycker att effekten är bra, men hur länge effekten satt i ökade inte med tiden. Patienterna föredrog is framför nervblockad, trots att nervblockad var bästa bedövningen, men den gjorde ondast att få.
Acknowledgement

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Also want to thank Martin Gillstedt for helping me with the statistical analysis.
References


## Appendix A

### DERMATOLOGY LIFE QUALITY INDEX

<table>
<thead>
<tr>
<th>Hospital No:</th>
<th>Name:</th>
<th>Address:</th>
<th>Date:</th>
<th>Diagnosis:</th>
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The aim of this questionnaire is to measure how much your skin problem has affected your life **OVER THE LAST WEEK**. Please tick one box for each question.

1. Over the last week, how itchy, sore, **painful or stinging** has your skin been?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home or garden**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

   Not relevant ☐

4. Over the last week, how much has your skin influenced the **clothes** you wear?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

   Not relevant ☐

5. Over the last week, how much has your skin affected any **social** or **leisure** activities?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

   Not relevant ☐

6. Over the last week, how much has your skin made it difficult for you to do any **sport**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

   Not relevant ☐

7. Over the last week, has your skin prevented you from **working or studying**?
   - Yes ☐
   - No ☐
   - Not relevant ☐

   If "No", over the last week how much has your skin been a problem at **work or studying**?
   - A lot ☐
   - A little ☐
   - Not at all ☐

8. Over the last week, how much has your skin created problems with your **partner or any of your close friends or relatives**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

   Not relevant ☐

9. Over the last week, how much has your skin caused any **sexual difficulties**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

   Not relevant ☐

10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?
    - Very much ☐
    - A lot ☐
    - A little ☐
    - Not at all ☐

    Not relevant ☐

Please check you have answered EVERY question. Thank you.