Treatment of Axillary Hyperhidrosis with long-pulsed Nd:YAG laser or IPL treatment using Dynamic Optical Coherence Tomography Imaging of Laser-Tissue Interaction: *Protocol for a within-person randomised trial conditioning on treatment type*

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SUMMARY

Objective

To assess the efficacy of Neodymium-doped Yttrium Aluminium Garnet (Nd:YAG) laser or Intensed Pulse Light (IPL) treatment on eccrine sweat production in the axillae of persons experiencing excessive axillary hyperhidrosis.

Design

Randomised, within-person controlled clinical trial conditioning on two different types of laser.

Setting

One Dermatology Department, at a University hospital in Denmark, from 2020-2021.

Participants

A total of 20 participants enrolled and within person randomised after signing informed consent from the patients attending the hyperhidrosis clinic; in randomised order 10 patients will be treated with Nd:YAG laser, whereas the other 10 will be receive IPL treatment.

Interventions

Participants will be randomised to receive one Nd:YAG laser-treatment or one IPL treatment of either left or right axilla depending on the outcome of the randomisation (i.e. within person randomisation). The treated area will be cooled with ice after laser treatment. Prior to treatment, patients can use lidocaine-prilocaine 5% cream at the treatment site on an optional basis.

Main outcome measures

Primary outcome measure will be reduced excessive sweat production (%points) monitored by an iodine-starch test assessed at 1-month follow-up compared to baseline. A 30%point reduction in sweat production in the treated axilla relative to control, will be considered clinically significant.

Key secondary outcome measures include (1) weighing the sweat by gravimetric testing, (2) patient assessment of sweat production on a Hyperhidrosis Disease Severity Scale (HDSS) – also assessed at 1 month from baseline. All of the above will be tested for the contextual impact of type of intervention (Nd:YAG laser and IPL treatment, respectively), using a test for interaction. Safety around the use of Nd:YAG laser and IPL-treatment will be monitored by registering pain during treatment on a visual analogue scale, as well as monitoring adverse events immediately as well as one week after treatment. As for the purpose of further exploratory analyses (both benefits

and harms), all outcome measures will be re-collected 24 months after treatment.

Timelines and dissemination

For the collection of the primary data (i.e. primary endpoint being assessed after 1 month), First Patient First Visit (FPFV) will take place in January 2020 and Last Patient Last Visit (LPLV) will be in June 2020. We plan to present data internationally at e.g. the European Academy of Dermatology and Venerology as well as nationally to the Danish Dermatology Society and to the Hyperhidrosis Patient Association. Results will be published in an internationally recognised peer reviewed (biomedical) journal.

Trial registration: Danish Research Ethics Committee (approved, protocol number: SJ-689); ClinicalTrials.gov: NCT ???? pending.

INTRODUCTION

Background

Primary axillary hyperhidrosis is a condition with excessive secretion of sweat from the eccrine sweat glands of the armpits that affects between 1 and 5 % of the world's population[2]. Numbers may be underestimated since this chronical disease debuts during adolescence and is unmentionable in many cultures and social environments. Hyperhidrosis may lead to malodour and cause large sweat patches on clothes, thus affecting dressing behaviour, social activities and job opportunities. As a direct consequence, many patients experience affected psychological and social behaviour, increased mental stress and low self-esteem[3].

Several treatment modalities exist that may treat axillary hyperhidrosis. Systemic treatment with anticholinergic tablets is often reserved to hyperhidrosis that affects the entire body due to a substantial risk of adverse effects. Possible adverse effects (i.e. related to the intervention) include dry mouth and other mucous membranes, digestive problems, decreased ability to empty the bladder, visual disturbances and affected nervous system[4,5]. Localised axillary hyperhidrosis is often treated by injections of botulinum toxin. Although this method is effective in many patients the procedure is painful, expensive and has to be repeated since the effect only last from four to nine months [6]. Recently, heating of the sweat glands with microwave technology has shown promising efficacy with minimal adverse effects. However, this treatment is very expensive and is only available at a few sites in Denmark. Surgery has also been performed, yet short-term and long-term efficiency is inferior to other methods [6]. Therefore, there is a need for efficient, safe, affordable and widely available alternatives to treat axillary hyperhidrosis.

An alternative method that have been proposed, could be heating and destroying sweat glands by Neodynium Yttrium Aluminium Garnet (Nd:YAG) laser or intensed pulsed light (IPL). These types of non-invasive light devices are widely available at dermatological clinics in Europe and is well-known to treat vascular lesions and undesired hair growth. The IPL has a 640 - 800 nm wavelength and the Nd:YAG laser a 1064 nm wavelength that penetrates deeply into the skin and target the melanin of the hair shaft. By adjusting the pulse length according to the theory of extended photo-thermolysis, light energy can be delivered through the hair shaft into surrounding sweat glands[7]. A previous pilot study has demonstrated significant and lasting reduction of axillary hyperhidrosis in six patients treated with Nd:YAG laser[1].Treatments were reported safe and efficient without any side effects. Likewise, two studies of a comparable but invasive Nd:YAG laser technique reported only temporary mild adverse effects and significant sweat reduction for up to 43 months after treatment[8,9]. A single prospective study without a control group demonstrated increased sweat production following Nd:YAG laser treatment of

excessive hair growth[10]. Targeting hair and sweat glands is however not directly comparable due to different pulse lengths of the delivered energy.

Dynamic optic coherence tomography (d-OCT) is an imaging technique that utilizes infrared light to create two-dimensional horizontal or transverse images. Penetration depth is approximately 0.5 – 2 mm [11]. The d-OCT technique allows *in situ* visualization of dynamic changes in blood flow and superficial skin structures in vital skin. Thus, the eccrine sweat glands and the surrounding blood supply can be followed over time without taking invasive tissue biopsies. Previous studies of histological changes after laser treatment of eccrine sweat glands have only been able to demonstrate limited structural changes and therefore, there is a need for improved imaging techniques to visualize laser-tissue-interactions.

Aim & Objectives

This study aims to assess the efficacy and safety of experimental intervention (either Nd:YAG laser *OR* IPL treatment) of an axilla with hyperhidrosis, relative to the contralateral untreated side, and to visualise laser-tissue interactions by Dynamic Optical Coherence Tomography.

Primary efficacy objective: to assess the effect of one of the experimental interventions (either Nd:YAG laser or IPL) treatment on eccrine sweat production by comparing treated and contralateral untreated axillae in patients eligible for botulinum-toxin therapy due to axillary hyperhidrosis. Sweat production is to be assessed at baseline and at one-month follow-up primarily by the iodine-starch test and secondly by gravimetric testing and questionnaires.

METHODS

Patient research partners (PRPs)

The study is designed without the assistance of PRPs. Collaboration between patients and professionals in developing and disseminating research projects is relatively new and the explorative nature and easily quantifiable outcomes chosen in this study reduces the need for the use of PRP. Should the study support the use of the new treatment, larger confirmatory studies will be needed and these will naturally include softer patient-rerouted outcomes and PRP collaboration.[12]

Trial design and allocation ratio

In a prospective within-person randomised trial, patients will be randomly allocated to receive laser treatment or IPL of one axilla while the other serve as a control (i.e. Right-Left and Left-Right, respectively). Primary endpoint will be assessed after 1 month. Treatments are performed

with a combined platform of non-ablative 640 – 800 nm IPL and 1064 nm long-pulsed Nd:YAG laser (Lumenis M22 system, Lumenis Ltd.) and laser energy is applied according to patient skin type.

Participants and settings

Eligibility criteria for participants & body sites

Legally competent women and men of at least 18 years, Fitzpatrick skin type I-III, suffering from severe axillary hyperhidrosis characterised by a value of 3 or 4 on the HDDS scale. Patients will not be considered eligible for inclusion if they take photosensitizing medication or have received other active treatments for axillary hyperhidrosis within the last five months. Axillary skin must be intact without wounds, scars or skin disease. Previous surgery, laser or microwave therapy in the axilla is not allowed. Patients who are pregnant or lactating at the time of enrolment will not be considered eligible either.

Settings and locations where the data will be collected

This project will take place from autumn 2019 to spring 2021 in an established research environment in the Dermatologic Department at Zealand University Hospital Roskilde. All patients will be included from January 2020 to June 2020 and will if possible be re-evaluated two years later.

Professor, doctor in medical science and Head of Department Gregor Jemec is principal investigator. He is a highly qualified researcher with extensive counselling experience. Daily leader will be medical doctor, PhD Elisabeth Hjardem Taudorf (EHT), who works as a clinician and a researcher. Medical doctor and PhD-students Mattias Hennig and Linnea Thorlacius will participate in daily study activities. The department accounts for all study facilities and technical equipment. The study has been approved by the Danish Research Ethics Committee (protocol number: SJ-689). Before enrolling the first patient, the trial was registered with clinicaltrials.gov (NCT Identifier: Pending).

Interventions

The intervention under investigation is one treatment with 640 – 800 nm IPL or non-ablative long-pulsed 1064 nm Nd:YAG laser (Lumenis M22 systems, Lumenis Ltd.). Laser or IPL energy will be applied according to patient skin type. Skin will be cooled during and after treatment to reduce inconvenience. On an optional basis, patients may also choose to receive topical anesthesia by lidocaine gel prior to treatment (EMLA 5%, Astra-Zenica, København S, Danmark). All patients will receive one treatment and will be followed up after one month. If possible,

patients will be contacted in order to perform a long-time follow up after 24 months. After completion of the project, patients are offered laser or IPL treatment of the axilla, which served as a control in the study.

Outcomes

The primary efficacy end point will be reduction in sweat production assessed as the change from baseline in an iodine-starch test at one month after treatment (i.e. 1 month after baseline).

Key secondary endpoints are (1) gravimetric testing of sweat production, and (2) patient-reported sweat production assessed on a 4-point Hyperhidrosis Disease Severity Scale (HDDS) for each axilla independently. The dynamic in situ laser-tissue interactions are monitored at baseline and at one-month follow-up. If possible, for further exploratory analyses, follow-up assessments will be repeated after 24 months.

Adverse events to treatment are monitored by the patient filling in a visual analogue scale of pain during treatment, by the laser surgeon reporting the presence of redness, oedema or ulceration immediately after treatment and by the patients filling in a questionnaire regarding adverse events one-week post-treatment.

Power and Sample size considerations

A sample size calculation was performed based on the assumptions that the main outcome measurement (the iodine-starch test for sweat) is continuous in nature, fairly normally distributed, and that an additional improvement in the intervention side of 30%points (assumed standard deviation=25%) will be considered clinically relevant. For a paired t-test of a normal mean difference with a two-sided significance level of 0.05 ($p< 0.05$), assuming a common standard deviation of 25% on the iodine-starch test with a correlation of 0.5, a sample size of 8 pairs is required to obtain a power of at least 80% to detect a mean difference between pairs of 30% (the actual power is 82.8%). It was decided to include and (within-person) randomise 10 patients for each intervention in order to consider a potential risk of drop-outs; a sample size of 10 pairs has a power of 92% to detect the mean difference between pairs of 30%.

As an extra exploratory objective, we will explore whether the use of Nd:Yag laser or IPL treatment have a different outcome after assessing the overall benefit or “both of the experimental treatments”. Thus, it was decided for pragmatic reasons to include 20 patients in total; 10 of them treated with Nd:Yag laser on the experimental side, whereas the other 10 will receive IPL treatment on the experimental side.

Randomization and masking

Sequence generation, allocation concealment, and implementation

This is an intra-person study, comparing outcomes within participants. All participants will receive active treatment on one axilla (Active-Right|Control-Left and Control-Right|Active-Left, respectively). The implied subgroups of which axilla to receive active long-pulsed Nd:YAG treatment or IPL will also (like right/left) be selected based on a computer generated table of random numbers using SAS Proc Plan developed by an external collaborator/author (RC). The contralateral axilla will serve as control.

The randomisation sequence is prepared by an external biostatistician with no clinical involvement in the trial (RC). The allocation will be concealed in a password-protected computer file only accessible by the biostatistician. Individual allocations will be held in sealed, opaque, consecutively numbered digital files. Digital files will be forwarded individually to the principal investigator sequentially as an active feedback mechanism after receiving a scanned copy of the informed consent form.

This procedure will ensure that participants, study staff, and outcomes assessors at Department of Dermatology, Zealand University Hospital, Roskilde will remain blinded to subsequent treatment allocations throughout the trial (20 patients being randomised in total: 10 on the Nd:YAG and 10 on the IPL within person-randomisation, respectively).

The group to which the patients is assigned is directly communicated from the data manager to the daily leader of the project (EHT); i.e. the investigator will be informed about which treatment to apply (Nd:YAG or IPL) and which axilla (Right or Left) to treat just before the actual treatment: IPL or NdYAG and Active-Right|Control-Left OR Control-Right|Active-Left, respectively.

Blinding (masking)

Patients, physicians, outcome assessors, and data analysts will possibly be aware of the allocated groups.

Statistical methods

A detailed statistical analysis plan (SAP) will be developed during data collection while keeping the blind. In brief, the analyses will be based on mixed linear models, with a random effect for participant (1, 2, 3, …, to 20) with a fixed effect for group (active or placebo), axilla (right or left), and the experimental intervention of secondary interest (Nd:YAG or IPL). For the primary analyses the type of experimental intervention (Nd:YAG or IPL) will be included as a main effect only; secondarily if the primary test hypothesis is rejected ($p < 0.05$; H_0: $\mu_{Active} = \mu_{Placebo}$) we will

add a test for interaction to compare the net benefit for Nd:YAG *vs.* Placebo and IPL *vs.* placebo.

RESULTS COLLECTED (FOR REPORTING)

Table 1 | Characteristics of participants AND primary & key secondary end points.

	Baseline	**Follow-up (1 week from baseline)**	**Follow-Up (1 month from baseline)**
Age (years)	X	-	-
Sex: Female, no. (%)	X	-	-
Skin type	X	-	-
Family medical history	X	-	-
Personal medical history	X	-	-
Medication	X	-	-
Age of onset of hyperhidrosis	X	-	-
Previous history of hyperhidrosis	X	-	-
Primary Outcome Measure:			
Iodine-starch test incl. Photos (%)	X	-	X
Key Secondary Outcome Measures:			
Dynamic OCT imaging (photos)	X	-	X
Gravimetric testing (mg/5 min)	X	-	X
HDSS score for each axilla individually (4-point rang scale)	X	-	X
Binary questions for patient: 1) Effect from treatment? no. (%)	-	-	X
2) Adverse effects from treatment? no. (%)	-	-	X
3) Registration of whether the patient wish to receive laser treatment on control axilla after the study? no. (%)	-	-	X
Monitoring of adverse events			
Patient: VAS of pain during treatment (0-100 mm)	X	-	-
Physician: Report of redness, oedema and ulceration immediately after treatment (0-100 mm)	X	-	-
Patient: questionnaire of adverse effects (one-week post treatment)	-	X	-

OTHER

Perspectives and dissemination

Given a successful outcome of an investigation of long-pulsed Nd:Yag laser or IPL treatment for axillary hyperhidrosis, the laser treatment could potentially be implemented in the everyday practice, since Nd:YAG lasers and IPL devices are already widespread in European dermatological hospital departments and clinics.

We plan to present data internationally at e.g. the European Academy of Dermatology and Venerology as well as nationally to the Danish Dermatology Society and to the Hyperhidrosis Patient Association. Publication of results in an international scientific journal may lead to worldwide awareness of this new treatment, which hold the potential to provide long-lasting sweat reduction in patients suffering from axillary hyperhidrosis.

Patients may benefit from improved self-esteem, prevention of social anxiety and isolation, and better job opportunities, providing a positive personal development for patients, who presently suffer from a socially unacceptable and neglected chronic disease.

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