

Image guided targeted photoablation of eccrine glands for the treatment of localized hyperhidrosis

Detailed Protocol

I. Background and Significance

Hyperhidrosis is a condition in which sweating is in excess of that required for normal regulation of body temperature. It can be primary (not associated with any underlying condition), or secondary to drugs, endocrine disturbances, or certain malignancies. Commonly affected areas in primary hyperhidrosis include axillae, palms and soles. Secondary hyperhidrosis can affect scalp, face, neck, back, groin and legs.

The prevalence of primary hyperhidrosis in the United States has been estimated at 2.8%(1). Studies performed in other countries have reported higher estimates, including 13% prevalence of primary focal hyperhidrosis in Japan (2) and 28% prevalence of focal hyperhidrosis in Germany(3), but variation in study methodology may account for some of these differences.

Current methods of treatment all have limitations. Antiperspirants such as aluminum chloride provide only short-term relief and are often insufficient even for this. Iontophoresis of tap water or of aluminum chloride provides only several days of relief. Botox, which is approved for severe primary axillary hyperhidrosis, requires a large number of painful injections and must be repeated every three months. Glycopyrrolate, a systemic oral anticholinergic, can be helpful in hyperhidrosis but its use is frequently limited by systemic side effects. The MiraDry system, which is also approved for primary axillary hyperhidrosis, has significant comorbidity including neuropathy and pain. Neither Botox nor MiraDry is approved for treatment of areas outside of the axillae.

Iontophoresis is a noninvasive method using a weak electrical current to stimulate ions to pass into the skin. As noted above, iontophoresis of tap water or of aluminum chloride solution is used to treat hyperhidrosis. Iontophoresis of pilocarpine has long been used to stimulate sweating in the diagnosis of cystic fibrosis. Methylene blue is best known as an intravenously injected agent used in the treatment of methemoglobinemia. It has been known for decades that iontophoresis of methylene blue into the skin produces “pore patterns” centered on sweat-producing eccrine glands(4).

Fractional photothermolysis (FP) was introduced by the primary investigator as a method to obtain skin remodeling without the marked side effects typically associated with classic laser ‘layer’ resurfacing procedures (5). FP applies a dense pattern of microscopically small treatment zones (MTZs) to the skin. Within each MTZ the tissue is either thermally destroyed (nonablative FP) or removed (ablative FP). As

each of the individual MTZs is surrounded by undamaged tissue and the diameter of such MTZ is very small ($<300\text{ }\mu\text{m}$) the tissue is repaired very quickly. Also, in contrast to larger diameter lesions, the wound healing results in tissue regeneration rather than fibrosis. Fractional photothermolysis has been FDA approved for a number of indications, including skin resurfacing, treatment of wrinkles and furrows, and treatment of scars. The key element of FP is that the tissue surrounding individual MTZs remains unharmed.

In this pilot study, we propose to assess the ability of ablative fractional lasers to decrease sweating by selectively targeting sweat glands that have been labeled by iontophoretic delivery of methylene blue.

II. Specific Aims

To determine the safety and efficacy of iontophoretic methylene blue and laser therapy for the treatment of hyperhidrosis.

III. Subject Selection

We anticipate enrolling 15 subjects for this study.

Inclusion and exclusion criteria are as follows:

Inclusion criteria

1. Subjects of ages between 18 and 65 years.
2. Subjects with any Fitzpatrick skin type.
3. Subjects who are proficient in the English language.
4. Willingness to participate in the study.
5. Willingness to undergo experimental procedure.
6. Informed consent agreement signed by the subject.
7. Willingness to follow the follow-up schedule.
8. Willingness not to use any other hyperhidrosis treatment to the test sites during the study period (i.e. deodorant, at-home iontophoresis, Botox, MiraDry).
9. Patient rates symptoms at level “3” or “4” on the hyperhidrosis disease severity scale (HDSS, see below).
10. Subject answers “yes” to all exercise tolerance questions (see below).
11. No known allergy to iodine or potato starch. *If a prospective subject has a known allergy to iodine or potato starch, he or she is not excluded from the study. However, the subject will be excluded from the optional Minor’s test.

Exclusion criteria

1. Pregnancy
2. Subjects on systemic treatment for hyperhidrosis, such as anticholinergic drugs (e.g. glycopyrrolate), sedatives or tranquilizers, within the past 8 weeks.
3. Subjects who have undergone surgical excision of sweat glands or sympathectomy for hyperhidrosis.

4. Subjects with an underlying disorder, such as neurologic injury or disease affecting the autonomic system, vascular disorders and metabolic disorders (e.g. hyperthyroidism, diabetes mellitus) that can produce hyperhidrosis
5. Subjects with a history of coronary artery disease.
6. Subjects with a history of poor compliance or psychosis
7. Subjects taking SSRIs, SNRIs, TCAs, or MAOIs
8. Subjects with known hypersensitivity to lidocaine or methylene blue
9. Subjects with cardiac pacemaker or any other electrically powered implantable device.
10. Subjects not proficient in the English language.
11. Subject answers “no” to any of the exercise tolerance questions (see below).
12. Known allergy to iodine or potato starch.

IV. Subject Enrollment

Subjects will be recruited through email advertisements within the Partners system, and flyers posted on bulletin boards on the MGH campus and hospital. Additionally, patients who present to MGH Dermatology clinics with a complaint of hyperhidrosis will be informed of the study by their treating physician and asked if they would like to be contacted by study staff (Dr. Levin, Dr. DiGiorgio, or Dr. Anderson) about participating. The treating physician will emphasize that participation will be entirely voluntary and that a decision not to participate will not impact the care that the patient receives in the dermatology clinic. If a patient agrees to be contacted, the treating physician will provide study staff with the patient’s name and contact information.

No contact will be made by study staff until it is initiated by a prospective subject in response to a posted advertisement or until a patient agrees to be contacted by study staff when asked by a physician in the MGH Dermatology clinics as noted above.

When contact with study staff is made (either in response to a posted advertisement or through referral by a physician in the dermatology clinic), basic aspects of the study will be explained, and the prospective subject will be asked to schedule a screening visit with study staff.

V. Study Procedures

A. Screening Visit

The investigator will interview each subject, obtain a complete medical history and determine that the full selection criteria are met. The HDSS (below) will be completed to assess fulfillment of inclusion criterion #8. The consent form will be completed and, if agreed by the patient, signed. No study procedures will take place prior to obtaining informed consent. If the subject consents to participate in the study,

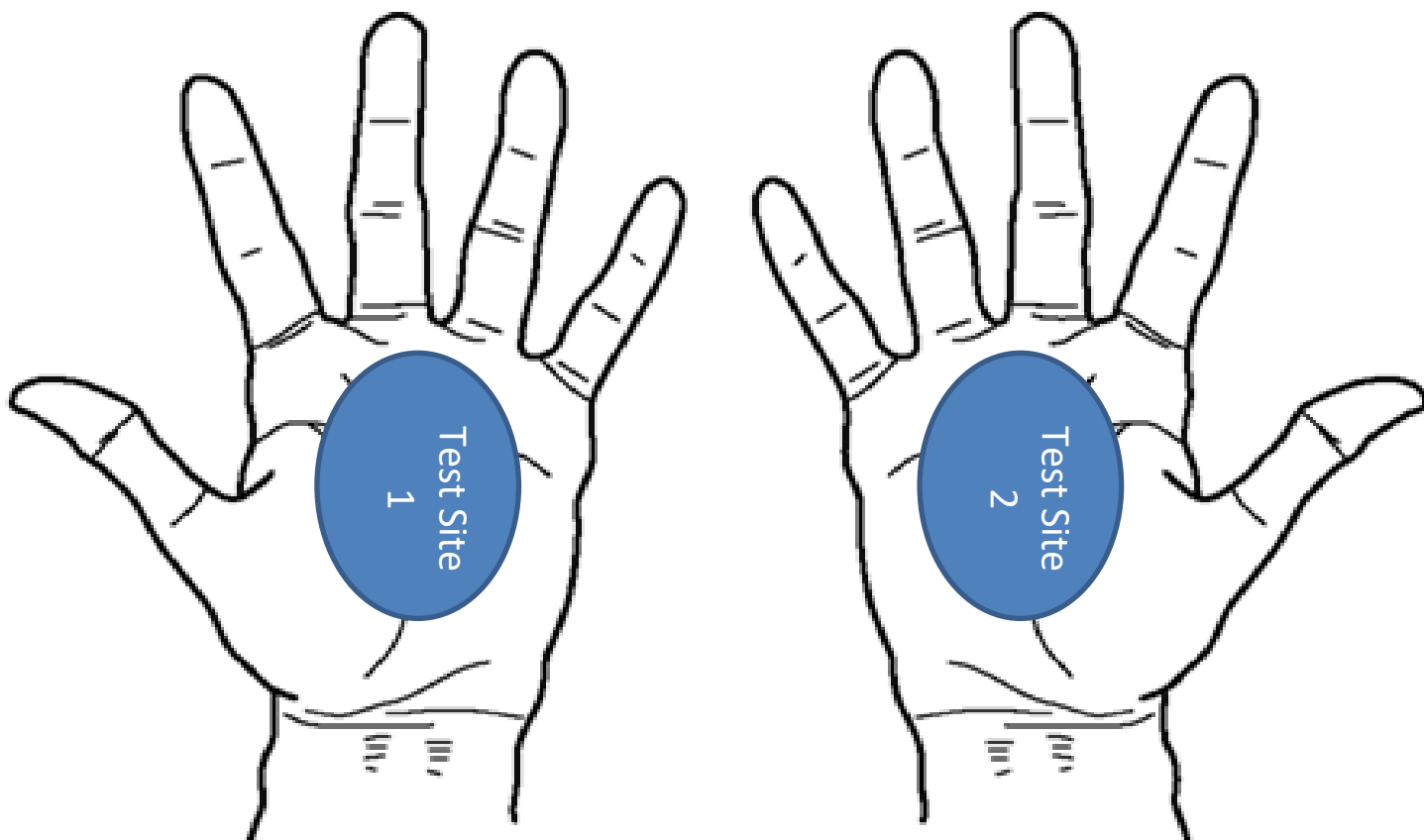
the initial treatment visit (Visit 1 below) may take place the same day as the screening visit at the subject's discretion.

Hyperhidrosis Disease Severity Scale	
“How would you rate the severity of your hyperhidrosis”	
☐ 1.	My sweating is never noticeable and never interferes with my daily activities
☐ 2.	My sweating is tolerable but sometimes interferes with my daily activities
☐ 3.	My sweating is barely tolerable and frequently interferes with my daily activities.
☐ 4.	My sweating is intolerable and always interferes with my daily activities

Exercise Tolerance Questions	
☐ Yes ☐ No	Can you climb a flight of stairs or walk up a hill?
☐ Yes ☐ No	Can you run a short distance?
☐ Yes ☐ No	Can you do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
☐ Yes ☐ No	Can you participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

B. Mapping of test sites (Study Visit 1)

Two test sites, each measuring 7.2 - 16.8 cm² (sizes of Iomed Gelsponges), will be chosen on the palms. One site will receive treatment and the other will serve as a contralateral untreated control. The chosen sites will be marked with easily removable ink and photographed. After photography, the ink will be removed with an alcohol wipe. Landmarks in the photograph such as fingers and skin creases will be used to identify the treatment and control sites at future visits.



Note: Test sites 1 and 2 will be randomized to left and right palms, respectively.

C. Measurement of sweat output (Study Visit 1, as well as Study Visits 2-6)

Sweating (pre-treatment and at follow-up visits) will be assessed as follows: Subjects will be asked to exercise using a stationary bike until sweating is observable. Gravimetric assessment of sweating will be performed (See sweat measurement protocol below). In addition, qualitative measurements using Minor's starch iodine test will be performed at follow-up visits in willing subjects at the investigator's discretion (when there is at least 50% reduction in sweat at control site relative to baseline) in order to illustrate the sweating.

D. Treatment (Study Visit 1)

All subjects will receive a single treatment. The test sites will be treated as follows:

Test Site 1:

Iontophoresis of Dye

The iontophoretic drug delivery system (Iomed, Inc., Salt Lake City, UT) is a battery operated compact iontophoretic device that delivers direct current. Iontophoresis is a procedure that uses low level electrical current to enhance delivery of drug ions into the skin. It is a safe and effective and rapid method of delivering water-soluble ionized (electrically charged) medications into the skin.

The subject's palm will be swabbed with alcohol and methylene blue will be delivered to site by iontophoresis (see iontophoresis protocol below).

Laser exposure

After 15 minutes the areas to be treated will be cleansed with alcohol and then air dried. Topical anesthesia, followed by ice packs, will be applied to the treatment area for 30 minutes in order to numb the area. Ice packs alone are commonly used when injecting neurotoxins into the palm to treat hyperhidrosis. This is generally preferred by patients over the alternative, which would be a regional nerve block to the hand. The Sciton Profractional laser will then be used to target the individual glands. The handpiece has an integrated camera that localizes the individual glands (blue dots) and passes their coordinates to the laser itself for targeted ablation. Laser exposures (pulse duration, energy per pulse) will be within ranges that are routinely used for the FDA-approved indication of skin resurfacing.

Test site 2 is a contralateral untreated control site for test sites 1.

E. Biopsy (Study visits 2 - 6)

Skin punch biopsies measuring 3 mm will be performed in willing volunteers when necessary according to the investigator's discretion (when there is decrease of at least 50% in sweating at treatment site versus control) using standard aseptic conditions. After completing the biopsy procedure, the biopsy sites will be sutured. The subject will be instructed to gently cleanse the surgical sites with soap and water and to apply petrolatum ointment twice daily. Sutures will be removed 10 days after the biopsy. The biopsies will be sent for routine hematoxylin and eosin processing. A maximum of 4 biopsies will be performed in a single subject.

F. Study Visits 2-6: Post treatment visits (Week 1 $\pm$ 3 days , week 2 $\pm$ 3 days, week 4 $\pm$ 5 days, months 3 $\pm$ 14 days and month 6 $\pm$ 14 days). The following procedures will be performed at each post-treatment visit:

- Clinical evaluation
- Photographs
- Sweat testing using stationary bike, gravimetric measurements, and (optionally) Minor's tests described above.

Iontophoresis Protocol:

Prior to the application of the electrodes, the skin is prepared by cleaning with isopropyl alcohol to remove any oily secretions or dead cells and also to disinfect. The sites for the active and inactive electrode is similarly cleaned.

The methylene blue is applied to the delivery electrode. The delivery electrode is then applied to the test site, while the inactive electrode is applied to skin 10-15 cm away. The iontophoretic device is connected such that the anode (positively charged) is attached to the delivery electrode, while the cathode is attached to the inactive electrode. The device

is switched on and the delivery current density and timer are set. Current amperage is increased to a maximum of 4 mA or maximum tolerated by the patient. Iontophoresis takes place for 15 minutes, after which excess solution is wiped away from the skin.

Sweat measurement Protocol:

(Gravimetric assessment and Minor's test):

Gravimetric Assessment: After drying the surface, a preweighted filter paper under occlusive dressing (Tegaderm) is applied to the test site for a period of time measured by a stopwatch. The paper is then weighed and the rate of sweat production is calculated.

Minor's Test: 2% iodine solution is applied to the test site. After drying, potato starch powder is applied. Sweating is then encouraged by exercise. Presence of sweating is indicated the appearance of a dark blue color.

VI. Biostatistical Analysis

Gravimetric measurements of sweat production will comprise the primary endpoint of the study; this endpoint has been used in other studies involving assessment of response to hyperhidrosis treatment(6).

A prior study (7) reports a coefficient of variation of 10.6% when using gravimetry to assess sweat production on the backs of individual subjects at two-week intervals. Using this as a conservative estimate of intra-subject variability, 10 subjects are needed in order to detect an 18% difference in sweat production between treatment site and untreated control with 80% probability at a one-sided 0.05 significance level. We are proposing 15 subjects in order to allow for attrition of subjects.

VII. Risks and Discomforts

Only physicians will perform the iontophoresis and operate the Sciton laser. These physicians include Drs. Anderson, Levin, and DiGiorgio. These laser operators have completed the MGH laser training and a credentialing process for the use of the Sciton profracional device, and have been approved as users on the MGH approved laser user list. Any risk of eye damage will be eliminated by the wearing of protective eyewear during laser use.

Subjects may experience a mild tingling or burning sensation during iontophoresis.

Subjects will wear protective goggles during the procedure to avoid eye injury.

Subjects may experience pain during the laser procedure. Measures are taken to mitigate or eliminate this pain.

Prior to the laser portion of the procedure, subjects will receive numbing using topical anesthesia followed by ice packs to mitigate pain during the procedure. Additionally, ice packs will be applied to the treatment area every few minutes during the procedure. Total elimination of pain cannot be definitively achieved.

The type of pain experienced during the laser procedure (when it is performed on a large area such as the entire face and with only topical anesthesia) is usually described as a series of pinpricks and/or heating/burning pain. In such a situation (treatment of entire face using only topical lidocaine), patients have described the pain associated with this procedure as stinging, pinprick-like, or burning. In one study using the fractional 2940 nm laser to treat periorbital and perioral wrinkles, maximum pain ratings following topical anesthesia and cold-air cooling were 4 (on a scale of 1-10) for periorbital and 3 for perioral resurfacing (Dierickx, et al. Micro-fractional ablative skin resurfacing with two novel erbium laser systems. *Lasers in Surgery and Medicine* 40:113-123 (2008)). In a study of full-face CO2 fractional ablative resurfacing using topical anesthesia (Berlin, et al. A Prospective study of fractional scanned nonsequential carbon dioxide laser resurfacing: a clinical and histopathologic evaluation. *Dermatologic Surgery* 35:222-228 (2009)), the authors reported "mild to moderate" pain from the procedure. We anticipate less pain with our proposed procedure than in a normal clinical (often cosmetic) situation because and because we are treating a smaller area and because we are using both topical anesthesia and ice packs for numbing. The reason for performing this procedure despite the risk of pain is that hyperhidrosis can be very concerning to patients, and sometimes quite debilitating in terms of employment, relationships, and other aspects of quality of life. There are currently no effective long-term treatments for localized hyperhidrosis that are painless or that require no pain control. For example, the MiraDry system, which is approved for treatment of axillary hyperhidrosis (but not palmoplantar or any other area), requires tumescent local anesthesia of the entire axilla. Even with this precaution, patients frequently experience pain with MiraDry.

The pain is caused by a very thin laser beam (250 micron diameter) that reaches depth of 1.5 mm. The energy of the beam is absorbed by water in the skin, which is instantly heated to a temperature at which it turns to vapor and exits in a plume. The amount of tissue that is vaporized for each microthermal treatment zone is 0.00029 cubic cm, a tiny volume. Our plan is to target this tiny ablation volume to the sweat glands themselves so that they are removed from the skin. Our goal is to determine whether and for how long we can decrease the sweating symptoms.

Overall, no more than 10% of the skin within the treatment area is exposed to the laser, which is significantly less than is usually used in the treatment of the many other conditions for which the device is cleared.

Other possible side effects include:

From the laser procedure:

Burns

The risk of a burn is minimized by proper use of the laser. However, the risk cannot be completely negated.

Swelling of the skin

This is a common but temporary side effect of using the laser and is improved by applying ice packs.

Redness of the skin

This is a common but temporary side effect of using the laser and is improved by applying ice packs.

Pigmentary Changes.

Laser exposure can cause pigmentary changes such as hyper- and hypopigmentation. Although this is usually temporary, it may be permanent.

Scarring.

As with any form of laser exposure, there is a small risk of scarring. However, this is minimized by proper technique and wound care.

Miliaria

Miliaria may develop. This results from obstruction of the sweat gland and can appear as vesicles or erythematous papules.

Alopecia

Permanent asymmetric hair loss is possible.

From the biopsy procedure:

Infections and scarring at biopsy sites.

Although unlikely, infections and scarring at biopsy sites may occur.

From the iontophoresis procedure:

Staining of treated area.

Blue staining of the treated area may persist for 2-4 weeks.

From the iodine test:

There may be temporary brown discoloration of the test areas on the skin, which could last up to four weeks.

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction to iodine are rash, itching, and other skin problems. Severe reactions such as swelling of the face and throat or trouble breathing have not been reported for the iodine test, but are theoretically possible.

Any serious adverse event will be reported within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem by telephone, fax or email followed by written report using the HRC Adverse Event Form within 10 working days/14 calendar days of the event. Mild or moderate adverse events will be summarized in progress report at the continuing review. Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines.

VIII. Potential Benefits

The subject will not benefit directly from participating in this study. If successful, there is a chance that the subject will experience relief from sweating in the small test areas.

If this modality proves to be effective, it will be a useful alternative to treating hyperhidrosis for future patients.

IX. Monitoring and Quality Assurance

All members of the study team have completed the Collaborative IRB Training Initiative (CITI), the mandatory tutorial on the responsible conduct of human subject research. The Principal Investigator (R Rox Anderson, MD) will oversee the implementation of this investigation and closely supervise all co-investigators throughout the study. A clinical investigator will assure the treatment safety by assessing for the incidence of adverse events at the exposure treatment session and at the follow up visits (and any other followup visits that may be requested by the investigator based on individual need.) The principal investigator shall review data on an ongoing and consistent basis throughout the duration of the study. There shall be no change in treatment or data evaluation and reporting procedures without prior IRB approval.

All source data, informed consent and case report form entries will be organized and filed into individual subject binders. Any pertinent notes to file regarding the subject shall be documented by a study investigator and kept in the applicable subject binder. The principal investigator shall review data on an ongoing and consistent basis throughout the duration of the study. All subjects must be assigned a study identification number that will be the only item that appears on the subject binder and photographs. In order to protect the privacy and confidentiality of subjects, binders will be stored in a locked room at the Wellman Center for Photomedicine (Bartlett Room 304F, where research binders for other studies are also stored.) The key to the code which links a subject's identity to the alphanumeric code will be maintained in an electronic file on a secured hospital server. The electronic digital images, labeled with the study identification number, will be stored in a different directory on a secured hospital server.

1. Strutton DR, Kowalski JW, Glaser DA, Stang PE. US prevalence of hyperhidrosis and impact on individuals with axillary hyperhidrosis: results from a national survey. *J Am Acad Dermatol* 2004;51(2):241-248.
2. Fujimoto T, Kawahara K, Yokozeki H. Epidemiological study and considerations of primary focal hyperhidrosis in Japan: from questionnaire analysis. *J Dermatol* 2013;40(11):886-890.
3. Augustin M, Radtke MA, Herberger K, Kornek T, Heigel H, Schaefer I. Prevalence and disease burden of hyperhidrosis in the adult population. *Dermatology* 2013;227(1):10-13.
4. Papa CM, Kligman AM. Mechanisms of eccrine anidrosis. I. High level blockade. *J Invest Dermatol* 1966;47(1):1-9.
5. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med* 2004;34(5):426-438.
6. Glaser DA, Coleman WP, 3rd, Fan LK, et al. A randomized, blinded clinical evaluation of a novel microwave device for treating axillary hyperhidrosis: the dermatologic reduction in underarm perspiration study. *Dermatol Surg* 2012;38(2):185-191.
7. Hayden G, Milne HC, Patterson MJ, Nimmo MA. The reproducibility of closed-pouch sweat collection and thermoregulatory responses to exercise-heat stress. *Eur J Appl Physiol* 2004;91(5-6):748-751.