Evolution of a New Treatment Modality for Primary Focal Hyperhidrosis

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Introduction

Hyperhidrosis is a condition of excess perspiration. While no specific diagnostic criteria exist to differentiate "normal" amounts of sweating from those individuals with a bona fide medical illness, in most cases, patients complaining of excess sweating have substantial symptoms and findings. These include persistent sweating, dripping or soaking moisture at rest, inability to perform certain daily functions such as handling paper due to wetness on the hands or vastly accelerated garment deterioration due to wetness. Hyperhidrosis may exist due to diseases or medications such as hyperthyroidism or anti-depressive agents and, in these cases, is known as secondary hyperhidrosis. Primary hyperhidrosis is diagnosed when no underlying medical condition or causative medication is found. Primary hyperhidrosis is typically a focal condition most commonly involving the axillae and reported to occur in 1.4% of the US population, although the prevalence is probably under-reported due to the social stigma of the disease.[1]

To date, no ideal treatment for focal hyperhidrosis exists. Current treatments have various limitations. High strength topical antiperspirants available over the counter or via prescription all contain aluminum salts which are at best, modestly effective for true medical hyperhidrosis and have been associated with some risks when used long term.[2,3] Botulinum toxin injections show good efficacy but last less than 12 months and are a painful procedure. Systemic anticholinergic agents have a broad array of side effects and limited efficacy.[4, 5] Various surgical procedures have their own specific morbidities such as scars, pain and importantly, compensatory hyperhidrosis.[6]

The ideal treatment for hyperhidrosis would be focally deliverable, non-invasive, long-acting and with minimal adverse effects. A technology based on focused heating of sweat gland tissue using microwave energy has been developed and refined for clinical use. The engineering, pre-clinical and clinical work conducted to develop this product will be reviewed here.

Technology

A microwave-based technology has been developed and optimized which implements several features in its design to precisely deliver energy to the depth of the sweat glands. An integrated vacuum system lifts the skin and underlying tissue a few millimeters into the treatment chamber. During the treatment cycle (consisting of energy delivery time and post-cool time) cooling fluid flows through a chamber in contact with the skin, protecting the epidermis and upper dermis from excess heating (see Figure 1). Structures deeper than the sweat glands are protected from heat injury due to the limited penetration depth of microwave energy. Limited penetration is achieved by tailoring the frequency and antenna structure such that the radiated microwave energy is focused at the dermal/hypodermal interface.

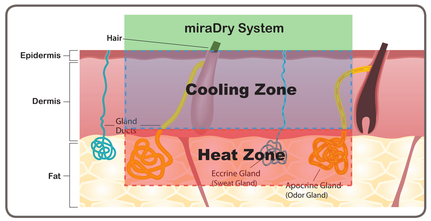

Figure 1. The miraDry System creates a heat zone at the level of the sweat glands and a protective cooling zone at the dermis.

Pre-Clinical Studies

Multiple pre-clinical studies were conducted in the Yorkshire porcine model. All studies used the belly/flank of the pig as the target area; there are no eccrine (sweat-producing) glands but the dermis and subcutaneous fat allowed safety evaluation of the various tested devices and settings as well as confirmation of the depth of penetration and heat zone. Multiple interations varying the power output as well as the antennae that transmit the microwave energy were tested to arrive at a combination that produced a well-controlled zone of heat injury at the correct depth.[7]

Figure 2 shows a representative result of testing with the system approximately one week after energy was applied. The dark areas show the zone with the bulk of the damage, indicating that the energy indeed is concentrated at the dermal/hypodermal interface. There is no sign of damage to the epidermis or upper dermis.

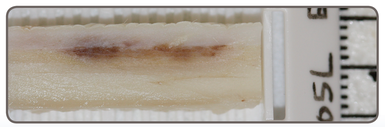

Figure 2. Effect of energy delivery on porcine model.

Procedure

To perform the treatment, subjects receive infiltrative local anesthesia in a grid pattern to the entire axilla. The treatment is provided via serial placement of the handpiece, with an active area of approximately 10mm by 30mm. After placement of the handpiece, the treatment cycle is activated. Upon activation, a vacuum is created which gently draws the skin against the thin ceramic treatment plate. Chilled fluid passes behind the plate providing cooling to the superficial levels of the skin. Sensors ensure that the skin is in close apposition to this cooling surface. Microwave energy is then applied non-invasively in a very directed fashion via multiple antennae within the handpiece. The energy is delivered over approximately 30 seconds followed by a 20 second post-cool period. Upon completion, the vacuum is released and the cessation of the audio signal indicates the end of the treatment cycle. The handpiece is then moved by the operator to the next adjacent treatment area and the process is repeated.

Based on the clinical testing described below, two procedure sessions approximately 3 months apart are recommended for optimal efficacy results.

Clinical Studies

A series of clinical studies have been conducted to systematically demonstrate the safety and efficacy of the procedure, as well as to optimize the device and procedure for clinical use. All studies had very similar key inclusion/exclusion criteria which included:

- Adults only
- All subjects were required to have HDSS=3 or 4 (see Table 1)
- Aside from the feasibility study, the studies required gravimetric readings of at least 50mg of sweat / 5 min in each axilla
- No botulinum toxin injections in the axillae within the 6 months prior to enrollment

Table 1. Hyperhidrosis Disease Severity Scale (HDSS) Definition

The question asked is: How would you rate the severity of your hyperhidrosis?

HDSS Value	Definition
1	My underarm sweating is never noticeable and never interferes with my daily activities
2	My underarm sweating is tolerable but sometimes interferes with my daily activities
3	My underarm sweating is barely tolerable and frequently interferes with my daily activities
4	My underarm sweating is intolerable and always interferes with my daily activities

Table 2. Subject Demographic Comparison

		Feasibility Study (n=28)	Randomized Study (n=81 treated)	miraDry Study (n=31)
Age:	Median	34 years old	33 years old	33 years old
	Range	19 to 49	18 to 83	18 to 65
Gender:	Female	57%	53%	74%
Race:	Caucasian	77%	84%	87%
BMI:	Median	25.6	26.5	24.8

Feasibility Study

After pre-clinical studies had identified an optimal design with demonstrated safety, a human feasibility study was undertaken to gain efficacy information.[7] The first phase involved a small number of subjects that were treated in a small area in one axilla to demonstrate (via the starch-iodine test) local sweat elimination. The second phase (utilizing a modified device and handpiece with a larger active area, see Figure 3), was a titration study to treat full axillae; the goal was to optimize the device settings and establish methods to measure efficacy prior to a definitive efficacy study being conducted. The second phase study was conducted at 6 sites in the US; subjects were treated with one to three procedure sessions over 2 months. A total of 28 subjects were enrolled, treated and followed for three months post treatments. Major findings from the study include:

- Device settings that demonstrated efficacy with appropriate safety parameters were identified
- A reduction to an HDSS score of 1 or 2 in 82% of subjects (measured 30 days post-treatment)

Randomized Study

The device used and the settings determined from the prior study procedure were then implemented in a large, randomized sham-controlled study at 7 sites in the US.[8,9] A total of 120 subjects were randomized (81 in the active treatment group and 39 in the sham treatment group). Treatments were conducted in one to three procedure sessions, typically spaced 2 weeks apart. Subjects in the sham group were followed for 6 months. Subjects in the active group were followed for 12 months. The major findings from the study were:

- A reduction to an HDSS score of 1 or 2 in 89% of subjects (measured 30 days post-treatment) in the active group, and a statistically significant difference between active and sham group was seen ($p<0.001$)
- HDSS efficacy in the active group was relatively stable from 3 months (74%) to the last study visit at 12 months (69%)
- Gravimetric assessments (weight of sweat) also showed stability in efficacy from 3 to 12 months
- The procedure was well tolerated and a strong safety profile was established

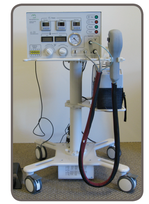

Figure 3. Investigational version of the miraDry System used in Feasibility and Randomized studies.

miraDry Study

Based on findings from the pre clinical animal studies as well as the two human clinical trials, a commercial version of the device, named the miraDry System (see Figure 4), was developed that added software control and automatic safety features. The energy delivery through the handpiece microwave antennas was also improved to eliminate potential gaps between the heated regions under each antenna.

Figure 4. Commercial miraDry System used in the miraDry study.

The miraDry procedure using the commercial device was tested in 2 sites in Canada in a single-group study of 31 subjects. These subjects were treated in one to three procedure sessions, with procedure sessions now being held two to three months apart. At the time of this writing, efficacy and safety data are available for up to 3 months post-treatment.[10] Subjects will be followed for 12 months. The major findings from this study were:

- A reduction to an HDSS score of 1 or 2 in 90% of subjects (measured 30 days post-treatment)
- The procedure and device improvements have stabilized the efficacy seen at later time points compared to prior studies; the last reported efficacy was 94% at 3 months post-treatment
- The average reduction in amount of sweat produced (measured by gravimetric assessment) was 82%.
- Patient satisfaction tracks very closely with efficacy and has been reported at >90%

A compilation of efficacy results for the three reported studies can be seen in Table 3 and plotted over time in Figure 5. The most recent miraDry study with the optimized device and procedure show greater than 90% efficacy.

Table 3. Comparison of HDSS Score Reduction Results for Three Reported Studies

Study	Reference	30 days	3 months	6 months	12 months
Feasibility	Kaminer	23/28=**82%**	18/28=**64%**	not available	not available
Randomized	Kilmer	72/81=**89%**	60/81=**74%**	54/81=**67%**	56/81=**69%**
miraDry	Lupin	28/31=**90%**	29/31=**94%**	(pending)	(pending)

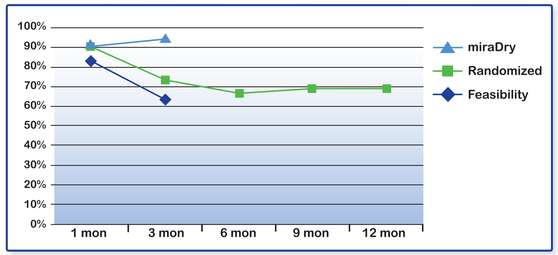

Figure 5. Percentage of subjects that had HDSS scores of 1 or 2 at the indicated follow-up visits for each study.

Finally, the safety data across all three clinical studies has been very good. Almost all subjects noted the expected mild, temporary swelling and discomfort in the treatment area post-treatment with an average duration of approximately one week; altered sensation in the treatment area can last several months. Treatment-related effects were apparent very soon after a procedure and have almost entirely been transient. Table 4 lists the side effects with incidence >5% of subjects seen in each study. Only interim data from the miraDry commercial device study is available as the study is still ongoing.

Table 4. Most Common Adverse Events in Each Study

Category	# of subj (%)	Severity (events)
Feasibility Study (n=28)		
Numbness or altered sensation outside treatment area	10 (36%)	10 mild, 3 moderate
Compensatory hyperhidrosis	2 (7%)	1 mild, 1 moderate
Randomized Study (n=81)		
Numbness or altered sensation outside treatment area	8 (10%)	8 mild, 1 moderate
Axillary pain requiring Rx medication or soreness	5 (6%)	4 mild, 1 moderate, 1 severe*
miraDry Study (n=31)		
Numbness or altered sensation outside treatment area	12 (39%)	16 mild
Edema in limb or chest	8 (26%)	5 mild, 3 moderate
Skin: Irritation or rash	3 (10%)	3 mild
Tenderness in arms	3 (10%)	3 mild

* One subject elected bedrest after the procedure which required a severe rating.

Conclusion

Primary focal hyperhidrosis remains a difficult clinical problem. Through deliberate engineering, study and clinical analysis, a novel device using microwave energy has been developed. This device focuses the energy at a specific depth and uses topical cooling to preserve the more superficial layers of skin. Clinical studies have shown:

- Significant overall efficacy with improvement at each stage of device development
- A highly acceptable safety profile with mild, generally self-limited changes
- An easy to perform clinical procedure
- The possibility that the improvement in hyperhidrosis may be long-lived compared to existing therapies

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