

A Randomized, Blinded Clinical Evaluation of a Novel Microwave Device for Treating Axillary Hyperhidrosis: The Dermatologic Reduction in Underarm Perspiration Study

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BACKGROUND Duration of effect and effectiveness limit current options for treating axillary hyperhidrosis. A new microwave procedure for treatment of axillary hyperhidrosis has been tested.

STUDY DESIGN/MATERIALS AND METHODS Adults with primary axillary hyperhidrosis were enrolled in a randomized, sham-controlled, blinded study. Subjects were required to have a Hyperhidrosis Disease Severity Scale (HDSS) score of 3 or 4 and baseline sweat production greater than 50 mg/5 min. Procedures were administered using a proprietary microwave energy device that isolates and heats target tissue. Responders were defined as subjects reporting a HDSS score of 1 or 2. Subjects were followed for 6 months (sham group) or 12 months (active group).

RESULTS Thirty days after treatment, the active group had a responder rate of 89% (72/81), and the sham group had a responder rate of 54% (21/39) ($P < .001$). Treatment efficacy was stable from 3 months (74%) to 12 months (69%), when follow-up ended. Adverse events were generally mild, and all but one resolved over time.

CONCLUSIONS The procedure demonstrated statistically significant, long-term efficacy in sweat reduction. As with any new procedure, findings from this first investigational device study identified optimization strategies for the future.

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Axillary hyperhidrosis (excessive underarm sweating) is a condition that can be a substantial burden, affecting work performance, relationships with other people, and self-esteem. One study that defined axillary hyperhidrosis as excessive or abnormal/unusual sweating found that 1.4% of the U.S. population met that definition.¹ A third-party survey found that 33% of the population reports that they sweat too much (in their underarms) (unpublished data). Duration of effect

(e.g., topical antiperspirants, injections of botulinum toxin²) and complications and effectiveness (surgical interventions, sympathectomy^{3,4}) limit current treatment options for axillary hyperhidrosis. Microwave devices, although not commonly used in dermatology, can be optimized to focus heat at the interface between the skin and subcutaneous tissue and cause irreversible thermolysis of apocrine and eccrine sweat glands that reside at that interface. In this study, a new early-generation

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microwave-based procedure for treatment of axillary hyperhidrosis was tested for long-term efficacy and safety.

Materials and Methods

Patients

One hundred twenty adults with primary axillary hyperhidrosis (PAH) were enrolled in a multicenter, randomized, sham-controlled study. Subjects were required to have a Hyperhidrosis Disease Severity Scale (HDSS)⁵ score of 3 or 4 (barely tolerable or intolerable sweating) and to have baseline axillary sweat production of greater than 50 mg/5 min as measured by gravimetric readings. Subjects were excluded if they had ever had prior surgery for PAH or botulinum toxin injections to treat PAH within the past 12 months.

The study was conducted in accordance with the Declaration of Helsinki, and all subjects signed an institutional review board-approved informed consent before any study procedures.

Sweat Assessments

The primary method of assessing level of underarm sweat was subject-reported HDSS score. Table 1 provides the definition of each of the four possible categories. Gravimetric assessment of sweat was

used as a secondary measure. Measurements were taken in a normal-temperature room with subjects at rest. Axillae were wiped with gauze or absorbent towels before the test, and a preweighed filter paper (Whatman #541, 90 mm, Maidstone, England) was placed in each axilla for 5 minutes, after which the difference in weight was calculated in milligrams.

Although not used for any study end points, the starch-iodine test was used in some treatment sessions to identify areas that still had active sweat glands. An alcohol-based iodine mixture was wiped on the skin of the axilla, and then corn starch was sprinkled on the area and gently brushed to create a thin uniform coating. Any sweat that appeared turned black (Figure 1). To protect study blinding, subjects wore an eye-mask during the starch-iodine test to preclude the possibility of seeing the extent of the sweat.

TABLE 1. Hyperhidrosis Disease Severity Scale Definition	
Score	How would you rate the severity of your hyperhidrosis?
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

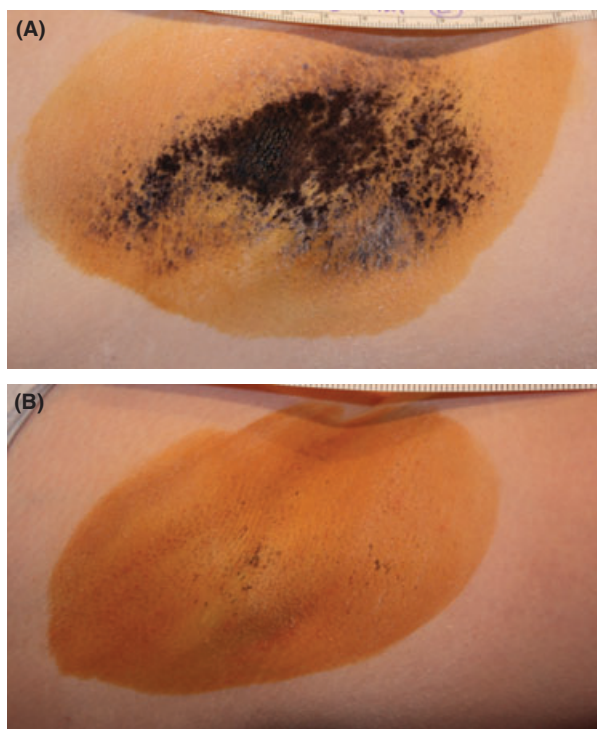


Figure 1. Photographs of starch-iodine tests of the left axilla of a subject who received treatment showing (A) baseline extent of sweating and (B) amount of sweat 12 months after treatment was complete.

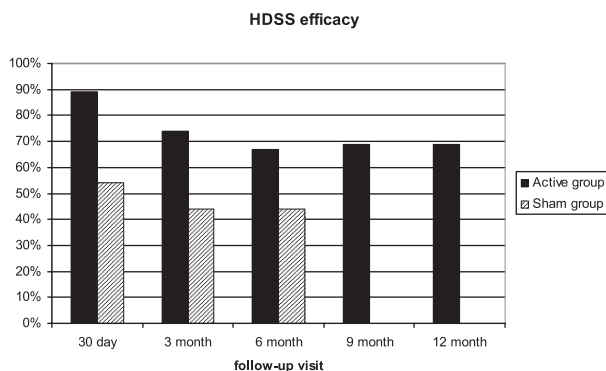


Figure 2. Hyperhidrosis Disease Severity Scale efficacy through the follow-up period. Sham subjects exited the study after the 6-month visit. The *P* value for the active-sham comparison was less than .05 for each visit.

Treatments

The study protocol was that subjects would typically undergo two procedure sessions, separated by approximately 2 weeks. Fewer procedure sessions were allowed if the subject's underarm sweat was eliminated with one session or if the subject declined further treatment. A third procedure session was allowed within a 30-day window if a subject still had a high level of sweating after two sessions. Procedures were put in place to protect blinding during the treatment period.

At the time of the first procedure session, subjects were randomized in a 2 to 1 ratio to a treatment group ($n = 81$) and sham group ($n = 39$). Each session included three steps: marking the axilla with a treatment template, injecting local anesthesia (1% lidocaine with 1:100,000 epinephrine) throughout the indicated area, and applying the microwave treatment. The microwave-based device included integrated vacuum and cooling (DTS G2 System; Miramar Labs, Sunnyvale, CA). Sham subjects experienced all steps of the procedure session, but microwave energy was not delivered.

In the first procedure session, the hair-bearing areas of both axillae were treated; 83% of subjects had a second procedure session approximately 2 weeks after the first session, as outlined in the protocol. The unblinded investigator determined

the extent of the area to be treated based on a starch-iodine test and sweat assessments (active group) or a defined area based on axilla size (sham group). All sham group subjects had two procedure sessions. Eleven subjects (9%) had only one session. Four of these subjects had a reduction of sweat after the first session to a level that required no further treatment (i.e., HDSS = 1 or 2 and sweat measurements <50% of baseline and no visible areas to treat on the starch-iodine test). Two subjects declined further treatment because of pain during or after the treatment; five subjects had ongoing side effects (swelling, pustules, or blisters) at the time of the scheduled second treatment (2 weeks after the first) and so did not receive any more treatment. Ten subjects (8%) had a third procedure session approximately 30 days after the second procedure session when it was seen that they still had high levels of sweat production (HDSS = 3 or 4 or sweat measurements >50% of baseline).

Blinded study personnel administered HDSS questionnaires and gravimetric assessments at each follow-up visit. The timing for all follow-up visits was calculated relative to the last procedure session. Sham group subjects had follow-up visits at 30 days, 3 and 6 months and then exited the study. Active group subjects had follow-up visits at 30 days and 3, 6, 9, and 12 months after treatment. All subjects and study staff were unblinded at the end of the 6-month study visit.

Study Efficacy Measures

For the primary endpoint, responders were defined as subjects reporting a HDSS score of 1 or 2 at the 30-day follow-up visit. Secondary analyses included the same measure at the 6-month follow-up visit and calculating the proportion of subjects that achieved a 2-point or greater decline in HDSS. Gravimetric efficacy success was defined as a greater than 50% reduction in weighed sweat from baseline data (average of right and left values). A second analysis was also performed to

evaluate a 75% or greater reduction in weighed sweat.

Statistical Analysis

Statistical analysis was performed using SAS (Version 9.1, SAS Institute Inc., Cary, NC). The analysis used all 120 enrolled subjects (intention-to-treat population); the method of last observation carried forward was used to impute missing data from missed visits. Comparisons between the randomized groups for demographic characteristics and responder percentages were made using the Cochran-Mantel-Haenszel test stratified according to investigational site. Statistical hypothesis testing was two sided, with significance inferred at $\alpha = 0.05$.

Safety Assessments

The investigator rated Adverse events that subjects reported in severity and how likely it was that the event was related to the study device or procedure. The expected local sequelae in the treated area were categorized separately from the adverse events.

Results

Demographics for all enrolled subjects are shown in Table 2. There were no statistically significant differences between the subjects in the active group and the sham group, although there was a substantial difference in the proportion of subjects with a HDSS score of 3 between the sham group (67%) and the active group (51%). One hundred one of the 120 subjects completed the study as planned; 13 active group subjects (16%) and six sham group subjects (15%) exited the study early, none because of adverse events.

Efficacy

Hyperhidrosis Disease Severity Scale efficacy results are shown in Tables 3 and 4. The primary efficacy endpoint was met, with 89% of the active group

TABLE 2. Subject Demographic Characteristics

	Active Group (n = 81)	Sham Group (n = 39)	Total (N = 120)
Age			
Median	33	31	31
<30, n (%)	17 (44)	40 (49)	57 (48)
30–45, n (%)	15 (39)	32 (40)	47 (40)
≥ 45, n (%)	7 (18)	9 (11)	16 (13)
Sex, n (%)			
Male	13 (33)	38 (47)	51 (43)
Female	26 (67)	43 (53)	69 (58)
Race, n (%)			
White	33 (85)	68 (84)	101 (84)
African American	4 (10)	4 (4.9)	8 (6.7)
Other	2 (5.1)	8 (9.9)	10 (8.3)
Baseline Hyperhidrosis Disease Severity Scale score, n (%)			
3	41 (51)	26 (67)	77 (64)
4	40 (49)	13 (33)	53 (36)
Baseline gravimetric reading, mg/5 min, average	180.5	177.2	179.4

Percentages may not add up to 100% due to rounding.

and 54% of the sham group meeting the definition of responder at 30 days ($P < .001$). For all time points with data from both groups (through the 6-month visit), the HDSS efficacy for the active group was statistically significantly greater than the efficacy for the sham group. For the active group subjects, the efficacy results continued to be stable for 1 year after treatment (to the time of the last follow-up visit; see Figure 2).

The summary of results from the gravimetric assessment of sweat production can be seen in Table 5. A reduction of 50% or more in sweat at the 30-day follow-up visit was seen in 80% of the active group and 67% of the sham group ($P = .07$). There was a statistically significant difference when success was defined as a 75% or greater reduction in sweat; the active group efficacy was 62%, and the sham group efficacy was 39% ($P = .01$). At later time points, there was no statistically significant difference in gravimetrically measured sweat reduction between the two groups,

TABLE 3. Hyperhidrosis Disease Severity Scale (HDSS) Efficacy Results Through the 6-Month Follow-Up Visit, Comparing Responder Rate in the Active ($n = 81$) and Sham ($n = 39$) Groups

Definition of Success	30-Day Visit %			3-Month Visit %			6-Month Visit %		
	Active Group	Sham Group	P-Value	Active Group	Sham Group	P-Value	Active Group	Sham Group	P-Value
HDSS score 1 or 2	89	54	<.001	74	44	=.001	67	44	.02
HDSS score reduced by ≥ 2 points	67	13	<.001	57	13	<.001	47	13	<.001

TABLE 4. Hyperhidrosis Disease Severity Scale (HDSS) Efficacy Results Through the 12-Month Follow-Up Visit for the Active Group ($n = 81$)

Definition of Success	30-Day Visit %	3-Month Visit %	6-Month Visit %	9-Month Visit %	12-Month Visit %
HDSS = 1 or 2	89	74	67	69	69
HDSS reduces by ≥ 2	67	57	47	42	38

TABLE 5. Gravimetric Efficacy Results Through the 6 Month Follow-Up Visit, Comparing Responder Rate in the Active ($n = 81$) and Sham ($n = 39$) Groups

Definition of Success, Reduction from Baseline	30-Day Visit %			3-Month Visit %			6-Month Visit %		
	Active Group	Sham Group	P-Value	Active Group	Sham Group	P-Value	Active Group	Sham Group	P-Value
$\geq 50\%$	80	67	.07	75	64	.20	63	59	.69
$\geq 75\%$	62	39	.01	52	44	.34	41	36	.60

although the reduction was greater in the active group.

Safety

There were no procedure-related serious adverse events reported in the study for any subject. Procedure-related adverse events were generally mild. There were 45 procedure-related adverse events in 23 (28%) active group subjects and five (13%) sham group subjects. The types and frequency of adverse events are shown in Table 6 according to randomization group. The most frequently reported adverse event (9.9% of treated subjects) was altered sensation in a moderately sized area (average 12 cm length at onset) in the skin of the upper arm. This was reported as a change in sensitivity, tingling, or numb-

ness and was most likely due to effects on cutaneous nerves. There was substantial variation in the duration of this mild effect, but all of these events resolved over time (median duration 25 days). A contributing factor to the longest-duration event was the subject's infrequent follow-up visits. For the other events shown in Table 6, all but one resolved with no permanent effects. As noted in Table 6, one subject with self-reported compensatory hyperhidrosis reported ongoing sweating of the face at study exit.

Post-treatment local sequelae that were common (>50% of subjects) were similar in the sham and active groups and included vacuum acquisition marks, tenderness or altered sensation in the treatment area, and soreness or discomfort.

TABLE 6. Procedure-Related Adverse Events in Each Study Group

Category	Total	Sham Group (N = 39)			Active Group (N = 81)		
	Events, n	Events, n	Subjects, n (%)	Duration, Days, Mean (range)	Events, n	Subjects, n (%)	Duration, Days, Mean (range)
Altered sensation in treatment limb	10	1	1 (2.6)	79.0 (79–79)	9	8 (9.9)	67.4 (4–225)
Pain or soreness	8	2	2 (5.1)	3.5 (3–4)	6	5 (6.2)	21.8 (1–74)
Swelling in the treatment limb*	7	2	1 (2.6)	2.5 (2–3)	5	4 (4.9)	8.6 (2–20)
Blisters, burns, or ulcerations	5	0	0	–	5	4 (4.9)	28.2 (12–40)
Skin: rash, irritation, or dermatitis	4	0	0	–	4	4 (4.9)	27.0 (3–87)
Axillary bumps or nodules	4	2	1 (2.6)	11.0 (10–12)	2	2 (2.5)	30.0 (8–52)
Compensatory sweating	2	0	0	–	2	2 (2.5)	52 [†]
Other	5	0	0	–	5	5 (6.2)	25.8 (2–46)
Total	45	7			38		

*This effect was rated as mild in all but one event, where the patient stayed in bed over a weekend, which required a severe severity rating.

[†]One subject reported ongoing, stable altered sweating of the face at study exit. No duration data were used.

Discussion

This study demonstrates a statistically significant reduction in subject-reported sweat severity after treatment with a novel microwave device than in subjects who received a sham treatment. This endpoint, defined as reaching a HDSS score of 1 or 2, means that subjects' sweat level has no or little remaining interference in their daily life, a clinically meaningful result. The statistically significant difference occurred for all follow-up visits through 6 months. The active group followed to 12 months after treatment showed stable efficacy through their final follow-up visit. There is evidence in the literature⁶ that sweat glands form only at the embryonic stage and that new sweat glands do not appear after birth. This suggests that a stable level of efficacy would continue.

The analysis of HDSS scores with a different criterion (requiring a ≥ 2 point drop in the HDSS scale) highlights that the randomization of the active and sham group yielded important differences in severity scores at baseline. A higher

proportion of subjects enrolled in the sham group (67%) than of the active group (51%) had a baseline HDSS score of 3. This meant that more sham group subjects could achieve success in the primary efficacy measure by dropping a single point (from 3 to 2). By applying the more-stringent criterion of dropping two or more points to both groups, the result (67% for the active group and 13% for the sham group at the 30-day visit, a 54% difference) is statistically significant ($P < .001$). This analysis also allows a more-direct comparison with the published results on treatment with botulinum toxin A (where a 2-point change in HDSS score was required for success),² which showed similar results at the 30-day visit of 75% for the treatment group and 25% for the placebo group ($P < .001$), a difference of 50%. In the same study, the average duration of botulinum toxin effect was 6.7 months.

The results from the gravimetric assessment of sweat reduction did not show a statistically significant difference at all time points. Inpatient variations of gravimetric testing have been noted previously^{7,8}

and may have affected the ability to obtain accurate measurement of sweat reduction. The study design also did not include taking multiple baseline measurements to account for subjects being more nervous at the initial screening visit, potentially leading to higher baseline readings and a resulting reduction in the amount of weighed sweat at follow-up visits for all subjects, regardless of intervention. Furthermore, the room conditions (temperature and humidity) and the time of day were not strictly controlled. These effects could have contributed to gravimetric measurement variability.

The safety profile of the procedure demonstrated low risk for the subjects. The mechanism of action of the procedure causes noninvasive focused heating of the tissue at the depth of the sweat glands with resulting thermolysis of the sweat glands. As would be expected with this mechanism, most subjects experienced local edema and mild discomfort in the treated area, on average lasting 9 days and usually easily controlled with use of ice and nonprescription antiinflammatories. A small percentage (~5%) of subjects required prescription pain management after treatment. Some of the side effects were of long duration but resolved; they also generally were mild and did not affect subjects' daily activities.

This study also provided the opportunity to identify potential areas for improvement in the procedure and device. The second procedure session took place approximately 14 days after the first session. In retrospect, waiting longer between procedure sessions to allow postoperative fibrosis to set in may have given a better indication of areas that were missed or undertreated at the first procedure session. Also, some subjects experienced side effects that were not resolved in this short period, so they only received one treatment. Waiting longer would have allowed more-complete treatment. In addition, the study design used fixed energy delivery. Given the favorable safety results at this fixed setting, it is expected that using a higher dose at a second session might deliver a greater benefit with little risk.

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