A novel lotion formulation of 20% oxybutynin hydrochloride for the treatment of primary palmar hyperhidrosis: A randomized, placebo-controlled, double-blind, phase III study

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Background: No previous controlled studies have been specifically designed or adequately powered to show the efficacy of topical oxybutynin for palmar hyperhidrosis by using quantitative measures.

Objective: To evaluate efficacy of 20% oxybutynin hydrochloride lotion (20% OL) in reducing palmar sweat volume in patients with primary palmar hyperhidrosis (PPHH).

Methods: In a randomized controlled trial, Japanese patients with PPHH aged 12 years and older received either 20% OL (n = 144) or placebo (n = 140) on both palms once daily for 4 weeks. Palmar sweat volume was measured by the ventilated capsule method. For the primary outcome, response was defined as a reduction of sweat volume of at least 50% from baseline.

Results: At week 4, the responder rate for sweat volume was significantly higher in the 20% OL arm than in the placebo arm (52.8% vs 24.3%, respectively; treatment difference, 28.5% [95% CI, 17.7% to 39.3%]; $P < .001$). No serious adverse events occurred, and no adverse events led to treatment discontinuation.

Limitations: The treatment period was only 4 weeks.

Conclusions: In patients with PPHH, 20% OL is superior to placebo in reducing palmar sweat volume. (J Am Acad Dermatol 2023;89:62-9.)

Key words: Hyperhidrosis Disease Severity Scale (HDSS); oxybutynin hydrochloride; perspiration meter; primary palmar hyperhidrosis; sweat volume; ventilated capsule method.

INTRODUCTION

In primary focal hyperhidrosis, excessive, bilateral, and relatively symmetric sweating occurs in the axillae, palms, soles, or craniofacial region.[1] Primary palmar hyperhidrosis (PPHH) manifests at younger ages than primary focal hyperhidrosis affecting other areas,[2-4] and an epidemiological study in Japan showed that the mean age of onset is 13.8 years.[2] According to the same study, PPHH affects 5.33% of the Japanese general population.

Sweating on the palm is not induced by ambient temperature but by mental stress (eg, doing mental arithmetic or undergoing mental testing), emotional stimuli (eg, fear or aversiveness), and physiological stimuli (eg, tactile stimulation of the hand or a loud noise).[5-7] Patients with PPHH have an impaired

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quality of life[4,8,9] because the condition causes difficulties in handling paper documents, holding onto objects with the hands, or touching other people (eg, shaking hands) in work and school life and can prevent the use of touch technologies (eg, computer keyboards, mobile phones, and touch screen interfaces).[8-10]

PPHH is treated with topical aluminum chloride, tap water iontophoresis, botulinum toxin injection therapy, sympathectomy, or systemic anticholinergics.[1,11,12] However, topical aluminum chloride may induce skin irritation, which can lead to interruption or discontinuation of its use.[10,13] The risk of skin irritation with topical aluminum chloride is further increased if it is applied at high concentrations (30% to 50%) or with occlusive dressings.[1,10-12,14,15] In addition, in Japan, topical formulations of aluminum chloride, which are not covered by insurance for the treatment of hyperhidrosis, are prepared in hospital pharmacies. Iontophoresis has the disadvantage that it needs to be provided regularly with a specific medical device.[14,16] One problem associated with the use of botulinum toxin is pain control during local injection.[13,16] Regarding adverse effects, sympathectomy and systemic anticholinergics are less recommended for the treatment of palmar hyperhidrosis.[1,9,11,12,14-21]

Recently, use of topical oxybutynin has been explored for the treatment of primary focal hyperhidrosis,[22] but no controlled studies have been specifically designed or adequately powered to show the efficacy of topical oxybutynin in PPHH. Therefore, we performed a randomized controlled study to evaluate the efficacy of HP-5070, a novel once-daily 20% lotion preparation of oxybutynin hydrochloride (20% OL) developed by Hisamitsu Pharmaceutical Co, Inc, in reducing palmar sweat volume in Japanese patients with PPHH.

CAPSULE SUMMARY

- The conventional treatments for PPHH, topical aluminum chloride and iontophoresis, have several disadvantages, so new approaches are needed.
- Topical 20% OL may be a promising new treatment option for PPHH.

METHODS

Trial design

This was a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted at 21 Japanese outpatient dermatology clinics and clinics with dermatology departments from October 19, 2020 to February 13, 2021. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Before the start of the study, the institutional review board of each participating institution approved the study protocol. All patients provided written informed consent before participation in the study; for patients under 20 years of age, a written consent form was also signed by their legal guardians. The study was registered with the Japan Registry of Clinical Trials (jRCT2031200142, date of registration; October 9, 2020) before enrollment of the first patient.

Treatment

This study consisted of a 1-week baseline period and a 4-week double-blind treatment period. During the baseline period, patients were not given study treatment. The eligibility of each patient was checked by the investigator at the time of informed consent and during the baseline period and was then confirmed by the patient registration center. The patient registration center randomized eligible patients to either the 20% OL arm or the placebo arm in a 1:1 ratio by using dynamic allocation with minimization methods in which the stratification factor was baseline sweat volume. All patients, investigators, monitors, and the study sponsor were kept blinded to the treatments assigned to individual patients throughout the study period. The placebo lotion was packaged in the same bottle and had the same characteristics as the active drug (20% OL). During the double-blind treatment period, patients applied 500 μL of 20% OL to the entire surface of both palms once daily before going to sleep. From the start of the baseline period until the end of the double-blind treatment period, any medications, therapies, and surgeries that could potentially affect the clinical evaluations were prohibited.

Patients

Eligible patients for this study were Japanese patients with PPHH aged 12 years or older who, in the opinion of the investigator, were able to receive pharmacological treatment to the palms. At screening, patients were excluded from the study if they were found to have received any treatment that might prevent assessment of their PPHH or to have any skin disorder or disease on their palms other than PPHH, and at the baseline assessment, patients were excluded if they fulfilled any of the following criteria: Hyperhidrosis Disease Severity Scale (HDSS)[23] score

Abbreviations used:

AE: adverse event
DLQI: dermatology life quality index
FAS: full analysis set
HDSS: hyperhidrosis disease severity scale
OL: oxybutynin hydrochloride lotion
PPHH: primary palmar hyperhidrosis

of 1; mean of sweat volume measurements taken on 3 different days (measured in the left palm whenever feasible) of less than 0.500 mg/cm^2/min; and any of 3 measurements taken to determine mean baseline sweat volume was 0.500 mg/cm^2/min higher or lower than the mean of the 3 measurements. The full exclusion criteria are listed in Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/pxkh7wzb4w/2.

Outcomes

The primary endpoint of the study was the proportion of responders in terms of sweat volume at week 4, defined as patients with a reduction of sweat volume from baseline of greater than or equal to 50%. During the 1-week baseline period, sweat volume was measured 3 times on 3 different days with a ventilated capsule perspiration meter (Model SKN-2000M,[5,24,25] SKINOS Co, Ltd); the mean value of the 3 measurements was defined as the baseline value. At week 4, sweat volume was also measured 3 times on 3 different days (in the last week of the double-blind treatment period) by the same method, and the mean value of the 3 measurements was calculated (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/pxkh7wzb4w/2).

In this ventilated capsule method, a cup-form capsule is placed on the skin and fed with ambient air, and sweat volume is calculated by determining the difference in humidity of the air before and after it has passed through the capsule.[5,24,26,27] During the measurement of sweat volume, participants remained seated, and sweat volume was continuously monitored for 3 minutes with the capsule placed on the base of the left thumb, whenever feasible. Mean sweat volume (as mg/cm^2/min) was automatically calculated and recorded by a computer (Supplementary Fig 1). Written procedures for measuring sweat volume were prepared before the start of the study and were followed by all participating institutions during the study. Before the start of the study, standard environmental conditions for sweat volume measurement were established at each institution within the ranges of 23 °C to 26 °C and 40% relative humidity (RH) to 60% RH. During the study, the environmental conditions were kept constant whenever possible.

Secondary endpoints included absolute and percent changes from baseline in sweat volume, HDSS score, and Dermatology Life Quality Index (DLQI) score.[28] The HDSS was assessed at baseline and weeks 2 and 4, and absolute and percent changes from baseline in sweat volume and the DLQI were evaluated at week 4. To determine the HDSS score, the investigator interviewed patients about the severity of their hyperhidrosis in the past week. To determine the DLQI score, patients completed the self-administered DLQI, which asks about the impact of the disease on quality of life in the past week. Responder rate for the HDSS score was defined as the proportion of patients with an improvement greater than or equal to 1 point or greater than or equal to 2 points, and responder rate for the DLQI score was defined as the proportion of patients with an improvement greater than or equal 4 points.

The safety assessments included adverse events (AEs), clinical laboratory tests (routine hematology, blood biochemistry, and qualitative urine analysis), vital signs, and 12-lead electrocardiography assessments.

Statistical analysis

The planned sample size for the study was calculated as follows: From the results of a previous phase II clinical study (unpublished data), the achievable responder rates for sweat volume were assumed to be 45% in the 20% OL arm and 25% in the placebo arm. On the basis of these assumptions, the smallest number of participants required to show a treatment difference at an alpha error rate of 5% with a statistical power of greater than or equal to 90% with two-tailed Fisher's exact test was calculated to be 256 in total (128 per arm). By assuming that 4 patients may be excluded from the full analysis set (FAS), we planned to enroll a total of 260 patients.

For the primary endpoint (responder rate for sweat volume at week 4), the FAS was used as the primary analysis population. The differences between the 2 treatment arms and its exact unconditional 95% CI were calculated, and the 2 arms were compared with Fisher's exact test. In this analysis, patients with missing sweat volume data at week 4 were considered as nonresponders. As a post hoc analysis, analyses of subgroups (baseline sweat volume, 0.500 to $<$1.000 mg/cm^2/min and $\geq$1.000 mg/cm^2/min) were performed for the primary endpoint and were analyzed in a similar way to that used for the primary endpoint.

Among the secondary endpoints, absolute and percentage changes in sweat volume from baseline to week 4 were subjected to analysis of covariance

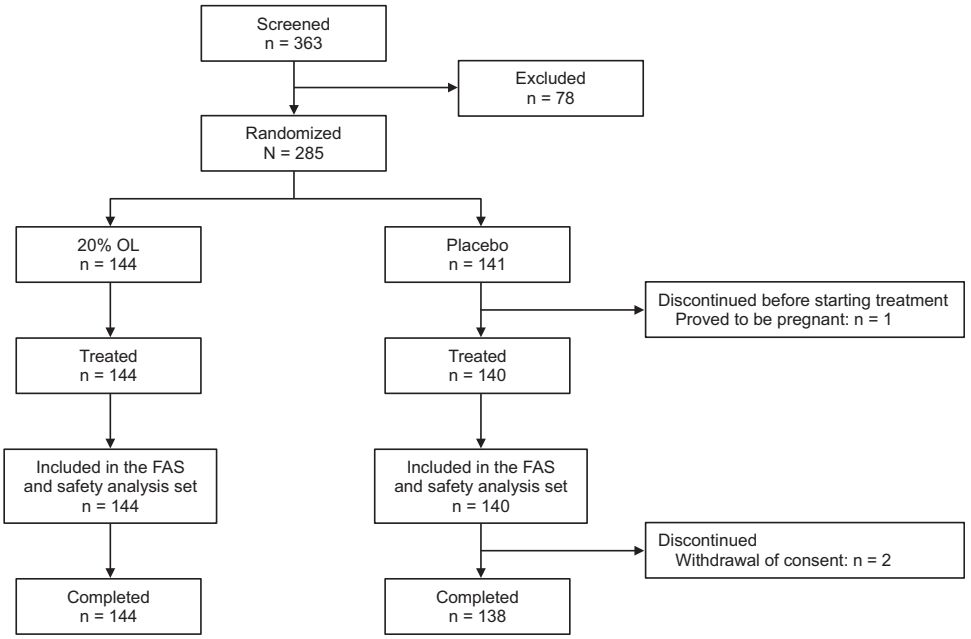

Fig 1. Primary palmar hyperhidrosis. Flow of patients through the study, *FAS*, Full analysis set; *OL*, oxybutynin hydrochloride lotion.

with a model that used *treatment* and *baseline sweat volume* as explanatory variables. Missing values of sweat volume at week 4 were imputed by baseline values. Responder rates for the HDSS and DLQI scores were analyzed in a similar way to that used for the primary endpoint.

The safety analysis set comprised patients who received at least 1 dose of the study treatment. AEs were coded according to the Medical Dictionary for Regulatory Activities version 23.1.

All statistical analyses were performed with SAS version 9.4. Data were considered statistically significant if the two-tailed *P*-value was less than .05.

RESULTS

Patients

Figure 1 shows the flow of participants through the study. The FAS included 144 patients in the 20% OL arm and 140 patients in the placebo arm. The demographic and baseline clinical characteristics of the patients were well balanced between the 2 treatment arms (Table I).

Efficacy

Efficacy results are summarized in Table II. The responder rate for sweat volume at week 4 (primary endpoint) was significantly higher in the 20% OL arm than in the placebo arm. This result was replicated in both subgroups as defined according to baseline sweat volume (Table III).

Absolute and percentage changes in sweat volume from baseline to week 4 also improved more in the 20% OL arm than in the placebo arm. The responder rates for HDSS score were higher for the 20% OL arm than for the placebo arm as early as at week 2. The responder rate for the DLQI score was not significantly different between the 2 treatment arms (Table II).

Safety

An overall summary of AE incidence rates is provided in Table IV. Most of the AEs reported in this study were mild. No serious AEs occurred, and no AEs led to discontinuation of the study treatment. In the 20% OL arm, application site AEs and thirst were reported in 13 patients (9.0%) and 5 patients (3.5%), respectively. All application site AEs were mild, except for 1 episode of moderate application site pruritus. All AEs of thirst were mild in severity and resolved during or within 3 days after the end of study treatment without therapeutic intervention. No abnormal changes were found in routine laboratory data, vital sign measurements, or ECG findings.

DISCUSSION

This randomized controlled study showed that 20% OL was superior to placebo in terms of responder rate for sweat volume at week 4 in Japanese patients with PPHH. To the best of our knowledge, this was the first randomized controlled study specifically designed to confirm the efficacy of topical oxybutynin with an objective, quantitative measure, ie, reduction of palmar sweat volume, in patients with palmar hyperhidrosis.

Table I. Demographic and baseline clinical characteristics of patients in the full analysis set

Characteristics	20% OL (*n* = 144)	Placebo (*n* = 140)
Sex, *n* (%)		
Male	81 (56.3)	87 (62.1)
Female	63 (43.8)	53 (37.9)
Age, mean (SD), y	34.1 (13.8)	35.7 (14.2)
Age, *n* (%)		
< 15 y	10 (6.9)	3 (2.1)
≥ 15 y	134 (93.1)	137 (97.9)
Weight, mean (SD), kg	62.79 (13.61)	64.52 (14.81)
BMI, mean (SD), kg/m^2	22.77 (4.17)	22.79 (3.97)
Age at disease onset, mean (SD), y	13.8 (8.8)	13.2 (6.9)
Duration of disease, mean (SD), y	20.33 (12.74)	22.48 (12.69)
Baseline sweat volume*, mean (SD), mg/cm^2/min	0.8651 (0.3719)	0.8803 (0.4536)
Baseline sweat volume*, *n* (%)		
0.500 to <1.000 mg/cm^2/min	109 (75.7)	107 (76.4)
≥1.000 mg/cm^2/min	35 (24.3)	33 (23.6)
Baseline HDSS score, *n* (%)		
2	74 (51.4)	64 (45.7)
3	58 (40.3)	60 (42.9)
4	12 (8.3)	16 (11.4)
Baseline DLQI score, mean (SD)	6.1 (4.4)	6.4 (5.1)

BMI, Body mass index; *DLQI*, Dermatology Life Quality Index; *HDSS*, Hyperhidrosis Disease Severity Scale.
*Mean of 3 measurements taken on 3 different days.

In the field of pain and Parkinson's disease, an expectation effect is considered as one of the causes of the placebo effect.[29-31] Psychological factors in response to the treatment process for PPHH may act as a placebo effect because sweating on the palm represents emotional sweating,[5-7] suggesting difficulties in verifying effects in a placebo-controlled study. In this study, sufficient reduction in sweat volume was observed in both the placebo and the active arms, providing evidence for a placebo effect in reducing sweat volume from baseline. Nevertheless, the study showed greater efficacy of 20% OL than placebo by using a quantitative and objective measure, the ventilated capsule method, which has been used extensively to assess sweat volume for research purposes.[5,25,32-37] The results also suggest efficacy of 20% OL even in patients with severe PPHH, ie, a baseline sweat volume greater than or equal to 1.000 mg/cm^2/min.[33,35,37]

In terms of DLQI score, although no significant difference in responder rate was found between the 2 arms, the mean change from baseline to 4 weeks in the 20% OL arm was −3.7, which represented an improvement close to the minimal clinically important difference of 4, whereas in the placebo arm it was −2.2 (Table II).[38] The difference in responder rate was not significant, but the change from baseline tended to show a clinically relevant improvement for the 20% OL arm.

Regarding safety, thirst—a known systemic AE of anticholinergic drugs—occurred in 5 patients (3.5%) in the 20% OL arm, but all episodes of thirst were mild enough to permit continued treatment with 20% OL. No pediatric patients (age, <15 years) experienced thirst. Meanwhile, a 12-week study, ie, a longer study than the present one, reported that the incidence of dry mouth was 70.5% with oral oxybutynin for the treatment of palmar hyperhidrosis.[20] In addition, another study found significantly lower incidences of dry mouth and constipation with transdermal oxybutynin than with oral anticholinergics.[39] Taken together with these findings, the results of the present study suggest a favorable safety profile of 20% OL. Long-term use of an anticholinergic drug has been implicated as a risk factor for the development of cognitive impairment.[40] Considering that some patients with hyperhidrosis may initiate treatment with an anticholinergic drug in childhood, the availability of topical 20% OL will have a significant clinical benefit because the formulation may reduce the long-term risk of cognitive impairment. Most of the application site AEs reported in this study were mild, and no AEs led to discontinuation of treatment, indicating that 20% OL has good cutaneous safety when applied for 4 weeks.

This study has several limitations. First, the experimental treatment was administered for only 4 weeks, but patients with hyperhidrosis need to be treated on a long-term basis. Second, the study enrolled only Japanese patients with PPHH, and the findings may not be generalizable to other ethnic populations. Despite these limitations, the results are

Table II. Summary of efficacy outcomes in the full analysis set

Efficacy outcomes	No. of patients	20% oxybutynin hydrochloride lotion	No. of patients	Placebo	Difference (95% CI)	*P* value (vs placebo)
Responder for sweat volume at week 4, *n* (%)						
≥50% reduction from baseline	144	76 (52.8)	140	34 (24.3)	28.5 (17.0-39.4)*	<.001†
LS mean (SE) percent change from baseline in sweat volume at week 4, %	144	−48.57 (2.54)	140	−26.60 (2.58)	−21.97 (−29.09 to −14.85)	<.001‡
LS mean (SE) change from baseline in sweat volume at week 4, mg/cm^2/min	144	−0.4457 (0.0235)	140	−0.2306 (0.0238)	−0.2152 (−0.2811 to −0.1493)	<.001‡
Responder for HDSS score, *n* (%)						
At week 2						
≥1-point improvement from baseline	144	61 (42.4)	140	36 (25.7)	16.6 (4.9-27.9)*	.0039†
≥2-point improvement from baseline	70§	15 (21.4)	76§	6 (7.9)	13.5 (−2.8 to 29.3)*	.0319†
At week 4						
≥1-point improvement from baseline	144	97 (67.4)	140	60 (42.9)	24.5 (12.8-35.5)*	<.001†
≥2-point improvement from baseline	70§	23 (32.9)	76§	10 (13.2)	19.7 (3.5-35.2)*	.0055†
HDSS score, *n* (%)						
At week 2						
1	143	21 (14.7)	139	6 (4.3)	NA	NA
2		97 (67.8)		84 (60.4)		
3		22 (15.4)		39 (28.1)		
4		3 (2.1)		10 (7.2)		
At week 4						
1	144	55 (38.2)	138	19 (13.8)	NA	NA
2		76 (52.8)		86 (62.3)		
3		12 (8.3)		26 (18.8)		
4		1 (0.7)		7 (5.1)		
Responder for DLQI score, *n* (%)						
≥4-point improvement from baseline at week 4	97‖	56 (57.7)	89‖	40 (44.9)	12.8 (−1.7 to 26.9)*	.1060†
Mean (SD) change from baseline in DLQI score at week 4	144	−3.7 (3.8)	138	−2.2 (3.4)	NA	NA

DLQI, Dermatology Life Quality Index; *HDSS*, Hyperhidrosis Disease Severity Scale; *LS*, least squares; *NA*, not analyzed.
*Exact unconditional 95% CI.
†Fisher's exact test.
‡Analysis of covariance with a model that used *treatment* and *baseline sweat volume* as explanatory variables.
§Patients with a baseline Hyperhidrosis Disease Severity Scale score ≥3.
‖Patients with a baseline Dermatology Life Quality Index score ≥4.

Table III. Subgroup analysis of the primary endpoint (responder rate for sweat volume at week 4) in the full analysis set

Subgroup	No. of patients	20% oxybutynin hydrochloride lotion	No. of patients	Placebo	Difference (95% CI)	*P* value (vs placebo)
Baseline sweat volume*, *n* (%)						
0.500 to <1.000 mg/cm^2/min	109	55 (50.5)	107	25 (23.4)	27.1 (14.2-39.7)*	<.001†
≥1.000 mg/cm^2/min	35	21 (60.0)	33	9 (27.3)	32.7 (9.0-54.3)*	.0081†

*Exact unconditional 95% CI.
†Fisher's exact test.

Table IV. Summary of adverse event incidence rates in the safety analysis set*

Summary of adverse events	20% oxybutynin hydrochloride lotion (*n* = 144)	Placebo (*n* = 140)
Any AE, *n* (%)	33 (22.9)	20 (14.3)
AEs occurring in ≥2 patients in either treatment arm (MedDRA PT)†, *n* (%)		
Application site AEs		
Application site dermatitis	6 (4.2)	0
Application site pruritus	3 (2.1)	1 (0.7)
Asteatosis	2 (1.4)	1 (0.7)
Application site eczema	2 (1.4)	0
Other AEs		
Thirst	5 (3.5)	1 (0.7)
Nasopharyngitis	5 (3.5)	0
Hand dermatitis	2 (1.4)	0
Glucose urine present	1 (0.7)	4 (2.9)
Blood pressure increased	0	2 (1.4)
Any treatment-related AE (adverse drug reaction), *n* (%)	18 (12.5)	12 (8.6)
Deaths, *n* (%)	0	0
Any serious AE, *n* (%)	0	0
AEs by severity‡, *n* (%)		
Mild	31 (21.5)	17 (12.1)
Moderate	2 (1.4)	2 (1.4)
Severe	0	1 (0.7)
Any AE leading to treatment discontinuation, *n* (%)	0	0
Any application site AE, *n* (%)	13 (9.0)	5 (3.6)

AE, Adverse event; *MedDRA*, Medical Dictionary for Regulatory Activities; *PT*, preferred term.
*If an adverse event occurred more than once in a patient during the study, the patient was counted only once.
†Adverse events were coded with preferred term according to the Medical Dictionary for Regulatory Activities, version 23.1.
‡A patient who had more than one adverse event during the study was counted only once for the adverse event with the worst severity.

promising, and future studies with longer treatment periods and in other ethnic groups are warranted.

CONCLUSION

When administered for 4 weeks, 20% OL is effective for the treatment of PPHH and has a favorable safety profile. Therefore, it may represent a promising treatment option for PPHH.

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Conflicts of interest

Dr Yokozeki and Dr Fujimoto received medical consultant fees from Hisamitsu Pharmaceutical Co, Inc. Dr Terahara and Mr Okawa, Mr Inakura, and Mr Hirayama are employees of Hisamitsu Pharmaceutical Co, Inc.

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