Dermatology Practical & Conceptual

Topical Oxybutynin 3% Gel Versus Aluminum Chloride 15% Lotion in Treatment of Primary Focal Hyperhidrosis

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Key words: aluminum chloride, hyperhidrosis, oxybutynin, therapy, topical

Citation: El-Agamy El-Samadony A, Hegab DS, El Maghraby GM, El-Maadawy IH. Topical Oxybutynin 3% Gel versus Aluminum Chloride 15% Lotion in Treatment of Primary Focal Hyperhidrosis. *Dermatol Pract Concept.* 2023;13(3):e2023192. DOI: https://doi.org/10.5826/dpc.1303a192

Accepted: February 11, 2023; **Published:** July 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Hyperhidrosis is excessive sweating beyond thermoregulatory needs. It is a potentially disabling condition with challenging management. Aluminum chloride is the established topical treatment; however, response remains unsatisfactory. Oxybutynin is an anticholinergic drug that stands as a therapeutic chance for hyperhidrosis.

Objectives: comparing the efficacy of topical oxybutynin 3% gel versus aluminum chloride 15% lotion in treatment of primary focal hyperhidrosis.

Methods: Forty patients with hyperhidrosis were randomly distributed into 2 equal groups treated by either topical oxybutynin 3% gel or topical aluminum chloride 15% lotion once daily night application for 4 weeks (both groups). Evaluation was done at 2 and 4 weeks of treatment and after 1 month of the end of treatment for follow up by Minor iodine starch test, hyperhidrosis disease severity scale (HDSS) and dermatology life quality index (DLQI).

Results: Both treatment modalities were effective with insignificant differences between patients of both groups regarding improvement in Minor iodine starch test and HDSS after 2 weeks of treatment (P = 0.561, 0.33 respectively). Oxybutynin 3% gel yielded significantly better improvement of Minor's test, HDSS and patient's quality of life at the end of 4 weeks of treatment with lower recurrence rate than aluminum chloride 15% lotion at 1 month follow up. Minimal adverse effects were noted in both studied groups.

Conclusions: Oxybutynin 3% gel could be considered as a promising treatment modality for hyperhidrosis with higher efficacy than aluminum chloride 15% lotion and lower recurrence rate.

Introduction

Hyperhidrosis is a dermatologic disorder characterized by sweating beyond what is necessary for thermoregulation in the person environment. Primary and secondary hyperhidrosis are the chief categories of the condition [1]. Diagnosis of primary hyperhidrosis is associated with hyperactivity of the sympathetic nervous system after exclusion of other pathologies that result in diaphoresis. By contrast, secondary hyperhidrosis is attributable to an underlying cause as neurologic, endocrine conditions, infectious, chronic diseases, or medication side effects [2].

In terms of social, psychological, professional, and emotional aspects, hyperhidrosis is quite embarrassing. The degree of impairment of quality of life is similar to that reported in chronic conditions including severe psoriasis and kidney failure [3]. The unpredictable and uncontrollable nature of the condition makes it very distressing for sufferers [4].

Typically, primary hyperhidrosis treatment follows an incremental, stepwise approach from less invasive therapies (eg, aluminum chloride and iontophoresis) to more invasive treatments such as botulinum toxin-A injection, oral anticholinergics or surgery. These treatments, however, have various limitations due to their inability to penetrate thick epidermal layers (topical treatments on palmoplantar areas), pain (injections), skin irritability (topical treatments on axillary areas) or systemic effects (oral therapies and invasive treatments) [5].

Topical treatment is the first recommendation because it is safe, cost-effective and non-invasive. Aluminum chloride can cause skin irritation due to formation of hydrochloric acid in the presence of water [6]. Oxybutynin, a small tertiary amine molecule, is well suited for use as a transdermal agent. The unionized free base form predominates at physiologic pH. Its serum half-life is 62-84 hours when applied topically suggesting that treatment may have a longer duration of action than existing topical therapies as aluminum chloride [7].

Objectives

To compare the efficacy of topical oxybutynin 3% gel versus aluminum chloride 15% lotion in treatment of primary focal hyperhidrosis.

Methods

This single-blinded, prospective, comparative study included 40 hyperhidrosis patients who did not receive any treatment for the condition during the preceding 6 months and were selected from the outpatient clinics of Dermatology and Venereology Department, Tanta University Hospitals. Patients were randomly allocated into two equal groups; patients of group A were treated with topical oxybutynin 3% gel (liquid crystalline gel containing oleic acid 20gm, tween eighty 30gm, ethanol 10gm, water 40gm and oxybutynin 3gm), and group B with aluminum chloride 15% lotion. All patients were instructed to apply the treatment once daily, at night (when sweating is diminished) for 4 weeks (adequate period for the optimal response of the topically applied drug to occur). Treatment was applied on the skin for 6 to 8 hours and was washed off in the next morning with avoiding contact of the gel or the lotion with the eyes, nose and mouth.

The study was declared for Ethical and Research approval by Tanta University Institutional Review Broad, approval code no: 34256 / 11 / 20. An informed written consent was obtained from all patients before the study.

Exclusion criteria were the presence of bacterial or viral infection at treated area, history of sensitivity to aluminum salts, history of hyperthyroidism or diabetes mellitus, other inflammatory or genetic skin diseases affecting the treated area (eg eczema, psoriasis or keratoderma), pregnancy, lactation and medications that induce hyperhidrosis as cholinesterase inhibitors, selective serotonin reuptake inhibitors, opioids or tricyclic antidepressants.

All patients were subjected to full history taking (present, past history and family history of hyperhidrosis), general and full dermatological examination and laboratory investigations including thyroid function tests and hemoglobin A1C.

Assessment of the severity of hyperhidrosis at the affected site and the efficacy of the treatment used was done through:

- Minor iodine starch test [8]: After cleaning the affected area, povidone-iodine solution was applied to dry skin and allowed to dry. A thin layer of starch powder was applied to the painted area. The test was monitored until formation of purplish sediment in the evaluated area. Different intensities of sweating were identified and recorded using digital photographs with 48 and 5-mega

pixel dual camera (Oppo F11, 2019), at baseline and after 2 and 4 weeks of treatment, then 1 month after stopping treatment for follow up assessment (a proper period for evaluation of the long term effect of the topically applied drug and to re-initiate therapy for patients who had recurrence thereafter). All photographs were graded by 2 blinded dermatologists by giving points to represent the degree of improvement as: 0 = no improvement, 1= minor improvement of < 25%, 2 = moderate improvement of 26 - less than 50%, 3 = major improvement of 51- less than 75%, 4= <75% improvement. Finally, the mean of the two evaluators scores was calculated at each time of evaluation.

- Hyperhidrosis disease severity scale (HDSS) [9]**:** Patients were asked to rate the condition severity by HDSS at baseline. A score of 1 indicated mild hyperhidrosis, 2 indicated moderate hyperhidrosis, and 3 or more (3 or 4) indicated severe hyperhidrosis. Response to treatment was assessed by calculating the change in HDSS from baseline to weeks 2 and 4 then 1 month after stoppage of treatment. The outcome was addressed by reduction of the HDSS by points ranging from zero to 4 points.
- Dermatology life quality index (DLQI) [10]**:** Quality of life was assessed with DLQI at baseline, at the end of treatment (after 4 weeks) and 1 month after stoppage of treatment.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (IBM Corp). The Shapiro-Wilk test was used to verify the normality of distribution. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was considered at 0.05.

Results

The demographic data of patients of both groups are summarized in Table 1. Evaluation of the degree of improvement of both groups according Minor iodine starch test, HDSS and DLQI at different periods of evaluation is summarized in Table 2 and Figure 1.

Regarding Minor test; in group A, the best degree of improvement was at the fourth week. Meanwhile in group B, the best degree of improvement was at the second week (Figures 1A, 2 and 3).

Regarding HDSS; in group A, the best level of decline of HDSS was at the fourth week. While in group B, HDSS declined significantly at the second week and that decline continued at the fourth week with no significant difference (Figure 1B).

Regarding DLQI; in group A, there was a statistically significant decline in DLQI score at the fourth week and at 1 month follow up. In group B, there was a statistically significant decline in DLQI score at the fourth week but with no significant difference between baseline and 1 month follow up (Figure 1C).

Comparison between the two studied groups according to Minor's test, HDSS and DLQI at different periods of evaluation is presented in Figure 4.

Regarding Minor test, at the fourth week, group A showed a statistically significant better improvement in comparison with group B. Both groups showed decline of improvement at 1 month follow up, but group A results were

Table 1. Comparison between the two studied groups according to demographic data (Group A: treated by topical oxybutynin 3% gel. Group B: treated by topical aluminum chloride 15% lotion).

	Group A (N=20)	Group B (N=20)	Test of significance	P value
Age; mean(SD)	15.8(5.3)	13.9(6.44)	U Mann Whitney test = 136.5	0.086
Gender; **N** (%) - Male - Female	 8 (40%) 12 (60%)	 5 (25%) 15 (75%)	χ^2= 1.026	0.31
Positive family history of hyperhidrosis; **N** (%)	8 (40)	11 (55)	χ^2= 0.902	0.34
Duration of hyperhydrosis (years); mean(SD)	7.7 (5.6)	6.4 (4.8)	U Mann Whitney test = 191	0.82
Site of hyperhydrosis; **N** (%) - Palmar - Plantar - Axillary	 12 (60) 7 (35) 1 (5)	 11 (55) 8 (40) 1 (5)	χ^2=0.388	1.0

SD = standard deviation.

Table 2. Evaluation of the degree of improvement of both studied groups according Minor iodine starch test, hyperhidrosis disease severity scale and dermatology life quality index at different periods of evaluation.

Degree of improvement according to Minor iodine starch test; mean (SD)	2 weeks	4 weeks	1 month follow up	Fr	P value
Group A (N=20)	2.9 (1.25)	3.7 (0.73)	2.7 (1.45)	17.59	<0.001
Significance between periods	P1=0.006, P2=0.693, P3=0.002				
Group B (N=20)	2.9 (1.6)	2.4 (1.9)	0.6 (1.3)	19.9	>0.001
Significance between periods	P1=0.874, P2=0.002, P3=0.003				

Degree of reduction of HDSS; mean (SD)	Baseline	2 weeks	4 weeks	1 month follow up	Fr	P value
Group A (N =20)	3.7 (0.5)	1.8 (1.07)	0.9 (0.9)	2.1 (1.02)	48.9	<0.001
P0		<0.001	<0.001	0.003		
Significance between periods	P1=0.017, P2=0.298, P3=0.001					
Group B (N =20)	3.9 (0.3)	2.2 (1.2)	2.3 (1.5)	3.6 (0.9)	35.3	<0.001
P0		<0.001	<0.001	0.501		
Significance between periods	P1=0.951, P2=0.002, P3=0.003					

DLQI; mean (SD)	Baseline	4 weeks	1 month follow up	Fr	P value
Group A (N=20)	19.9 (3.8)	1.6 (3.3)	5.05 (5.3)	37.3	<0.001
P0		0.001	0.001		
P3		0.014			
Group B (N=20)	21.2 (2.6)	12.2 (7.8)	19.5 (4.5)	24.3	<0.001
P0		0.001*	0.527		
P3		0.006			

Group A = treated by topical oxybutynin 3% gel; Group B = treated by topical aluminum chloride 15% lotion; Fr = Friedman test, Significance between periods was done using post-hoc test (Dunn); SD = standard deviation; P = P value for comparing between the three studied periods, P0 = P value for comparing between baseline and each other periods, P1 = P value for comparing between 2 weeks and 4 weeks, P2 = P value for comparing between 2 weeks and 1 month follow-up, P3 = P value for comparing between 4 weeks and 1 month follow-up.

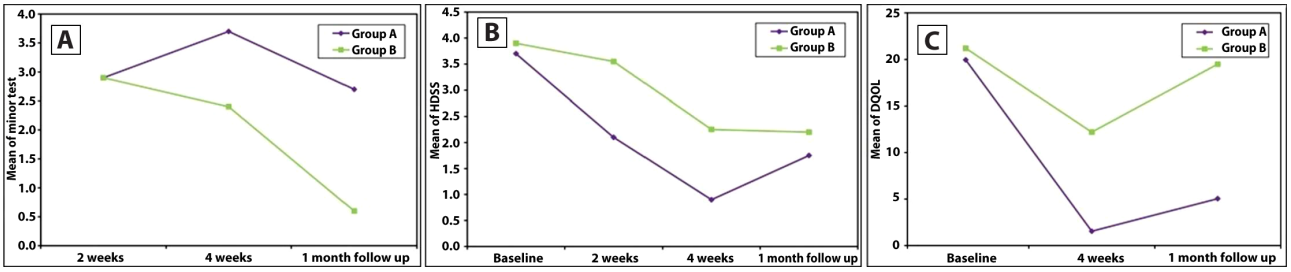

Figure 1. Comparison of the degree of improvement at different periods of evaluation. Group A treated with topical oxybutynin 3% gel. Group B treated with topical aluminum chloride 15% lotion. (A) According to Minor test. (B) B according to hyperhidrosis disease severity scale (HDSS). (C) According to Dermatology Life Quality Index (DLQI).

still significantly better (Figure 4A). Regarding HDSS, there was a significantly lower HDSS in patients of group A than in those of group B after 4 weeks of treatment (P = 0.004) and at 1 month follow up (P >0.001) (Figure 4B). Regarding DLQI, there was a significantly better score and less impact on patient's quality of life in group A than group B, after 4 weeks of treatment (P <0.001) and at 1 month follow up (P value < 0.001) (Figure 4C).

Regarding side effects, no side effects were reported except for mild irritation and scaling in one patient (5%) in group A and irritation with moderate dryness in another patient (5%) in group B.

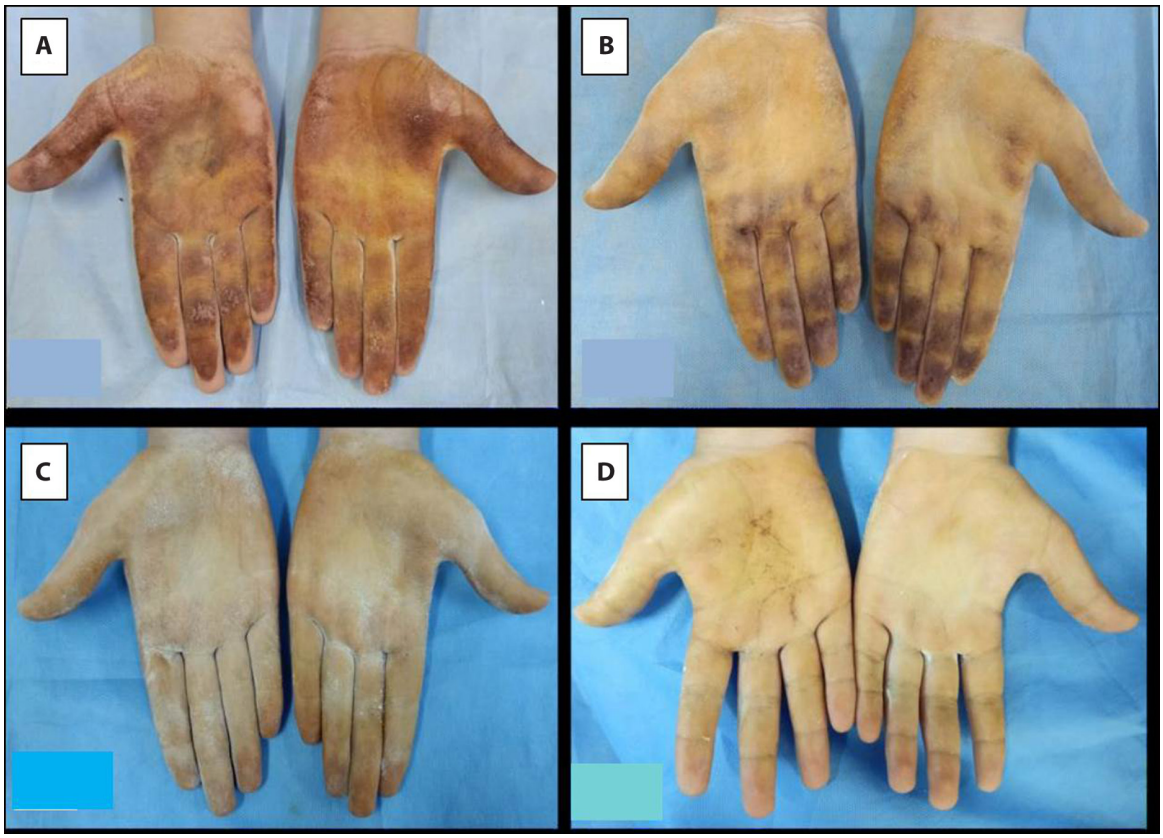

Figure 2. A 14- year old male patient with palmar hyperhidrosis of 2 years duration, group A, treated by topical oxybutynin 3% gel. (A_D) Minor iodine starch test. (A) Before treatment. (B) After 2 weeks of treatment. (C) After 4 weeks of treatment, showing more than 75 % improvement. (D) At 1 month follow-up after stoppage of treatment, showing no recurrence.

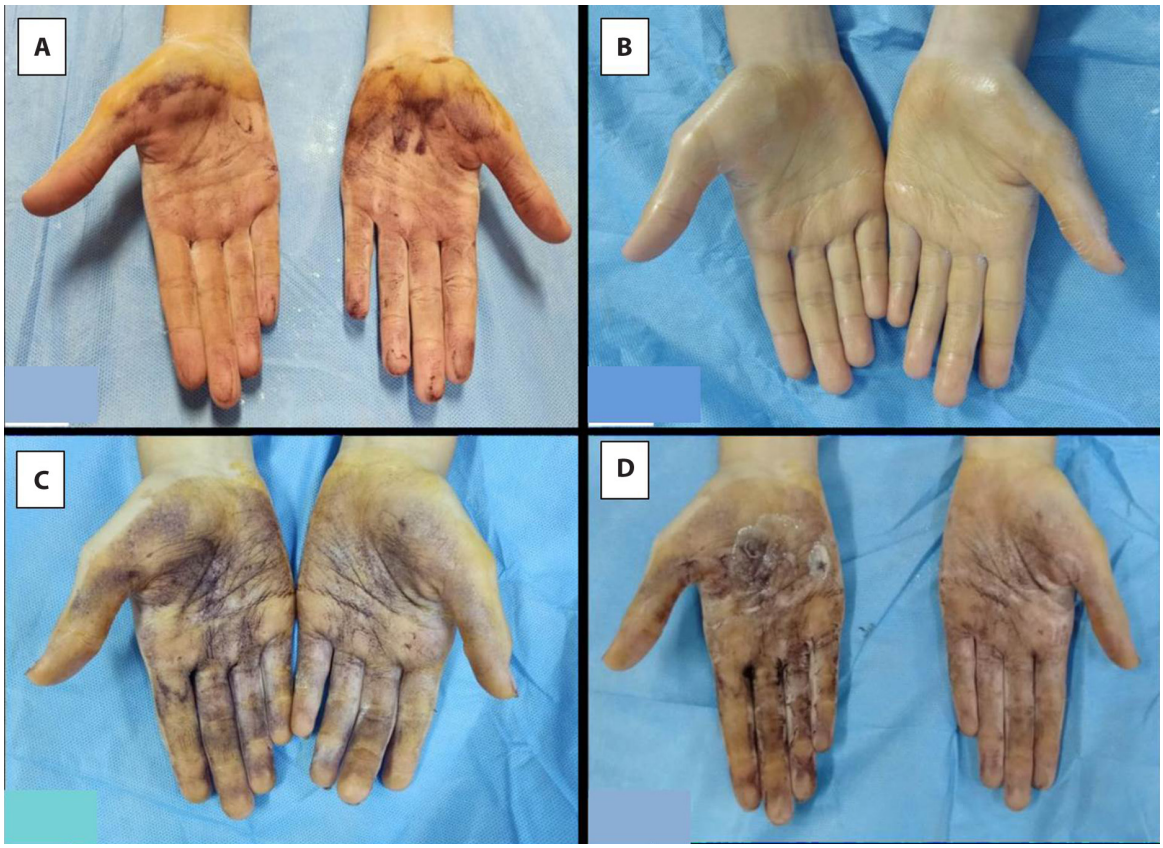

Figure 3. A 12-year old female patient with palmar hyperhidrosis of 5 years duration, group B, treated by topical aluminum chloride 15% lotion. (A-D) Minor iodine starch test. (A) Before treatment. (B) After 2 weeks of treatment (C) After 4 weeks of treatment, showing recurrence. (D) At 1 month follow-up after stoppage of treatment.

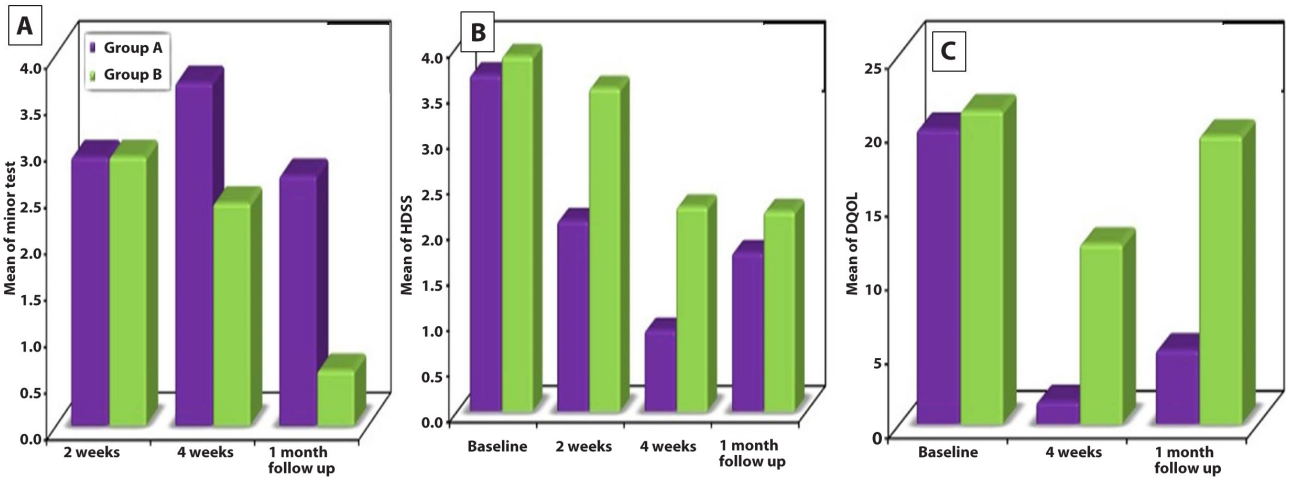

Figure 4. Comparison between the two studied groups at different periods of evaluation. Group A: treated by topical oxybutynin 3% gel, group B: treated by topical aluminum chloride 15% lotion. A: according to Minor's test. B: according to hyperhidrosis disease severity scale (HDSS). C: according to dermatology life quality index (DLQI).

Table 3. Correlation and relation between Minor test at 4 weeks of treatment and different patient parameters in both study groups.

	Minor test at 4 weeks			
	Group A (N=20)		Group B (N=20)	
	rs	P	rs	P
Age (years)	–0.367	0.112	0.349	0.131
Duration (years)	–0.149	0.532	–0.325	0.163
	n	Mean(SD)	n	Mean(SD)
Sex				
- Male	8	3.75(0.71)	5	3.8(0.45)
- Female	2	3.67(0.78)	15	1.93(1.94)
U, P	U=46, P=0.910		U=18.5, P=0.098	
Family history				
- Negative	12	3.67(0.78)	9	2.56(1.94)
- Positive	8	3.75(0.71)	11	2.27(1.9)
U, P	U=46, P=0.91		U=45, P=0.77	
Site of hyperhidrosis				
- Palmar	12	3.67(0.78)	11	2.73(1.85)
- Plantar	7	4(0.0)	8	1.88(2.03)
- Axillary	1 [a]	2 [a]	1	3 [a]
U, P	U=35, P=0.59		U=32.5, P=0.4	

Group A = treated by topical oxybutynin 3% gel; Group B = treated by topical aluminum chloride 15% lotion; R = Spearman coefficient; SD = standard deviation; U = Mann Whitney test; P = P value for comparing between the different categories. [a] Excluded from the comparison due to small number of case (N = 1).

There was no statistically significant correlation between percentage of improvement in Minor test after 4 weeks of treatment and either patient's age or hyperhidrosis duration in the two studied groups (Table 3).

Moreover, no statistically significant relations were detected between the percentage of improvement in Minor's test at 4 weeks of treatment and either the patient's sex, family history or hyperhidrosis site (Table 4).

Table 4. Relation between Minor's test at 4 weeks and different parameters in each group.

	Minor's test at 4 weeks			
	Group A		Group B	
	N	Mean(SD)	N	Mean(SD)
Sex				
- Male	8	3.75(0.71)	5	3.8(0.45)
- Female	2	3.67(0.78)	15	1.93(1.94)
U, P	U=46. P=0.910		U=18.5, P=0.098	
Family history				
- Negative	12	3.67(0.78)	9	2.56(1.94)
- Positive	8	3.75(0.71)	11	2.27(1.9)
U, P	U=46, P=0.91		U=45, P=0.77	
Site of hyperhidrosis				
- Palmar	12	3.67(0.78)	11	2.73(1.85)
- Plantar	7	4(0.0)	8	1.88(2.03)
- Axillary	1#	2#	1	3#
U, P		U=35, P=0.59		U=32.5, P=0.4

Group A: treated by topical oxybutynin 3% gel. **Group B:** treated by topical aluminum chloride 15% lotion. **SD:** Standard deviation. **U:** Mann Whitney test. **P:** P value for comparing between the different categories. **#:** Excluded from the comparison due to small number of case (n = 1).

Discussion

Regarding the site of hyperhidrosis in the present study, palmar hyperhidrosis was the most predominant with a percentage of 60% and 55% in groups A and B respectively, followed by plantar hyperhidrosis with a percentage of 35% in groups A and 40% in group B. This was in contrast to the study carried out by Artzi et al in which axillary hyperhidrosis was most predominant (38%) [10]. Many authors reported that axillary hyperhidrosis has the highest incidence among primary focal hyperhidrosis patients [9,11,12]. The higher prevalence of palmar hyperhidrosis in our study could be explained by the young age of the patients (5-28 years) in whom excessive hand sweating might hinder their daily scholar and life activities. Moraites et al [11] and Wolosker et al [13] suggested that when the condition occurs in prepubertal individuals, the palmar or plantar variety generally manifests (88.9%), with less presentations in the axillary (15.5%), facial (6.6%), abdominal and dorsal (4.4%) regions. Moreover, in our culture, palmar and plantar hyperhidrosis were of more concern to patients secondary to their impact on quality of life in contrary to axillary hyperhidrosis which is usually perceived as an extreme physiological form of sweating.

In the present study, oxybutynin gel was used in a concentration of 3% was to ach optimal tolerability and lower side effects.

It should be noted that the duration of treatment (4 weeks) and follow up (additional 4 weeks after the end of treatment) in the present study are near to those in several previous studies investigating lines of treatment of hyperhidrosis [6,7].

Regarding the treatment outcome in the present study, oxybutynin 3% gel achieved statistically significant better outcome than aluminum chloride 15% lotion in reducing hyperhidrosis symptoms after 4 weeks of treatment according to Minor test, HDSS and DLQI. It was noted that none of the patients in group A showed failed treatment, whereas 20% of group B patients failed to respond to aluminum chloride lotion.

The response obtained from oxybutynin gel was sustained, even improved, throughout the 4 weeks of treatment in 100% of patients of group A. This was in contrast to the response to aluminum chloride lotion which showed diminishing efficacy after 2 weeks and potential recurrence of hyperhidrosis symptoms despite continued treatment in 15% of patients of group B.

The superiority of oxybutynin over aluminum chloride may be explained by its relatively longer half-life which extends to 84 hours when applied topically and hence it has a longer duration of action [14]. On the other hand, the superficial plugs formed by aluminum chloride in the distal eccrine sweat gland ducts are thought to remain in place for around 24 hours and to be washed away over time, when the sweat output returns. Therefore, re-application was previously recommended for maintenance of its effect [15].

The results of oxybutynin gel in the present study came in accordance with those of Artzi et al [10] who evaluated

the efficacy of twice daily application of oxybutynin 10% gel versus placebo in treatment of primary focal hyperhidrosis (palmar, plantar or axillary). They reported a significant sweat reduction in the drug-treated areas in comparison with placebo-treated areas with a statistically significant mean improvement in HDSS and DQLI pre- and post-treatment (P = 0.001 for both). Seventy four percent of their patients reported moderate-to-high satisfaction.

In a similar context, the study conducted by Nguyen et al reported that a daily application of oxybutynin 3% gel reduced primary axillary hyperhidrosis symptoms according to the HDSS in all included seven patients [7]. Also, DLQI scores improved in all patients who completed the study. They also reported that all patients with concurrent palmoplantar hyperhidrosis experienced improvement in at least one untreated site and that could be attributed to the passive diffusion of the gel across the stratum corneum and its systemic absorption [10].

Regarding aluminum chloride lotion, several studies reported its efficacy in the treatment of primary focal hyperhidrosis (axillary, palmar and plantar) with concentrations ranging from 6.25% to 40% and several investigators consider aluminum chloride hexahydrate in alcohol solution as the first-line treatment for axillary hyperhidrosis [16-18].

On the other hand, some authors declared that aluminum chloride might be less rewarding in palmar and plantar hyperhidrosis than in axillary hyperhidrosis and they suggested that if aluminum chloride solutions are to be used on the palms or soles, the concentration must be raised up to 30% [1,16,19]. This could explain the lower efficacy of aluminum chloride noted in the current study as cases of palmar and plantar hyperhidrosis were most predominant and the used concentration was 15%. Some authors suggested that if aluminum chloride solutions are to be used on the palms or soles, the concentration must be raised up to 30% [1,16]. In contrast, a previous study showed that aluminum chloride 12.5% was as effective as 30% for the treatment of plantar hyperhidrosis [17].

Regarding the frequency of treatment application, the current study showed that only once nightly application of oxybutynin gel 3% was effective with comparable results to the twice daily application (morning and evening) adopted by Artzi et al in reducing over sweating at the application sites [10]. This suggested that morning application might be of limited value and that night-time application was more effective due to the low sweat output during sleep which allowed the drug to remain in place with longer contact duration and better diffusion into the sweat glands.

Similarly and in accordance with application regimen in the current study, many authors recommended a night-time application aluminum chloride lotion, just before sleep (when sweat is at its lowest level) to be washed off after 6 to 8 hours. This should result in efficient plug formation, limit skin irritation, increase efficacy, and limit clothing damage [1,19,20].

Regarding the drug concentration, the current study showed that oxybutynin 3% gel had comparable efficacy to the 10% gel used in the study conducted by Artzi et alat the application sites [10]. However, the higher concentration might be associated with higher systemic absorption and hence better efficacy at distant untreated sites. The effect on distant sites was not evaluated in the current study and could be an area of potential future research.

Regarding the adverse events in the present study, no remarkable side effects were reported in the two groups except for mild irritation, scaling and dryness in only 5% of cases. No systemic adverse events were noted, and no serious adverse effects that led to withdrawal from the study were encountered.

In a previous study, the use of oxybutynin 10% gel was associated with transient headaches in the first week in 3.8% of patients, 47.8% of axillary hyperhidrosis patients reported erythema and pruritus, 50% of plantar hyperhidrosis patients reported that the product was “sticky” and unpleasant to use and 11.3% of the patient population withdrew from the study secondary to adverse effects [10]. The higher incidence of adverse effects in comparison with the present study might be related to higher concentration of the gel used.

In a previous small pilot study carried out on 10 patients with severe axillary hyperhidrosis who were treated with topical oxybutynin 3% gel, 7 patients completed the study and 33.3% of them experienced mild systemic adverse event; where 22.2% reported xerostomia during the first week, and 11.1% reported constipation and blurry vision which was associated with opioid use after elective surgery and probably not related to the study drug [7]. The authors recommended further large, prospective, placebo-controlled studies to assess safety and efficacy of oxybutynin 3% gel.

Regarding aluminum chloride lotion, it has been previously reported that skin irritation and most adverse effects were correlated with higher concentrations [1] which were avoided by the use of 15% lotion in the current study.

The present study had some limitations including the relatively small sample size, being a single center study, in addition to the short period of patients follow-up. Therefore, more studies with larger sample size on different types of focal hyperhidrosis, whether affecting one site or several sites at the same time, are recommended to evaluate the effect and safety of oxybutynin gel and its influence on distant untreated sites.

Conclusions

Oxybutynin 3% gel tended to reduce hyperhidrosis severity and improve quality of life in patients with primary focal hyperhidrosis. It might be more effective than aluminum chloride 15% lotion at relieving hyperhidrosis symptoms with no tachyphylaxis and lower recurrence rate after stoppage of treatment and minor side effects. Hence, it should be considered as a possible added efficient topical treatment for primary focal hyperhidrosis besides topical aluminum chloride. Further studies on oxybutynin gel on a larger number of patients and for longer duration of follow up are needed to confirm its efficacy and safety in treatment of primary focal hyperhidrosis.

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