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High Versus Low Concentration of Aluminium Chloride Hexahydrate Iontophoresis on Primary Palmar Hyperhidrosis

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ABSTRACT

Background: Primary palmar hyperhidrosis (PH) often develops throughout infancy or adolescence and lasts the entirety of one's life. Although its cause is uncertain, it is believed to be caused by localised sympathetic hyperactivity on otherwise healthy eccrine sweat glands, which is typically brought on by emotional or temperature stimulus.

Objective: To evaluate the therapeutic efficacy, tolerability and side effects of the low concentration (1%) versus high concentration of aluminium chloride hexahydrate (20%) iontophoresis for primary palmar hyperhidrosis.

Patients and Methods: Thirty patients of both genders who established diagnosis of primary palmar hyperhidrosis with age ranged 10-30 years were selected randomly from dermatology outpatient clinic of Ain Shams General Hospital, Cairo, Egypt. The included subjects were randomly distributed into two equal groups; Group (A) consisted of 15 patients (9 females and 6 males) with palmar hyperhidrosis were treated with iontophoresis of low concentration 1% aluminum chloride for 3 days per week for 4 weeks. Group (B) consisted of 15 patients (8 females and 7 males) were treated with iontophoresis of high concentration 20% of aluminium chloride hexahydrate at the same time.

Results: Both groups of the study showed a significant decrease in hyperhidrosis from the 3rd day until the 4th week post-treatment ($p < 0.05$) throughout the follow-up period. However, comparing between both groups revealed that improvement in group B was slightly better than group A ($P < 0.04$), but with more side effects like dermatitis and low endurance, some patients might stop the treatment sessions.

Conclusion: application of low concentration iontophoresis; 1% of aluminium chloride hexahydrate compared to a high concentration approach (20%) results in a significant reduction in the rate of palmar sweating with extended endurance and no skin irritation.

Keywords: Iontophoresis, Low concentration 1% Aluminum Chloride Hexahydrate, High concentration 20% Aluminum Chloride Hexahydrate, Primary palmar hyperhidrosis.

INTRODUCTION

Primary focal hyperhidrosis is an idiopathic illness that often affects the axillae, palms, soles, and cheeks and is characterised by excessive perspiration that exceeds thermoregulatory demands. Most of the time, there is no underlying illness, and typically, emotional stress worsens it rather than heat or exercise [(1)].Up to 1% of the general population may be afflicted, and there are serious medical, psychological, and occupational consequences. Currently used treatments include topical aluminium salts, tap-water iontophoresis, anticholinergic medications including botulinum toxin, local surgical procedures, and sympathectomies. However, the relatively high prevalence of side effects and problems has restricted these therapies. Primary hyperhidrosis (PHH) is typically treated with aluminium chloride applied topically [(2)].

Regardless of the severity, aluminium chloride-based antiperspirants are a well-established first-line treatment for all forms of primary focal HH. The mode of action involves blocking the eccrine sweat gland ducts with aluminium salts, which causes functional and structural deterioration of the glandular secretory cells and the ductal epithelial cells, finally halting sweat output [(3)].

For the treatment of aluminium chloride solution to be successful, large concentrations of up to 30% may need to be applied for 6–8 hours. However, some persons are unable to endure the dermatitis that the high concentration solution might induce despite the fact that it can be extremely effective [(4)].

Since the sweat glands serve as the primary entry point for medications, iontophoresis can successfully drive the aluminium salt to enter the sweat glands. The shared mechanism for the effect of topically applied aluminium salt and direct electrical current administration is sweat gland blockage; this would support the application of aluminium salt via iontophoresis [(5)].

Applying direct current alone can reduce perspiration, but since the effects are frequently transient (lasting only a few days), continual treatment is necessary. Topical aluminium chloride application to the control hand likewise caused a considerable reduction in hyperhidrosis, though still with limited endurance. Particularly for patients with sensitive skin and palmar hyperhidrosis who cannot tolerate extended contact with topical treatments, iontophoretic application of aluminium salt might be thought of as a non-invasive and secure alternative therapy option [(6)].

The aim of this study was to evaluate the therapeutic efficacy, tolerability and side effects of the low concentration (1%) versus high concentration of aluminium chloride hexahydrate (20%) iontophoresis for primary palmar hyperhidrosis.

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PATIENTS AND METHODS

Design of the study:

A prospective, single blind, parallel group, post-test randomized controlled trial with a 1:1 allocation ratio was conducted from September 2021 to September 2022. Thirty patients of both genders who established diagnosis of primary palmar hyperhidrosis with age ranged from 10 to 30 years were selected randomly from dermatology outpatient clinic of Ain Shams General Hospital, Cairo, Egypt.

The included patients were randomly distributed into two equal groups in numbers, **Group (A)** consisted of 15 patients (9 females and 6 males) with palmar hyperhidrosis were treated with iontophoresis of low concentration 1% aluminum chloride for 3 days per week for 4 weeks. **Group (B)** consisted of 15 patients (8 females and 7 males) were treated with iontophoresis of high concentration 20% of aluminium chloride hexahydrate for 3 days per week for 4 weeks.

Before each participant was requested to provide an informed written permission to participate in the investigation, the goal of the study and the steps involved were thoroughly and simply described to them. The trial coordinator routinely verified protocol adherence, handled data with care, and performed quality control on screening.

Inclusive criteria:

- Age ranged between 10-30 years for both genders.
- Patients with primary palmar hyperhidrosis, score 3 and 4 on the hyperhidrosis disease severity scale (HDSS), to the extent that their palms were moist for the most of the day.
- The informed consent was signed by every patient included in the trial or by his parent if he was child.
- Dermatologists conducted medical examinations on each subject before the trial began.

Exclusive criteria:

- Patients with medical conditions that maybe associated with hyperhidrosis e.g., diabetes mellitus, spinal cord injury, brain damage, hyperthyroidism, anxiety, menopause, heart failure, and parkinsonism.
- Patients who received any other medications that might affect the sweat output e.g., anxiolytics, thyroxine or topical potassium permanganate for at least 4 weeks preceding the study.
- Patients with sensory disorders.
- Patients with fungal infection of palms.
- Patients with any cardiac problem or with pacemaker.
- Patients who had a local wound, severe eczema and local burn.
- Female patients who were pregnant or lactating.

Randomization and blinding:

The random distribution of individuals into two groups of equal size using a dice roll was made by a third party. Group A (when the dice gave an even number) and group B (when the dice revealed an odd number). Blocks were permitted during the randomization process to guarantee that each group had an equal number of participants. After randomization, there was no drop out. A single-blind clinical investigation was conducted. Group assignment and evaluation were done in secret. The treatment allocation was hidden from the lead researcher and the biostatistician.

Measurement procedures:

- All patients underwent a complete history taking including personal history e.g., name, age and sex. In addition, they were asked about any past history. Detailed analysis of the present history e.g., palmar hyperhidrosis and also the medical history including all the drugs taken.
- Measurements have been taken as following: Gravimetric test was applied pretreatment, post 2 weeks and post 4 weeks of treatment, while iodine-starch test and hyperhidrosis disease severity scale (HDSS) were applied pre and post treatment.
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    - ***Starch-Iodine Test (The Minor's Test):***
      It is an easy and affordable way to detect perspiration, pinpoint the region that is afflicted, and gauge how severe the sweat overproduction is [(7)]. Prior to and during treatments, the approach was most beneficial for mapping regions of focused sweating [(8-10)].
      It was done to qualitatively identify the places where the palms sweat excessively. A dry surface was treated with an iodine solution (1–5%), which was then covered in starch. Sweat caused the starch and iodine to mix, producing purple sediment that might be seen in photos [(11)]. The more sweating area is detected, the more purple sediment was shown.

    - ***Gravimetry Test:***
      It is a simple and quick process for determining how much sweat is produced during a specific amount of time. We measured the weight of a typical filter paper using a high-precision scale (with the accuracy of 0.001 g). In order to take the weight off the upper limb, the patient's hand was then put on the paper with the forearm resting on the table with the elbow flexed. The paper was weighed once more after exactly one minute, showing the milligrammes per minute sweat secretion rate [(9)].

- ***The Hyperhidrosis Disease Severity Scale (HDSS):***

  A four-point scale was used to assess the severity of hyperhidrosis [(10)]. The following scale rated how annoying and disruptive sweat is to daily life: 1) Tolerable/never gets in the way = 1 (lack of HH). 2) Acceptable/occasionally interferes = 2 (moderate HH). 3) Hardly tolerable/constantly obstructs = 3 (severe HH). 4) Intolerable/always interfering = 4 (severe HH) [(11)].

  It is one of the primary validated questionnaires used in clinical studies to assess the severity and quality of life of palmar hyperhidrosis. Based on how the ailment impacts everyday activities, it offers a qualitative assessment of the severity of the patient's condition. The patient chooses the claim that most accurately describes his experience with perspiration in each area assessed. This is a useful diagnostic tool that is straightforward and simple to use, can be swiftly given, and has strong association with other survey modes [(12-17)].

Therapeutic procedures:

Application phase:

- Iontophoresis of aluminum chloride hexahydrate (1%) was applied to both hands of patients of group (A), using a galvanic stimulator (Enraf Nonius, Dynatron 438, Netherlands) with intensity adapted according to patients' sensation for 30 min.
- The treatment was repeated for 12 sessions (3 times/week).
- Patients of group (B) were regarded as treated with iontophoresis of aluminum chloride hexahydrate (20%) to both hands using a galvanic stimulator (Enraf Nonius, Dynatron 438, Netherlands) with intensity adapted according to patient's sensation for 30 min.
- The palmar surface of the hand, from the metacarpophalangeal (MCP) crease to the distal wrist crease, was covered by the active electrode. On the front of the forearm's anterior surface, the neutral electrode was positioned. The active electrode was decided upon as an anode.
- To minimise any potential adverse effects, a modest dose of aluminium chloride hexahydrate, 1%, was used in this study.
- Patients were told to cease the therapy if they experienced any uncomfortable feelings.
- The fluid was kept under the electrodes by using a thin layer of absorbent pad [(12)].

Ethical approval:

The Faculty of Physical Therapy at Cairo University granted approval for the study (P.T.REC/012/003292). All study participants or their caregiver in case of children participants, gave their written consent after being informed of the objectives of our investigation. The worldwide medical association's code of ethics, the Declaration of Helsinki for Humans, was adhered to throughout the course of this study.

Sample size calculation:

Two groups of high and low concentrations with three types of measurements (pre, after two weeks, and after 4 weeks) were used in the study. G-power analysis- for estimating appropriate sample size- was employed. The researcher anticipated an effect size of at least 0.25 with lower limit of 0.8 for detecting the effect. So, using level of significance=0.05, power=0.8 and effect size=0.25, G-power software analysis estimated the minimum required sample size to be 28 subjects. Based on this, a sample size of 30 subjects was chosen for analysis in the study.

Statistical analysis

With the help of the SPSS (Statistical Package for the Social Sciences) version 24 for Windows®, the obtained data were coded, processed, and analysed. To explain the demographic impact on sweat output mass, a descriptive study of the patients' physical features was conducted. The difference in sweat production mass for the gravimetry measure was evaluated using the independent samples t-test and within subject contrast tests. The difference in sweat output mass for the HDSS measure was evaluated using the independent samples t-test, paired t-test, and percent of improvement change. P value less than 0.05 was regarded as significant.

RESULTS

Thirty patients of 13 males and 17 females were found eligible to participate in the study. The demographic characteristics of patients were displayed in the following two tables:

As revealed from the table, There was no significant difference between both groups in their ages (P-value=0.74 >0.05). Confidence Intervals of mean age for both groups represented by Error Bar are heavily overlapped, then it is concluded that there is no significance difference between the two groups with respect to age.

Table (1): Comparison of mean age of groups A and B

Items	Group A		Group B		Comparison		Sig
	Mean	±SD	Mean	±SD	t-value	P-value	
Age (years)	20.21	±3.17	23.147	±2.97	0.19	0.74	NS

As revealed from table 2, there was no significant difference between both groups with respect to sex.

Table (2): Comparison of sex distributions between groups A and B

	Group A	Group B	χ^2	p-value	Sig
Females	**9 (60%)**	**8 (53.3%)**	**0.457**	**0.357**	**NS**
Males	**6 (40%)**	**7 (46.7%)**			

Using gravimetry measure, it is concluded that for group A, there was a decrease in sweat output mass for both hands after 2 weeks of treatment to (0.071±0.003) with mean reduction of 0.8%, and there was a decrease in sweat output mass for both after 4 weeks of treatment to (0.070±0.002) with mean reduction of 1.3%. The results of repeated measure ANOVA revealed that the decrease for all post treatments evaluations (after 2 weeks and after 4 weeks) for group A were significant.

It is also concluded that for group B, there was a decrease in sweat output mass for both hands after 2 weeks of treatment to (0.071±0.003) with mean reduction of 0.7%, and a decrease in sweat output mass after 4 weeks of treatment to (0.071±0.002) with mean reduction of 0.8%. The results of repeated measure ANOVA revealed that the decrease for all post treatments evaluations (after 2 weeks and after 4 weeks) for group B were significant.

As revealed from table 3 there was no significant difference between both groups in sweat output mass at pretreatment, after 2 weeks, and after 4 weeks.

Table (3): Independent Samples t-Tests for Gravimetry measure

Sweat mass concentration	t-test for Equality of Means			
	t	Df	Sig.(2-tailed)	Mean Difference
Concentration_pre	-.705-	28	.487	-.0008-
Concentration_2 weeks	-.943-	28	.354	-.0009-
Concentration_4 weeks	-1.104-	28	.279	-.0010-

Within subjects analysis for group A indicated that there was significant difference in sweat mass after 2 weeks treatment compared to pre-treatment with p-value=0.002. Also, there was significant difference after 4 weeks treatment compared to pre-treatment with p-value <0.05.

Within subjects analysis for group B indicated that there was significant difference in sweat mass after 2 weeks treatment compared to pre-treatment with p-value=0.008. Also, there was significant difference after 4 weeks treatment compared to pre-treatment with p-value=0.003.

The effect size was used to compare post treatments to pre-treatment in both groups of high and low concentrations. This measure indicated that there was large effect or large improvement after applying the treatment in both groups and that effect or improvement were relatively bigger for (after 4 weeks evaluation) compared to (after 2 weeks evaluation) in both groups. Table 4 displays the results of within subject tests for gravimetry measure.

Table (4): Comparison of the effect of treatment on gravimetry measure within each group

Group		Sum of Squares	df	Mean Square	F	Effect size	Sig
Low (A)	after 2 weeks vs. pre	6.144E-6	1	6.144E-6	15.426	0.724	0.002
	after 4 weeks vs. pre	1.500E-5	1	1.500E-5	28.075	0.816	0.000
Error	after 2 weeks vs. pre	5.576E-6	14	3.983E-7			
	after 4 weeks vs. pre	7.480E-6	14	5.343E-7			
High (B)	after 2 weeks vs. pre	3.996E-6	1	3.996E-6	9.875	0.657	0.008
	after 4 weeks vs. pre	1.008E-5	1	1.008E-5	13.665	0.715	0.03
Error	after 2 weeks vs. pre	5.261E-6	13	4.047E-7			
	after 4 weeks vs. pre	9.590E-6	13	7.377E-7			

Table (5): Improvement change in within group analysis for gravimetry measure

Group		Gravimetry	
		Pre treatment	Post treatment (4 weeks)
A	Mean±SD	0.071±0.002	0.070±0.002
	Mean	0.001	
	Percentage	1.3%	
B	Mean±SD	0.071±0.003	0.071±0.002
	Mean	0.0007	
	Percentage	1.1%	

Using HDSS measure with assignment of patients in high concentration and low concentration groups after converting the scores of severity disease measure, it is concluded that for group A, there was a decrease in sweat output mass after 4 weeks of treatment with mean reduction of 1.4%. The results of paired t-test revealed that the decrease for post treatment evaluation (after 4 weeks) for group A was significant.

For Group (B), there was a decrease in sweat output mass after 4 weeks of treatment to (0.071±0029) with mean reduction of 1.6%. The results of paired t-test revealed that the decrease for post treatment evaluation (after 4 weeks) for group B was significant.

Using independent t-test for pre-treatment and post – treatment on group A and B indicated that there was no significant difference for pre –treatment. Also, there was no significant difference for after 4 weeks treatment. Table 6 displays the results of the independent t-tests for HDSS measure.

Table (6): Independent Samples Test

	t-test for Equality of Means			
	T	df	Sig.(2-tailed)	Mean Difference
Concentration pre	-0.789	28	0.257	-0.0002
Concentration_2 weeks	-1.247	28	0.367	-0.0001

For within subjects group analysis, paired t-tests were used to determine the difference in sweat output mass at pretreatment, and after 4 weeks of treatment between Groups (A) and (B). The following table displays the results of paired t-tests for HDSS measure.

The findings showed a significant difference in matched paired t-test between pre and post treatment values, as shown in table 7. Additionally, a matched paired t-test comparing before and after therapy revealed a significant change.

Table (7): Comparison of the effect of treatment before and after therapy.

	Paired Differences		T	Df	Sig. (2-tailed)
	Mean	Std. Deviation			
Concentration_pre_low-concentration_4 weeks_low	0.0008	0.0005	5.29	14	0.000
Concentration_pre_high-concentration_4 weeks_high	0.0009	0.001	3.697	14	0.003

Percentage of improvement was used as other criteria for quantifying the difference within subject analysis. Percentage of improvement indicated that improvement in Group B was greater than corresponding improvement in group A for post treatment evaluation. The following table displays within group improvement change for HDSS measure:

Table (8): Improvement change in within group analysis for HDSS measure

Group		HDSS	
		Pre	Post
A	Mean	0.0628	0.0620
	±SD	0.0023	0.0023
	Mean difference	0.0008	
	Percentage of	1.4%	
B	Mean	0.0631	0.0621
	±SD	0.0025	0.0026
	Mean difference	0.0009	
	Percentage of	1.6%	

DISCUSSION

Typically, primary palmar hyperhidrosis appears during childhood or adolescence and persists for the remainder of a person's life. Although the exact aetiology is unknown, it is thought to be induced by localised sympathetic hyperactivity on healthy eccrine sweat glands, which is often triggered by emotional or thermal stress [(14)].

Regardless of the severity, aluminium chloride-based antiperspirants are a well-established first-line therapy for all forms of primary focal hyperhidrosis (HH). The mechanism of action involves obstructing the eccrine sweat gland ducts with aluminium salts, which weakens the glandular secretory cells and the ductal epithelial cells structurally and functionally before stopping sweat production [(3)].

Iontophoretic application of aluminium salt may be considered as a non-invasive and secure alternative therapeutic option, especially for individuals with palmar hyperhidrosis and sensitive skin who cannot withstand extended contact with topical therapies [(6)].

Patients with primary hyperhidrosis are at risk of developing disease and the therapeutic efficacy of high concentration versus low concentration was compared using gravimetry and HDSS measures.

In comparison regarding gravimetry measure between the two groups of high and low concentration, the test revealed significant difference after 2 weeks treatment compared to pre-treatment in favor of group A compared to group B. Also, the test revealed significant difference after 4 weeks treatment compared to pre-treatment in favor of group A compared to group B. In comparison regarding HDSS measure between the two groups of high and low concentration, the test revealed significant difference after 2 weeks treatment compared to pre-treatment in favor of group A compared to group B. Also, the test revealed significant difference after 4 weeks treatment compared to pre-treatment in favor of group A compared to group B.

The results of the study showed an improvement after 4 weeks of treatment but with different percentages for every method of evaluation and for every group.

As for gravimetry test, group A has percentage of improvement of 1.3% after 4 weeks and group B has percentage of improvement of 1.1% after 4 weeks. While as for HDSS test, group A has percentage of improvement of 1.4% after 4 weeks and group B has percentage of improvement of 1.6% after 4 weeks.

Iontophoresis is a noninvasive technique used to accelerate the penetration of ions through the epidermal layers, according to **Oliveira *et al.*** [(15)] research, which is in agreement with and supported by the findings of our investigation. Two electrodes, the anode (positive electrode) and cathode (negative electrode), which are attached to the skin, are used to add regulated voltage and/or charge to an electrolytic solution (negative electrode).

Furthermore, according to the findings of this study, which are in line with the works reported by **Thomas *et al.*** [(7)], iontophoretic application of aluminium salt can be thought of as a non-invasive and secure alternative treatment method, particularly for patients who have sensitive skin and palmar hyperhidrosis and cannot tolerate prolonged contact with topical solutions.

The current study's findings were in agreement with those of **Togel *et al.*** [(16)]**,** who looked at the effectiveness and persistence of hypohidrosis caused by modest concentrations of aluminium chloride hexahydrate (1%), administered by 30 min of iontophoresis in individuals with primary palmar hyperhidrosis.

In the current study, group B was given a high dose of 20% aluminium chloride hexahydrate, which similarly caused a considerable decrease in hyperhidrosis but still had low endurance and more side effects including dermatitis. Therefore, the long-lasting hypohidrosis that was caused in the current experiment is probably attributable to the cumulative impact of both components that were present during the iontophoresis of 1% aluminium chloride at a low concentration. This may cause group A to experience a more severe and protracted blockage of the sweat glands than group B.

Additionally, no study has documented a deterioration of palmar hyperhidrosis in individuals receiving 1% aluminium chloride iontophoresis at low concentrations. The study's scope was restricted to patient physical and mental health issues that could influence diagnosis and therapy.

LIMITATIONS

- Small sample size.
- The impact of environmental factors during therapy, such as an illness or condition that is not explicitly specified.
- The patient's physical and mental state at the time of the examination and treatment would have an impact on the outcomes.
- Cooperation of the patient,
- Possible human error in measurement.
- Individual differences in patients and their influence on treatment program.
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CONCLUSION

According to the previous discussion of our results and reports of research studies in the field related to the present study, the results of this study support the expectation that low concentration aluminium chloride hexahydrate (1% iontophoresis) is shown to significantly reduce the palmar sweating rate with longer endurance and no skin irritation compared to high concentration method.

RECOMMENDATIONS

1. For patients with palmar hyperhyidrosis, it was advised to include a low concentration (1%) of aluminium chloride hexahydrate in their regimen.
2. More research is required to examine the efficacy of using aluminium chloride hexahydrate in low and high dosages to treat palmar hyperhydrosis.
3. Further studies are needed with larger sample size to investigate the effectiveness of treatment, providing better statistical analysis of data.
4. Further studies are needed to detect the effect of treatment on patient’s quality of life.

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