METHOTREXATE IONTOPHORESIS VERSUS COAL TAR OINTMENT IN THE TREATMENT OF PRIMARY HYPERHIDROSIS

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Abstract

Objectives: To assess the therapeutic effect of methotrexate iontophoresis and coal tar ointment on laboratory mass scale 'sweat output' and hyperhidrosis disease severity scale in primary palmer hyperhidrosis. **Design:** A single-blinded randomized clinical study. **Setting:** Outpatient-setting. **Subjects:** Sixty participants with primary palmer hyperhidrosis (15-35 years old) were allocated randomly into two groups. Group (A) received methotrexate iontophoresis; Group (B) received coal tar ointment. **Intervention:** 30 minutes per session, three sessions a week for four weeks for group A; and while group B received coal tar ointment. **Outcome measures:** Laboratory mass scale 'sweat output' and hyperhidrosis disease severity scale was measured pretreatment, after 6 sessions (post I) and after 12 sessions (post II). **Results:** Sixty patients with hyperhidrosis participated in this study. There was no significant difference between groups in age and sex distribution ($p > 0.05$). There was a significant decrease in sweat output in both groups at post II compared with that pretreatment and post I ($p < 0.01$) and a significant decrease at post I compared with pretreatment ($p < 0.001$). There was a significant decrease in HDSS in both groups at post II compared with that pretreatment and post I ($p < 0.001$) and a significant decrease at post I compared with pretreatment in group A ($p < 0.001$) while there was no significant difference between pretreatment and post I in group B ($p > 0.05$). There was no significant difference between groups pretreatment ($p > 0.05$). There was a significant decrease in sweat output and HDSS of group A compared with that of group B at post I and post II ($p < 0.001$). **Conclusion:** Application of four consecutive weeks (30 minutes per session, 12 sessions, 3sessions/week) of methotrexate iontophoresis has a significant improvement in severity of symptoms and sweat output that is better compared to coal tar ointment in improving sweat output and symptoms severity in primary palmar hyperhidrosis.

Keywords: Primary palmer hyperhidrosis, Methotrexate iontophoresis, Laboratory mass scale, Hyperhidrosis disease severity scale.

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INTRODUCTION:

Primary palmar hyperhidrosis is a common idiopathic disorder that is globally represented by 2.8% of worldwide populations. It is marked by excessive palms sweating beyond physiological need where nearby 37.9% of worldwide patients suffering from adverse effects on their quality of life.[1] The excessive sweating is mediated by the vegetative nervous system and often begins primarily at the level of the upper extremities.[2]

Palmar Hyperhidrosis in response to thermal and emotional stimuli, but also spontaneously without apparent trigger, thus it affects symmetrical areas of the body and tends to involve palms although other areas might be affected.[3] Palmar hyperhidrosis leads to numerous negative psychological and social interactions impacts, as well awful influences on their daily activities, devastating emotional and mental health, in addition to express extra stress and anxiety.[4-5] Clinically, palmar hyperhidrosis is an excessive sweating that is associated with being nervous or unhygienic that feedback across patients` social interactions creation of an uncertainty and reduce mental health resulting in a sense of unhappiness and feeling depressed.[6] Almost, onset of palmar hyperhidrosis is identified by 25 years with earliest average onset at 13 years old. [7-8]

Numerous topical treatments are the first line therapy in palmar hyperhidrosis. Unless, both patients and clinicians consider them ineffective and side-effects as problematic, dry mouth, urinary retention, accommodation disorders, constipation and memory impairments.[9-10] Antiperspirants should be applied at night to increase efficacy, limit skin irritation and minimize destruction of clothes. Furthermore, prolonged applications are required and clinical effect is usually noted after 1-2 weeks.[5]

Previous studies used a variety of physical therapy procedures to treat chronic palmar hyperhidrosis, such as Iontophoresis that is a non-invasive involves usage of electric energy for ion local transfer (phoresis) or delivery of ionized (ionto) medicated. several clinical trials stated a positive outcome among the participants. It should be administered three times a week until satisfactory sweat reduction is achieved and then once a week as maintenance therapy, [6,11] and adding anticholinergics in the tap water required for iontophoresis resulting in a more efficient reduction of sweat production compared to only water iontophoresis.[12-13]

According to the literature, palmar hyperhidrosis could be responded to 20"/o aluminum chloride in anhydrous ethanol, also coal tar those were monographed by the FDA as grade I category because reported safety and effectiveness.[14] A major side-effect of treating palms with botulinum toxin type A is weakness in fingers or wrists impacting grip ability. Side-effect could be reduced by using botulinum toxin B on thenar eminences of the palms.[15]

To the best of the authors' knowledge, there have been no such research on management of palmar hyperhidrosis not only reduces sweat production increases quality of life and ultrasound to the conventional physical therapy program has been studied.[13] As a result, the authors hypothesized that methotrexate iontophoresis and coal tar ointment improves both laboratory mass scale ‘sweat output’ and hyperhidrosis disease severity scale in primary palmer hyperhidrosis.

MATERIALS AND METHODS

This study was a pre-test/post-test, single-blinded (assessor), prospective randomized clinical trial. The patients were recruited from outpatient clinics from EL KASR EL-AINI in Cairo Governate, Egypt, from December 2022 to March 2023. The research ethical committee of Faculty of Physical therapy, Cairo university approved the study (approval No.: NCT05875285). All participants involved in this study provided informed consent, with the promise that their data would be kept confidential and utilized anonymously in the analysis for the purpose of the study only. The participants had been knowledgeable about the objective, study benefits, were free to leave the study at any moment. This study was reported according to CONSORT guidelines.

Participants:

Sixty patients, who had been clinically diagnosed with palmar hyperhidrosis were invited to participate in this study. The patients were composed of 12 and 14 men and 18 and 16 women for both groups A and B, respectively, as both groups A and B mean± standard deviation of age were 24.20± 6.87 and 23.43±5.91, respectively. Patients with chronic palmar hyperhidrosis were referred by their certified dermatologist based on their history and detailed dermatological examination, which included standard diaper of approximately 30 grams and laboratory mass scale ‘sweat output’.[16]

The following were the inclusion criteria: Patients with primary palmar hyperhidrosis to extend that their palms were wet during most of the day whom score 3 and 4 were included, their age range was 15-35 years and they were examined and referred by certified dermatologist.[17]

Patients were excluded if they had associated medical conditions, such as hyperthyroidism, diabetes mellitus, parkinsonism, spinal cord injury, brain damage, congestive heart failure, anxiety, alcoholism and/ or menopause. Participants had received any medicines affecting sweating involving thyroxin or anxiolytics if not stopped at least 4 weeks before preceding our study. As well, those with cardiac disorders including arrhythmia, ischemic heart disease, low tolerance or low respiratory reserve and pregnancy or lactating females, also whom have local wound, sever eczema or sever palm fungal infections and whom have sensory disorders were excluded from the study.[13,18]

Intervention:

The patients were allocated into two equal groups at random (N 30). Verbal explanation about the study aims, importance and approach were instructed to every patient in both groups. Every patient has given his /her written informed consent before beginning of the study. All patients were asked to stop any medications used for the treatment of hyperhidrosis before the beginning of the study by at least 4 weeks, then dermatologist recheck after the end of the study and continue their medical management.

Group (A) received twelve sessions three times per week every session those were consisted of 30 minutes application of methotrexate iontophoresis using continuous direct current.[20]

Group (B) received coal tar ointment was putted direct on patients affected skin after describing the instruction

and method of application and time of application and activated alarm instead not to forget.

Outcome measures:

The author, who was blinded to the allocation, evaluated laboratory mass scale 'sweat output' and hyperhidrosis disease severity scale was measured pretreatment, after 6 sessions (post I) and after 12 sessions (post II).[21]

STATISTICAL ANALYSIS

SPSS (Version 25) for Windows was used to analyze the data. Subjects' demographic characteristics and outcome variables were described using the mean and standard deviation. To analyze the differences in the mean values of the variables under investigation among both groups, t-test "paired and unpaired" with Bonferroni, Mann-Whitney and Wilcoxon signed ranks test was performed. The level of significance between groups was fixed at alpha < 0.05.

RESULTS

▪ **Subject characteristics**:

Sixty patients with hyperhidrosis participated in this study. Table (1) showed the subject characteristics of group A and B. There was no significant difference between groups in age and sex distribution (p > 0.05).

Table (1). Basic characteristics of participants.

	Group A	Group B			
	Mean ± SD	**Mean ± SD**	**MD**	**t-value**	**p-value**
Age (years)	24.20 ± 6.87	23.43 ± 5.91	0.77	0.46	0.64
Sex, N (%)					
Females	18 (60%)	16 (53%)		(χ^2 = 0.27)	0.60
Males	12 (40%)	14 (47%)			

SD: standard deviation; χ^2: Chi squared value; p-value, level of significance.

▪ **Effect of treatment on sweat output and HDSS:**

- **Within group comparison**

There was a significant decrease in sweat output in both groups at post II compared with that pretreatment and post I (p <0.01) and a significant decrease at post I compared with pretreatment (p <0.001). (Table 2).

There was a significant decrease in HDSS in both groups at post II compared with that pretreatment and post I (p <0.001) and a significant decrease at post I compared with pretreatment in group A (p <0.001) while there was no significant difference between pretreatment and post I in group B (p >0.05). (Table 3).

- **Between group comparison**

There was no significant difference between groups pretreatment (p > 0.05). There was a significant decrease in sweat output and HDSS of group A compared with that of group B at post I and post II (p <0.001). (Table 2-3).

Table (2). Mean sweat output at pretreatment, post I and post II of group A and B.

Sweat output (gm)	**Group A**	**Group B**			
	mean ± SD	**mean ± SD**	**MD**	**t- value**	**p-value**
Pre treatment	0.59 ± 0.14	0.61 ± 0.12	-0.02	-0.28	0.77
Post I	0.46 ± 0.12 [a, b]	0.54 ± 0.13 [a, b]	-0.08	-2.46	0.01
Post II	0.37 ± 0.10 [a, b]	0.50 ± 0.12 [a, b]	-0.13	-4.23	0.001
F- value	98.76	69.74			
p-value	***p = 0.001***	***p = 0.001***			

SD, standard deviation; MD, mean difference; p-value, level of significance, a significant difference with pretreatment; b significant difference between post I and post II.

Table (3). Median values of HDSS at pretreatment, post I and post II of group A and B.

HDSS	**Group A**	**Group B**		
	Median (IQR)	**Median (IQR)**	**U- value**	**p-value**
Pre treatment	4 (4-3)	4 (4-3)	420	0.60
Post I	3 (3-2) [a, b]	4 (4-3) [b]	154	0.001
Post II	2 (2-2) [a, b]	3 (3-2) [a, b]	225	0.001
χ^2- value	50.06	69.74		

p-value	***p = 0.001***	***p = 0.001***

IQR, interquartile range; U value: Mann-Whitney test value; χ2: chi-squared value; p-value, level of significance, a significant difference with pretreatment; b significant difference between post I and post II.

DISCUSSION:

The findings showed that there was a significant decrease in sweat output and HDSS in both groups at post II compared with that pretreatment and post I ($p < 0.01$ and < 0.001, respectively) and a significant decrease at post I compared with pretreatment ($p < 0.001$), while there was no significant difference between pretreatment and post I in HDSS in group B ($p > 0.05$). There was a significant decrease in sweat output and HDSS of group A compared with that of group B at post I and post II ($p < 0.001$).

Primary palmar hyperhidrosis is a dermatologic disorder of excessive sweating, where eccrine glands of palm secrete inappropriate large quantities of sweat. Primary hyperhidrosis creates significant physical, emotional and/ or social discomfort those lead to a negative impact on sufferers' quality of life.[22]

Nawrocki and Cha,[23] had stated that populations with primary hyperhidrosis usually considered idiopathic. Where, eccrine glands seem morphologically and functionally normal, unless they were stimulated by emotion and stress not during sleep or sedation.

Primary hyperhidrosis might have physiological consequences such as cold and clammy hands, dehydration and dermal infections secondary to maceration.[5]

Up to date, primary palmar hyperhidrosis treatment remains a challenge and a logical approach must be taken to individualize therapy based on the degree of functional impairment. Numerous therapeutic approaches available for hyperhidrosis such as topical antiperspirants, intradermal botulinum toxin injections, systemic treatments and surgical interventions.[22]

The current study aimed to assess the effectiveness of methotrexate iontophoresis and coal tar ointment on laboratory mass scale 'sweat output' and hyperhidrosis disease severity scale in primary palmer hyperhidrosis.

Most of previous studies focused on the direct current iontophoresis efficacy, but to the best of the authors' knowledge no recent clinical trial had been proven for primary palmar hyperhidrosis.

Cruddas and Baker,[24] had reported that daily application of various topical pharmacological agents might fail to adequately achieved control of hyperhidrosis, including boric acid, anticholinergic medicines, resorcinol, 2-5% tannic acid solutions, potassium permanganate, formaldehyde, methenamine and glutaraldehyde.

Approved FDA as an effective semisolid by-product obtained in the destructive distillation of bituminous safe coal tar as an ingredient for primary palmar hyperhidrosis treatment.[15]

Shayesteh,[20] had stated specific topical agents could use as maintenance therapy depending on iontophoresis that addressed as a non-invasive boosting high concentration of a charged topical pharmacological agents transdermally by repulsive electromotive force using a small electrical current is not fully understood, yet.

The aim of iontophoresis for primary palmar hyperhidrosis is to transport topical medicines deeper inside focused skin area thus its entry portal is primarily sweat glands that resulting in a more efficient reduction of hyperhidrosis symptoms severity.[6]

Methotrexate iontophoresis is an inexpensive safe suitable approach enhance efficient induce hyperkeratosis of eccrine glands` pores therefore permits obstruction of sweat flow and excess sweat secretion. Thus, it aids in controlling severity of primary palmar hyperhidrosis symptoms, which almost reported by 3rd life decade whom manifested at childhood and adolescence.[25]

Iontophoresis is a well-known physical therapy modality that based on application of application of 15 to 20 mA to aimed site for 20-30 minutes per session, where adding methotrexate as a topical pharmacological medicine assists in the impairment of the electrochemical gradient of sweat secretion and a biofeedback mechanism that ensured in most primary palmar hyperhidrosis population by the 4th decade of life.[24]

According to Voelker,[22] who proved that methotrexate iontophoresis as a conservative noninvasive approach depends upon a direct electric current to increase the penetration of ionic methotrexate substances into dermal area for therapeutic purposes. In addition, numerous clinical trials had found iontophoresis approach has therapeutic benefit to increase administrated quantity and depth of topical medicines` ionic substances.[26]

According to Rajagopal and Mallya,[27] had evaluated sixty primary hyperhidrosis patients whom randomly allocated into two groups. Their used topical pharmacological agent botulinum toxin type A 100 units per each palm was compared to digital iontophoresis with topical application of aluminum chloride hexahydrate lotion along four weeks, with additional period for whom had recorded no improvements, plus extended six months as a follow up. They had stated that iontophoresis gained around 47% improvements for initially improved patients, plus 17% for whom crossed over. we could explain their unimproved populations could managed through just

was activated alarm instead not to forget such maintenance therapy.

According to Romero et al.,[25] who had stated that hyperhidrosis disease severity scale as an excellent clinical outcome measure for primary hyperhidrosis, which easily and quick practical applied in a simple understood manner. HDSS held a good diagnostic correlation scale if associated with nearby 50% reduction was defined laboratory mass produced in form of sweat output.

According to a recent Pakistanian clinical trial of Rahim et al.,[26] whom compared efficacy of iontophoresis therapy versus aluminum chloride hexahydrate in treatment of seventy pakistanian participants with palmoplantar hyperhidrosis along six weeks, where iontophoresis group received three sessions per week. Their recorded remarkable reduction in hyperhidrosis clinical manifestations severity from 3.40± 0.65 to 1.48± 0.78 by percent of improvement 2.9%, 25.7%, 48.6% and 22.9%, respectively (p value 0.001) without any reported adverse effects for iontophoresis.

According to Gregoriou et al.,[28] managing primary palmar hyperhidrosis prevent any remarkable negative impact on patients` quality of life that was moderately or severely affected emotionally. As well, Cruddas and Baker,[24] ensured usage methotrexate for managing palmar primary hyperhidrosis, but no significant decrease in palmar sweating was recorded.

According to Wade et al.,[29] numerous efforts exerted globally for discovering more efficient with minimal risk for managing of primary palmar hyperhidrosis. However, discomfort in form of burning or tingling sensation could be experienced, also erythema, dryness and vesiculation in the treated area those not reported along current clinical trial. Therefore, we concluded iontophoresis 'US FDA-approved device' that facilitates faster delivery of involved topical pharmacological agents.

According to the current study results, it is important that physical therapists and other health professionals should consider the impact of adding methotrexate iontophoresis in treatment of primary palmar hyperhidrosis. However, the authors of this study emphasize that more research will be needed before this can be considered definitely effective.

LIMITATIONS

The current study has some limitations, including the inability to blind the patients due to the nature of therapeutic intervention. Another issue was the lack of follow-up for participants in both groups. As a result, future research should be conducted to investigate extended follow up of methotrexate iontophoresis on primary palmer hyperhidrosis patient outcomes. Furthermore, the individuals for this study were recruited from a single governate in Egypt. As a result, extrapolation of the findings to the entire Egyptian population might be limited.

CLINICAL MESSAGE:

According to the findings of this study, methotrexate iontophoresis had a notable efficacy in improving both laboratory mass scale 'sweat output' and hyperhidrosis disease severity scale in primary palmer hyperhidrosis.

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