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TOPICAL VERSUS CONTINUOUS BETAMETHASONE DIPROBIONATE PHONOPHORESIS IN THE TREATMENT OF ATOPIC DERMATITIC PATIENTS

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ABSTRACT

Purpose: The purpose of this study was to compare Topical versus Continuous Betamethasone Diprobionate Phonophoresis in the Treatment of Atopic Dermatitic Patients

Methods: Forty six patients atopic dermatitis were participated in this study and were randomly assigned to one of two groups. Phonophoresis group received continuous 0.05% betamethasone dipropionate phonophoresis, three sessions per week for 4 weeks, and control group received topical betamethasone dipropionate cream daily. Measurements were carried out by ultrasonography and SCORAD score.

Results: results revealed that there was a significant difference between both groups as regard to primary outcomes (SCORAD score) as well as secondary outcomes (skin thickness measurements).

Conclusion: it was concluded that continuous betamethasone diprobionate phonophoresis is a safe and effective modality more than topical cream for the treatment of atopic dermatitis.

Keywords: Phonophoresis, betamethasone dipropionate phonophoresis, SCORAD score, ultrasonography, Atopic dermatitis.

INTRODUCTION

Atopic Dermatitis (AD) is a chronic (long-lasting) disease that affects the skin. The word "Dermatitis" means inflammation of the skin. "Atopic" refers to a group of diseases that are hereditary (that is, run in families) and often occur together, including asthma, allergies such as hay fever. In atopic dermatitis, the skin becomes extremely itchy and inflamed, causing redness, swelling, cracking, weeping, crusting, and scaling[1.] Any chronic illness can have major impact on the sufferer's life. Atopic disease have become a major health problem. Its chronic course with extreme pruritus and loss of sleep affects the whole family**.** AD may have profound effects on the quality of life, social relationships and development. It also interferes with school and physical activities. Treatment may be demanding with frequent hospital attendances[2].

Topical corticosteroid such as betamethasone phonophoresis is effective in patients with AD. Although topical corticosteroids have been the mainstay of treatment for the past 40 years, they have local and systemic side effects. Local effects include skin atrophy, telangiectasias, hypopigmentation, rosacea, perioral dermatitis and acne. Systemic side effects include adrenal suppression, cataracts, glaucoma and growth retardation in children. These effects cause anxiety for both patients and clinicians and this is the main reason for patients' poor compliance with treatment[3].

The major barrier to the delivery of transcutaneous drugs is the skin. Pharmaceutical companies are continually involved in research to try to find new

ways to enhance the delivery of topical drugs. Although complex chemical enhancers have been integrated into some transdermal delivery systems, physical agents such as electricity and ultrasound (US) are becoming increasingly popular as enhancers. The use of electricity as an enhancer is referred to as iontophoresis, and the use of US as an enhancer is referred to as phonophoresis or sonophoresis[4].

Phonophoresis (PH), has been claimed to enhance the percutaneous absorption of certain pharmacological agents such as anti-inflammatory, steroids and local anesthetics from intact skin into the underlying subcutaneous structures by ultrasound, therefore improving their effectiveness. PH offers the potential advantage of delivering a pharmacologic agent in a relatively safe, painless, and easy manner to structures that lie somewhat deep within the body [5].

Phonophoresis (PH) has been studied in vivo with several anti-inflammatory drugs, including hydrocortisone [6], benzydamine [7], dexamethasone [8], and salicylates [9]and with anesthetics, such as lidocaine [10], with variable results. However, no study in literature review conducted to study the efficacy and safety of betamethasone dipropionate phonophoresis in patients with AD. Therefore, we used 0.05% betamethasone dipropionate cream on daily bases as the reference for comparing and evaluating the efficacy and safety of phonophoresis 0.05% betamethasone dipropionate applied every other day in young adult with AD.

PATIENTS AND METHODS

Subjects

This study was carried out on 46 patients with mild to moderate atopic dermatitis. Signed informed consent was obtained from each participant before enrollment in the study. History & clinical examination were done for all subjects and diagnosis of AD was made according to criteria proposed by Hanifin and Rajka, modified diagnostic criteria[11].

Reasons for exclusion were patients had severe AD, known sensitivity to the study treatments or eczema confined to the face or nappy area. Patients were excluded if they had received any therapy for AD other than emollients or antihistamines within four weeks before the start of the study. Treatment was stopped when the SCORAD system [12] was below 9 (clinically healed) or ultimately after 4 weeks.

All subjects were participated in single blind, randomized, controlled trial. To detect a 50% reduction in SCORAD index scores at the 5% significance level with 80% power, 23 patients per group are required. We recruited a larger number to allow for an estimated 10% withdrawal rate. A computerized random number list was generated and the subject allocation sequence was created from the list. The patients met with the blinded investigators who conducted the assessments. Following their assessments, the patients were assigned into 2 groups of equal number. PH - group received 0.05 % Betamethasone Dipropionate phonophoresis (BDP). Control group received 0.05 % Topical Betamethasone Dipropionate (TBD).

Measurements

All measurements have been recorded by blinded investigators who did not know the assignment groups. Primary outcome measurement included assessment of AD severity using SCORAD. The SCORAD have been collected at baseline (Pre) after 2 and 4 weeks. 2-week follow-up period with basic skin care only served to evaluate the AD and whether a rebound occurred. Secondary outcome included assessment of the thickness using ultrasonography, and safety analysis via measuring cortisol exertion in urine.

Severity of AD using SCORAD

The clinical severity of AD was evaluated by using the SCORAD index that developed by the European Task Force on atopic dermatitis (1993) [13]. It defines a score of three parameters: extent,

intensity and subjective symptoms. Extent is calculated with the rule of nines. Intensity items are erythema, edema/papulation, oozing/crust, excoriation, lichenification and dryness of non involved skin (0 to 3 points for each item). Subjective symptoms are pruritus and sleep loss for the last 3 days or nights (0 to 10 points for each item). The final score is then calculated according to the following equation: A/5 + 7B + C, where, A represents extent, B represents intensity and C represents subjective symptoms. The SCORAD is considered mild AD is less than 25, moderate lies 25-50 and severe AD is above 50.

Ultrasonography Measurements

Throughout this study the depth of the lesions was evaluated using a high-resolution ultrasound system dedicated to skin applications [14]. A Derma Scan C Ver. 3 (Cortex Technology ApS, Hadsund, Denmark) was used. The system frequency was at 20 MHz and with 10 mm penetration. The size of the probe was 19X33 mm and the scan length 12.1 mm. The principle of ultrasound imaging is based on the ultrasonic wave being partly reflected at the boundary of adjacent structures when traveling through tissue. The strength of this reflection depends on differences in the density of such structures, which leads to an amplitude variation of the reflected signal. Finally, processing of the signal received from multiple ultrasound pulses over an area of the skin forms a two-dimensional image; a so-called B-scan

Safety Analysis

Three 24-hour urine sample were collected for urinary-free cortisol/creatinine analysis at the beginning (baseline), the last day of the treatment period and at follow up. The 24-hour urine collections were mixed and stored frozen at-20^{0}C until they were analyzed in the clinical laboratory department [15].

Treatment Procedures

Continuous Betamethasone Dipropionate phonphoresis has been conducted through Ultrasound device (Nonius, Sonopuls 434, SN 03-202 type 1463.900, Enraf, Holland) , three sessions per week for 4 weeks. The patients assumed a comfortable position, then therapist clean and hydrate the body part under treatment. Adjust the US frequency to 1MHz, with intensity 1.5 W/cm^2 and the time of treatment was 5 min [16]. For control group: The patients were instructed to apply the ointment to the selected area once daily.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Student t test was used to assess the difference between the studied parameters in two groups. Paired t test was used to analyze the thickness of the skin within the group. We analyzed severity scores by using a repeated measure analysis of variance. Cortisol excretion between the two groups was compared using the Mann-Whitney U test, and compared in time within each of the two treatment groups using the Wilcoxon test. Analysis was performed using SPSS/PC software (SPSS Inc., Chicago, IL, USA). All p values less than 0.05 were considered to be statistically significant.

RESULTS

Baseline Characteristics of the Patients

Fifty-five patients enrolled in the study. Of these, 46 completed the study and nine dropout (3 patients in the PH -group and 6 in the control group). At baseline, the demographic characteristics, disease severity thickness of lesion and cortisol level were similar in both treatment groups. Table 1 lists the baseline characteristics.

Table 1: Characteristics of the patients in the two groups

	PH –**group (n=23)**	**Control group (n=23)**	***P-value***
Age (years)	22±4.74	21.83±4.86	0.9
Sex(male/females)	15/8	13/10	0.7
Positive family history	15(65%)	14(61%)	0.1
Duration of AD(months)	6.52± 3.39	6.17±3.63	0.7
Initial SCORAD	32.75± 4.71	33±5.09	0.87
Initial Thickness	15.55± 1.73	15.8± 1.6	0.63
Cortisol level (µg cortisol/g creatinine)	35.55± 14.7	34.8± 11.6	0.1

Results of the Primary Outcome SCOARD

No differences were observed in the SCORAD at the beginning of the study between the groups. Analysis of variance demonstrated significant difference in the mean downward linear trend of SCORAD within each group at 4 weeks compared to baseline and 2 weeks respectively.

After 2 week of the treatment, the SCORAD (mean ± SD) significantly decreased in both treatment groups (PH: 17.04 ± 9.72, control: 19.56 ± 5.62). In spite of the marked improvement after 2 week, only 9 patients in the PH -group was scored as clinically healed (SCORAD < 9), and 3 patients was scored as clinically healed in the control group.

At the 4 weeks of the treatment, the improvement of AD was more pronounced in the US-group. The mean SCORAD had dropped significantly to 8.08 ± 2.72 for US group compared with 14.26± 6.52 for the control group. There were 27 subjects with a SCORAD of 9 or less (17 in the PH -group and 10 in the control group). Two weeks after discontinuation of active treatment, the mean SCORAD had increased to 13 ± 9 (PH group) and 21 ± 7 (control group).

Table 2: Number of patients scored as clinically healed (SCOARD<9) in the course of the study

Week	PH **-group (n=23)**	**Control (n=23)**
Week 2	9	3
Week 4	17	10

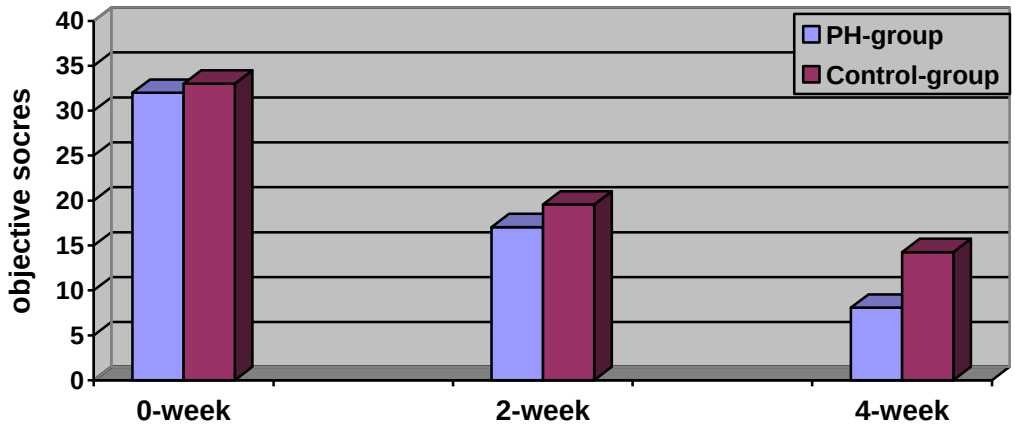

Figure1. Mean SCORAD for both groups according to the weeks

Results of Secondary Outcomes

Skin Thickness

Unpaired t test revealed no significant difference between both groups at the beginning of the study. The mean value of skin thickness was (PH; 15.64±1.67, and control; 15.78 ±1.64, p=0.77). After 4 weeks of the treatment, there was significant decrease of skin thickness compared to baseline in both groups, with the trend of significant ($p<0.05$) decline being greater in the PH -group (9.13±1.09) compared with control group (12.12±1.38). The percentage of skin thickness reduction was significantly greater for US-group 6.5% versus 3.6% for control group.

Table 3: Skin thickness (mean ± SD), in both groups

variables	PH -group (n=23)		Control (n=23)		P-values between groups
	0-week	4-week	0-week	4-week	
Skin thickness	15.64±1.67	9.13±1.09	15.78 ±1.64	12.12±1.38	0.79
P-value within group	0.01		0.03		0.01

Safety of the Study

Urinary cortisol excretion was not significantly different between the two treatment groups at the beginning of treatment (35.55± 14.7 *versus* 34.8± 11.6, *P* = .8), at the end of treatment (39.4± 6.4 *versus*38.55± 16.3, *P* = .8), and at the end of follow-up (34.4± 14.4 *versus* 33.25± 16.3, *P* = .9)

Fig. 2. Comparing the 24-hour urinary cortisol excretion at the beginning with the excretion at the end of treatment (PH -group: *z* = –1.1, *P* = 0.3; Control group: *z* = –0.4, *P* = 0.7) and at the end of follow up (PH-group: *z* = –0.4, *P* =0.7; Control group: *z* = –1.2, *P* = 0.2) there were no significant changes.

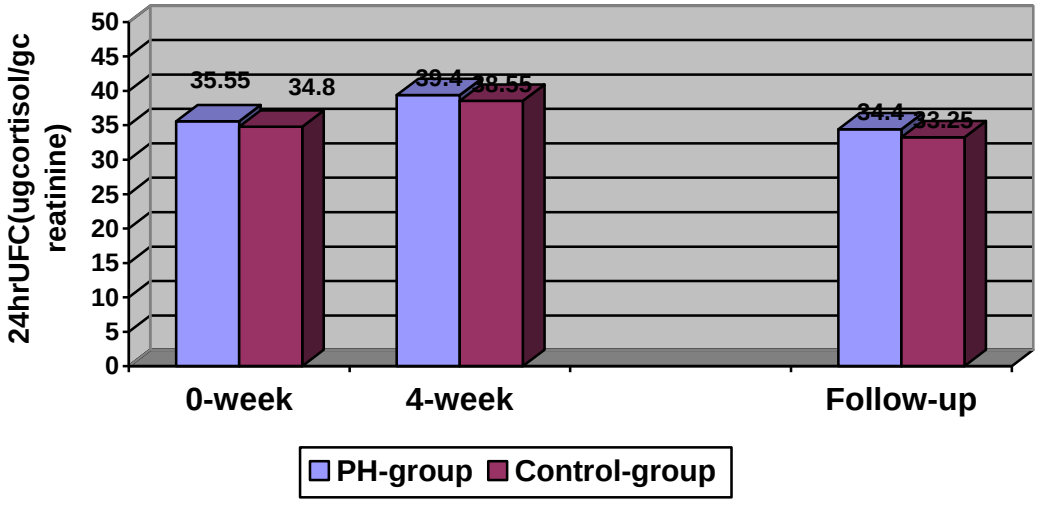

Figure 2: Twenty-four-hour urinary cortisol excretion in both groups

DISCUSSION

In this randomized controlled study, the results revealed that there was a significant difference between both groups as regard to primary outcomes(SCORAD) measurements) with the trend of significant ($p<0.05$) and the number of patients healed after 4 weeks were 17&10 for PH and control group respectively.

The results of the study also revealed that there was a significant difference between both groups as regard to the secondary outcomes (skin thickness measurements) with the trend of significant ($p<0.05$) as the mean skin thickness

after 4 weeks of treatment for PH and control group was 9.13±1.09 & 12.12±1.38 respectively. These results confirm the effectiveness of ultrasound in enhancing transfer of betamethasone diprobionate so enhancing healing and treatment of atopic dermatitis patients.

Numerous studies[16-18]have since demonstrated that US is generally safe, with no negative long- or short-term side effects, but the mechanisms by which US works as an enhancer are less clearly understood. The simplest explanation for the effectiveness of US as an enhancer of drug delivery is based on its heating effects. Heat increases the kinetic energy of the drug molecules and the proteins, lipids, and carbohydrates in the cell membrane. Temperature changes of approximately 5°C are necessary to cause measurable changes in cell membrane permeability. This level of increase in heating only predictably occurs when the US intensity is 1.5 W/cm^2or higher [19.]

Overall, the reviews of the research on the efficacy of phonophoresis are promising. Some of the studies, however, suffered methodological constraints that limit generalizability (eg, no control group, the experimenters were not blinded, the US delivery system was not calibrated, methods of documenting effectiveness were not objective, a small number of subjects were studied, or the topical drug used was not checked to ensure that it transmitted US (transmissivity). All these constraints were avoided in our study. And the transmissivity of betamethasone diprobionate was tested by Cameron MH and Monroe LG [20.]

Bommannon and colleagues[17] concluded that high-frequency US was effective as an enhancer of transcutaneous drugs and could be used safely for short periods of time. When 16-MHz US is used for more extensive periods of time, it is possible that the bubbles of the micronuclei begin to grow, then collapse and self-destruct (cavitation), secondarily enhancing drug penetration.

Tyle and Agrawala [21] reviewed the effects of drug delivery by phonophoresis in 1990 and concluded that US effectively enhanced localized and systemic drug delivery. Friberg[24] reported that some of the studies that showed increases in drug diffusion with US were correlated with damage to the stratum corneum. This damage was either part of the pathology designated for treatment (eg, psoriasis, dermatitis, and ulcer) or it was an outcome of the US treatment itself or the use of a stationary sound head.

Draper and Prentice [22] reported that the thermal effects of ultrasound increase tissue permeability, and the acoustic pressure created by the ultrasound beam drives the medication into the tissue. Naik et al.,[23] reported that both the thermal and nonthermal effects of US increase cell permeability. Also Abd El Baky and Waked[24] concluded in their study that phonophoresis is an effective method to enhance the delivery of ibuprofen and so enhance the improvement of grip strength.

Barbara.,[25] documented that both the thermal and nonthermal characteristics of high-frequency sound waves can enhance the diffusion of topically applied drugs. Heating from US increases the kinetic energy of the molecules in the drug and in the cell membrane, dilates points of entry such as the hair follicles and the sweat glands. And increases the circulation to the area sonicated. These physiological changes enhance the opportunity for drug molecules to diffuse through the stratum corneum and be collected by the capillary network in the dermis**.**

In order to assess the safety of the study, Comparing the 24-hour urinary cortisol excretion at the beginning with the excretion at the end of treatment for both groups and the results revealed that there was no significant difference between the beginning and the end of treatment in both groups.

CONCLUSION

Finally, according to the results of our study and reports of other investigators in similar studies, It can be concluded that, betamethasone diprobionate phonophoresis is a safe and effective modality more than topical cream for the treatment of atopic dermatitis.

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