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Effectiveness and Safety of Topical Emollients in the Treatment of PUVA-Induced Pruritus

Skuteczność i bezpieczeństwo stosowania miejscowo emolientów w leczeniu świądu powstałego w wyniku zastosowania metody PUVA

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Abstract

Background. In this study we tried to assess the efficacy of topical emollients in the treatment of patients with PUVA-induced pruritus.

Material and Methods. 41 patients over 18 years of age, who received PUVA treatment in the phototherapy unit, were included in the study. Patients were randomly divided into two groups; Group I was administered with a 4% urea lotion and Group II was administered with liquid petrolatum. The follow-up period was minimum 4 weeks. During the first 2 weeks, patients were administered topical emollients and received PUVA treatment together. The next 2 weeks, they continued PUVA treatment without any medication.

Results. When time-dependent changes in the visual analogue scale scores for pruritus of both groups were considered, both treatment methods were found to be remarkably successful ($p < 0.0001$). In addition, an insignificant group-time interaction was identified ($p = 0.753$).

Conclusions. Topical emollients were found to be effective in the treatment of PUVA-induced pruritus. Both forms of medication can be successfully administered and increase the patient's compliance with medication (*Adv Clin Exp Med* 2013, 22, 5, 715–720).

Key words: emollients, pruritus, PUVA therapy, visual analogue scale, Likert scale.

Słowa kluczowe: emolienty, świąd, leczenie PUVA, wizualna skala analogowa, skala Likerta.

PUVA, which is a combination of psoraline and UV light, is an effective treatment method commonly used to cure various skin diseases [1–3]. Development of new irradiation techniques and equipment gave rise to gradual increase of photochemotherapy indications which made PUVA become more widely used day by day. In addition to that, PUVA has some long or short term side effects in its own right as well [4, 5]. Pruritus, which is a short term significant adverse effect, can sometimes be strong and make it hard for the patients to comply with medication [6, 7]. The mechanism for

PUVA-induced pruritus is not precisely known. It manifests itself frequently after few treatments. Pruritogenic substance production, lowered pruritic threshold, increased skin dryness have been emphasized as possible causes [7–9].

There is still no treatment method for PUVA-induced pruritus the efficacy of which has been proved with controlled trials. Despite the wide use of topical emollients, there is no controlled trial which would reveal their efficacy. In this study, we tried to assess the effect of topical emollients in the treatment of PUVA-induced pruritus.

Cases and Methods

Subjects

53 patients over 18 years of age receiving PUVA treatment in the Phototherapy Unit of our clinic were included in our study. 12 patients who did not appear for control examination and had to start a topical or systemic treatment to alleviate itching complaints were excluded from the study. Hence, a total of 41 patients were included in the assessment. The study group constituted of 20 psoriasis vulgaris, 16 vitiligo, and 5 alopecia areata patients that were planned to receive long term PUVA treatment and developed itching thereafter. After having questioned cases about receiving any medication that would reduce or trigger itching, we included in the study only those that did not receive any topical treatment and/or any systemic retinoid treatment, antihistaminic treatment, or systemic steroid treatment in the last 3 months that would have affected pruritic complaints.

Cases were randomly divided into two groups, and one group (Group I) was administered with 4% urea lotion and the other group (Group II) was administered liquid petrolatum. They were followed for a period of four weeks. During the initial two weeks, they received topical emollients along with the PUVA treatment (not just before the treatment) and the next two weeks patients continued to receive PUVA treatment without emollients.

Clinical Measures

Before the treatment, all cases were tested for complete blood count, liver and kidney functions, electrolyte levels, lipid profile, serum urea, creatinine, alkaline phosphatase, and sedimentation levels. They were dermatologically examined in each treatment session to evaluate pruritic scores.

Waldmann UV 8001K unit (Waldmann Lichttechnik GmbH, Schweningen, Germany) was used in the treatment and all cases were given 8-methoxypsoralen before taking UV light. Pruritic magnitude and changes in time were evaluated in each treatment session (2–3 weeks) and recorded in forms printed for each case separately. Hemogram, liver, and kidney functions were periodically reviewed over the treatment period due to possible side effects of PUVA.

Pruritus Measures

We used slightly different measures of pruritus to assess patients' pruritic complaints. A visual analogue scale (VAS) is usually a horizontal line of 100 mm, anchored by the terms 'no itching' at the

0 point to 'strongest itching' at the 10 end of the scale [10]. A 5-point Likert scale was used to assess pruritus over the past 24 hours, with responses from Grade I ('no itching') to Grade V ('severe itching, often discomforting, and sleep disturbing').

Statistical Analysis

Statistical analyses were made with SPSS for Windows (version 11.5, SPSS Inc., Chicago, IL, USA). Variables with Gaussian distribution were shown as mean \pm SD and variables with non-Gaussian distribution were shown as median (25th and 75th percentiles). Student's *t* test was used to compare the means of two independent groups, whereas paired-samples *t* test was used to compare the means of two dependent groups. Yates' χ^2 test was used to compare the proportions between independent groups whereas McNemar test was used to compare the proportions between dependent groups. Repeated-measures ANOVA analysis was used to test the statistical significance of differences of variables between and within the groups. Statistical significance was $p < 0.05$ (two-tailed).

Results

The main demographic features and dermatological examinations of the study population were shown in Table 1 and 2. A total of 12 cases received PUVA treatment twice a week and 29, thrice a week. The median cumulative PUVA doses were 56 J/cm² for Group I and 68 J/cm² for Group II. Cases were assessed on the basis of VAS score and Likert scale for a period of two weeks before the treatment and another two weeks after the treatment. According to the results, VAS score of 42 ± 19 in Group I declined to 22 ± 15 and the VAS score of 41 ± 18 of Group II went back to 23 ± 14 (Fig. 1).

Change of pruritic complaints in time based on Likert scale is shown in Table 3. Although the frequency of the patients displayed Grade I or Grade II increased significantly after treatment in Group I ($p = 0.008$), it did not increase significantly after treatment in Group II ($p = 0.687$).

Repeated-measures ANOVA analysis for VAS score showed a significant time-effect ($F = 60.9$; $p < 0.0001$), whereas an insignificant group-time interaction ($F = 0.1$; $p = 0.753$). These results indicated that both emollients were more effective in the treatment, but the difference between the two treatment protocols was not statistically significant when compared in terms of treatment efficacy. As for the medical efficacy, cases reported benefits from the medication within one week at the latest.

Table 1. Demographic data of the groups

| | Group I (n = 23) | Group II (n = 18) | <i>p</i> |
|-------------|---------------------|----------------------|-----------|
| Age (years) | 39 ± 13 | 46 ± 14 | = 0.096* |
| Male/Female | 12/11 | 6/12 | = 0.375** |

* *p*-value was computed using Student's *t* test.

** *p*-value was computed using Yates' χ^2 test.

Discussion

Photochemotherapy is a widely used and effective treatment in a number of skin disorders including psoriasis, atopic dermatitis, vitiligo and photodermatoses. PUVA treatment has some acute adverse effects, such as erythema-burning, pruritus, nausea, pseudoporphyria, PUVA pain, maculopapular rash [11]. The largest series about PUVA therapy was reported by Henseler et al. In the multicenter study 3175 severe psoriasis patient went on photochemotherapy and pruritus side effect was reported with a rate of 25.6% [12]. Another series of cases dealing with the side effects of photochemotherapy were reported by Melski and colleagues. They analyzed the side effects seen in 1308 patients undergoing treatment of oral methoxalen photochemotherapy and reported observing PUVA-induced pruritic complaints at a rate of

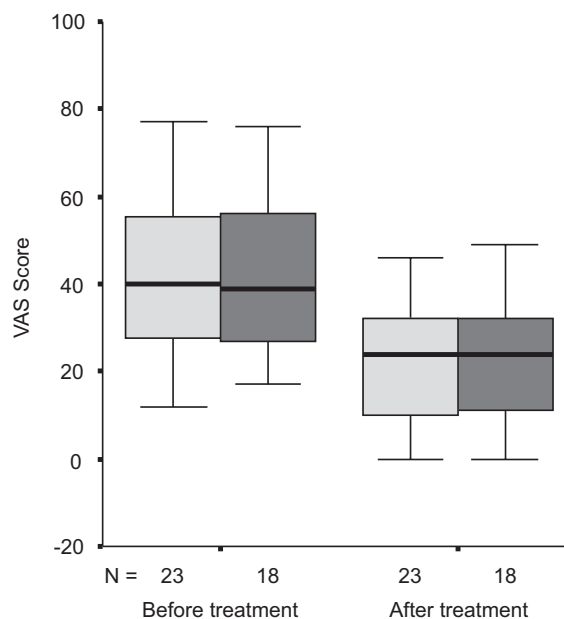


Fig. 1. Box-plots showing the values of VAS scores of the groups before and after treatment (dotted and patternless for Group I; dotted and patterned for Group II). Decrease in VAS scores for both Group I and Group II after the emollients is shown

14.03% out of the total number of treatment sessions. Nearly half of these cases developed a manifestation of generalized itching (6.4%). A very small group of patients (0.44%) manifesting severe itching required the discontinuation of the treatment [6].

Table 2. Results of dermatological assessment of the study population

| | Group I (n = 23) | Group II (n = 18) | All cases (n = 41) |
|--------------------------------------|---------------------|----------------------|-----------------------|
| Percentage of Involvement (%) | 15 (10–20) | 15 (10–20) | 15 (10–20) |
| Cumulative doze (J/cm ²) | 56 (38–126) | 68 (40–89) | 66 (39–104) |
| Disease diagnosis, | | | |
| Vitiligo, n (%) | 12 (52.2) | 8 (44.4) | 20 (48.8) |
| Psoriasis, n (%) | 9 (39.1) | 7 (38.9) | 16 (39.0) |
| Alopecia Areata, n (%) | 2 (8.7) | 3 (16.7) | 5 (12.2) |
| Magnitude of disease | | | |
| Minor, n (%) | 2 (8.7) | 0 (0) | 2 (4.9) |
| Mild, n (%) | 5 (21.7) | 4 (22.2) | 9 (22.0) |
| Moderate, n (%) | 10 (43.5) | 9 (50.0) | 19 (46.3) |
| Severe, n (%) | 6 (26.1) | 5 (27.8) | 11 (26.8) |
| Number of weekly sessions | | | |
| 2, n (%) | 7 (30.4) | 5 (27.8) | 12 (29.3) |
| 3, n (%) | 16 (69.9) | 13 (72.2) | 29 (70.7) |
| Treatment dose | | | |
| 2, n (%) | 5 (21.7) | 2 (11.1) | 7 (17.1) |
| 3, n (%) | 7 (30.4) | 6 (33.3) | 13 (31.7) |
| 4, n (%) | 3 (13.0) | 4 (22.2) | 7 (17.1) |
| 5, n (%) | 2 (8.7) | 3 (16.7) | 5 (12.2) |
| 6, n (%) | 6 (26.1) | 3 (16.7) | 9 (22.0) |

Table 3. Cross table showing before and after treatment Pruritic Scores Likert item frequencies

| | Pruritic score likert | Before treatment | After treatment | <i>p</i> |
|----------|----------------------------|------------------|-----------------|----------|
| Group I | Grade I or II, n (%) | 10 (43.5) | 18 (78.3) | = 0.008* |
| | Grade III, IV, or V, n (%) | 13 (56.5) | 5 (21.7) | |
| Group II | Grade I or II, n (%) | 9 (50.0) | 11 (61.1) | = 0.687* |
| | Grade III, IV, or V, n (%) | 9 (50.0) | 7 (38.9) | |

* *p*-value was computed using McNemar test.

Grade I – No itching.

Grade II – Mild itching, but not remarkably discomforting or sleep disturbing.

Grade III – Moderate itching, sometimes discomforting, but not sleep disturbing.

Grade IV – Moderate itching, often discomforting, but not sleep disturbing.

Grade V – Severe itching, often discomforting, and sleep disturbing.

The exact cause of PUVA-induced pruritus is not known. Substance P, which has been implicated as a primary neuropeptide involved in the itch sensation, may be the mediator. It can be released from terminal nerve endings by noxious stimuli including UV light [13]. Also, a lowered pruritic threshold, and especially increased skin dryness, have been emphasized as possible causes [7–9]. PUVA induced pruritus may necessitate discontinuation of treatment. Most of the patients respond to emollients and antihistamines, but there are no controlled trials of which emollient is most effective in the treatment of PUVA-induced pruritus. Topical emollients like urea, petrolatum, glycerine, olive oil, Balmandol have been in use in the treatment of pruritus for long years. Emollients are used to break the dry skin cycle, retain water in the stratum corneum and serve as a barrier against transepidermal liquid loss. It is still not known how these lipids manifest their antipruritic effects [14].

Having assumed that the dry skin played a fundamental role in the development of PUVA-induced pruritus, in our study we aimed to reduce the skin dryness with the use of topical emollients. Both the 4% urea lotion and the liquid petrolatum revealed a significant recovery of PUVA-induced pruritic complaints at the end of the study. Results indicated that both treatment methods decreased itching at the same level and neither of them was superior over the other. Having started antipruritic effects in the first two weeks, both forms of medication were well tolerated by the patients. This study is the first to document emollient effectiveness on PUVA-induced pruritus.

For the assessment of patients pruritic complaints we used two scales. The grade of pruritus was assessed on the basis of VAS and Likert scale for a period of two weeks before the treatment and another two weeks after the treatment. According to the results, VAS score showed a significant time-

effect ($F = 60.9$; $p < 0.0001$), whereas an insignificant group-time interaction ($F = 0.1$; $p = 0.753$). These results indicated that both emollients were effective in the treatment, but the difference between the two treatment protocols was not statistically significant when compared in terms of treatment efficacy.

Likert scale score showed an improvement in the pruritic complaints of the patients in Group I. So, the frequency of the patients displaying Grade I or Grade II increased after the emollients significantly ($p = 0.008$). However, pruritus severity was not improved significantly after emollients in Group II ($p = 0.687$).

Both VAS and Likert scale have some advantages and disadvantages. There are many studies that compare the reliability, validity, user-friendliness and responsiveness of these scales with different results. Du Toit et al. suggest that VAS is more sensitive to detect small differences than the Likert scale [15]. Some researchers claim that it is easier to use and to understand. Furthermore, some other studies suggested that VAS has better responsiveness than the Likert scale and might also be more reliable and valid [16]. We can explain the difference between Group I and Group II, which was assessed with the Likert scale, as the pooriness of assessment method.

Zamiri et al. claimed that axon reflex was impaired following PUVA treatment. A patient, who complained of skin pain after the second session of PUVA treatment, was administered an intradermal histamine injection on the site of the pain and identified to have formed no ring of edema and to have given no response of axon reflex. The condition was explained with reference to the increase in dermal nerve endings. However, the claim was then criticized by Johansson, who further claimed the condition not to have been related with the neurons [17]. Jordon put forward that these patients

could be tested for histamine and claimed that in the case of no axon reflex response, the use of antipruritic medication would not have been beneficial [9]. Some products, such as urea, glycerol and lactic acid, increase desquamation by degrading the corneodesmosomes accumulated due to the corneodesmolytic effect. Decreased hydration in dry skin and abnormal accumulation of these cohesive proteins on the upper layers of stratum corneum can change the mechanical properties of stratum corneum, producing an itching effect by the mechanical stimulation of the underlying neural fibers [18].

Rogers and colleagues assessed the increased pruritic complaints of 12 psoriasis patients under PUVA treatment objectively via nocturnal extremity movements. In four patients an increase in the upper extremity movements was noted which was aligned with the itching movement and an increase in the lower extremity movements which was aligned with the uneasiness. They also put forward the possible effect of neurotransmitters on the PUVA-induced itching mechanism [7]. Still, there is no treatment method which has been shown to be effective in the treatment of PUVA-induced pruritus by controlled studies. Topical emollients have been widely used to prevent dehydrative effect of PUVA as well as to reduce its itching effect on the skin. However, no controlled study has yet been carried out to show their efficacy.

Grade of PUVA-induced pruritus varied from patient to patient. In some patients itching occurred at a level that is very hard to endure, disturbing their daily activities, producing itching-associated insomnia, resisting against treatment and bringing about a significant reduction in their quality of life, whereas in some patients it occurred on a localized and temporary basis. Some patients described itching to have hit as severe attacks at intervals. Itching did not require quitting treatment in any of the cases.

A decrease of PUVA-induced pruritic complaints by the use of topical emollients without any antihistaminic intake suggests that pruritus might be related to skin dryness. However, our experience showed us that the use of emollients did not completely eliminate pruritus. This situation suggests that other mechanisms might have played a role in the etiopathogenesis. As a result, 4% urea preparation and petrolatum both make an effective, reliable and cost-effective treatment method in curing PUVA-induced pruritus. Use of topical emollients by patients receiving photochemotherapy during the treatment period reduces pruritic complaints and increases patient compliance in the long run. For a more effective treatment period, it would be beneficial to use topical emollients alone or in combination with antihistaminic preparations in patients who have developed pruritic complaints.

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