Research Article / Araştırma Makalesi

Efficacy and Safety of Local Psoralen-UVA Treatment in Palmoplantar Dermatoses: A Single-Center Retrospective Study

Palmoplantar Dermatozlarda Lokal Psoralen-UVA Tedavisinin Etkinliği ve Güvenliği: Tek Merkezli Retrospektif Bir Çalışma

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Özet: Lokal PUVA palmoplantar dermatozlarda dirençli vakalarda kullanılan tedavilerden biridir. Bu çalışmada palmoplantar dermatozların tedavisinde lokal PUVA'nın etkinliğini ve güvenilirliğini değerlendirmeyi amaçladık. Palmoplantar dermatoz (palmoplantar psoriasis, kontakt dermatit, palmoplantar keratoderma, dishidrotik ekzema) tanısıyla lokal PUVA ile tedavi edilen toplam 115 hasta çalışmaya dahil edildi. Ortalama maksimum doz 4.83 ± 2.55 ve ortalama kümülatif UVA dozu 171.30 ± 176.77 idi. Tedavi yanıtı değerlendirildiğinde 58 (%74.35) hastada tam yanıt, 15 (%19.23) hastada kısmi yanıt alınırken, 5 (%6.41) hastada yanıt alınamadı. Gruplar arasında cinsiyet, yaş dağılımı, hastalık süresi, ortalama tedavi süresi, seans sayısı ve tedaviye yanıt açısından hastalıklar arasında anlamlı fark yoktu. En sık görülen yan etki eritemdi ve hastaların 16'sında (%13.9) görüldü. Sonuç olarak lokal PUVA tedavisi palmoplantar dermatozlarda topikal steroid ve sistemik tedavi ihtiyacını azaltan etkili ve güvenli bir tedavi seçeneğidir.
Anahtar Kelimeler: Fototerapi, PUVA, psoriasis, ekzema

Abstract: Local PUVA is one of the treatments used for resistant cases in palmoplantar dermatoses. In this study, we aimed to evaluate the efficacy and safety of local PUVA in the treatment of palmoplantar dermatoses. A total of 115 patients who were treated with local PUVA with the diagnosis of palmoplantar dermatosis (palmoplantar psoriasis, contact dermatitis, palmoplantar keratoderma, dyshidrotic eczema) were included in the study. The mean maximum single dose was 4.83 ± 2.55 and the mean cumulative UVA dose was 171.30 ± 176.77. Treatment response was evaluated in 78 (67.8%) of the patients; 37 (32.2%) patients were lost to follow up. When the treatment response was evaluated, 58 (74.35%) patients achieved a complete response; 15 (19.23%) patients achieved a partial response, and 5 (6.41%) patients had no response to the treatment. There was no significant difference between diseases in terms of gender and age distribution, disease duration, mean duration of treatment, number of sessions and response to treatment between groups. Erythema was the most common adverse effect and was observed in 16 (13.9%) of the patients. In conclusion, local PUVA treatment is an effective and safe treatment option in palmoplantar dermatoses that reduces the need for topical steroids and other systemic treatments.
Keywords: Phototherapy, PUVA, psoriasis, eczema

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1. Introduction

Some dermatoses are located specifically on the palmoplantar region and negatively affect the quality of life of patients. Some of these dermatoses are warts, eczema, keratoderma, psoriasis, hand-foot-mouth disease, piezogenic pedal papule, pityriasis rubra pilaris, and idiopathic palmoplantar hidradenitis. Palmoplantar psoriasis, eczema, and keratoderma are more common among them (1,2).

In the first-line treatment of palmoplantar dermatoses moisturizers, topical corticosteroids, calcipotriol, and salicylic acid are generally used. However, in many cases topical treatments can fail or side effects may develop. In these resistant cases, phototherapy or systemic treatments such as retinoids, methotrexate, cyclosporine, biological agents are needed (3). Phototherapy is one of the oldest treatment methods in dermatology practice. It is used in the treatment of a large number of dermatoses, such as psoriasis, atopic dermatitis, vitiligo, and mycosis fungoides. It has anti-proliferative, anti-inflammatory, immunosuppressive, and immunomodulatory effects. It can be applied in various ways such as ultraviolet (UV) A1, psoralen plus UVA (PUVA), narrow-band UVB, and targeted phototherapy (4, 5).

Local PUVA is one of the treatments used for resistant cases in palmoplantar dermatoses. It is considered as an effective safe treatment option; it does not have the side effects that may occur with oral psoralen intake (3,6). There are limited number of studies in the literature evaluating the efficacy and safety of local PUVA in palmoplantar dermatoses (2,3,7-9). In this study, we aimed to evaluate the efficacy and safety of local PUVA in the treatment of palmoplantar dermatoses.

2. Materials and Methods:

One hundred and fifteen patients who were treated with local PUVA with the diagnosis of palmoplantar dermatosis between 2008-2018 were evaluated retrospectively. Sociodemographic characteristics, diagnoses, duration of the disease, number of phototherapy sessions, concomitant treatments, response to treatment, and side effects were recorded. The study protocol was approved by Eskişehir Osmangazi University Ethics Committee.

Phototherapy protocol

The UVA irradiation was administered using a local UVA system (Daavlin Spectra, M series, 311/350 model UV device), three times weekly on alternate days. In all cases, an oil-in-water emulsion of 8-MOP 0.1% was applied to the affected areas 15 minutes before the application of UVA radiation. The initial dose was 0.25 or 0.50 J/cm ^{2} and then increased by 0.25 to 0.50 J/cm ^{2} for each successive treatment, as tolerated until the skin was clear or a maximum of 10 J/cm ^{2} was reached. All patients used topical emollients and 21 patients were treated with oral acitretin additionally. Patients were also warned to avoid using topical photosensitizing agents.

Evaluation of clinical response

The clinical response to therapy was determined by the decrease in the erythema, edema, infiltration, desquamation, hyperkeratinization, dyshidrosis, fissures, and pustules. The regression of all findings and complaints of more than 75% was evaluated as a "complete response". An improvement between 25% and 75% in the clinical findings was considered a "partial response", and less than 25% was considered an "no response". The time at which the frequency of topical PUVA administration was reduced from three times weekly to twice weekly was designated as the point of maximal response.

Statistical analysis

Continuous data are defined as mean ± standard deviation (SD), and median (Q1-Q3). Categorical data are given as frequency and percentage (%). Compatibility with normal distribution was tested with the Shapiro-Wilk test. In analyzing categorical data, the Pearson exact (Exact) Chi-Square test was used. SPSS 21.0 package program was used in the application of the analysis. The statistical significance level was accepted as a $p < 0.05$ criterion value.

3. Results

A total of 115 patients who were treated with local PUVA between 2008-2018 with the diagnosis of palmoplantar dermatosis were included in this study. Sixty-nine (60%) of the patients were female and 46 (40%) were male. The mean age of the patients was 47.66 ± 14.20 (10-74) years. The mean disease duration was 5.76 ± 9.17 (3 months-50 years) years. When patients are evaluated clinically and histopathologically; 65 (56.5%) of the patients were palmoplantar psoriasis (PPP), 39 (33.9%) of contact dermatitis (CD), 7 (6%) of palmoplantar keratoderma (PPK), 3 (2.6%) of dyshidrotic eczema (DE), 1 (0.9%) of pityriasis rubra pilaris (PRP). Of the patients who had phototherapy, 54 (47%) patients had palmoplantar involvement, 42 (36.5%) patients had only palmar involvement, and 19 (16.5%) patients had only plantar involvement. When the previous treatments of the patients were evaluated; all patients (100%) had received topical treatments including emollients, corticosteroids, and calcineurin inhibitors; 3 (2.61%) patients had received phototherapy, 28 (24.35%) patients had received systemic treatments including corticosteroid, acitretin, methotrexate, cyclosporine, and adalimumab. During local PUVA treatment, all patients were given topical moisturizers and intermittently topical corticosteroids. Oral acitretin treatment was added to 21 (18.26%) of the patients to increase the effectiveness of the treatment (Table 1).

The mean maximum single dose was 4.83 ± 2.55 J/cm^2 and the mean cumulative UVA dose was 171.30 ± 176.77 J/cm^2. Treatment response was evaluated in 78 (67.8%) of the patients. Four patients discontinued the treatment on their requests, and 23 patients were lost to follow-up of the treatment. The treatment was discontinued due to adverse effects in 13 patients, although a partial response was obtained from 3 of them. When the treatment response was evaluated, 58 (74.35%) patients received a complete response; 15 (19.23%) patients received a partial response and, 5 (6.41%) patients received no response to the treatment (Table 2).

When the response to treatment was compared among the diseases, there was no significant difference between diseases in terms of gender and age distribution, disease duration, mean duration of treatment, and number of sessions. Best response was obtained from CD patients; 66.7% of them had complete response. This was followed by PPP with 63.1%, PPK with 57.2% and DE with 33.3%. PRP was not included in this assessment since there was only one patient. However, there was no statistically significant difference between the diseases in terms of response to treatment (complete and partial response). There was a significant difference between diseases in terms of maximum single dose and cumulative doses. Maximum single dose and cumulative UVA doses were highest in PPK patients (Table 3).

Of the 21 patients whose acitretin was added to the treatment, 16 were PPP, 4 were CD and 1 was PPK. It was observed that the response to the treatment increased and a complete response was obtained in 11 of the patients. Treatment was discontinued in 4 of them due to side effects, 5 of them lost to follow-up of the treatment and 1 of them discontinued the treatment on his request.

Adverse effects were observed in 16 (13.9%) of the patients. Erythema was the most common adverse effect and was seen in 16 (13.9%) of the patients. In addition, bullae, localized edema, and hyperpigmentation were detected in 2 patients for each (1.7%). In 13 of the 16 patients, treatment was discontinued due to side effects. While 3 of the patients whose treatment was discontinued due to side effects responded to the treatment; in the remaining 10 patients, the treatment had to be discontinued before the response to the treatment could be evaluated.

Table 1. Demographic and clinical features of patients

		n (%)
Sex	Female	69 (60%)
	Male	46 (40%)
		Mean ± SD (min-max)
Age (year)		47.66 ± 14.20 (10-74)
Disease duration (year)		5.76 ± 9.17 (0.25-50)
		n (%)
Diagnosis	Palmoplantar psoriasis	65 (56.5%)
	Contact dermatitis	39 (33.9%)
	Palmoplantar keratoderma	7 (6.1%)
	Dishidrotic eczema	3 (2.6%)
	Pityriasis rubra pilaris	1 (0.9%)
Involvement	Palmar	42 (36.5%)
	Plantar	19 (16.5%)
	Palmoplantar	54 (47%)
Previous treatments	Topical	100 (100%)
	Phototherapy	3 (2.61%)
	Systemic treatment	28 (24.35%)
Current treatments	Topical	100 (100%)
	Systemic treatment	21 (18.26%)

Table 2. Treatment features and response rates of the patients

		Mean ± SD (min-max)
Treatment duration (month)		5.02 ± 5.07 (0.25-25)
Number of treatments		41.93 ± 38.43 (1-197)
Maximum single dose (J/cm^2)		4.83 ± 2.55 (0.25-10)
Cumulative UVA dose (J/cm^2)		171.30 ± 176.77 (0.25-844)
		n (%)
Treatment response	**No response**	5 (6.41%)
	Partial response	15 (19.23%)
	Complete response	58 (74.35%)

Table 3. Comparison of demographics, treatment characteristics and response rates according to diseases

	PPP	**CD**	**PPK**	**DE**	**PRP**	**p***	**Multiple comparison p****
Sex, n (%)							
Female	44 (%67.69)	18 (%46.15)	4 (%57.14)	2 (%66.66)	1 (%100)	0.243	
Male	21 (%32.30)	21 (%53.84)	3 (%42.85)	1 (%33.33)	0		
Age (mean ± SD)	48.72 ± 13.49	46.30 ± 13.23	47.00 ± 23.87	51.33 ± 16.92	25	0.823	

Disease duration (year) (mean ± SD)	6.17 ± 10.22	4.58 ± 7.29	6.50 ± 8.02	10.37 ± 13.61	-	0.673	
Treatment duration (month) (mean ± SD)	5.18 ± 5.95	4.74 ± 3.59	5.57 ± 3.74	4.66 ± 5.92	2.5	0.965	
Number of sessions (mean ± SD)	40.63 ± 40.33	42.56 ± 37.16	53.28 ± 33.64	39.33 ± 43.92	31	0.876	
Maximum single dose (median, interquartile range) (mean ± SD)	3.50 (3.50-7.00) 5.03 ± 2.55 (1)	3.50 (3.50-3.50) 4.03 ±2.31 (2)	7.50 (5.75-9.00) 7.07 ±2.26 (3)	3.50 (3.25-4.75) 4.17 ± 1.61 (4)	10.0 (10.0-10.0) 10.0 ± -	0.016	2-3:0.003 1-3:0.037 1-2:0.045
Cumulative UVA dose (median, interquartile range) (mean ± SD)	101 (22.5-7.00) 164 ±172 (1)	99.8 (38.5-221) 147 ± 141 (2)	298 (161-491) 353 ± 284 (3)	33.3 (26.4-287) 198 ± 297 (4)	215 (215-215) 215 ± -	0.039	2-3:0.004 1-3:0.007
Treatment response **Complete** **Partial** **None**	28 (%43,1) 13 (%20) 1 (%1,5)	26 (%66,7) - 3 (%7,7)	3 (%42,9) 1 (%14,3) 1 (%14,3)	1 (%33,3) - -	1 (%100) - 0	0.072	

**One-way analysis of variance **Tukey multiple comparison test*
PPP:palmoplantar psoriasis
PPK:palmoplantar keratoderma
CD:contact dermatitis
DE:dyshidrotic eczema
PRP:pityriasis rubra pilaris

4. Discussion

Some dermatoses specifically affect the palmoplantar region. Although topical treatments such as emollients, corticosteroids, and calcipotriol are used in the treatment of palmoplantar dermatoses; these treatments sometimes may not be sufficient and resistance can develop. Systemic treatments such as retinoids, methotrexate, cyclosporine, and phototherapy can be needed (1-3).

Local PUVA is one of the treatments used for resistant cases in palmoplantar dermatoses. It is generally used to treat patients whose disease cannot be controlled with topical steroids. It is also an alternative or additional treatment method for patients who are not suitable or resistant to systemic therapy. It is a treatment method that is well tolerated, reliable, and inexpensive (3,10,11).

PUVA photochemotherapy can be applied after administration of systemic (8-MOP or 5-MOP) or topical (8-MOP) psoralen. It shows its effects by inducing a delayed erythemal reaction peaking 96 hours after irradiation of psoralen-sensitized skin. In palmoplantar local PUVA, treatment is started with 40% of MFD or 0.5-1 J/cm ^{2} UVA, 15 minutes after the photo-stabilizer 8-MOP is applied to the area to be treated. Treatment is continued with an increase in the dose of 0.5-2 J / cm ^{2}. Topical PUVA is safer than systemic PUVA since it avoids short and long-term side effects of oral psoralen (2,4,11).

In our study, we found that the 74.35% of the patients received a complete response; 19.23% of the patients received a partial response and, 6.41% of the patients received

no response to the treatment. There are several studies in the literature evaluating the efficacy of local PUVA in palmoplantar dermatoses; the response rates of these studies appear to be similar to our study (2,3,7-9). Davis et al. evaluated the efficacy of local PUVA on palmoplantar dermatoses in 35 patients. Ten of the patients were diagnosed with psoriasis vulgaris, 8 with pustular psoriasis, 5 with dyshidrotic eczema, and 12 with other types of eczema. They observed that 40% of the patients had complete remission, 40% had clinically significant improvement and 6% had no response (7). Riad et al. retrospectively evaluated 125 patients who were treated with local PUVA with the diagnosis of palmoplantar dermatosis. They divided the patients into three groups (hyperkeratotic, pustular, and exudative dermatitis) according to their dominant clinical appearance. It was seen that 69% of the patients received a good response (complete or partial response) (3). Carascosa et al. also reported 48 palmoplantar psoriasis patients treated with local PUVA treatment. They reported that the treatment was effective in 63% of patients (9).

In a retrospective study conducted in Austria, Bretterklieber et al. investigated the bath PUVA treatment results of 79 chronic palmoplantar dermatosis patients (palmoplantar psoriasis, dyshidrotic eczema, hyperkeratotic-ragadiform eczema). They reported that 14 patients (18%) completely recovered and 37 patients (47%) clinically improved. They also evaluated the long-term effects of the treatment with a questionnaire after an average of 4.3 years. Among the responders, 36% of the patients reported that their lesions improved, the frequency and severity of itching and redness decreased, 29% continued complete remission, 79% decreased topical steroid use and 67% increased their quality of life. They showed that bath PUVA positively affects the course of the disease in resistant and chronic palmoplantar dermatoses both in the short and long term (8). Although there are similarities between this study and our study in terms of getting significant response rates, we do not have any data that can be evaluated in terms of the long-term results of treatment.

We also evaluated the response to treatment among the diseases. Although, there was no statistically significant difference between the diseases in terms of response to treatment; the best response was obtained from CD patients. Maximum single dose and cumulative UVA doses were highest in PPK patients. The higher maximum single dose and cumulative UVA doses detected in PPK patients may be related to the thicker lesions compared to other dermatoses. In literature exudative dermatitis and hyperkeratotic rhagadiform eczema patients had been found to have the highest treatment responses in two different studies (3,8).

The combination of PUVA and acitretin shows a synergistic effect and is used as an effective treatment option in patients who are resistant to phototherapy (12). In the study conducted by Carrascosa et al, acitretin was added to the treatment of patients who did not respond to the local PUVA treatment and it was found that the response to the treatment increased in these patients (9). In our study, similarly, the response to the treatment increased in 11 of 21 patients who had added acitretin to their treatment.

PUVA treatment has several acute and chronic side effects. PUVA erythema can be seen in 10-32 % of the patients. The most common side effect of topical PUVA is phototoxicity, hence, photoprotection is important after sessions. Topical psoralen can also cause pigmentation (4). In our study, adverse effects were observed in 13.9% of the patients. Erythema was the most common adverse effect and was seen in 13.9% of patients. Bullae, localized edema, and hyperpigmentation were detected in 1.7% of the patients. In a retrospective study conducted in Israel, the most common adverse effect was found to be transient superficial skin burns in 8 % of the patients (3). Davis et al. reported that mild localized erythema was seen in 16 (46%) patients; among these patients, 1 patient developed blisters and 1 had solar urticaria (7). Similarly, Carrascosa et al. reported adverse effects in 25% of the patients; mild erythema was present in 18% of cases as the most common adverse effect (9). In a study evaluating the response of chronic palmoplantar dermatoses to bath PUVA

therapy, in 5.06% of the patients, severe phototoxic reactions were reported as adverse effects (8).

Adverse effects sometimes can cause cessation of the phototherapy. In our study, treatment was discontinued due to side effects in 13 of the 16 patients. Riad et al. reported that the most common adverse effect was transient superficial skin burns in 8% of the patients and treatment was discontinued due to a second-degree burn in 1 patient, acute paronychia in 1 patient, and palmar hyperpigmentation in 2 patients (3). In the study conducted by Carrascose et al., although the adverse effects were reported in 25% of the patients; treatment was discontinued in only one patient (9).

Our study has several limitations. We evaluated patient data retrospectively. Response to treatment was evaluated on a monthly examination by different dermatologists. Although examinations were performed by experienced physicians, examination findings and records can vary according to the dermatologist. Another limitation is there is no data on the follow-up of patients and relapse rates.

In conclusion, local PUVA treatment is an effective and safe treatment option in palmoplantar dermatoses that reduces the need for topical steroids. Further prospective and large-scale studies are warranted to elucidate our result.

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Toros University (Decision no: 10, Date: 3.7.2018).
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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