Combination Topical PUVAsol with Methotrexate Versus Methotrexate in the Treatment of Palmoplantar Psoriasis

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ABSTRACT

Background

Non-pustular palmoplantar psoriasis (PPP) is chronic and disabling dermatosis. Topical psoralen and solar ultraviolet - A therapy (PUVAsol) is efficacious and safe therapy in psoriasis management.

Objective

To study the efficacy and adverse clinical effect profile of topical PUVAsol along with methotrexate in PPP.

Method

This is a prospective, randomized, clinical trial conducted among 54 patients with moderate to severe PPP. Patients were grouped into two categories. Group I was treated with weekly oral methotrexate only while group II had additional soak PUVAsol therapy twice weekly for a total of three months. Modified palmoplantar psoriasis area severity index (mPPPASI) score was used for quantification of severity. Patients were followed up monthly for the efficacy and adverse clinical event profile for 3 months; additionally patients were followed up monthly for next three months for assessment of relapse.

Result

The mean age of patients with PPP was found to be 38.7 ± 13 years and male: female ratio was 1.1:1. In comparison to group I patients, statistically significant improvement was observed among group II patients in the third month follow up (p= 0.039). Fifteen patients (35%) achieved mPPPASI 75 during the treatment period. No significant difference was noted among the mPPPASI score during relapse assessment. Eleven (29%) patients had evidence of relapse (mPPPASI more than 25% of baseline) during follow up period. No statistically significant adverse clinical events were noted.

Conclusion

Topical PUVAsol is an efficacious, safe and cost effective modality in moderate to severe PPP. It could be employed in rotational or maintenance therapy of psoriasis.

KEY WORDS

Palm, psoriasis, PUVA therapy

INTRODUCTION

Palmoplantar psoriasis (PPP) is a common acquired keratoderma.[1] It is a chronic idiopathic entity localized to palms and soles and is characterized by well to ill-defined scaly plaques with erythema, fissuring and scaling.[2] The entity is further distinct from another similar variant of psoriasis localized to palms and soles, palmoplantar pustulosis. PPP is often met distinctly and may be associated with other forms of psoriasis. We are unaware why this form of psoriasis is localized to the palms or soles. Repeated trauma resulting in koebnerization could cause recurrence. It has significant negative impact on quality of life and frequently leads to persistent pruritus or pain.

Topical agents, alone offer limited benefit in the management of PPP because of lower penetration. Psoralen and ultraviolet irradiation (PUVA) therapy is a well-established therapeutic modality in the treatment of psoriasis.[3] Systemically administered PUVA therapy poses problems with early and late complications. Psoralen along with solar irradiation as the source of UVA (PUVAsol) can be employed among those who cannot visit hospital frequently or with economic constraints.[4] Soak PUVAsol, paint PUVAsol and bath PUVAsol are the topical forms commonly employed to reduce the systemic effects.

PPP has received little attention in modern literature. The prevalence of palmoplantar lesions in psoriasis has been reported to be 17.4% among 3065 psoriasis cases.[5] Population studies have revealed equal gender prevalence and the disease can occur at any ages. The present study aims to study the efficacy and adverse clinical effects of soak PUVAsol in moderate to severe PPP.

METHODS

This is a prospective, randomized, clinical trial conducted among 54 patients. Prior ethical consideration was taken (IRC no. 136/16; IRC-KUSMS). Envelope method was employed for categorizing the participants into two groups; group I and group II. The study was conducted for a period of one and half year (August 2015 – February 2017).

Patients presenting with clinical evidence of moderate to severe plaque type palmo-plantar psoriasis (non-pustular variant) attending the outpatient department of dermatology department, Dhulikhel hospital, Kavre, Nepal were enrolled in the study. A written informed consent was obtained from all participants regarding the use of the data for publication purpose. The modified Palmoplantar Psoriasis Area Severity Index (mPPPASI) for palms and soles was used to clinical scoring of the plaques (Table 1).[6] Plaques involving at least 50% of a single palmar or plantar surface were considered to be moderate to severe grade PPP.[7] Only moderate to severe plaque PPP were selected for systemic therapy; mild disease was managed with topical agents only. Age of the patient between 16 to 65 years

Table 1. Modified Palmoplantar Psoriasis Area Severity Index (mPPPASI) for clinical assessment of palmoplantar psoriasis. Clinical severity: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. Extent of involvement 0=none, 1≤10%, 2=10 to<30%, 3=30 to<50%, 4=50 to<70%, 5=70–90% and 6=90–100%

Clinical Severity	Right Palm	Left Palm	Right Sole	Left Sole
1. Erythema	0-4	0-4	0-4	0-4
2. Infiltration	0-4	0-4	0-4	0-4
3. Desquamation	0-4	0-4	0-4	0-4
Extent of Involvement	0-6	0-6	0-6	0-6
Total Extent	Max:6X0.2	Max:6X0.2	Max:6X0.3	Max:6X0.3
Max score = Total clinical score X Total Extent	A	B	C	D
Total mPPPASI=A+B+C+D				

and patients who could come for follow up were the other inclusion criteria. A wash out period of 2 weeks for topical agents and 4 weeks for systemic agents was permitted for any previous treatment. Patients with history of alcohol consumption, uncontrolled diabetes mellitus, pregnancy, lactation, deranged hemogram, liver or renal function test were excluded from the study.

Complete hemogram, random blood sugar, liver and renal function test, HIV 1 and 2 serology and chest radiograph to exclude tuberculosis were the prior investigations performed. Figure 1 represents a biopsy of the palmar psoriasis lesion from one of our patient. Women of child bearing age were advised for contraceptive use. Clinical assessment was done monthly till 3 months. Complete hemogram, liver function test and random blood sugar were repeated at 4 weeks and 12 weeks. Relapse assessment was done monthly for next 3 months. As a concomitant therapy; topical petrolatum, tablet folic acid 5 mg the as a part of methotrexate therapy and tablet levocetirizine 5 mg were only allowed.

Patients of group I (N = 24) were treated with oral methotrexate 0.25 mg/kg given once weekly for 3 months (maximum 25 mg per week). No doses alteration was allowed after the initial dosing. Patients of group II (N = 30) were treated with oral methotrexate in a similar fashion. Additionally soak PUVAsol was prescribed two times a week (eg: Wednesday and Saturday). Two 10 mg tablets of 8-methoxypsoralen (8-MOP) was dissolved in 6 litres of water making a concentration of 0.03% 8-MOP.[8] The patients were then advised to soak hands and feet for next 20 minutes. Then patients had to immediately expose the soaked parts to natural sunlight. As recommended by Sornakumar L et al. the exposure time was initially set to 5 minutes which was increased by 1 minute weekly up to a maximum of 15 minutes.[9] The time advised for sun exposure was between 15:00 to 16:00 hrs.[10] Change in mPPPASI score at 12 weeks or mPPPASI90 whichever was earlier was considered to be the primary end point.

Treatment related adverse effect was the secondary end point of the study. During relapse assessment, increment in the mPPPASI score of more than 25% from the mPPPASI at 12 weeks was considered to be a relapse case.

For all continuous variables, arithmetic mean, standard deviation and range were calculated. For categorical variables, frequencies were calculated. The Mann-Whitney test and Chi-square tests were used to evaluate for the statistical significance of differences observed between groups for continuous and categorical variables respectively. A 5% margin of error (p-value < 0.05) was considered to be significant statistically. For all statistical analyses, the Statistical Package for Social Sciences (SPSS) version 16.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

Table 2 compares the baseline characteristics of the study group. No significant difference was noted among the study groups. The overall male: female ratio of PPP was 1.1: 1. The mean age was 38.7 ± 13 years (range: 20-72 years). The average duration of disease was 10.07 ± 11.83 months (range: 1-48 months). Nineteen patients (35.2%) had evidence of psoriatic lesions elsewhere. Family history was reported by 3 (5.5%) patients only. Similarly 12 (22.3%) patients had involvement of nails and 9 (16.7%) patients had history of arthralgia. Figure 2 and 3 represents the improvement of patients of group I and II respectively.

Table 2. Comparison of the baseline characteristics among study groups.

Characteristics		Group I (N=24)	Group II (N=30)	p-value
Age	Years	37.20 ± 13.27	39.9 ± 12.45	0.44
Gender	Male	15 (62.5%)	13 (43.3%)	0.16
	Female	9 (37.5%)	17 (56.7%)	
Disease duration	Months	12.04 ± 13.17	8.5 ± 10.6	0.27
Prior treatment	Yes	19 (79.2%)	26 (86.6%)	0.46
	No	5 (20.8%)	4 (13.4%)	
Involvement of other sites	Yes	7 (29.2)	12 (40%)	0.40
	No	17 (70.8)	18 (60%)	
Family History	Yes	1 (4.1)	2 (6.7%)	0.69
	No	23 (95.9%)	28 (93.3%)	
Nail Involvement	Yes	3 (25%)	9(20%)	0.12
	No	21 (75%)	21 (80%)	
Arthralgia	Yes	5 (20.8%)	4 (13.4%)	0.46
	No	19 (79.2%)	26 (86.6%)	
mPPPASI Score		14 ± 9.8	17.15 ± 8.6	0.21
Methotrexate dose	Per week	12.125 ± 3.65	11.875 ± 3.79	0.80

A total of 11 patients lost follow up (7 from group I and 4 from group II) for reasons unrelated to the study. Table 3 compares the mPPPASI scores among two groups during the first 3 months of treatment. In comparison to group I patients statistically significant improvement was observed among group II patients at the end of 3 months (p= 0.039).

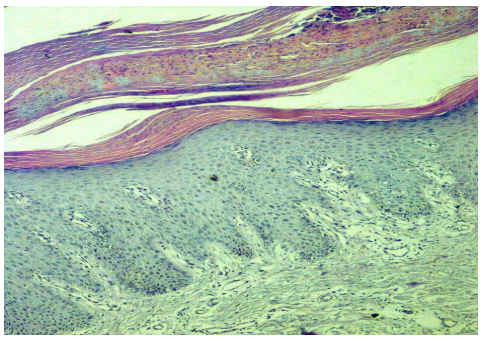

Figure 1. Histology of palmoplantar psoriasis demonstrates orthokeratosis, parakeratosis, focal collection of neutrophils (right upper end), thinning of granular layer, psoriasisform epidermal hyperplasia and clubbing of rete ridges.

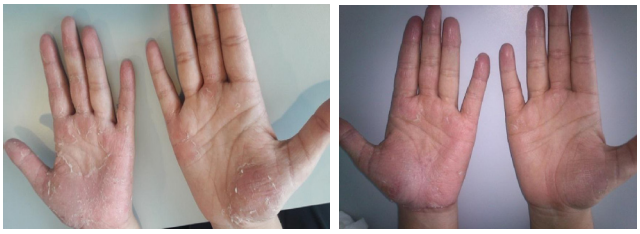

Figure 2. Improvement in one of group I patient after 3 months of therapy (left: before therapy and right: after therapy)

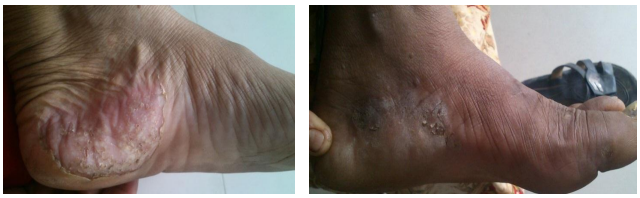

Figure 3. Improvement in one of group II patient after 3 months of therapy (left: before therapy and right: after therapy)

Table 3. Comparison of mPPPASI score during the first three months of treatment.

Weeks	mPPPASI (Group I)	No. of patients (Group I)	mPPPASI (Group II)	No. of patients (Group II)	p-value
0	14 ± 9.8	24	17.15 ± 8.6	30	0.21
4	11.55 ± 6.52	20	12.7 ± 7.15	28	0.55
8	11.9 ± 6.86	19	9.46 ± 4.14	27	0.09
12	8.9 ± 6.73	17	5.8 ± 2.64	26	0.039

Table 4 compares the mPPPASI scores between the study groups during period of relapse assessment. No significant difference was noted among the mPPPASI score during the relapse assessment period. Figure 4 compares the mPPPASI scores during the entire study period. A total of 15 patients (35%) had more than 75% improvement in the mPPPASI score at the end of 3 months (figure 5).

Table 4. Comparison of mPPPASI score during the period of relapse assessment

Weeks	mPPPASI (Group I)	No. of patients (Group I)	mPPPASI (Group II)	No. of patients (Group II)	p-value
12	8.9 ± 6.73	17	5.8 ± 2.64	26	0.039
16	6.71 ± 5.52	17	4.96 ± 3	25	0.19
20	5.2 ± 3.16	16	5.81 ± 4.22	23	0.62
24	7.83 ± 4.67	15	8.28 ± 5.7	23	0.77

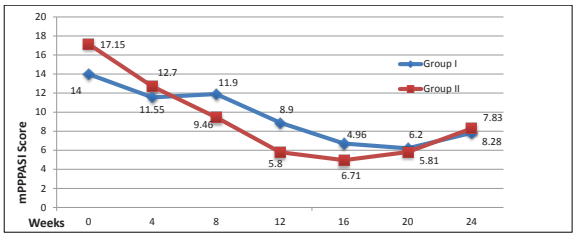

Figure 4. Comparison between the mean mPPPASI scores during the entire study period.

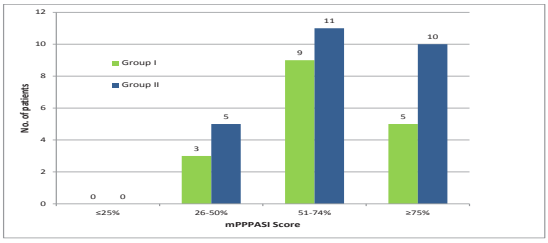

Figure 5. mPPPASI response to treatment.

DISCUSSION

The non-pustular variant of psoriasis involving the palms and soles is a common condition and is therapeutically challenging.[1,2,5] There are no consensus guidelines for treatment. Topical agents have been widely used for the management. Psoralen and UVA therapy is a well-established modality in the treatment of psoriasis.[3] Topical PUVA therapy is safer and more convenient as compared to oral psoralen.[4] They offer a number of advantages over systemic PUVA including better compliance, insignificant nausea, ocular or central nervous system effects and lower cumulative UVA dose. Systemic conventional agents too did not demonstrate optimal cure in plaque and pustular palmoplantar psoriasis.[6] Use of biological agents have been attempted.

The disease causes significant quality-of-life concerns.[7] The hyperkeratotic plaque type variant is the commonest form. Hand foot eczema, palmoplantar variant of lichen planus, lichen simplex and focal keratoderma are some of the common differentials. However, a definite morphology of well-defined fissured, scaly plaques predominantly involving the instep area, involvement of knuckle area, psoriatic lesions elsewhere, nail changes and family history could aid in the diagnosis. Further biopsy could help in the diagnosis. Aydin O et al. had compared 17 biopsy samples of non-pustular palmoplantar psoriasis with 25 All patients consumed the drugs for 3 months; there was no any untimely termination. There was no statistically significant difference between the total cumulative dose of methotrexate among the study groups at the end of 3 months (p=0.67). Eleven out of 38 (29%) patients had evidence of relapse (mPPPASI more than 25% of baseline) in the follow up period (table 5). Table 6 enlists the reported and noted adverse clinical events. No untimely termination of therapy had to be considered because of adverse clinical events.

Table 5. Relapse assessment of patients during follow up

Weeks	Group I	Group II	p-value
16 weeks	0	0	-
20 weeks	3 (18.75%)	4 (17.4%)	0.91
24 weeks	5 (33.3%)	6 (26%)	0.63

Table 6. Adverse clinical effects noted among study groups.

Adverse clinical effect	Group I (N=17)	Group II (N=26)	p-value
Dyspepsia	2	3	0.98
Deranged LFT	3	3	0.57
Mucositis	0	1	0.41
Headache	1	0	0.21
Anemia	0	1	0.41
Leucopenia	2	2	0.65
Burning Sensation over lesions	0	0	-
Erythema over lesions	0	0	-

samples of eczematous dermatitis.[11] The results suggested that apart from vertical alterations of parakeratosis and orthokeratosis, there were no any statistical difference in histologic features, suggesting that the histological differentiation is equally challenging.

Among very limited studies relating non-pustular variant of palmoplantar psoriasis, the present study is a unique of its kind. No literature could be found for appropriate comparison of results. Psoriasis involving more than 10% body surface area, disabling disease of palms or soles and severe scalp involvement are considered to be severe form of psoriasis and has been recommended to be treated with systemic agents.[12] Studies from early 1980s demonstrated effectiveness of acitretin or etritinate in psoriasis of palm and soles.[13] PUVA has shown moderate efficacy in the treatment of psoriasis yielding a Physician Global Assessment (PGA) score 0 or 1 in 62.5 % PPP patients.[14] Topical PUVA (bath, soak and cream PUVA) further offers a wide range of advantages. Cooper EJ et al. have demonstrated that bath PUVA decreases the cumulative effects of Oral PUVA therapy by 2 to 6 fold.[15] In general psoriasis, 60 to 80% clearance of lesion have been reported with PUVA therapy. Further it is considered to be an agent that prolongs the remission period of

psoriasis with minimal adverse effects.[12] Berneburg M et al. studied 74 patients of psoriasis vulgaris comparing bath PUVA and systemic PUVA.[16] There was 73.8% median PASI improvement with bath PUVA than 62% with systemic PUVA in 6 weeks. Similarly bath PUVA was found to be more efficacious than narrow band ultraviolet-B therapy yielding an improvement of 85.4% median PASI and 58.7% median PASI respectively.[17]

In the present study, the disease appears to involve middle aged population, with equal gender prevalence. The average duration of disease is quite long which reflects the morbidity of the disease. No precipitating agents were reported. However, there is a significant history (83.3%) of prior treatment with multiple agents in the past. Table 3 has shown a statistically significant improvement in group treated with oral methotrexate and topical PUVAsol in the third month follow up. A recent published meta-analysis on the use of methotrexate on psoriasis has confirmed methotrexate to be a highly efficacious and safe agent in psoriasis including its palmoplantar variant.[18] No statistical significant difference was observed among the study groups during the relapse assessment period. However a significant proportion of patients (35%) had relapse with increase in mPPPASI score of more than 25%. This further points the gravity of the disease. Inadequate therapy, lack of a maintenance therapy, repeated koebnerization could be the responsible factors. Topical PUVAsol could be easily used in this period which could decrease this proportion. Finally the therapy appeared to be safe, cost effective and home based.

This study is a single center study with limited sample size. Observer bias and lack of blinding could be the potential limitations. However, a larger scale study could further acknowledge the potential of topical PUVAsol therapy.

CONCLUSION

The present study has demonstrated better efficacy of soak PUVAsol along with methotrexate as compared to a methotrexate monotherapy. Soak PUVAsol appears to be a safe, promising and cost effective adjuvant in the treatment of moderate to severe PPP. Further it may also prolong the remission period of such recalcitrant disease. This property could be employed in rotational or maintenance therapy of the disease.

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