

## A COMPARATIVE STUDY OF EFFICACY OF HAND FOOT PSORALEN-ULTRAVIOLET A THERAPY VERSUS SEQUENTIAL THERAPY OF TOPICAL CLOBETASOL PROPIONATE WITH TOPICAL CALCIPOTRIOL OINTMENT IN PALMOPLANTAR PSORIASIS

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### ABSTRACT

#### BACKGROUND

Palmoplantar psoriasis that accounts for 3% - 4% of all psoriasis cases produces significant functional and social disability. Reduction of pain and improvement in the function of limbs are more important therapeutic goals than complete clearance. This prospective, randomised, controlled study was conducted in Coimbatore Medical College, a tertiary care centre in Tamilnadu.

We conducted the study on 50 patients from September 2011 to November 2012.

Aims and Objectives- The aims and objectives of the study was to compare the efficacy, to observe the reduction in percentage of psoriasis area and severity index score (PASI SCORE) above 50% and to observe the adverse effects in first 6 months and duration of remission in the next 6 months.

#### MATERIALS AND METHODS

We divided all patients into two groups- Who had taken phototherapy was Group A and Who had taken sequential therapy was Group B. SPSS (Statistical Package for Social Sciences) Ver. 20 was used to perform statistical analysis. T-test for equality of means was conducted to compare the two groups.

#### RESULTS

In Group A 81.8% of the patients and in Group B 91.6% of the patients showed more than 50% reduction of PASI score. The initial PASI score and percentage reduction was compared with 8<sup>th</sup> week score, 16<sup>th</sup> week and 24<sup>th</sup> week of treatment of both groups. The 't' test result of percentage reduction showed significant difference at the end of 8<sup>th</sup> week ('t' value 2.618, P < 0.01), 16<sup>th</sup> week ('t' value= 3.288, P < 0.05), and 24<sup>th</sup> week ('t' value= 3.324, P < 0.05).

#### CONCLUSION

Efficacy of sequential manner is better than topical PUVA. Patients on PUVA therapy group developed more adverse effects and the duration of remission maintenance was short.

#### KEYWORDS

Palmoplantar Psoriasis, PASI Score, PUVA, Sequential Therapy, Calcipotriol Ointment.

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#### BACKGROUND

Palmoplantar psoriasis produces significant functional and social disability.<sup>[1]</sup> Psoriasis Area Severity Index score was first described in 1978. The severity of psoriasis is assessed by PASI score. According to Carlin et al, PASI score reduction of 50% corresponds to a clinically significant endpoint in assessment of palmoplantar psoriasis.<sup>[2-5]</sup>

#### Clinical Variants of Palmoplantar Psoriasis according to Nobel Classification<sup>[6]</sup>

1. Sharply demarcated erythematous patches and covered by adherent psoriatic scales.

2. Diffuse mild hyperkeratosis with scales.
3. Very thick hyperkeratotic layer resembling hereditary type of palmoplantar keratoderma.
4. Diffuse erythema.

#### Multi-Modality Therapeutic Strategies

Topically, treatment may be given in different ways like combination therapy, rotational therapy<sup>[7]</sup> and sequential therapy.<sup>[8]</sup> Our study was based on sequential therapy. It has three steps. They are clearing or quick phase, transitional phase and maintenance phase.

#### Topical Calcipotriol and Clobetasol Propionate Ointment

The effect of calcipotriol ointment is slower than topical corticosteroid. For rapid activity, calcipotriol is combined with steroid. Calcipotriol is a synthetic vitamin D derivative, which acts by binding to vitamin D receptor.

#### PUVA Therapy

FDA gave approval for PUVA therapy in 1982. The mechanism of action has three steps.<sup>[9,10]</sup> Psoralen binds with DNA double strand before irradiation. After UVA exposure bind with pyrimidine base to form cyclobutane monoadducts

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(MA). After absorbing a second photon, psoralen-DNA crosslink is formed by 4MA. The reactive oxygen species are formed by this crosslink; it damages cell membrane and inhibits DNA replication which causes cell cycle arrest. So, there is alteration of cytokine and cytokine receptor, which causes apoptosis of lymphocytes and keratinocytes.

**Soak PUVA**

To avoid the side effects of systemic PUVA, topical PUVA is useful. Hand and/or foot soak in 8 Methoxypsoralen 2.5 mg/L for 15 minutes followed by UVA irradiation weekly two or three times is effective; 1 mL contains 5 mg of 8 MOP.<sup>[11]</sup> In the literature, there is no specific data regarding the initial dose of UVA irradiation for palmoplantar psoriasis. It depends upon the severity of the disease and higher UVA doses are recommended to treat the thicker skin of palmoplantar psoriasis.

Moisturisation is needed before phototherapy in elderly populations, because phototherapy itself can aggravate xerosis and pruritus.<sup>[12]</sup> The emollients will decrease the total UVA dose required to clear psoriasis.<sup>[13,14]</sup>

PUVA therapy has three phases. They are clearing, maintenance and tapering phase. In clearing phase, radiation is given up to 90% clearance of lesions. In maintenance phase, the irradiation is maintained until clearance of remaining lesions. Then taper the radiation dose weekly once, two weeks once, three weeks once, four weeks once and then stop the treatment.

**MATERIALS AND METHODS**

We conducted prospective, randomised, controlled study by convenient sampling method. We took 50 patients as sample size who attended Outpatient Department of Dermatology in Coimbatore Medical College Hospital from September 2011 to November 2012. The treatment duration was six months and the followup period was six months. The results were tabulated and appropriate tests of significance were worked up. SPSS (Statistical Package for Social Sciences) Ver. 20 was used to perform statistical analysis. T-test for equality of means was conducted to compare the two groups.

**Inclusion Criteria**

Patients aged between 18 - 60 years with written consent and who had not used other forms of topical treatment during the previous four weeks.

**Exclusion Criteria**

Age less than 18 years and who had not given consent. Pregnant and lactating women were also excluded.

Patients were evaluated with complete history, dermatological and systemic examination. Biopsy was also done in doubtful cases.

**Treatment Protocol**

The 50 patients were randomly arranged and by using computer generated random table. They were divided into Group A and Group B and each constituted of 25 patients.

**Group A**

25 patients were included in this group; 0.5 mL of 1% 8-Methoxypsoralen lotion was diluted in two litres of water. Hands and feet were soaked in that solution for 15 minutes.

Then patient was advised to mop both palms and soles and to apply emollients followed by UVA exposure, 30 minutes after soak. Initial dose of UVA is 1 J/cm<sup>2</sup> with increment dose of 0.5 J/cm<sup>2</sup> on every visit with a frequency of two times per week for six months. Eyes were protected by using goggles during treatment.

**Group B**

25 patients were included in this group. Sequential therapy of 0.05% Clobetasol propionate ointment with 0.005% Calcipotriol ointment was given for six months.

**Phase 1**

Combination of clobetasol propionate and calcipotriol ointment once a day application in the first month.

**Phase 2**

Clobetasol propionate for weekends and calcipotriol for week days once a day application in the second and third month.

**Phase 3**

Calcipotriol ointment once a day application in the fourth, fifth and sixth month.

**Treatment Assessment**

Severity and extent of disease were calculated by using "Psoriasis Area Severity Index Score" (PASI Score) and PASI percentage reduction score. PASI score was calculated before treatment at the end of 8<sup>th</sup> week, 16<sup>th</sup> week and 24<sup>th</sup> week.

PASI score for Palmoplantar psoriasis.

$$PASI = 0.2 (EU + IU + DU) AU + 0.4 (EL + IL + DL) AL$$

Area of Psoriatic involvement for Palms and Soles were calculated as 1. It means 10% of area was involved. Severity of Erythema, Induration, Desquamation was calculated as follows" 0- None, 1- Slight, 2- Moderate, 3- Severe, 4- Very Severe.

**RESULTS**

Out of 25 patients selected for Group A and Group B, 22 patients came for treatment till twenty four weeks in Group A, 24 patients came for treatment till twenty four weeks in Group B. Only those patients were included for analysis.

Sl. No.	PASI Percentage (%) Reduction at the End of Treatment	Group A	Group B
1	10 - 20	-	-
2	21 - 30	-	-
3	31 - 40	-	-
4	41 - 50	4	2
5	51 - 60	8	2
6	61 - 70	7	4
7	71 - 80	3	11
8	81 - 90	-	5
	<b>Total</b>	<b>22</b>	<b>24</b>

**Table 1. PASI Percentage Reduction at the End of Treatment**

**PASI Reduction Score and Percentage Reduction**

The mean PASI score before treatment for Group A and Group B were 3.4 and 3.1 respectively. The 't' test results did not show any significant difference in the average initial score between Group A and Group B, (t value= 0.753, P > 0.05).

After 8 weeks of treatment, the mean PASI score for both groups were 2.7 and 2.2 respectively (t value= 10.035 P < 0.01 and t= 8.571 P < 0.01). After 16 weeks of treatment, the mean PASI score for both groups were 2.1 and 1.5 respectively (t value= 12.889 P < 0.01 and t= 9.603 P < 0.01). After 24 weeks of treatment, the mean PASI score for both groups were 1.4 and 0.9 respectively (t value= 13.754 p < 0.01 and t = 9.843 P < 0.01). T test conducted for Group A and Group B comparing initial scores with scores at 8<sup>th</sup>, 16<sup>th</sup> and 24<sup>th</sup> week showed significant reduction in the scores at all three periods.

After 8 weeks of treatment, the mean PASI percentage reduction for both groups were 21.28% and 29.55% respectively. After 16 weeks of treatment, the mean PASI percentage reduction for both groups were 40.06% and 50.56% respectively. After 24 weeks of treatment, the mean PASI percentage reduction for both groups were 60.50% and 70.77% respectively.

		Mean	S.D	T Value	P Value
After (8 Weeks)	A	21.28	9.30	2.618	P < 0.01
	B	29.55	11.83		
After (16 Weeks)	A	40.06	10.90	3.288	P < 0.05
	B	50.56	10.74		
After (24 Weeks)	A	60.50	10.26	3.324	P < 0.05
	B	70.77	10.66		

**Table 2. Statistics Table for PASI Percentage Reduction**

According to 't' test on the basis of more than 50% reduction in PASI score, the p value showed < 0.01 and < 0.05 after 8<sup>th</sup>, 16<sup>th</sup> and 24<sup>th</sup> weeks of treatment. As the 'p' value was significant, this difference in the treatment regimen was not merely by chance. Sequential therapy regimen had a definitive role in treatment of palmoplantar psoriasis than PUVA therapy.

In Group A, out of 22 patients 18 (81.8%) showed more than 50% reduction of PASI. None of the patients showed complete clearance of both palmar and plantar psoriasis. Four patients showed complete clearance of lesion in the palms. Two patients showed complete clearance of lesion in the soles. The average period of clearance of lesions was at 19 weeks. In six months followup period, 3 patients showed relapse after 15 weeks of average period of remission.

In Group B out of 24 patients, 22 (91.6%) showed more than 50% reduction of PASI score. Here also none of the patients showed complete clearance of both palmar and plantar psoriasis. Seven patients showed complete clearance of lesion in the palms and five patients showed complete clearance of lesion in the soles. The average period of clearance of lesions was at 20.3 weeks. In six months followup period, 2 patients showed relapse after 20 weeks of average period of remission.

**Adverse Effects**

**Group A**

4 patients (18.18%) developed adverse effects during treatment. Two patients developed erythema over palms and soles, two patients developed burning sensation.

**Group B**

3 patients (12.5%) developed adverse effects during treatment. One patient developed erythema over soles and two patients developed itching and burning sensation over soles.

Group	Adverse Effect
A	4 Patients (18.18%)
B	3 Patients (12.5%)

**Table 3. Adverse Effects**

**Image 1. PUVA Therapy**



**Before Treatment**



**20 Weeks After Treatment**

**Image 2. Calcipotriol Combinations**



**Before Treatment**



**17 Weeks After Treatment**

**Image 3. Side Effect**



**Diffuse Erythema due to PUVA Therapy**

## DISCUSSION

In our study on the treatment of palmoplantar psoriasis with topical PUVA therapy and sequential treatment with topical calcipotriol and clobetasol ointment, the mean age of the patients presented with palmoplantar psoriasis was 43.32 years; 68% of patients were males and 32% were females and the mean duration of the disease was 17 months. Response to treatment were assessed based on reduction in PASI score and its percentage at 8<sup>th</sup>, 16<sup>th</sup> and 24<sup>th</sup> week.

### Topical PUVA (Group A)

The starting dose of UVA therapy was 1 J/cm<sup>2</sup> with an increment of 0.5 J/cm<sup>2</sup> on subsequent visit. The maximum dose reached was 24.5 J/cm<sup>2</sup> for some patients. In our study, the Group A patients were treated with 8-methoxypsoralen solution along with ultraviolet A therapy twice weekly showed reduction in PASI score of 21.28%, 40.06%, 60.50% at the end of 8<sup>th</sup>, 16<sup>th</sup> and 24<sup>th</sup> week respectively. Maximum improvement was observed at 24<sup>th</sup> week.

There are many studies in literature about the topical PUVA in the treatment of palmoplantar psoriasis, but the results were not consistent. Various studies conducted for the treatment of palmoplantar psoriasis are-

1. Wilkinson JD, Ralfs IG et al, in this study 67% of patients showed considerable improvement with topical application of methoxypsoralen along with UVA.<sup>[15]</sup>
2. Abel EA et al, in this study 5 (35.7%) out of 14 patients had complete clearance of lesions after 15 to 40 treatments.<sup>[16]</sup>
3. Norbert J. Neumann et al, showed 64.64% reduction of PASI score.<sup>[17]</sup>
4. Tsankov N et al, this study showed 40% of patients had marked improvement after 15 sessions of PUVA therapy.<sup>[18]</sup>
5. Petty A et al, reported the most commonly used therapeutic options for palmoplantar psoriasis are long-term treatment with topical corticosteroids and hand-foot PUVA, but the disease become resistant to these modalities after sometime.<sup>[19]</sup>
6. Tsankov N et al, showed no statistically significant difference between the combination of calcipotriol with UVA phototherapy and PUVA in regard to the therapeutic effect.<sup>[20]</sup>

In our study for the treatment of palmoplantar psoriasis with PUVA therapy, 4 out of 22 patients (18.18%) had complete clearance of palmar psoriasis and 2 patients (9.09%) had complete clearance of plantar psoriasis after 34 to 44 treatment sessions; 18% of patients developed adverse effect during treatment. In the followup period, 3 patients developed relapse after 15 weeks of remission. These findings in our study are comparable to the above mentioned studies conducted for the treatment of palmoplantar psoriasis with PUVA therapy.

The disadvantages of PUVA are unavailability of PUVA chamber in many centres, repeated hospital visits and long-term side effects.

### Combination of Calcipotriol with Clobetasol Propionate Ointment (Group B)

The topical calcipotriol and clobetasol propionate ointment was given in a sequential manner for 6 months. In this group maximum percentage reduction of PASI score was 29.55%, 50.56% and 70.77% at the end of 8<sup>th</sup>, 16<sup>th</sup> and 24<sup>th</sup> weeks respectively. The maximum improvement was observed at the end of 16<sup>th</sup> and 24<sup>th</sup> weeks.

Studies related to the treatment of palmoplantar psoriasis with combination of topical calcipotriol and steroids were very less, but many studies were done with combination of calcipotriol and steroids for the treatment of other type of psoriasis.

These combinations showed better results for the treatment of localised plaque type of psoriasis. Even though the onset of action of calcipotriol is slow, steroid will trigger its action and reduces the irritant potential of calcipotriol. The advantage of calcipotriol is that it can be given safely for children, diabetics and hypertensive patients.

In a randomised, double-blinded, controlled trial of Van der Vleuten CJ et al,<sup>[21]</sup> 71.2% of patients achieved "absent" or "very mild" disease with the two-compound scalp formulation, compared to 64% with betamethasone dipropionate and 36.8% with calcipotriene alone. But the disadvantage is pruritus in the combination.<sup>[21,22]</sup>

The efficacy of occlusive topical calcipotriol therapy is better than non-occlusive therapy. The study by Duweb et al showed better efficacy with occlusive calcipotriol applied for 6 weeks; twice-weekly occlusive calcipotriol ointment was as effective as the twice-daily application.<sup>[23]</sup>

A study by Lebwohl M and Menter A et al, revealed that a high-potency topical corticosteroid in combination with vitamin D analog gave better efficacy, although it does not appear to be as effective as super potent corticosteroid used alone.<sup>[24,25]</sup> A combination with super potent topical clobetasol or halobetasol gave better results than with high potent topical betamethasone ointment.

In a similar study by Koo J, Blum RR and Lebwohl M (2006) et al with the combination of topical calcipotriol with clobetasol, there was a 92% clearance of skin lesions after 6 months of therapy.

In our study, 66.7% of patients showed more than 70% clearance of psoriatic skin lesions after 6 months of therapy with topical calcipotriol and clobetasol with least side effects. Seven patients (29.16%) showed 100% clearance of palmar psoriasis and five patients (20.83%) showed 100% clearance of plantar psoriasis after six months of therapy, which is comparable with the study done by Koo J, Blum RR, Lebwohl M (2006) et al.

#### CONCLUSION

1. Efficacy of topical calcipotriol ointment and steroid used in sequential manner is better than the topical psoralen ultraviolet A therapy.
2. 22 patients (91.6%) in calcipotriol and steroid combination group showed more than 50% reduction of PASI score. But in PUVA therapy group, 81.8% of patients showed more than 50% reduction of PASI score.
3. On comparing the adverse effects, patients on PUVA therapy group developed more adverse effects than the patients on calcipotriol and steroid combination group.
4. The duration of remission maintenance was long in calcipotriol and steroid combination group when compared to PUVA therapy group.

In our study, we arrived at the conclusion that topical therapies used in a sequential manner was more effective and it may be considered as a first line therapy for the treatment of patients with palmoplantar psoriasis.

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