

Randomized double blinded placebo controlled comparative study of topical steroid plus bath PUVA versus bath PUVA and placebo cream

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Abstract

Background The trend in psoriasis therapy in recent years has been to combine different agents in the hope that the combination will deliver better results. Topical corticosteroids are frequently used along with PUVA (Psoralen+ ultraviolet A) therapy in the treatment of psoriasis. But there is no consensus whether they enhance the therapeutic response of phototherapy. Our aim was to assess the effect of topical corticosteroids in combination with bath PUVA therapy on psoriasis with respect to time of clearance & duration of remission.

Methods It was a double blind randomized placebo controlled study. Twenty patients were divided into two groups by block randomization. One group was treated with bath PUVA and betamethasone propionate cream in (30/70) dilution cream while the other group was treated with PUVA and placebo cream. Bath PUVA was given for 15 treatments or until 90% clearance of disease whichever is earlier. The assessment was done by PASI_{TUL} scoring at the baseline, 3rd, 6th, 9th, 12th and 15th sittings.

Results Complete remission was achieved in all patients of steroid group and 8 patients of placebo group. The mean baseline PASITUL score decreased from 19.7 to 0.4 in steroid group and from 23.9 to 1.5 in placebo group. The mean cumulative UVA dose used in steroid and placebo groups were 32.85 Joules/cm² and 40.60 Joules/cm² respectively. The median number of UVA exposures used for >90% clearance in steroid group was 11 and for placebo group was 14 (p=.035). Out of 10 patients of steroid group 7 patients relapsed within six months while only 1 out of 8 patients who cleared completely in placebo group relapsed before 6 months (P=.023).

Conclusion While there was tendency of early clearance in steroid group, there was no statistically significant difference in overall clearance and mean cumulative dose of UVA used. There were early relapses in steroid group which was statistically significant.

Key words

Bath PUVA, topical steroid, randomized double blinded, placebo controlled.

Introduction

The trend in psoriasis therapy in recent years has been to combine different agents in the hope that

the combination will deliver better results and reduce side effects. The use of topically applied corticosteroids both as monotherapy and in combination with other treatments is an established mode of treatment in psoriasis and is being extensively used. This benefit may be attributed to their anti-inflammatory & anti-mitotic properties. Concerns regarding their prolonged use in psoriasis include tachyphylaxis, atrophy, striae & post treatment

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rebound flare.

Phototherapy is another popular modality of treatment for psoriasis. The various phototherapy treatments available include narrow band ultraviolet B (NB-UVB), oral psoralen combined with ultraviolet A irradiation (PUVA), bath PUVA and targeted phototherapy. Bath PUVA is among the popular modalities of phototherapy as side effects of systemic psoralen are avoided. Topical corticosteroids are used frequently in conjunction with PUVA therapy. Conflicting studies exist on the therapeutic response of phototherapy.^{1,2} Most of the previous studies evaluate topical corticosteroids in association with UV-B, very few studies exist in English literature evaluating steroid along with PUVA. Some investigators have even suggested that concomitant use of topical corticosteroids may even reduce length of remission that follows phototherapy treatment.^{3,4} The routine protocol in our hospital is either to give bath PUVA alone or to use diluted topical corticosteroids (betamethasone dipropionate in cream base 30/70) along with bath PUVA in treatment of psoriasis. In this double blind placebo controlled study, we aim to assess the effect of topical corticosteroids in conjunction with PUVA therapy on psoriasis with respect to time of clearance and duration of remission.

Aim and objectives

1. To assess the efficacy of both the regimens in the treatment of psoriasis
2. To compare the phototoxic side effects of both the regimens
3. To compare the remission time in both the regimens

Materials and methods

This was a randomized double blinded single centre study. Institutional ethical committee

clearance was obtained prior to starting the study.

Inclusion criteria

1. Patients of both sexes and age above 18 years.
2. Patients with psoriasis involving > 20% body surface area (BSA).
3. Patients not on any systemic therapy for psoriasis in past 4 weeks or topical steroid therapy for past 2 weeks.
4. Patients not on any systemic drugs known to exacerbate psoriasis.

Exclusion criteria

1. Pregnant and lactating women.
2. Patients with photosensitivity dermatitis or on photosensitizing drugs.
3. Pustular psoriasis/ erythrodermic psoriasis.
4. Patients not willing to give informed written consent.

A total of 24 patients with plaque type psoriasis meeting the inclusion and exclusion criteria for the study were enrolled. An informed written consent was obtained from all the patients involved in the study. Block randomization was done and six groups were made each having four patients. In each group 2 patients were randomly treated with bath PUVA and placebo cream while 2 patients were treated with bath PUVA and topical corticosteroid. The placebo cream and topical corticosteroid were dispensed by pharmacist after coding. The steroid used was a 30/70 dilution of betamethasone propionate cream. The placebo was also dispensed as a cream preparation so that no bias could occur. Neither the patients nor researchers knew the topical prescription dispensed. The patient was instructed to apply the coded cream twice a day; once in the morning at 8 am and then at night at 8 pm.

The equipment used for treatment was Waldmann PUVA 1000 unit equipped with 26 UVA lamps of 6 feet length, featuring a radiation spectrum of 315nm to 400nm with a maximum at 355 nm and an output of 9 mw/sq.cm.

Bath water PUVA was administered 2-4 days/week. 37.5 ml of 1% 8-methoxy psoralen (8-MOP) was dissolved in 100 L of water in a bath tub to obtain a final concentration of 3.75 mg/dl. Patients were asked to soak the entire body (neck below) for 10 minutes each in the supine and prone positions. After a total of 20 minutes of soaking, patient exited the tub, gently pat dried his skin and was immediately exposed to UVA in whole body phototherapy chamber. The starting dose of UVA was 1J/sq.cm and was increased by 0.5J/sq.cm on every sitting depending on the development of erythema as follows:

No erythema- UVA dose was increased.

Mild (barely perceptible erythema)- dose was not increased and the previous dose was maintained.

Moderate erythema (well defined asymptomatic)- Treatment was postponed until recovery and then continued with the previous dose.

Severe erythema (erythema with edema or blistering)- Treatment was stopped until recovery & further treatment was given by reducing exposure dose by half.

The treatment was given for 15 treatments or until 90% clearance of disease whichever was earlier. Patients were objectively assessed using PASI_{TUL} (Psoriasis area Severity Index- Trunk, upper and lower limb) at the baseline, 3rd, 6th, 9th, 12th and 15th sittings. Head and neck were

not evaluated as patients were treated with 8-MOP bath which spared the head. After clearing of the skin the patients were given only emollients to apply.

The improvement in patients was noted on a 3 point scale

1. Complete remission- More than 90% reduction in PASI score.
2. Partial remission- 50-90% reduction in the PASI score.
3. Treatment failure- <50% reduction in PASI score.

Side effects if any during the treatment schedule were noted. Patients were seen 1 month after clearing & contacted by telephone for further follow up. Patients were seen next at the time of flare with relapse being defined as recurrence of disease with involvement of more than 10% BSA.

Results

Twenty four patients were enrolled in the study. Two patients each in steroid and placebo groups dropped out of the study due to reasons unrelated to the study; thus a total of 20 patients completed the study with 10 patients in each group. Of the 20 patients 18 were males & 2 were females. The mean age of patients in the steroid group was 41.30±12.4 years and in the placebo group was 48.20±12.2 years. The duration of disease in the steroid group and placebo group were 8.10±6.8 and 7.60±6.5 years respectively. The BSA in the steroid group and placebo group were 46.70±19.6 and 50.70±19.3 respectively. The skin type of patients as per FitzPatrick skin typing in both groups were either Type IV or type V. The patient characteristics in the steroid and placebo groups are shown in **Table 1 & 2** respectively.

Table 1 Patient characteristics in steroid group

S.No	Age	sex	Fitz Patrick Skin type	BSA	Remission	Remission achieved at sitting	UVA dose (J/cm ²)	Relapse (weeks)	Relapse within 6 months
1	48	M	IV	30	CR	15	56	12	Yes
2	54	M	V	50	CR	15	51.5	12	Yes
3	39	F	V	25	CR	9	27	48	No
4	40	M	V	30	CR	12	35	8	Yes
5	25	M	IV	40	CR	8	20	6	Yes
6	43	M	IV	25	CR	10	20	16	Yes
7	60	M	IV	52	CR	9	22	4	Yes
8	42	M	V	75	CR	12	50	NR at 36 weeks	No
9	44	M	V	70	CR	12	31	NR at 36 weeks	No
10	18	M	IV	70	CR	8	16	12	Yes

BSA-body surface area, CR- complete Remission, PR-Partial remission, NR-No relapse

Table 2 Patient characteristics in placebo group

S.No	Age	Sex	Fitz Patrick Skin type	BSA	Remission	Remission achieved at sitting	UVA dose (J/cm ²)	Relapse	Relapse within 6 months
1	55	M	V	75	PR	PR	43	NA	NA
2	50	F	IV	75	CR	12	35	56	No
3	30	M	IV	25	CR	10	25.5	48	No
4	34	M	V	50	CR	14	50	40	No
5	70	M	IV	40	CR	12	33	NR at 40 weeks	No
6	42	M	IV	50	CR	12	42	NR at 32 weeks	No
7	38	M	V	40	CR	12	50	22	Yes
8	60	M	V	22	PR	PR	45	NA	NA
9	42	M	V	60	CR	15	42.5	NR at 24 weeks	No
10	56	M	V	70	CR	14	40	NR at 24 weeks	No

BSA-body surface area, CR- complete Remission, PR-Partial remission, NR-No relapse, NA-Not applicable

Table 3 Efficacy of treatment in steroid and placebo groups

Group	No. of patients	Complete Remission	Partial Remission	Treatment failure
Steroid	10	10	0	0
Placebo	10	8	2	0

Both treatments were highly effective in clearing the disease and no treatment failures were seen in either group (**Table 3**).

There was no statistical difference in the overall clearance caused by both treatments. All ten patients in steroid group and 8 out of 10 patients in placebo group achieved complete remission (**Figures 1-4**). Two patients in the placebo group attained partial remission.

The mean baseline PASITUL score decreased from 19.7 to 0.4 in steroid group in comparison to the placebo group which was from 23.9 to 1.5. Comparison of the mean PASITUL score at different sittings is shown in **Table 4** and **Figure 5**.

The sitting wise improvement in PASITUL in the steroid and placebo groups are described in **Tables 5 & 6** respectively.



Figure 1 Pre-treatment in steroid group in complete remission



Figure 2 Post treatment in steroid group in complete remission



Figure 3 Pre-treatment in placebo group in complete remission



Figure 4 Post treatment in placebo group in complete remission

Table 4 Comparison of the mean PASI_{TUL} score at different sittings in steroid and placebo groups

Sitting	Category	Mean	Std. Deviation
0	Placebo	23.9400	9.66818
	Steroid	19.7300	7.95097
3	Placebo	18.1500	5.44084
	Steroid	13.4300	5.72830
6	Placebo	12.5800	4.46039
	Steroid	7.8000	4.76748
9	Placebo	7.9200	3.58261
	Steroid	4.2200	4.40878
12	Placebo	3.9900	3.11892
	Steroid	1.5500	1.95349
15	Placebo	1.5900	2.60190
	Steroid	.4000	.84327

The mean cumulative UVA dose in the steroid group was 32.85 Joules/ sq.cm while in the placebo group was 40.60 Joules/ sq.cm (**Tables 1 & 2**).

No significant difference was seen in the mean cumulative UVA dose between the two groups (p=.15). However the median number of exposures used for >90% clearance in steroid and placebo groups were 11 and 14 respectively,

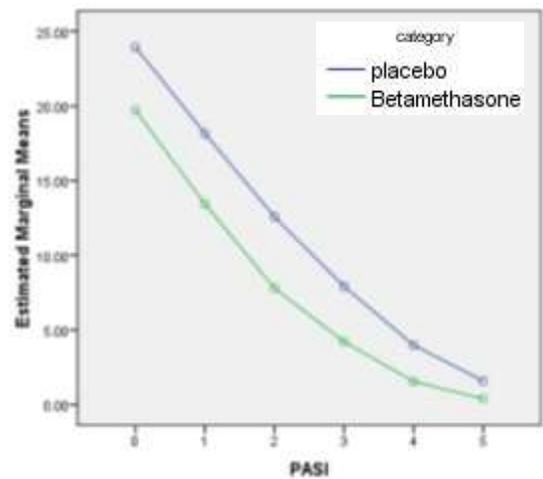


Figure 5 Mean PASI_{TUL} score at different sittings in steroid and placebo groups

which was statistically significant (p=0.035).

Most of the patients tolerated bath PUVA well. The common side effects noticed due to bath PUVA were erythema, itching and burning

Table 5 Improvement in PASITUL in steroid group

S.No	Day 0	PASI at sitting				
		3 rd	6 th	9 th	12 th	15 th
1	22.8	19.2	13.8	10.8	4.4	2
2	23	18	14	11.4	5	2
3	12	7.6	4	1	0	0
4	13.3	10.7	6.4	3	1	0
5	8.4	5.6	1.4	0.4	0	0
6	10	6	2.8	0.5	0	0
7	21	15.6	7.6	1.5	0	0
8	27	15.6	9	6	2.7	0
9	33.2	22	14	7.6	2.6	0
10	24.6	14	5	1.2	0	0

Table 6 Improvement in PASITUL in placebo group

S.No	Day 0	PASI at sitting				
		3 rd	6 th	9 th	12 th	15 th
1	27.1	20	16.2	12	9.5	6.1
2	47.5	28.7	19.5	10	3.6	0
3	16	10	6.4	2	0.5	0
4	16	12.6	6.3	3	1.8	0
5	19.4	15	10	6	1.9	0
6	25.6	20.8	12.2	7.2	1.6	0
7	22.2	20	14.8	11.9	6.2	2
8	14	13.4	12	10	8.8	6.6
9	22.8	21	17.6	10.8	3	1.2
10	28.8	20	10.8	6.3	3	0

Table 7 Side effects in steroid and placebo group

Group	Side effects				
	Nil	Erythema	Itching	Erythema + Itching	Erythema + Burning sensation
Steroid group	5	3	1	0	1
Placebo group	5	1	3	1	0
Total	10	4	4	1	1

Table 8 Relapse in the steroid group

S. No.	Remission	Relapsed after
1.	CR	12 weeks
2.	CR	12 weeks
3.	CR	48 weeks
4.	CR	8 weeks
5.	CR	6 weeks
6.	CR	16 weeks
7.	CR	4 weeks
8.	CR	NR (after 36 weeks)
9.	CR	NR (after 28 weeks)
10.	CR	12 weeks

CR- complete Remission, NR-No relapse

Table-9 Relapse in the placebo group

S. No.	Remission	Relapsed after
1.	PR	-
2.	CR	56 weeks
3.	CR	48 weeks
4.	CR	40 weeks
5.	CR	NR (after 40 weeks)
6.	CR	NR (after 32 weeks)
7.	CR	24 weeks
8.	PR	-
9.	CR	NR (after 24 weeks)
10.	CR	NR(after 24 weeks)

CR- complete Remission, PR-Partial remission, NR-No relapse

Note: Partial remission patients were not considered for relapse as per study criteria

sensation (**Table 7**). None of the side effects warranted discontinuation of therapy. There was no statistical difference among side effects between both groups. Side effects were not reported from either of the topical preparations.

Only patients who achieved complete remission were considered for relapse estimation. All patients in steroid group and 8 out of 10 patients in placebo group had complete remission. Relapse rates were higher and earlier in the steroid group than in the placebo group. Out of the ten patients in steroid group, 7 patients relapsed within six months while only 1 out of 8 patients in placebo relapsed before 6 months (P=.023) (**Tables 8 & 9**).

Discussion

Topical steroids along with moisturizers are often the mainstay of treatment for psoriasis especially mild to moderate psoriasis where it is considered to be the cornerstone of management.^{5,6} Remissions induced by only topical steroid are considered to be short-term. Combination therapy is very popular in the management of psoriasis. The combination of phototherapy and topical steroids being one of the popular modalities of treatment. The benefit of combination therapy include earlier remissions, prolonged remission period and

decreased side effects. In this study, both the treatments were found to be highly effective in producing clearance of psoriasis. All patients in steroid group and 8 patients in placebo group achieved > 90% clearance. There was no significant difference in the reduction of mean PASI and mean cumulative UVA dose used in two groups. However, the median number of exposures used for >90% clearance in steroid group was 11 & for placebo group was 14 which was statistically significant (p=.035).

The combination of phototherapy with topical corticosteroids has yielded conflicting results in previous conducted studies, with some authors claiming shorter remission period and others longer remission period.^{2,3} Most of the studies evaluating the efficacy of steroid and phototherapy combination have involved the use of UV-B rather than UVA. Studies involving combination of UV-B and steroid usually show lack of benefit from steroid addition.⁶⁻⁸ On the other hand some studies have showed a beneficial effect of steroid when used in combination with UV-A.^{3,7-10} Most studies have involved Western population. Studies on Asian skin especially South Asian skin types are lacking in this sphere.

In a study conducted by M. Schmoll *et al.*, evaluating 90 patients with psoriasis categorized patients into 3 groups: first group received PUVA only, second group received only topical steroids under occlusion and third group received a combination of both.³ Approximately 15 PUVA treatments were required for clearance in groups receiving photochemotherapy. Topical steroid only group produced rapid clearing of the skin but group also exhibited early relapses (in 50% of the patients after 3 weeks). PUVA cleared the disease more slowly. However, 50% of the patients remained free of psoriasis for approximately 10 weeks after clearance. Psoriasis treated with steroids under occlusion

together with PUVA showed a significantly faster remission as compared to PUVA. But as in PUVA only treated patients, relapses occurred after approximately 12 weeks in this group. In our study relapse in steroid group was noticed only after a mean of 14.75 weeks of remission (Range 4 to 48 weeks) whereas in the placebo group it was a mean of 42 weeks (range 24 to 56 weeks).

In a study done by Dutta *et al.* comparing PUVASOL with PUVASOL with topical triamcinolone acetonide ointment showed a quicker resolution of lesions at the end of 4 weeks in 66% of patients of steroid group versus 26.6% in non-steroid group.⁹ At the end of 8 weeks 60% of patients in steroid group had complete clearance of lesions as against 16.6% in the non-steroid group. Five patients in the non-steroid group showed a relapse at the end of one year follow up, while none of the patients in the steroid group showed any relapse. This was contrary to our study which showed relapses to be more and earlier in the steroid group than in the non-steroid group. The study done by Dutta *et al.*, however failed to describe the criteria for relapse.

In a half and half study done by Hanke *et al.* comparing PUVA and PUVA with betamethasone valerate showed a faster clearing of the steroid treated side as against the PUVA only side in 10/12 patients whereas two patients showed equal clearing.⁷

A study done by Dover *et al.* comparing the effect of topical corticosteroids vs placebo in conjunction with UVB phototherapy showed a slightly more rapid response in topical corticosteroid treated group in comparison to the placebo group but there was no difference in number of treatments or UVB dose required to achieve clearance. Remissions were seen to be longer in steroid group as against the placebo

group (183 vs 116 days). Relapse at 6 month were seen in 62% of emollient treated group in comparison to 42% of topical steroid group.¹

A study done by Horwitz *et al.* to compare the effect of topical corticosteroid (hydrocortisone valerate cream) and placebo along with modified Goeckerman regimen in treatment of psoriasis showed a significant difference in the remission period of two groups. The average duration of remission for patients treated with steroid and placebo were 5.9 and 17.9 weeks respectively.²

Levine and Parrish in a bilateral, paired comparison study of topical corticosteroids with UVB concluded that the addition of topical corticosteroids does not hasten the clearance of psoriatic plaques.¹¹ Although the steroid side attained faster improvement in the initial sittings, the number of sessions of phototherapy were the same. Perhaps the possibility of systemic absorption of topically applied steroids might be the reason for absence of variation in phototherapy vs phototherapy and steroid groups. Remission period was not calculated in this study. In our study, the use of steroid resulted in faster resolution and reduced number of PUVA sittings.

Petrozii *et al.* evaluated the effect of steroids along with UV-B rays showed that there was no difference of steroid use along with phototherapy in obtaining resolution of lesions.¹² Among the patients who had complete remission, the average duration of remission was 7.75 weeks for both treatment and control sites. It was concluded that corticosteroids did not alter the remission duration.

A double blind placebo controlled study conducted by Larkö *et al.* also showed that the steroid group tend to show improve earlier, but the number of sessions of phototherapy required were the same in both the groups.¹³ A shorter

remission period was seen in patients using topical corticosteroids along with UVB which was consistent with our study which demonstrated that topical corticosteroids resulted in early relapses.

In our study out of 10 patients of betamethasone group 7 patients relapsed within six months while only 1 out of 8 patients who cleared completely in placebo relapsed before 6 months (P=.023); a statistically significant difference. In our study relapse rates were calculated only for patients who had complete remissions. A standard definition of relapse is not commonly understood. Following effective therapy for psoriasis, it is not uncommon for a few small psoriatic plaques to recur, particularly on the elbows, knees, lower legs & scalp. From a practical point of view, one could consider relapse to have occurred when the psoriatic lesions have returned to the point where therapy should be reinstated. In most of the above studies definition of relapse was not clearly defined. In our study, we had defined relapse as more than 10% of body surface area involvement and found significant difference in the time of relapse in two groups.³

Conclusion

1. Bath PUVA with or without topical steroids is highly effective for clearance of psoriatic lesions
2. There was no significant statistical difference in the reduction of mean PASI and total cumulative UVA dose in both the groups. But number of treatments required to clear the disease was less in topical corticosteroid group
3. The use of topical corticosteroids along with Bath PUVA was associated with significant early relapses.
4. Studies with larger population maybe required to validate the findings of our study.

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