Chapter 8
Clinical Studies

8.1 Introduction

Topical glucocorticoids (TG) are the most frequently prescribed drugs by dermatologists. Their clinical effectiveness in the treatment of psoriasis and atopic dermatitis is related to their vasoconstrictive, anti-inflammatory, immunosuppressive and anti-proliferative effects. Treatment with TG formulations is effective, easy to administer, acceptable to patients and safe when used correctly.

The TG pharmacodynamic response is the ability to produce vasoconstriction of the microvasculature of the skin, leading to skin blanching (whitening) at the site of application. This "vasoconstrictor assay" was first described by McKenzie and Stoughton in 1962. Since that time, the method has been modified and extended to provide a reliable means to test TG and their formulations. The intensity of skin blanching has been correlated with drug potency and the degree of drug delivery through the Stratum Corneum. The vasoconstrictor assay has been used to measure the BA/BE of corticosteroid formulations in healthy volunteers and has been adopted in 1995 for BE determination by the U.S. Food and Drug Administration (FDA), in a Guidance document "Topical Dermatologic Corticosteroids: *In-vivo* Bioequivalence". Since 1962, many studies have been performed to verify and optimize this bioassay method . Techniques that are reliable and reproducible have been developed either by taking advantage of reflectance spectrophotometers to measure the skin color or by simple visual assessment of the skin blanching response.

The formulation is applied for various times (dose durations) up to 6 h to manipulate the amount of steroid delivered. At the end of the treatment period, the skin blanching response is measured with a chromameter over the

next 24–28 h. From the resulting response versus time profiles, the areas above the response curves (AARC) are calculated and plotted as a function of dose duration to obtain dose/response-like relationships.

The human skin blanching (vasoconstriction) assay for the assessment of topical corticosteroids uses the skin pallor induced at the site of application as an indicator of the potency of the drug or efficacy of the delivery vehicle. Usually several volunteers and several visual observers are used in the bioassay to counteract the subjectiveness of the methodology.

The assay procedure reported by Haigh and Kanfer employs 12 healthy, men and women who have not received corticoids, either systemically or topically, for at least 6 weeks before the study. Blanching is difficult to discern on highly pigmented or tanned skin, presumably because the melanocytes obscure the underlying vasculature, and it is barely visibleon black skin, even when exposed to potent, fluorinated corticoids. The application of corticosteroids to human skin does not induce pallor in all individuals.

The formulations remain in contact with the skin for 6 h, after which the guards, occlusive strips, and demarcating labels are carefully removed. Residual formulation is gently washed from the sites with soap and warm water, and the skin patted dry with a towel. The puckering of the skin, due to hydration, and slight erythema that results from adhesive tape removal usually subsides within 30 min. Thereafter, three trained observers independently assess the degree of induced blanching at each site at regular intervals. Observations are typically made at 7,8,9,10,12,14,16,18,28, and 32 h after initial application. Standard overhead fluorescent lighting is used to illuminate the horizontally placed arms of the volunteers.

Nevertheless, despite its limitations, the vasoconstrictor assay remains the standard procedure to assess the BA/BE of TG. In summary, therefore, apart from the vasoconstrictor assay, which is clearly restricted, at this time, to TG, there are currently no non-invasive or minimally invasive techniques for the assessment of BA/BE of topically applied drugs that are acceptable to the regulatory bodies (Haigh et al, 1997, Mckenzie et al, 1962, Leopold, 2003 and Schwarb et al, 1999)

Accurate assessment of the extent and severity of atopic dermatitis (AD) is essential for quantitating 1) the baseline clinical disease burden and 2) the effectiveness of a treatment regimen being tested. There are several systems for outcome measures of atopic dermatitis.

The principle of integrating disease extent and sign severity to describe disease has led to the definition of the eczema area and severity index (EASI). The Eczema Area and Severity Index (EASI) involves an assessment of disease extent on a scale of 0 to 6 in 4 defined body regions plus an assessment of erythema, infiltration and/or papulation, excoriation, and lichenification each on a scale of 0 to 3. A formula is then used to calculate the total score for each of the 4 regions, which are then added together. The individual components of EASI (i.e. body region involvement, severity) can be separated and evaluated independently or in combination to provide a more complete assessment of the patient. The extent of AD is usually determined by examining the patient's skin and estimating the percentage involvement of affected areas, while severity is determined by grading specific signs of eczema (e.g. erythema, induration/edema/papulation, excoriation, lichenification, scaling, and oozing/weeping/crusting), and by eliciting the symptomatic intensity of pruritus. EASI excludes non-key signs such as xerosis and scaling, oozing and crusting, and subjective parameters such as

pruritus and sleep loss in order to focus the index on key disease signs and to avoid mixing objective parameters with subjective symptoms. Regional body surface area tabulation was used to assess the severity of dermatitis over four body areas. In cohort 1 (older patient group), the head and neck (H), upper extremities (U), trunk (T), and lower extremities (L) were assigned proportionate body surface areas of 10% (H), 20% (U), 30% (T), and 40% (L), roughly consistent with the "rule of nines" Each of the four body regions was assessed separately for the key signs of erythema, induration/papulation/edema, excoriations, and lichenification. The average degree of severity of each sign in each of the four body regions was assigned a score of 0 to 3 (none, mild, moderate, and severe, respectively) (Hanifin et al, 2001).

The Rajka and Langeland scoring system is a simple scale measuring clinical course, intensity, and extent of atopic eczema that was published in abstract form in 1989. The original index proposed by Rajka and Langeland graded the disease activity of AD into mild, moderate and severe categories based on composite evaluation of disease intensity, clinical course and extent of examined AD (Charman, 2000). The recently described refined version of the index (Nottingham Eczema Severity Score) uses a 5-point rather than a 3-point grading system for clinical course and intensity, giving the potential for increased sensitivity to change while still being easy to administer. It still includes a measure of disease extent but uses a tick-box system corresponding to sites commonly affected by atopic eczema to simplify the assessment. The observer is instructed to tick each box on the surface diagram if more than 2 cm^2 (the size of a 10 pence coin) was involved in any given area. The number of involved areas is then calculated as a sum, with a score of 1–5 attributed according to the total number of involved sites.

The Nottingham Eczema Severity Score (NESS) provides an assessment of clinical severity of atopic eczema using a single practical evaluation based on the following parameters: (i) clinical duration of AE; (ii) intensity as measured by average sleep disturbance; and (iii) extent of disease involvement. The evaluation is intended to allow cases to be graded into the categories of mild, moderate and severe based on a combination of clinical symptoms in the past 12 months and a single clinical examination. Each parameter has been given equal weighting and is graded on a five-point scale from 1 to 5. The score for each parameter is added to produce a final total score. The minimum score is therefore 3 and the maximum 15 (Emerson et al, 2000).

8.2 Methods

8.2.1 Skin Blanching Assay

A double blind skin blanching bioassay study on normal human volunteers was carried out for comparative evaluation of halobetasol propionate formulations at Skin and V.D department, Baroda medical College under the supervision of qualified dermatologist. The formulation A was halobetasol propionate cream 0.05% (marketed product) while the formulation B was Microemulsion based Halobetasol propionate cream 0.035%. The study was carried out according to the protocol described below with 12 human volunteers and evaluation for blanching scores was done by three independent observers. The applied cream was removed from the application at different time viz. after 2 h, after 4 h, after 6 h and then blanching response was recorded for further 24 hours after removal of cream

8.2.2 Protocol for comparative skin blanching bioassay of Halobetasol propionate formulations.

A double blind study for comparative evaluation of halobetasol propionate Cream formulations.

Products:

1. Halobetasol Propionate (0.035%) ME cream
2. Halobetasol Propionate (0.05%) cream

Inclusion criteria:

1. 10 Volunteers male or female
2. Volunteers not having any skin disease such as mycotic or viral infections, irritant or allergic dermatitis
3. Age: >14 -70 yrs

Exclusion Criteria:

1. Volunteers unwilling to be a part of trial
2. Volunteers below 14 years of age will be excluded from the study.
3. Pregnant or lactating females
4. Volunteers with known hypersensitivity to drug
5. Volunteers with other co-existing severe medical disease including diabetes
6. Volunteers on any other concomitant medication

Study period: ~ 30 h

Evaluation criteria: Visual scoring of the corticosteroid induced skin blanching.

Procedure: Volunteers fasted overnight allowing only water intake. They were asked not to be exposed to sun light and not to use any substance that could have masked or changed the color of the skin. They were requested not to wash or wet the treated parts and not to engage in excessive physical activity, during the study periods. All volunteers were processed sequentially at 5-min intervals in order to minimize any possible effects of environmental variables, such as temperature and humidity. Volunteers were housed in controlled environment with temperature and humidity control. The skin blanching recordings was done half an hour prior to start of study and at start of the study to derive the 0 (zero) hour reading. Adhesive labels, from which circular area (area: 1 cm^2) had been punched, were applied to the flexor aspect of both forearms to demarcate a total of 3 application sites per arm of each volunteer. Each formulation (qty: 250 mg) was applied uniformly using a glass rod to three of the six demarcated sites After a contact time of 2h, 4h and 6h the protective covers and adhesive labels were removed The application site was then cleaned gently using tissue paper. Standard overhead fluorescent lighting was used to illuminate the horizontally-placed arms of

the volunteers. The Blanching is recorded immediately after removal of formulation Further recordings are made at an interval of 1h, 2h, 4h, 6h, 8 h, 12 h, 18 h, 24 h after removal of the formulation Blanching responses were graded subjectively by each of the three independent observer using an ordinal scale where the scores are as follows. The volunteers were allowed standard food and water intake during the course of the study. Any major side effect, if observed during the study was recorded.

Blanching Scores:

0: No blanching

1: Slight diffuse blanching with no distinct outline

2: More intense blanching with half of the drug treated site perimeter outlined

3: Marked general even blanching with distinct outline

4: Intense blanching with distinct margins on all sides

The blanching response was calculated as percentage of the total possible score (% TPS). The Plot of % TPS versus time to be used to calculate AUBC – area under blanching curve. This will allow a comparative evaluation between the different application time and the two formulations.

Data sheet for blanching study of halobetasol propionate formulations:

Volunteer's name:

Age:

Sex:

Occupation:

Date of commencement of treatment:

Blanching score card:

Formulation A/B : Right arm / Left arm

Forml. Appl. Time:	(Removal at 2 h) site		(Removal at 4 h) site		(Removal at 6 h) site	
	Time	score	Time	score	Time	score
0.5 hour before start						
At start of study						
Immediately after removal						
After 1 h						
After 2 h						
After 4 h						
After 6 h						
After 8 h						
After 12 h						
After 18 h						
After 24 h						

Observer Name and signature:

8.2.3 Pilot Study in Dermatitis Patients

A 3 week single blind study was carried out for comparative evaluation of Halobetasol Propionate Cream Formulations which included a microemulsion based halobetasol cream (0.035%) and a plain halobetasol propionate cream (0.05% - marketed preparation). The placebo's for the two formulations were also included in the study (placebo for the marketed preparation was provided by manufacturer). The patients were enrolled voluntarily in the study after informed consent. The patients were given Placebo to apply in their first week of enrollment for the study followed by two weeks of active treatment. The Right – left policy was used in patients having dermatitis on both sides of the body so as to have a comparative observation with respect to placebo. The study was carried out at Sir Sayajirao General hospital, Skin and V.D. department, Vadodara under the supervision of a qualified dermatologist. The grading system used was a combination of Nottingham Eczema Severity Score (NESS) and eczema area and severity index (EASI). Patients were evaluated for clinical course (1-5 score), disease intensity evaluation (1-5 score), extent of body surface (1-5 score) and key signs and symptoms :eythema, oozing/crusting, excoriation, oedema/induration/papulation, scaling, lichenification, pruritus on a scale of (0-3). Patient and physician global assessment criteria was used for overall evaluation.

Grade - 1 Complete/Excellent improvement (more than 80% improvement in symptoms).

Grade -2 Very good improvement (more than 70% to 80% improvement)

Grade -3 Good improvement (50% to 70% improvement).

Grade -4 No significant improvement (Less than 50% improvement)

Grade -5 Worsening of signs and symptoms or development of signs and symptoms.

8.2.4 Protocol for Comparative Evaluation of Halobetasol formulations in treatment of steroid responsive dermatoses.

A 3 week single blind study for comparative evaluation of Halobetasol Propionate Cream Formulations.

Products: 1. Halobetasol Propionate ME Cream (0.035%) and placebo

2. Halobetasol Propionate Cream (0.05%) and placebo

Inclusion criteria: 6-9 patients in each group. (Age: >14 -70 yrs) diagnosed with moderate to severe dermatitis

Exclusion Criteria: Any obvious infection or severe oozing. Patients below 14 years of age will be excluded from the study.

Study period: 3 week study including 2 week active treatment, one week preceding treatment.

Evaluation criteria: based on Nottingham eczema severity score (NESS) and Eczema area severity index(EASI) patients to be evaluated for

clinical course (1-5 score)

Disease intensity evaluation (1-5 score)

extent of body surface (1-5 score)

and key signs and symptoms :eythema, oozing/crusting, excoriation, oedema/ induration / papulation, scaling, lichenification, pruritus.

Any local or systemic side effects

Patient and physician global assessment criteria to be used for overall evaluation

Data sheet for clinical study of halobetasol formulations:

Patient's name:

Age:

Sex:

Occupation:

Provisional diagnosis:

Details of previous treatment:

Systemic:

Local:

For Duration:

Details of present treatment:

Date of commencement of treatment:

Drugs co- administered if any,

Clinical course of the disease: (on a scale of 1-5):

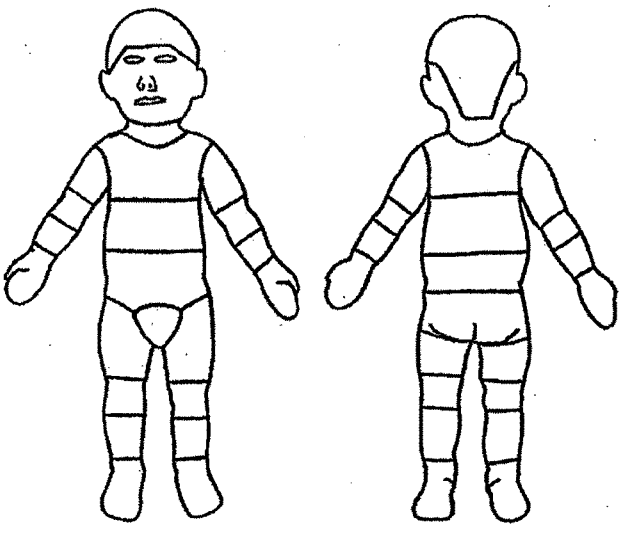
Score	Clinical course	Observation
1	Present for less than 6 weeks in total	
2	Present for between 6 weeks and less than 3 months in total	
3	Present for between 3 months and less than 6 months in total	
4	Present for between 6 months and less than 9 months in total	
5	Present for more than 9 months in total	

Disease intensity evaluation (based on sleep loss due to itch) (on a scale of 1-5):

Score	Clinical course	Observation
1	Sleep is not usually disturbed	
2	1 night per week on average	
3	2 or 3 nights per week on average	
4	4 or 5 nights per week on average	
5	6 or more nights per week on average	

Extent of the body surface involved: (on a scale of 1-5) (based on number of involved tick boxes)

Score	No. of tick boxes involved	Observation
1	0-2	
2	3-5	
3	6-10	
4	11-20	
5	>20	



Front ticks Back ticks

Attached herewith a real time trace of the affected area and its regression /progression during the course of treatment.

Changes in key signs and symptoms: (on a scale of 0 to 3)

Symptom	Initial / basal	Day 7	Day 10	Day 14	Day 17	Day 21	Day 28
Erythema,							
Oozing/ crusting,							
Excoriation,							
Oedema/induration/papulation							
Scaling,							
Lichenification,							
Pruritus							

0: none, 1: slight , 2: moderate, 3: severe

Adverse Effect profiling:

Adverse effect	Initial/ basal	Day 7	Day 10	Day 14	Day 17	Day 21	Day 28
Atrophy							
Striae							
Hyper-pigmentation							
Any other specify							

0: none, 1: slight , 2: moderate, 3: severe

Patient's global assessment at the end of treatment:

Physician's global assessment at the end of treatment:

Chief investigator:

Investigator:

Co-investigator:

8.3 Results

8.3.1 Skin Blanching Bioassay

For drug removal at 2 h: after application of formulations under occlusion for 2 hours, they were removed and skin blanching profiling was done for the next 24 hours. The results from the observations are depicted graphically below and the relevant statistics are also shown.

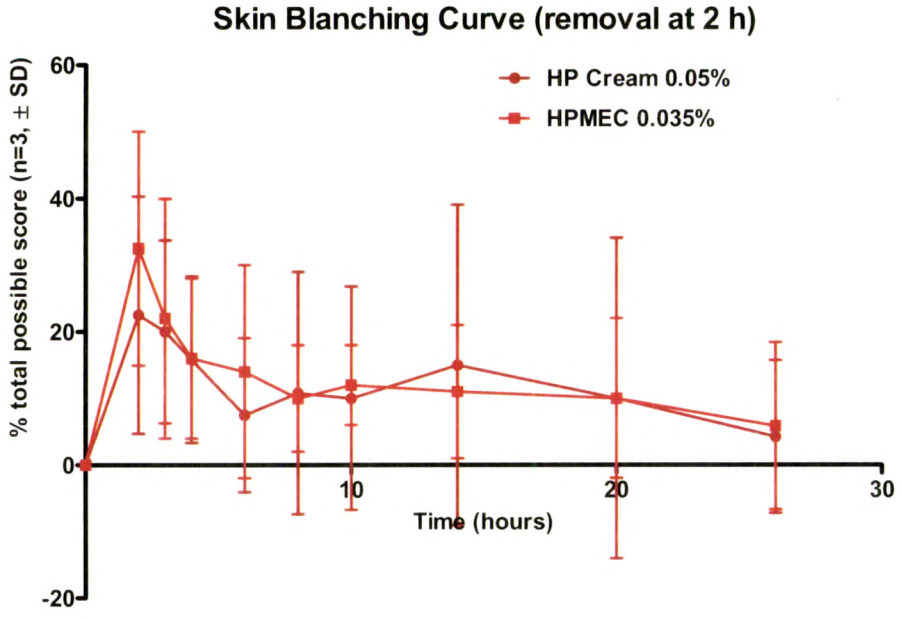


Fig. 8.1: Skin blanching curve for HP cream 0.05% and HPMEC 0.035% after 2 h of application

Area under the Blanching Curve (AUBC) Details

	HP cream 0.05%	HPMEC 0.035%
Total Area	291.7	311.3

Paired t test

(Formulation A : HP cream 0.05% vs HPMEC 0.035%)

P value	0.1904
Are means signif. different? (P < 0.05)	**No**
One- or two-tailed P value?	Two-tailed

For drug removal at 4 h: after application of formulations under occlusion for 4 hours, they were removed and skin blanching profiling was done for the next 24 hours. The results from the observations are depicted graphically below and the relevant statistics are also shown.

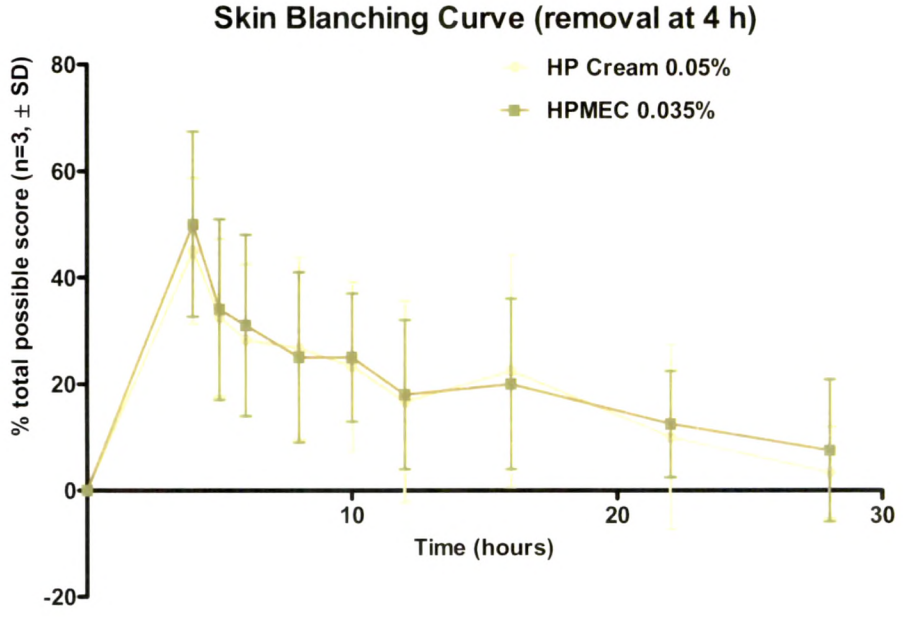


Fig. 8.2: Skin blanching curve for HP cream 0.05% and HPMEC 0.035% after 4 h of application

Area under the Blanching Curve (AUBC) Details

	HP cream 0.05%	HPMEC 0.035%
Total Area	520.0	557.0
Paired t test		
(HP cream 0.05% VsHPMEC 0.035%)		
P value		0.0820
Are means signif. different? (P < 0.05)		**No**
One- or two-tailed P value?		Two-tailed

For drug removal at 6 h: after application of formulations under occlusion for 6 hours, they were removed and skin blanching profiling was done for the next 24 hours. The results from the observations are depicted graphically below and the relevant statistics are also shown.

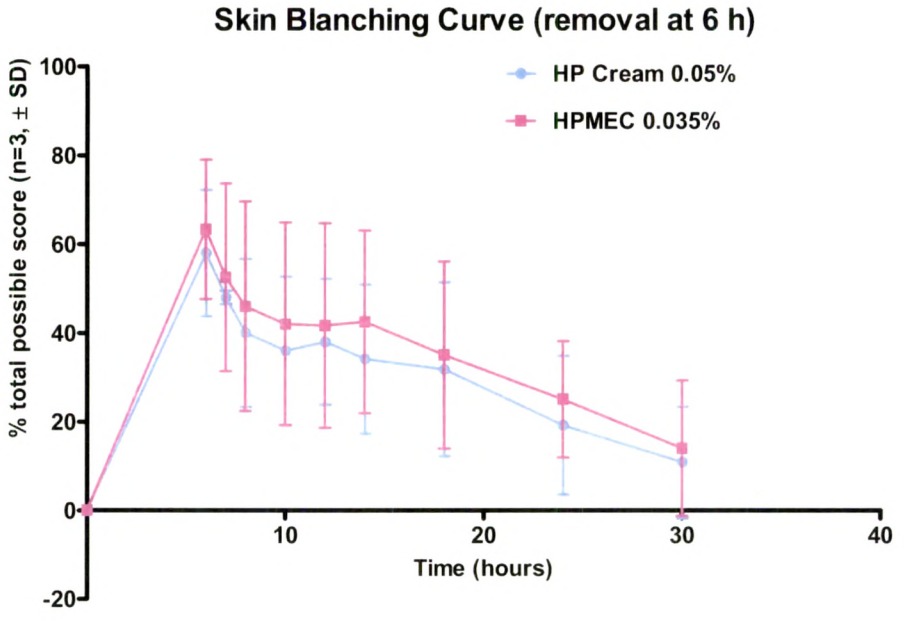


Fig. 8.3: Skin blanching curve for HP cream 0.05% and HPMEC 0.035% after 6 h of application

Area under the Blanching Curve (AUBC) Details

	HP cream 0.05%	HPMEC 0.035%
Total Area	867.9	1003
Paired t test		
(HP cream 0.05% Vs.HPMEC 0.035%)		
P value		0.0003
Are means signif. different? (P < 0.05)		**Yes**
One- or two-tailed P value?		Two-tailed

8.3.2 Pilot Clinical Studies

Table 8.1: Disease severity score comparison between the two groups.

	Group 1: HPMEC (0.035%) (n=6)	**Group 2: HP Cream (0.05%) (n=7)**
Mean score ± SD	8.83 ± 1.47	9.29 ± 1.25
No. of males	3	3
No. of females	3	4
Mean age ± SD (years)	50.6 ± 19.1	61 ± 5.4

*: P<0.05, significant (t –test)

Table 8.2: Change in key signs and symptoms during the course of study for Group 1: HPMEC (0.035%)

Time/ parameter	**Erythema**	**Oozing/ crusting**	**Excoriation**	**Oedema**	**Scaling**	**Lichenification**	**Pruritus**
0 day	0.667 ± 0.6	0	0.333± 0.3	0.167± 0.4	1.500± 0.5	1.500± 0.8	2.667± 0.5
7 day	0.583± 0.5	0	0.333±.0.3	0.167± 0.4	*0.833± 0.5	1.417± 0.8	*2.167± 0.5
14 day	0.167± 0.2	0	0.167± 0.2	0.083± 0.2	*0.417± 0.4	*1.000± 0.8	*1.167± 0.2
21 day	0.042± 0.1	0	0.083± 0.2	0	*0.083± 0.2	0.625± 0.4	*0.833± 0.2

Mean ± SD, n=6, *: P<0.05, significant (Paired t –test)

Table 8.3: Change in key signs and symptoms during the course of study for Group 2: HP cream (0.05%)

Time/ parameter	Erythema	Oozing/ crusting	Excoriation	Oedema	Scaling	Lichenfication	Pruritus
0 day	0.286 ± 0.2	0	1.071 ± 0.6	0	1.500 ± 0.8	2.357 ± 0.5	2.785 ± 0.4
7 day	0.286 ± 0.2	0	1.071 ± 0.6	0	*1.286 ± 0.6	2.286 ± 0.4	*2.250 ± 0.3
14 day	0.143 ± 0.2	0	*0.679 ± 0.4	0	*0.786 ± 0.5	*1.964 ± 0.4	*1.286 ± 0.4
21 day	0	0	0.429 ± 0.4	0	*0.357 ± 0.4	*1.571 ± 0.5	1.071 ± 0.2

Mean ± SD, n=7, *: P<0.05, significant (Paired t –test)

Table 8.4: Change in key signs and symptoms during the course of study for Group 1A: Microemulsion based placebo cream

Time/ parameter	Erythema	Oozing/ crusting	Excoriation	Oedema	Scaling	Lichenfication	Pruritus
0 day	0.250 ± 0.5	0	0.500 ± 0.6	0	1.500 ± 0.6	2.000 ± 0.0	2.750 ± 0.5
7 day	0.250 ± 0.5	0	0.500 ± 0.6	0	*0.750 ± 0.6	1.875 ± 0.25	2.250 ± 0.6
14 day	0	0	0.375 ± 0.5	0	0.500 ± 0.4	1.875 ± 0.25	2.125 ± 0.6
21 day	0	0	0.250 ± 0.5	0	0.250 ± 0.3	1.875 ± 0.25	2.062 ± 0.7

Mean ± SD, n=4, *: P<0.05, significant (Paired t –test)

Table 8.5: Change in key signs and symptoms during the course of study for Group 2A: Plain placebo cream

Time/ parameter	Erythema	Oozing/ crusting	Excoriation	Oedema	Scaling	Lichenfication	Pruritus
0 day	0.333 ± 0.5	0	1.000 ± 0.6	0	1.750 ± 0.9	2.250 ± 0.4	2.750 ± 0.4
7 day	0.333 ± 0.5	0	1.000 ± 0.6	0	*1.333 ± 0.7	2.250 ± 0.4	*2.208 ± 0.3
14 day	0.167 ± 0.2	0	0.917 ± 0.7	0	*1.333 ± 0.5	2.250 ± 0.4	1.958 ± 0.1
21 day	0.167 ± 0.2	0	0.833 ± 0.7	0	*0.833 ± 0.5	2.250 ± 0.4	1.792 ± 0.2

Mean ± SD, n=6, *: P<0.05, significant (Paired t –test)

Table 8.6: Percentage reduction in signs and symptoms at the end of treatment (21 days)

Parameter	Group 1: (n=6)	Group 2: (n=7)	Group 1a: (n=4)	Group 2a: (n=6)
Erythema	95.83 ± 4.167	100	100	100
Excoriation	75.00 ± 25.00	*55.56 ± 15.91	50.00 ± 50.00	20.00 ± 20.00
Scaling	95.83 ± 4.167	*76.67 ± 8.333	81.25 ± 11.97	77.00 ± 10.20
Lichenification	57.50 ± 7.50	*34.40 ± 5.25	6.250 ± 6.250	0
Pruritus	69.44 ± 1.757	60.95 ± 2.974	26.04 ± 8.736	33.75 ± 5.017

Mean ± SEM, *: P<0.05, significant (t –test), Group 1: HPMEC (0.035%), Group 2: HP cream (0.05%),

Group 1A: Microemulsion based placebo cream, Group 2A: Plain placebo cream

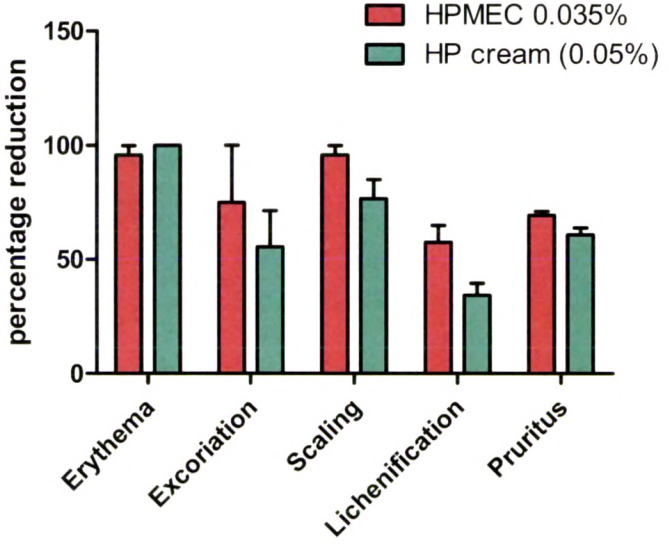


Fig. 8.4

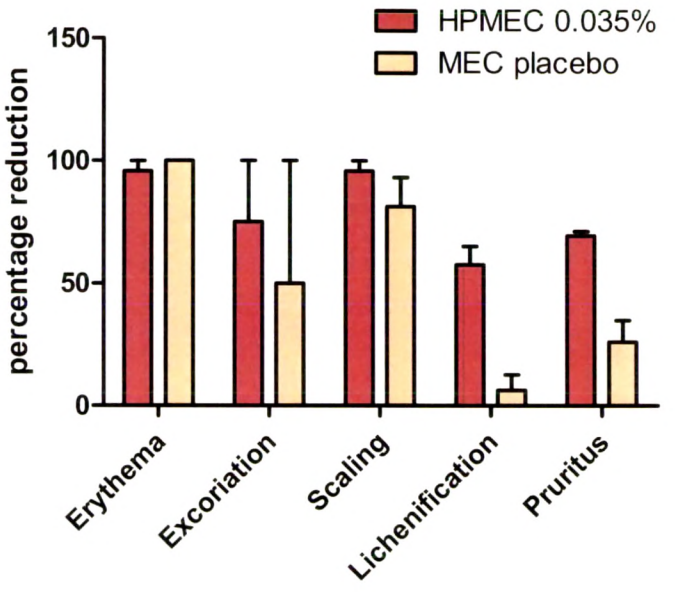


Fig 8.5

Fig. 8.4: Comparative percentage reduction in signs and symptoms at the end of treatment for HPMEC 0.035% and HP cream 0.05%

Fig. 8.5: Comparative percentage reduction in signs and symptoms at the end of treatment for HPMEC 0.035% and MEC placebo

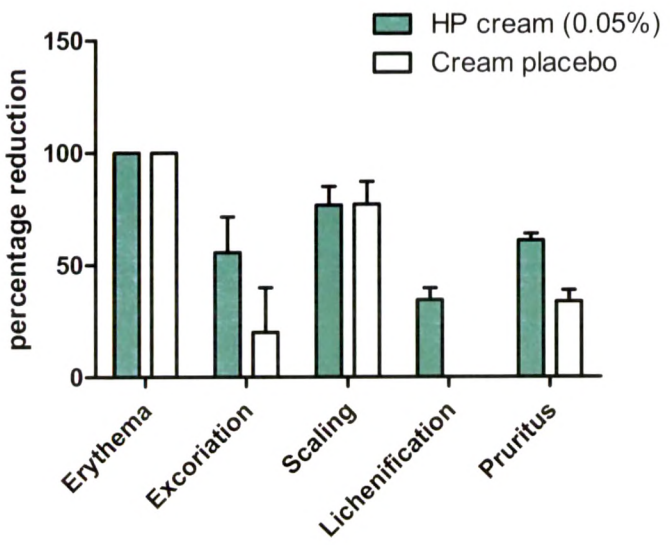


Fig. 8.6

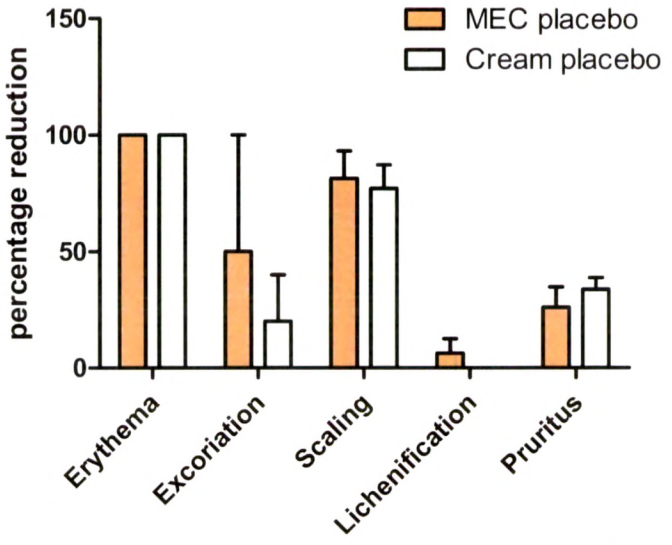


Fig.8.7

Fig. 8.6: Comparative percentage reduction in signs and symptoms at the end of treatment for HP cream 0.05% and Cream Placebo

Fig. 8.7: Comparative percentage reduction in signs and symptoms at the end of treatment for MEC Placebo and Cream Placebo

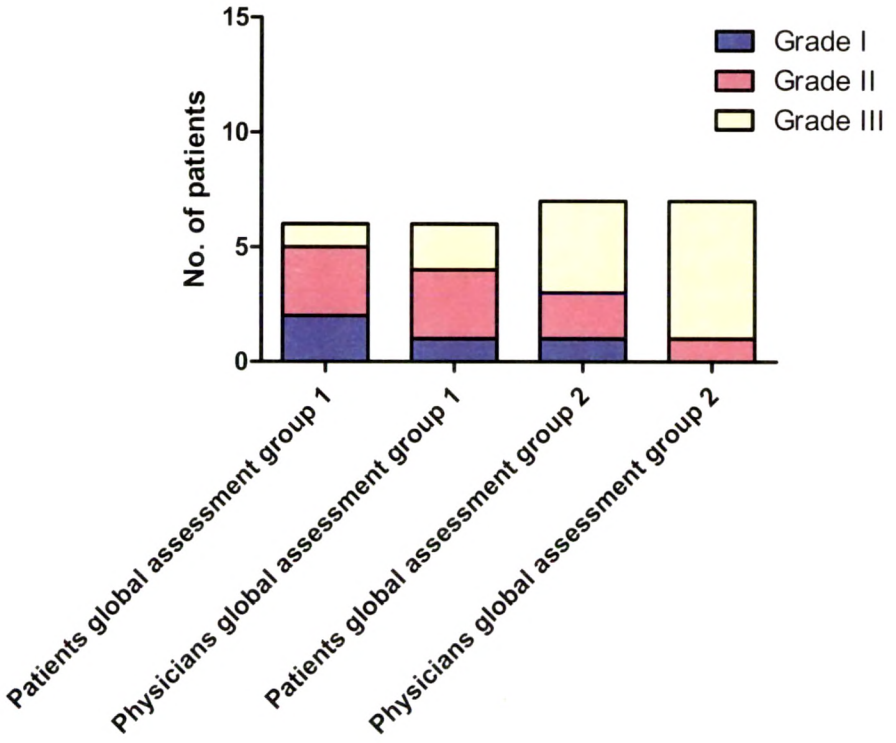


Fig. 8.8: Comparative overview of patient & physician global assessment for group1: HPMEC 0.035% and group2: HP Cream 0.05%

8.4 Discussion

Skin Blanching Bioassay

The vasoconstrictor assay or the skin blanching bioassay study was carried out for HPMEC 0.035% in comparison to HP cream 0.05% in healthy human subjects. The results show an improvement in efficacy of the product when formulated as microemulsion based cream. The pharmacodynamic response was seen to elicit faster in case of the nanotechnology based product. It was observed that the skin blanching lasted longer, suggesting an increased permeation and retention of the drug and hence, enhanced therapeutic efficacy of the product thus giving an equivalent response even in lower dose (Fig. 8.1- 8.3) (Schwarb et al, 1999).

Pilot study in dermatitis patients

Group 1: Microemulsion based halobetasol propionate cream (0.035%)

Group 2: Plain halobetasol propionate cream (0.05%)

Group 1A: Microemulsion based placebo cream

Group 2A: Plain placebo cream

The disease severity score based on the clinical course, disease intensity and extent of body surface involved was statistically similar in the two groups viz. microemulsion based cream 0.035% and plain cream 0.05% group. The scores indicated a moderate to severe progression of disease in the patient groups (Table 8.1). The mean age was 50.6 ± 19.1, 61 ± 5.4 years for the two groups (Table 8.1). This can be interpreted as the patients enrolled for the study had moderate dermatitis and the overall demography in each group was similar.

The percent reduction of erythema from the baseline level, at the end of study when compared between group 1 and 2 and also with their placebo (1A and

2A) respectively was almost equivalent, achieving a near complete control over the symptom (Table 8.6).

The % reduction of excoriation form the baseline level at the end of study although was not statistically significant between the two groups (1 and 2, 1A and 2A), but the mean values indicated effectiveness of microemulsion based cream over plain cream (Table 8.6). The reduction in excoriation in group 2 was statistically significant in the second week of treatment. (Table 8.3) when comparing the reduction in excoriation between medicated preparations (group 1 and 2) and their respective placeboes (group 1A and 2A), it is observed that placeboes don't have any significant impact on alleviating excoriation and the medicated preparations are more effective. The reduction in scaling and pruritus in group 1 continued through all the 3 weeks of study indicating effectiveness in reducing scaling and thus the resultant pruritus (Table 8.2). In group 2 reduction in scaling and pruritus continued through all the 3 weeks. But reduction in pruritus was not significant in the last week of study (Table 8.3). The % reduction of scaling at the end of study was higher with the microemulsion based cream as compared to plain cream (Table 8.6). The % reduction of pruritus at the end of study was slightly higher with the microemulsion based cream as compared to plain cream (Table 8.6) and significantly higher from their respective placebos.

The reduction in lichenification in group 1 and 2 was significant only after the second week when the active treatment started (Table 8.2, 8.3). The % reduction of lichenification at the end of study in group 1 was significantly more than group 2 (Table 8.6) and significantly higher from their respective placebos. The reduction in the key signs and symptoms in the two placebo groups (1A and 2A) showed no significant change during the three weeks except in case of scaling and erythema. (Table 8.4 and 8.5) The two placebos

were almost equally effective in control of erythema, scaling and lichenification (Table 8.6). The patient's global assessment of the treatment revealed that more number of patients experienced better control over disease with the use of HPMEC 0.035% as compared to HP cream 0.05%. The patients and physicians both reported higher number of patients with grade I improvement in global assessment (Fig. 8.8). Thus these studies clearly demonstrate the effectiveness of low dose HPMEC 0.035% over HP cream 0.05% in dermatitis patients and presents a scope for dose reduction of a high potency corticosteroid (Bhankharia et al, 2004, Saple et al, 2003, Mukhopadhyay et al, 2010).

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