

EFFICACY AND SAFETY OF TOPICAL CALCIPOTRIOL PLUS BETAMETHASONE DIPROPIONATE VERSUS TOPICAL BETAMETHASONE DIPROPIONATE ALONE IN MILD TO MODERATE PSORIASIS

ABSTRACT

Psoriasis is one of the prototypic papulosquamous skin diseases characterized by erythematous papules or plaques. This disease is chronic in nature with a tendency to relapse. In this disease the skin keeps scaling as flakes called psoriatic plaques due to rapid and excessive multiplication of epidermis cells which look like fishy skin and finally peels off as exfoliation. Betamethasone Dipropionate is 17, 21-dipropionate ester of betamethasone, a synthetic glucocorticoid with metabolic, immunosuppressive and anti-inflammatory actions. Betamethasone dipropionate binds to specific intracellular glucocorticoid receptors and subsequently binds to DNA to modify gene expression.

The study duration was 6 weeks. A total of 60 study participants of both sexes diagnosed with mild to moderate psoriasis were included in the study. They were randomized into two groups. Group A – topical calcipotriol plus betamethasone treatment group consisting of 30 patients and Group B – topical betamethasone alone also consisting of 30 patients and a total of 28 patients in topical calcipotriol plus betamethasone treatment group and 28 patients in topical betamethasone group completed the study.

Keywords: calcipotriol plus, betamethasone dipropionate, moderate psoriasis

INTRODUCTION

Psoriasis is a common autoimmune skin disease is derived from Greek word “psora” which means “itch”^[1]. It is characterized by round, circumscribed, dry, scaling plaques of varying sizes and covered by greyish white or silvery white scales, affecting approximately 2% of the population and leads to considerable impairment of the quality of life of the affected patients^[1-2]. The most commonly affected sites are the scalp, tips of fingers and toes, palms, soles, umbilicus, gluteus, under the breasts and genitals, elbows, knees, shins and sacrum^[3].

Psoriasis affects both sexes and can occur at any age. It can occur in people of all races. Whites suffer more than blacks^[4]. Psoriasis has a genetic basis and studies clearly signify a genetic association in psoriasis, with the incidence being greater amongst first-degree and second-degree relatives of patients^[4]. The genetics of psoriasis are known to be complex, with ten or more susceptibility loci, and these probably interact with various environmental factors that act on the skin or immune system.

It is a T-lymphocyte mediated autoimmune disease. T-lymphocytes, both CD4⁺ and CD8⁺ cells, are activated (HLA DR⁺ and CD25⁺). In dermis the CD4⁺ cells predominate, while CD8⁺ cells prevail in the epidermis. One of the earliest events in the psoriatic plaques is the influx of activated CD4⁺ cells. In resolving plaques an influx of CD8⁺ cells predominates, while there is a decrease of CD4⁺ cells^[5]. The induction of T-cell activation by psoriatic epidermal cells is highly dependent on the population of CD1a-DR⁺ dendritic cells, while CD1a⁺ Langerhans cells, HLA-DR⁺ keratinocytes and dermal dendrocytes might also be relevant APCs in psoriasis. Activated T-lymphocytes produce two different patterns of cytokines by (1)Th1 cells produce IL-2 and IF- γ , (2)Th2 cells produce IL-4, IL-5, and IL-10.

Abnormal activation of leukocytes leads to the accumulation of T cells and other

immune cells in developing skin lesions. T cells secrete proinflammatory cytokines which cause keratinocyte hyper proliferation and altered differentiation^[6]. The turnover time of the epidermis speeds up significantly and leads to the characteristic psoriatic lesions^[7].

Corticosteroids have an anti-inflammatory and immunomodulating effect. Corticosteroids inhibit different proinflammatory cytokines^[8]. They also inhibit production of cytokines (IL -1, IL-6, IL-8, tumor necrosis factor- α , interferon- γ), reduce mediators of inflammation (prostaglandins, leukotrienes, nitric oxide), decrease the abnormal CD4:CD8 ratio and the number and activity of Langerhans cells. When compared to systemic corticosteroids, topical corticosteroids have lesser side effects^[9].

The active form of vitamin D3 is known to play an important role in the stimulation of cellular differentiation, inhibition of proliferation and immunomodulation^[10]. This makes vitamin D3 a potential candidate for treatment of psoriasis. However, oral administration of parent vitamin D3 might not be suitable for treating psoriasis due to potential for hypercalcemia. Hence, several vitamin D3 analogues have been developed for treatment of psoriasis. Vitamin D analogues bind to the vitamin D receptor, thus causing biological actions on both keratinocytes and on immune-competent cells in the skin^[11]. Calcipotriol is a synthetic vitamin D3 analogue formulated as a cream and scalp solution. Calcipotriol regulates the proliferation and differentiation of keratinocytes^[12]. The calcipotriol cream is effective and statistically significant in treating psoriasis than the placebo alone^[13].

For decades, topical corticosteroids, particularly high- potency steroids, have been the mainstay in the topical treatment of psoriasis. Psoriatic patients with thick plaques often require treatment with the highest potency corticosteroids and are prone to multiple side effects with long term use^[14]. Safe and effective therapeutic options for plaque psoriasis are limited and the results are not satisfactory to some extent. Hence the treatment plan should include obtaining rapid control of the disease and maintaining that control. The combination therapy has synergistic or additive effects thereby showing superior efficacy and is better tolerated than monotherapy.

The purpose of the present study was to compare the efficacy and safety of calcipotriol combination

therapy with betamethasone dipropionate and betamethasone monotherapy.

MATERIALS & METHODS

The study was conducted in Sree Balaji Medical College and Hospital, Chennai during the period from March 2016 to September 2016 in accordance with declaration of Helsinki and ICH-GCP guidelines. The study protocol was reviewed and approved by the Institutional Ethics Committee and all trial participants have been informed about the study procedures and written informed consent was obtained.

The Drug Therapy was given free of cost to the patients and they were given assurance that any withdrawal from the study would not affect their future treatment in the same hospital. Patients diagnosed to have mild to moderate psoriasis by the physician based on Psoriasis severity index score (PASI score) who meets the inclusion criteria and are willing to give consent for the study were selected. Total of 98 patients were screened in that 11, refused to participate and remaining 27 didn't meet the inclusion criteria.

All the 60 patients selected were randomized with the help of a statistical software SPSS version 16 and allotted a treatment group. Participants received either one of the study drug for a period of 4 weeks. The baseline features like demographic data, general, systemic and local examination were carefully noted in the case report form. Contact numbers of the investigators and Emergency physicians were provided to all the study participants for any queries during the study period and for reporting of any adverse events.

There were four scheduled visits during the study, baseline visit, after 2weeks, then after 4weeks and after 6weeks (end of study visit)

Drug Dosage:

Study Group I:

Topical Calcipotriol plus betamethasone dipropionate

Topical Calcipotriol (50microgram/g) plus betamethasone dipropionate (500microgram/g) once daily for 4 weeks

Study Group II:

Topical Betamethasone dipropionate

Topical Betamethasone dipropionate (500 microgram /g) alone once daily for 4 weeks

RANDOMIZATION:

All 60 subjects are randomized to two treatment groups in 1:1 ratio using computer generated randomization with Statistical Package for the Social Sciences (SPSS) version 16.

LABORATORY INVESTIGATIONS:

The following Laboratory investigations are done during screening i.e. baseline visit ("0" weeks) Blood Biochemistry (Complete blood profile was tested)

STATISTICAL ANALYSIS:

Data analysis was done using Statistical Package for the Social Sciences (SPSS) version 16. "Intent to treat" principle was employed; meaning all volunteer participants who had received at least one dose of study medication was included in the statistics. Independent "t" test was done between the two study groups. Paired "t" test was done for comparing measurements within each group. The statistical significance was reported based on the p value, where value <0.05 was considered to be significant.

RESULTS AND DISCUSSION

A total of 98 patients were screened for this study, out of which 38 patients were excluded where 11 patients refused to participate and 27 patients didn't meet the inclusion criteria of our study.

The selected population of 60 patients was randomized to two groups and the treatment started as and when they reported to the hospital. Two patients from topical betamethasone group and 2 patients from topical calcipotriol plus betamethasone group failed to complete the study. One patient from betamethasone group couldn't be reached from the first week. One patient from calcipotriol plus betamethasone group requested to remove from the study during his 1st visit (2 weeks) and withdrew his consent. There was no discontinuation or withdrawal due to an adverse event.

All statistical analysis was done in SPSS version 16 and intent to treat principle is employed for analysis. Results were distributed in demographics, treatment comparison, and adverse event profile.

CALCIPOTRIOL PLUS BETAMETHASONE GROUP (N=30)

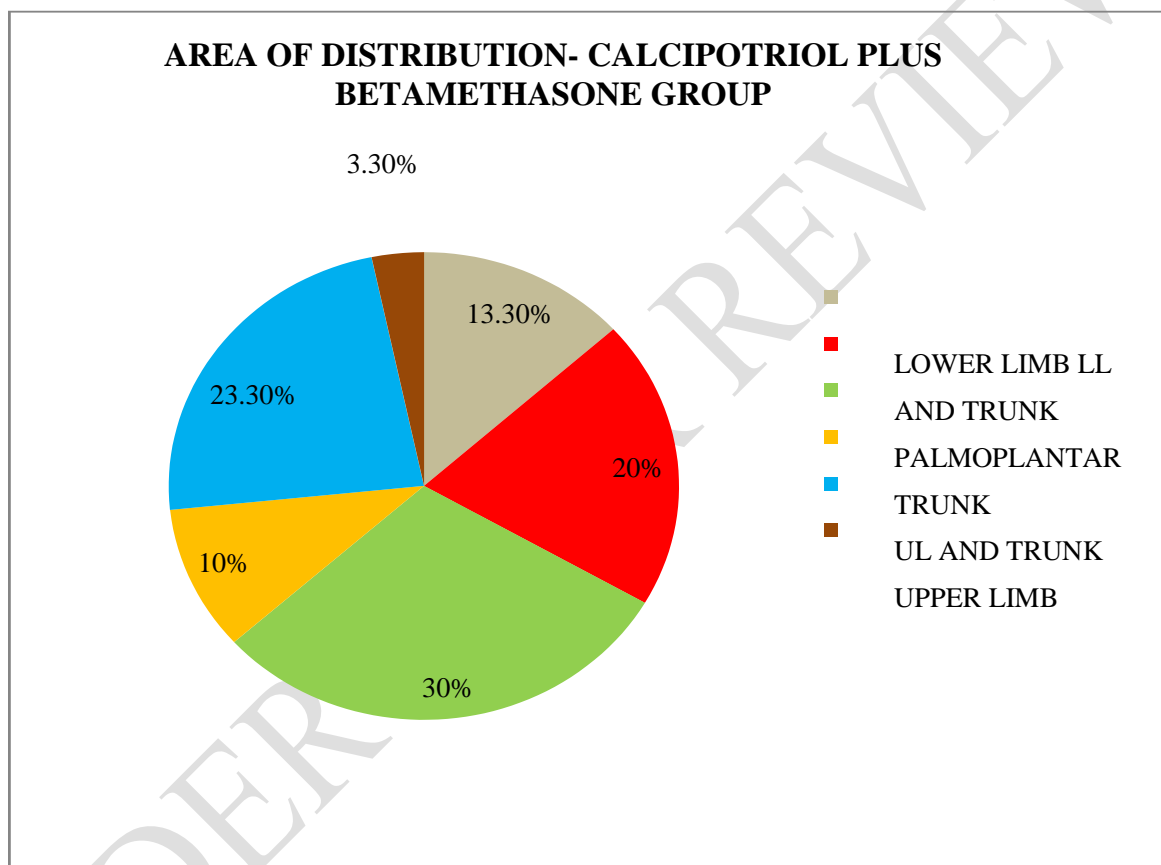
AGE:

The mean age is 43.83 years with standard deviation of 13.16 years (MEAN \pm S D DEVIATION= 43.83 \pm 13.16) with minimum age of 20 years and a maximum of 63 years.

SEX:

This group had 15 males (50%) and 15 females (50%) as participants.

Figure-1: Area of distribution in group I

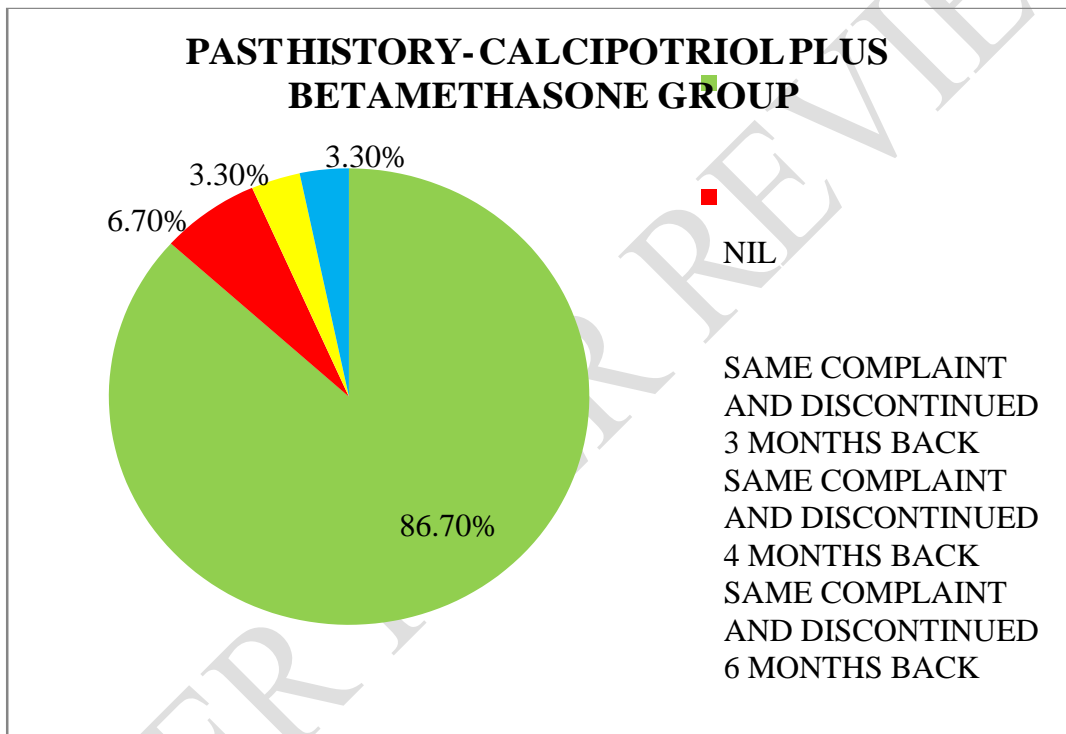


PAST HISTORY:

Majority of them N=26 (86.7%) did not have any past history.

Two of them (6.7%) had same complaint and discontinued treatment 3 months before. One patient (3.3%) had same complaint and discontinued treatment 4 months before. One patient (3.3%) had same complaint and discontinued treatment 6 months before.

Figure-2: Past history among group I



COMPLETED TREATMENT AND FOLLOW UP:

28 patients had completed treatment (93.3%) and follow up after 2 weeks of the study whereas 2 patients discontinued the treatment. (6.7%)

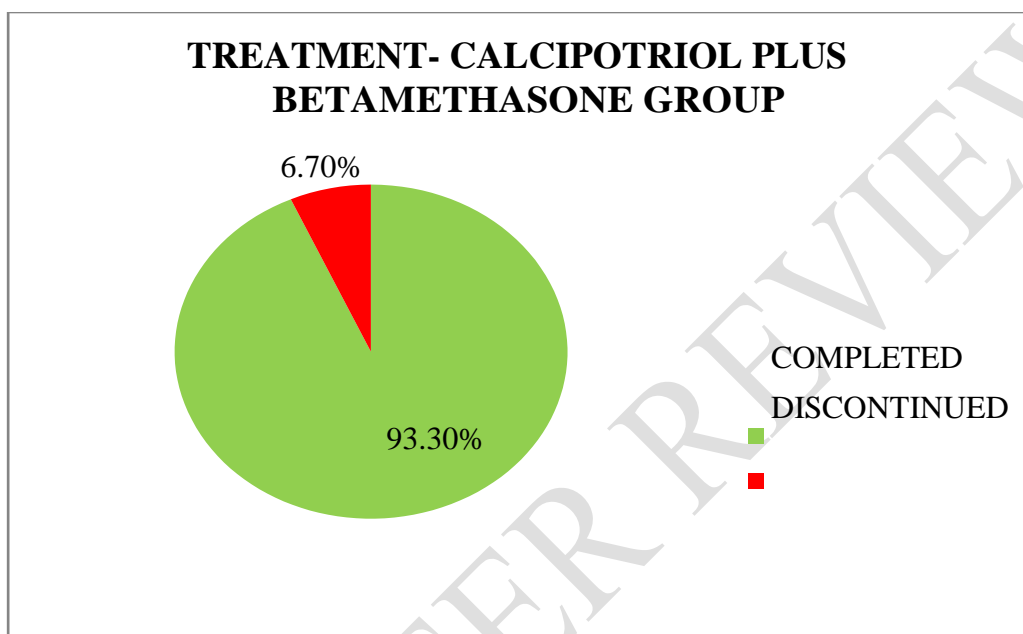


Figure-3: Completion of treatment among group I

ADVERSE REACTIONS:

1 patient (3.3%) had a hypopigmented patch whereas other 29 patients (96.7 %) developed no reactions.

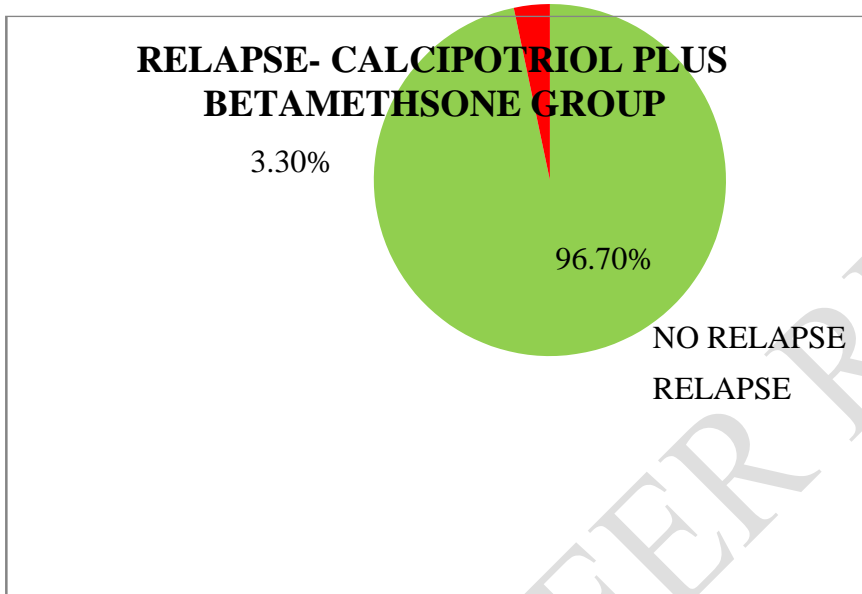
Table-1: Adverse reactions among group I

ADVERSE REACTIONS	FREQUENCY	PERCENTAGE
NIL	29	96.7%
HYPOPIGMENTATION	1	3.3%

RELAPSE:

29 patients had no relapse (96.7%) whereas 1 patient (3.3%) developed relapse.

Figure re-4: Relapse among group I



BETAMETHASONE GROUP (N=30):

AGE:

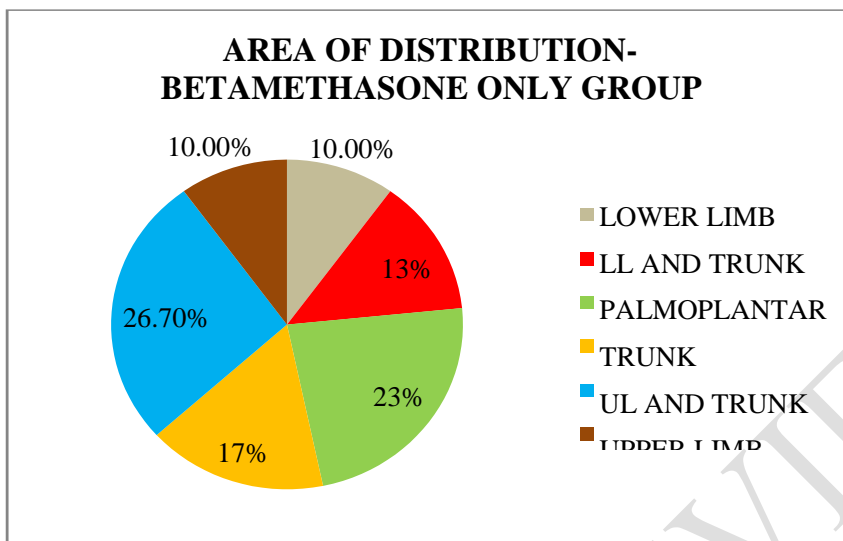
The mean age is 42.70 years with standard deviation of 11.72 years (MEAN ± STD DEVIATION= 42.70 ± 11.72)

with minimum age of 26 years and a maximum of 61 years.

SEX:

This group had 13 males (43.33%) and 17 females (56.66%) as participants.

Figure-5: Area of distribution in group II



Majority of them N=27 (90%) did not have previous past history.

PAST HISTORY:

Two of them (6.7%) had same complaint and discontinued treatment 4 months before. One patient (3.3%) had same complaint and discontinued treatment 6 months before.

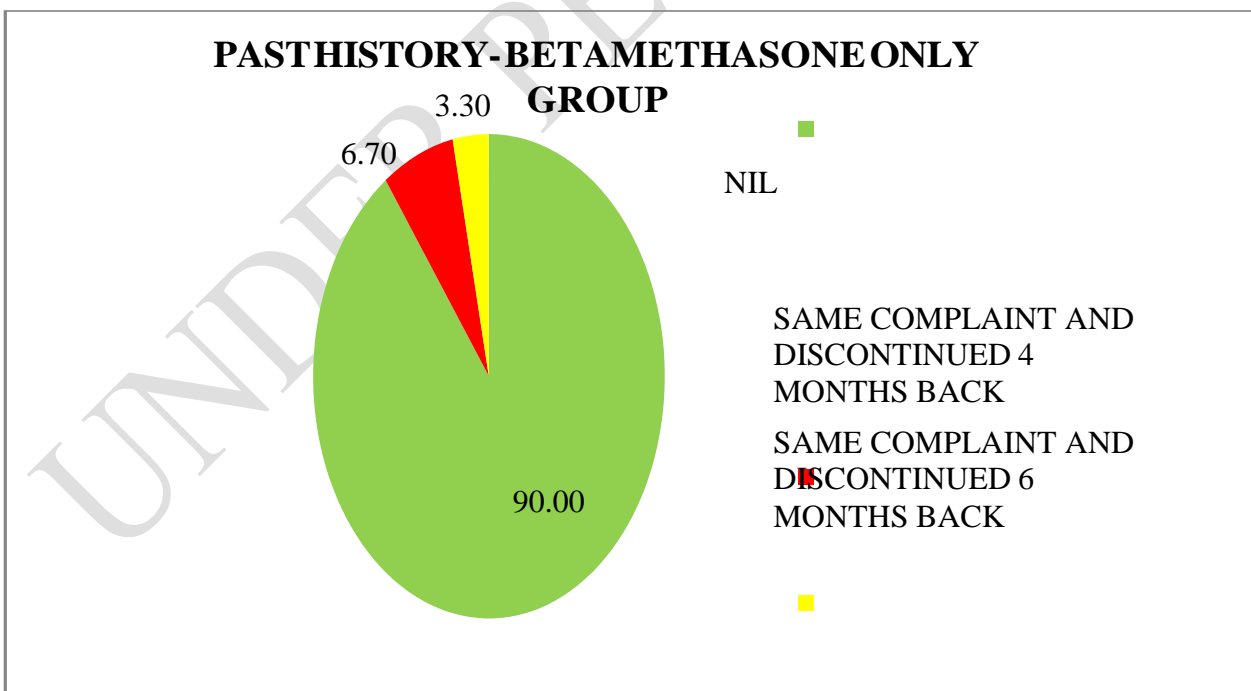


Figure-6:Past history among group II.

PSORIASIS SCORE INDEX:

PASI 0 WEEK:

The mean PASI score of 30 patients at 0 week is 9.447 with standard deviation of 0.768 (Mean \pm SD = 9.447 \pm 0.768). The minimum score was 7.2 and maximum score was 10.8

PASI 2 WEEK:

The mean PASI score of 29 patients (one patient discontinued) at 2 weeks is 5.786 with standard deviation of 0.769 (Mean \pm SD = 5.786 \pm 0.769). The minimum score was 4.2 and maximum score was 7.4.

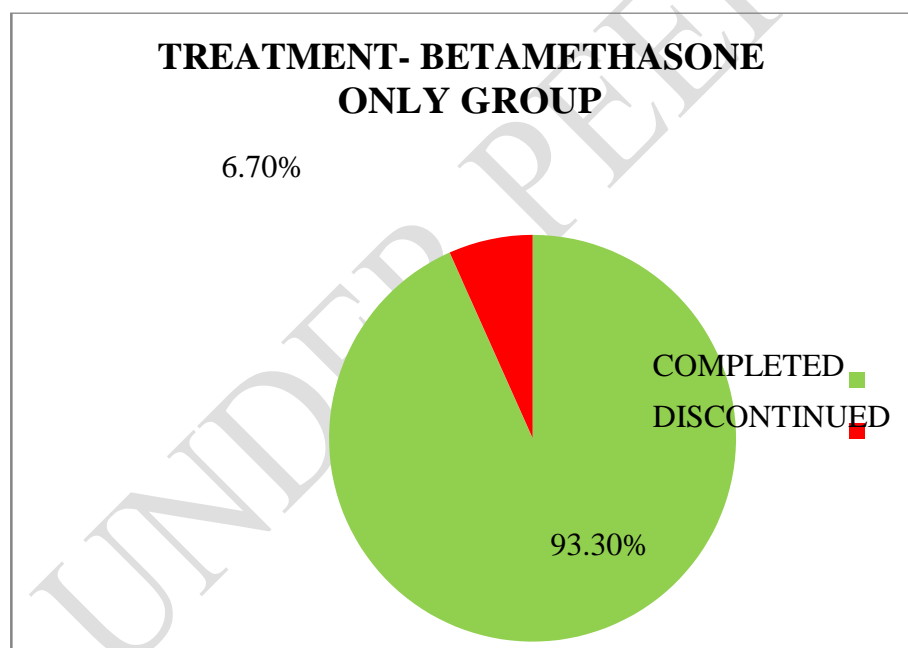
PASI 4 WEEK:

The mean PASI score of 28 patients (Two patients discontinued) at 4 weeks is 3.732 with standard deviation of 0.520 (Mean \pm SD = 3.732 \pm 0.520). The minimum score was 2.4 and maximum score was 4.8.

COMPLETED TREATMENT AND FOLLOW UP:

28 patients had completed treatment (93.3%) and follow up after 2 weeks of the study whereas 2 patients discontinued the treatment. (6.7%)

Figure7: completion of treatment among group II



ADVERSE REACTIONS:

There were no adverse reactions in the 30 patients.

RELAPSE:

28 patients had no relapse (93.3%) whereas 2 patients (6.7%) developed relapse.

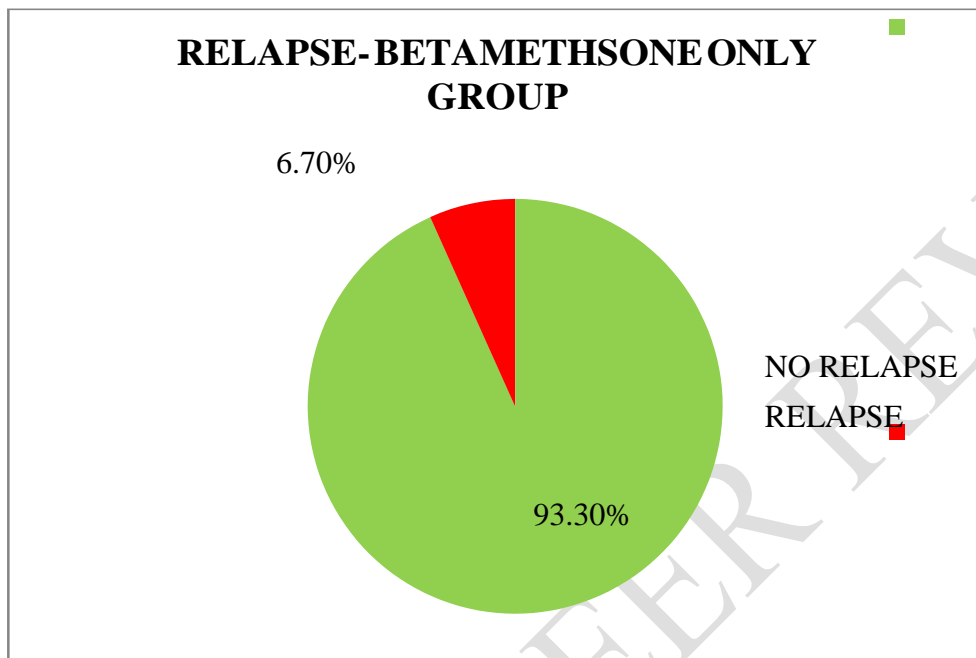


Figure-8: Relapse among group II

BASELINE INVESTIGATIONS:

Baseline investigations remains similar in both the groups and are within normal limit

PASI SCORE AT 0 WEEK:

Table- 2: Comparison of Psoriasis Area and Severity Index (PASI) in Group I and Group II (Baseline)

Two- sided confidence interval 95%			
	Sample Size	Mean	Standard Deviation
Group I	30	9.293	0.7697
Group II	30	9.447	0.7682
Results	t statistics	df	p-value¹
Equal Variance	-0.775654	58	0.4411

This result shows that PASI score at 0 week ($p= 0.44$) is not significant.

EFFECT OF DRUG ON PASI SCORE AFTER 2 WEEKS:

Table- 3: Comparison of Psoriasis Area and Severity Index (PASI) in Group I and Group II (2 weeks).

Two- sided confidence interval 95%				
	Sample Size	Mean	Standard Deviation	PASI score Percentage Reduction
Group I	30	5.314	0.711	42.81%
Group II	30	5.786	0.7694	38.75%
Results	t statistics	df	p-value¹	
Equal Variance	-2.46775	58	0.01657	

This result shows that PASI score after 2 weeks of the treatment ($p= 0.01$) is statistically significant.

EFFECT OF DRUGS ON PASI SCORE AFTER 4 WEEKS:

Table- 4: Comparison of Psoriasis Area and Severity Index (PASI) in Group I and Group II (4 weeks).

Two- sided confidence interval 95%				
	Sample Size	Mean	Standard Deviation	PASI Score Percentage Reduction
Group I	28	2.989	0.5087	67.83%
Group II	28	3.732	0.52	60.49%
Results	t statistics	df	p-value ¹	
Equal Variance	-5.40465	54	0.000001505	

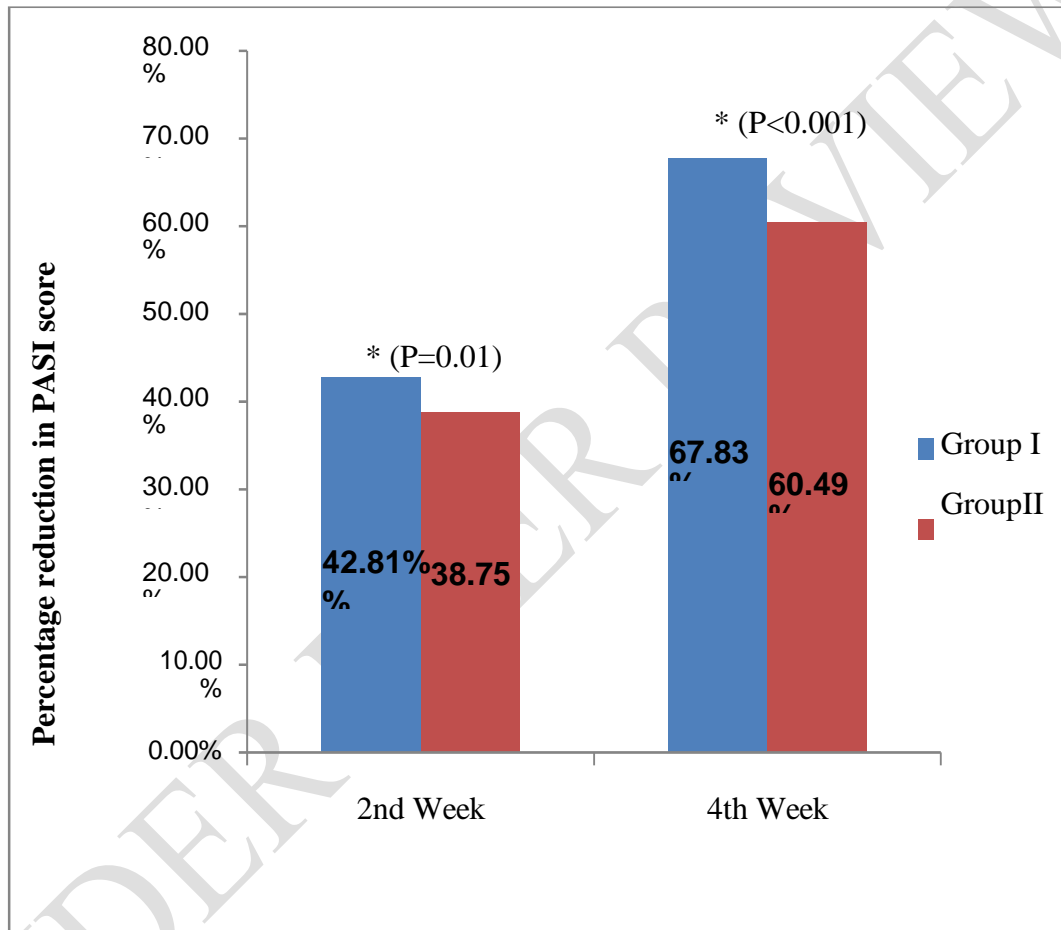
These results show statistically significant reduction in PASI score from base line after 4 weeks of treatment in both treatment groups ($p < 0.001$).

The significant reduction in PASI score in group I is mainly due to the combined action of calcipotriol and betamethasone dipropionate. Betamethasone produce prolonged anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties without curing the underlying condition. Calcipotriol induces differentiation and suppresses proliferation of keratinocytes, thus reversing the abnormal keratinocyte changes in psoriasis. Thus the combination of calcipotriol plus betamethasone not only produce symptomatic relief but also aids in curing the underlying condition thereby leading to normalization of epidermal growth.

GROUP I- TOPICAL CALCIPOTRIOL PLUS BETAMETHASONE

GROUP II- TOPICAL BETAMETHASONE ALONE

Figure-9: Psoriasis Area and Severity Index (PASI) Percentage Reduction in Group I and Group II after 2 weeks and 4weeks.



These results shows that there is statistically significant percentage reduction in PASI score after 2 weeks (p=0.01) and 4weeks (p<0.001) of treatment in both groups.

Psoriasis is a chronic disease where treatments are often needed throughout the life. Hence quality of patient's life is often affected. The availability of studies relating to the management of Psoriasis is limited when compared to the prevalence of its complications. Topical therapies are the mainstay of treatment for chronic plaque psoriasis. These include keratolytics, coal tar, corticosteroids, topical PUVA, calcipotriol alone and in combination with topical steroids.

The antipsoriatic effect of betamethasone and calcipotriol has been individually reported in a number of studies. Calcipotriol, a vitamin D analogue has proven to be highly efficacious in limited chronic plaque psoriasis. There are few trials comparing its efficacy with other topical agents such as steroids and coal tar. Sharma et al., reported >50% reduction in ESI score at week 4 in 60% of lesions treated with calcipotriol compared to 23.3% of lesions treated with coaltar ($P < 0.01$) [16]. Another study found the efficacy of calcipotriol/ Betamethasone formulations to be better than calcipotriol alone at 2 and 4 weeks follow-up and showed a greater reduction in mean PASI in combined formulation group (68.6% in once daily, 73.8% in twice daily group) than in the twice daily calcipotriol alone group (58.8%) and the vehicle group (26.6%).

The two - compound formulation of calcipotriol with betamethasone has been found to be superior to either component used alone^[17]. In this study effectiveness in reduction of psoriasis score index (PASI) was compared between the treatments with topical calcipotriol plus betamethasone (combined therapy) and betamethasone. Both group's topical calcipotriol plus betamethasone (Group I) and topica betamethasones (Group II) were well-matched in terms of pretreatment characteristics. The mean age was (43.83 ± 13.16) years and (42.70 ± 11.72) years in Group I and II respectively. There were 15 males (50%) and 15 females (50%) in group I and 13 males (43.33%) and 17 (56.66%) females as participants in group II. Family history of same disease was found in 10 patients (33.3%) in group I and 12 patients (40%) in group II.

The current study shows that topical calcipotriol plus betamethasone (Group I) and topical betamethasone (Group II) significantly reduced PASI. The Mean PASI score of Group I and Group II at baseline was (9.293 ± 0.7697) and (9.447 ± 0.7682) respectively. After 2 weeks of the treatment, mean PASI score was reduced to (5.314 ± 0.711) for Group I and (5.786 ± 0.7694) Group II. The mean difference in PASI score was

statistically significant ($p=0.01$) between both groups After 4 weeks of the treatment, score further decreased to (2.989 ± 0.5087) and (3.732 ± 0.52) in Group I and Group II. Topical calcipotriol plus betamethasone treated patients show very much significant ($p<0.001$) reduction in their PASI as compared to betamethasone alone treated patients

In our study, the mean percentage of PASI reduction after 4th week of the treatment was 67.83% in the topical calcipotriol plus betamethasone group and 60.49% in the betamethasone group respectively ($p<0.001$). These results shows that topical calcipotriol plus betamethasone to be more effective than betamethasone. Therefore combination therapy is more effective in reducing the psoriatic lesions thereby decreasing the psoriasis score index.

These findings were consistent with other studies. Dahri *et al.*, carried out a trail with 60 patients and divided into two equal groups namely group A and group B. The improvement in the parameter of PASI observed in group A was 67.89% i.e. the mean change from 14.08 ± 0.33 to 4.52 ± 0.22 ; while improvement in the parameter of PASI observed in group B (Calcipotriol plus Betamethasone) is 81.495%, the mean change from 12.81 ± 0.35 to 2.37 ± 0.36 . The results are highly significant i.e. ($p<0.001$) and showing great improvement in patient's symptoms^[18,19].

One patient in Group I (3.3%) reported hypopigmented patch and no other adverse effects were observed. Molin *et al.*, conducted a study with 421 patients and randomized either to treatment with calcipotriol (210 patients) or betamethasone (211 patients)^[20]. Adverse events were more frequent with calcipotriol than betamethasone. This shows that Calcipotriol plus Betamethasone therapy is safer as it produces less adverse effects than calcipotriol alone.

Calcipotriol has antipsoriatic action through inhibition of epidermal proliferation and inflammation and enhancement of normal keratinization^[15]. They can also affect the local immune system by triggering apoptosis in inflammatory cells, inhibiting T helper (Th) 1 cytokine production, and induction of a Th1 to Th2 switch. Topical corticosteroids have anti-inflammatory and antiproliferative effects^[15]. Betamethasone inhibits production of cytokines and reduces mediators of inflammation. Calcipotriol plus Betamethasone two compound formulation provides better compliance

for patients than monotherapy due to the combined action of vitamin D3 analogues on keratinocyte differentiation with the anti-inflammatory effect of steroids.

Thus combination of Calcipotriol plus Betamethasone has a more rapid onset of action compared to betamethasone alone there by leading to significantly faster clinical improvement and patient satisfaction.

CONCLUSION

This study revealed that topical calcipotriol plus betamethasone is efficacious compared to betamethasone alone in patients with mild to moderate psoriasis. Both treatment groups provided symptomatic relief in psoriasis. But the reduction in PASI score was high in topical calcipotriol plus betamethasone when compared with topical betamethasone alone. There was no serious adverse effect noted in both the groups.

To conclude combination therapy of topical calcipotriol plus betamethasone provide a promising role in the treatment of mild to moderate psoriasis.

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UNDER PEER REVIEW