Journal of Pharmaceutical Research International

33(23A): 28-38, 2021; Article no.JPRI.66785
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Efficacy and Safety of Topical Calcipotriol Plus Betamethasone Dipropionate Versus Topical Betamethasone Dipropionate Alone in Mild to Moderate Psoriasis

M. Sindhuja[1] and N. S. Muthiah[1*]

[1]Department of Pharmacology, Sree Balaji Medical College and Hospital, Chennai -600 044, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i23A31406
Editor(s):
(1) Dr. Giuseppe Murdaca, University of Genoa, Italy.
Reviewers:
(1) Asita Elengoe, Lincoln University College, Malaysia.
(2) Lukman Muslimin, Sekolah Tinggi Ilmu Farmasi Makassar, Indonesia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/66785

Original Research Article

Received 04 February 2021
Accepted 11 April 2021
Published 14 April 2021

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. 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. 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. 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. As a conclusion, the combination therapy of topical calcipotriol plus betamethasone provided a promising strategy for the treatment of mild to moderate psoriasis.

**Corresponding author: E-mail: muthiah.ns@bharathuniv.ac.in;*

Keywords: Calcipotriol plus; betamethasone dipropionate; moderate psoriasis.

1. 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. A 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 immunomodulation 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 in Flammarion (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 hyperkalemia. 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 corneocytes 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 immunotherapy. The purpose of the present study was to compare the efficacy and safety of calcipotriol combination therapy with betamethasone propionate and betamethasone immunotherapy.

2. MATERIALS AND 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 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 (P ASI 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 (selected using the computer aided randomized chart) 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).

2.1 Drug Dosage

2.1.1 Study group I

2.1.1.1 Topical calcipotriol plus betamethasone dipropionate

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

2.1.2 Study group II

2.1.2.1 Topical betamethasone propionate

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

2.2 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.

2.3 Laboratory Investigations

The following Basic Laboratory investigations (such as vitals and other parameters) are done during screening i.e. baseline visit ("0" weeks) Blood Biochemistry (Complete blood profile was tested).

2.4 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.

3. RESULTS AND DISCUSSION

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.

3.1 Calcipotriol Plus Betamethasone Group (N=30)

3.1.1 Age

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

3.1.2 Sex

This group had 15 males (50%) and 1 5 females (50%) as participants.

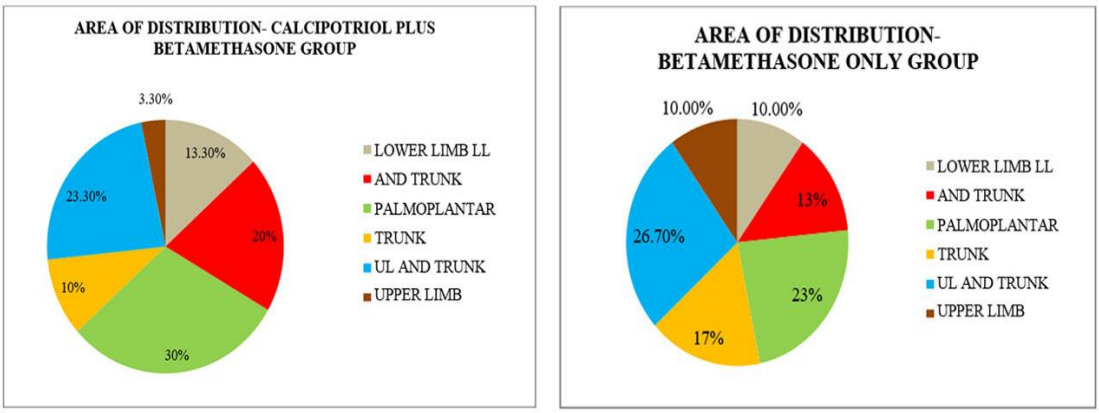

Fig. 1. Area of distribution in group I

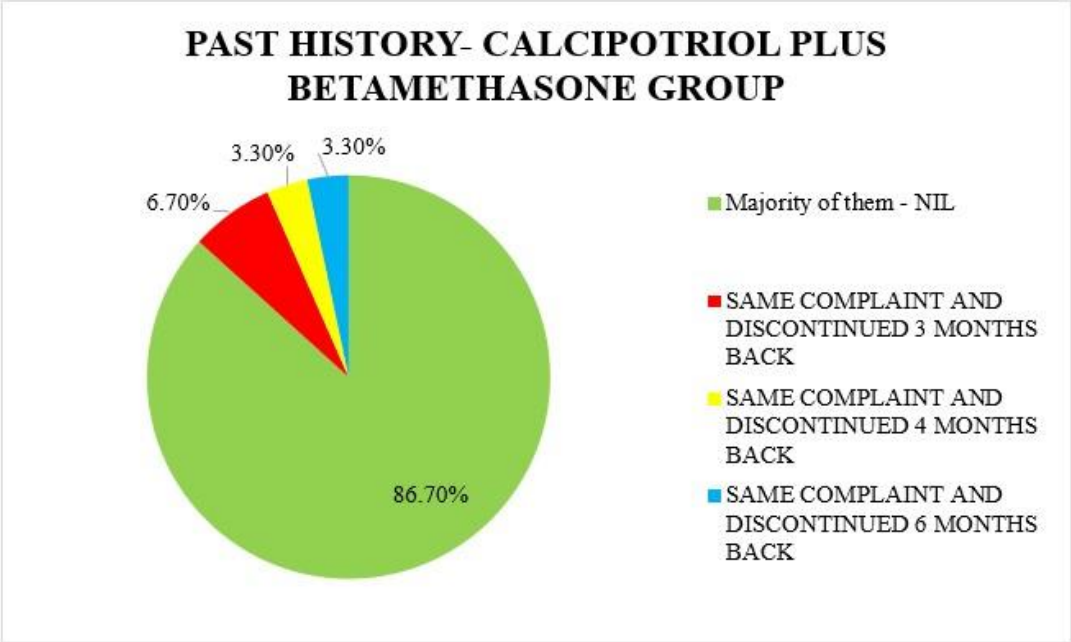

Fig. 2. Past history among group I

3.2 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.

3.3 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%).

3.4 Adverse Reactions

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

3.5 Relapse

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

3.6 Betamethasone Group (N=30)

3.6.1 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.

3.6.2 Sex

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

3.7 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.

3.8 Psoriasis Score Index

3.8.1 Pasi 0 week

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

3.8.2 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 ± SD = 5.786± 0.769). The minimum score was 4.2 and maximum score was 7.4.

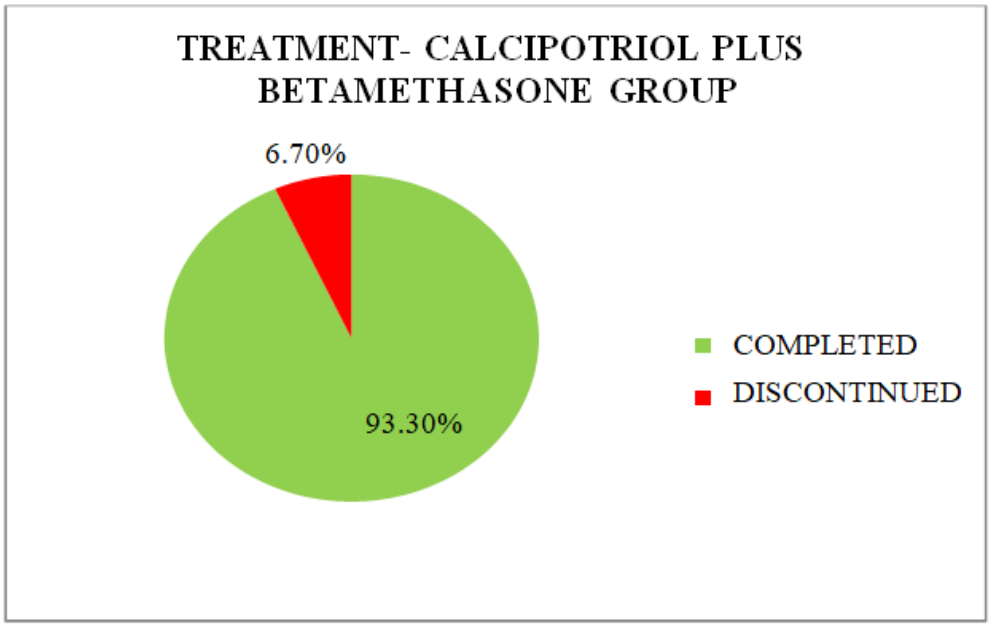

Fig. 3. Completion of treatment among group I

Table 1. Adverse reactions among group I

Adverse Reactions	Frequency	Percentage
Nil	29	96.7%
Hypopigmentation	1	3.3%

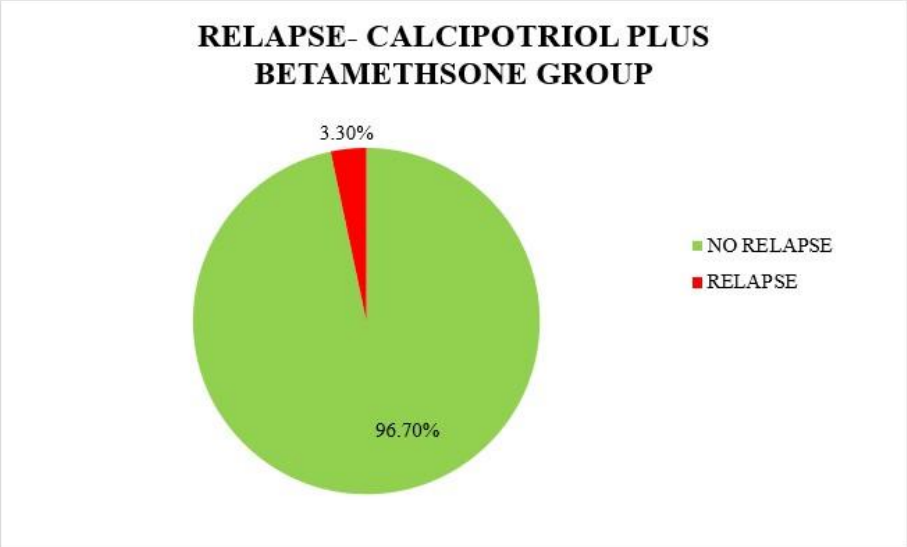

Fig. 4. Relapse among group I

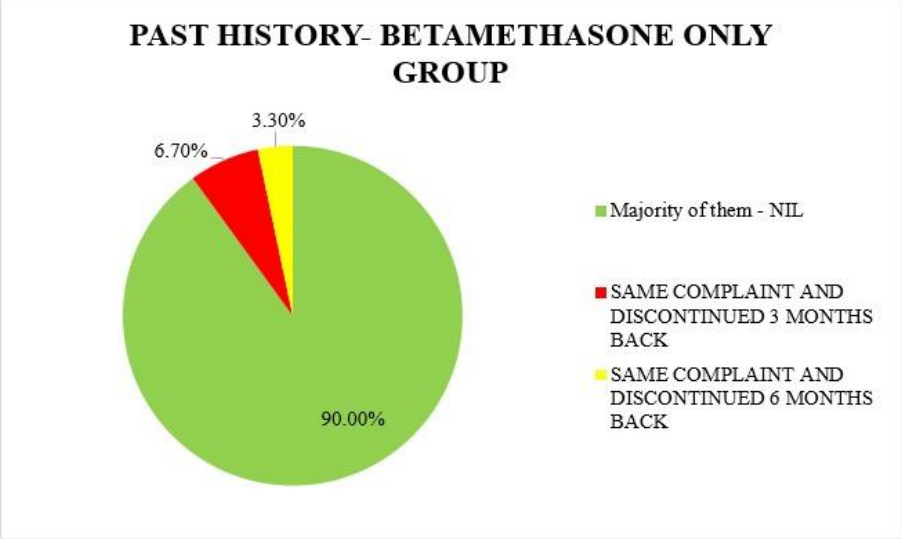

Fig. 5. Past history among group II

3.8.3 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 ± SD = 3.732 ± 0.520). The minimum score was 2.4 and maximum score was 4.8.

3.9 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%).

3.10 Adverse Reactions

There were no adverse reactions in the 30 patients.

3.11 Relapse

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

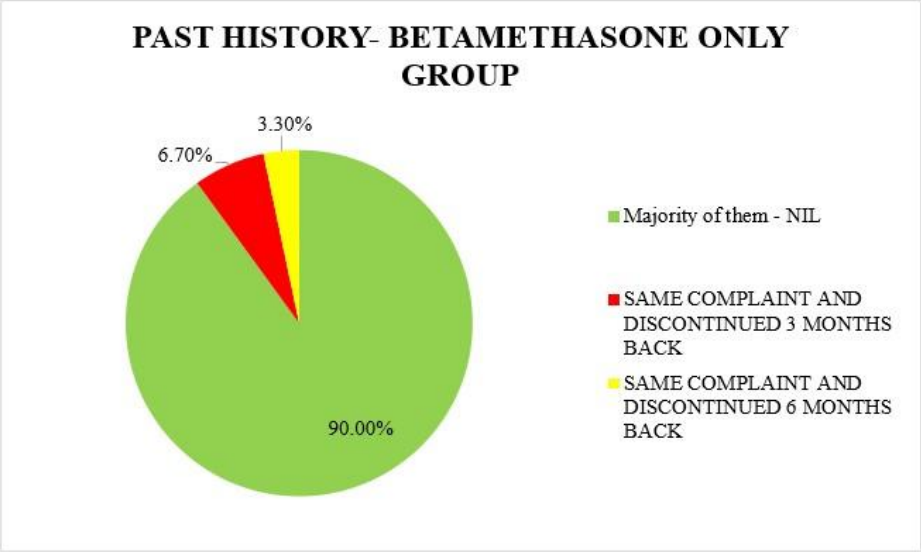

Fig. 6. Completion of treatment among group II

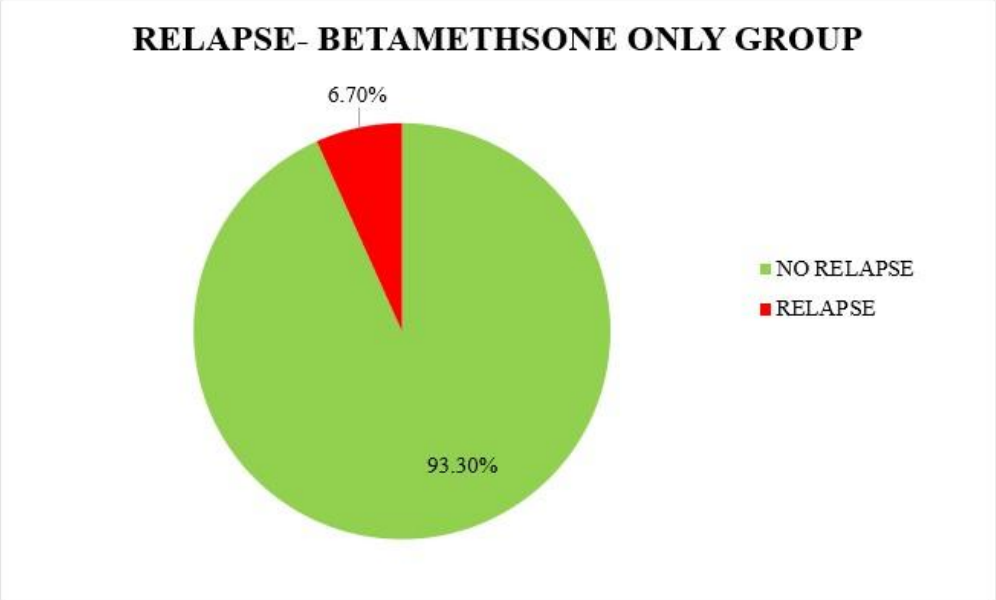

Fig. 7. Relapse among group II

3.12 Baseline Investigations

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

3.12.1 Pasi score at 0 week

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

3.13 Effect of Drug on PASI Score after 2 Weeks

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

3.14 Effect of Drugs on Pasi Score after 4 Weeks

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 am 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

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

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**	**do**	**p-value[1]**
Equal Variance	-0.775654	58	0.4411

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-value[1]**	
Equal variance	-2.46775	58	0.01657	

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	

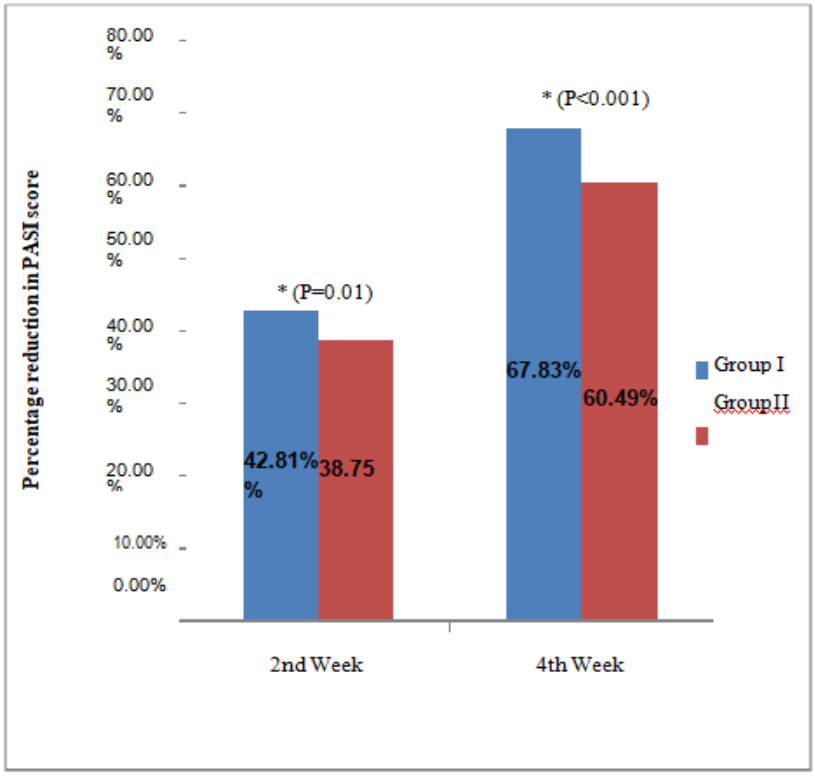

Fig. 8. Psoriasis area and severity index (PASI) percentage reduction in group i and group II after 2 weeks and 4 weeks

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 coal tar (P <0.01) [15]. 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 [16]. 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 topical 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 were15 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 12patients (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 [17,18].

One patient in Group I (3.3%) reported hypo pigmented patch and no other adverse effects were observed. Molin *et al*. conducted study with 421 patients and randomized either to treatment with calcipotriol (210 patients) or betamethasone (211 patients) [19]. 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 [20]. 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 ant proliferative effects [20]. Betamethasone inhibits production of cytokines and reduces mediators of inflammation. Calcipotriol plus Betamethasone two compound formulation provides better compliance for patients than immunotherapy 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. Meanwhile, the sample number is the main limitation of the present study. The heterogeneity nature of the data could be reduced by increasing the sample numbers.

4. 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.

CONSENT AND ETHICAL APPROVAL

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.

ACKNOWLEDGEMENTS

The encouragement and support from Bharath University, Chennai is gratefully acknowledged. For provided the laboratory facilities to carry out the research work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Smith CH, Barker JNWN. Psoriasis and its management. BMJ: British Medical Journal. 2006;333(7564):380-384.
2. Ahmad GK, Choudhury AM, Khondker L, Khan MS. Comparative safety of topical calcipotriol (0.005%) versus topical corticosteroid (betamethasone 0.1%) in plaque type psoriasis. Journal of Pakistan Association of Dermatology. 2016;23(4): 394-400.
3. Kuchekar AB, Pujari RR, Kuchekar SB, Dhole SN, Mule PM. Psoriasis: A comprehensive review. International Journal of Pharmacy & Life Sciences. 2011;2(6).
4. Chandran V. Genetics of psoriasis and psoriatic arthritis. Indian Journal of Dermatology. 2010;55(2):151-156.

5. Griffiths CE, Voorhees JJ. Psoriasis, T cells and autoimmunity. Journal of the Royal Society of Medicine. 1996;89(6): 315.
6. Li J, Li X, Hou R, Liu R, Zhao X, Dong F, Wang C, Yin G, Zhang K. Psoriatic T cells reduce epidermal turnover time and affect cell proliferation contributed from differential gene xpression. The Journal of dermatology. 2015;42(9):874-80.
7. Torsekar R, Gautam MM. Topical therapies in psoriasis. Indian dermatology online journal. 2017;8(4):235.
8. Luba KM, Stulberg DL. Chronic plaque psoriasis. South African Family Practice. 2006;48(9):30-6.
9. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Molecular and Cellular Endocrinology. 2011;335(1):2-13.
10. Vakirlis E, Kastanis A, Ioannides D. Calcipotriol/ betamethasone dipropionate in the treatment of psoriasis vulgaris. Therapeutics and Clinical Risk Management. 2008;4(1):141-148.
11. Trémezaygues L, Reichrath J. Vitamin D analogs in the treatment of psoriasis: Where are we standing and where will we be going? Dermato - endocrinology. 2011;3(3):180-186.
12. Segaert S, Duvold LB. Calcipotriol cream: A review of its use in the management of psoriasis. Journal of dermatological treatment. 2006;17(6):327-37.
13. Al Raddadi AA, Fatani MI, Shaikh YH, Thaci D, Al Reshaid AA, Al-Eisa AM, Alghamdi WA, Abdulfattah HY, Al Belbisi ZM, Atawi AC, Alajroush WA. Adopted guidelines of care for the topical management of psoriasis from American and German guidelines. Journal of the Saudi Society of Dermatology & Dermatologic Surgery. 2011;15(1): 5-13.
14. Hougeir FG, Cook-Bolden FE, Rodriguez D, Berlin JM. Critical considerations on optimizing topical corticosteroid therapy. The Journal of Clinical and Aesthetic Dermatology. 2015;8(Suppl1):S2-S14.
15. Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: A systematic review. British Journal of Dermatology. 2002;146(3):351-64.
16. Patel NU, Felix K, Reimer D, Feldman SR. Calcipotriene/betamethasone dipropionate for the treatment of psoriasis vulgaris: An evidence-based review. Clinical, Cosmetic and Investigational Dermatology. 2017; 10:385.
17. Dahri GM, Samdani AJ, Qazi N, Laghari MJ, Mashori GR, Wagan MA. To compare the role of calcipotriol alone versus combination with betamethasone in mild to moderate psoriasis. Sindh University Research Journal - SURJ (Science Series). 2010;42(1).
18. Ahmed GK, Khandker L, Nessa M, Alam MN, Chakraborty A, Yeasmin F. Comparative Efficacy of Topical Calcipotriol (0.005%) Versus Topical Corticosteroid (Betamethasone 0.1%) in Treating Plaque Type Psoriasis. Medicine Today. 2015;26(2):88-94.
19. Ashcroft DM, Po AL, Williams HC, Griffiths CE. Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. Bmj. 2000;320(7240):963-7.
20. Dhoke SP, Dwivedi RR, Harisha CR, Vyas MK, Sah M. International journal of universal pharmacy and bio sciences. Papp KA, Guenther L, Boyden B, Larsen FG, Harvima RJ, Guilhou JJ, Kaufmann R, Rogers S, van de Kerkhof PC, Hanssen LI, Tegner E. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. Journal of the American Academy of Dermatology. 2003; 48(1):48-54.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/66785