Original Paper

EFFICACY OF TOPICAL CALCIPOTRIOL VERSUS COMBINATION OF TOPICAL CALCIPOTRIOL PLUS BETAMETHASONE IN THE TREATMENT OF PLAQUE TYPE PSORIASIS

Khan MSI[1], Uddin MN[2], Khan AL[3], Ara R[4], Khondker L[5]

Abstract

Introduction: The effectiveness of various topical agents for the treatment of plaque psoriasis is limited and the results are somewhat not satisfactory to some extent. Topical Calcipotriol can be used either monotherapy or combination therapy with betamethasone. This topical agent has "corticosteroid-sparing" benefit and reduction of side effects, duration of treatment and also relapse rates when used as combination therapy for the treatment of psoriasis.

Objectives: The present study was conducted to compare the clinical efficacy between the topical Calcipotriol and combined formulation of topical Calcipotriol plus Betamethasone in the treatment of plaque type psoriasis.

Materials and Methods: A clinical trial was carried out from January 2011 to Jan 2014 in outpatient department of Dermatology and Venereology, combined military hospital- Dhaka and Jessore Cantonment and Bangabandhu sheikh Mujib Medical University, Dhaka. Patients of plaque type psoriasis were the study population. Consequitive type of non-probability sampling method was followed in this study. Patients were divided into two groups.Group A was treated with topical Calcipotriol (0.005%) ointment and group B with combination of topical Calcipotriol plus Betamethasone ointment.

Results: The mean percentage of Psoriasis Area and Severity Index (PASI) reduction after 4th week of treatment was 39.4 and 35.4 in group A and group B (p value >0.05) and after 8th week of therapy was 59.6 in-group A and 60.7 in-group B respectively. The mean baseline PASI score was 6.7±4.5 and after 8th week it was 2.0 ±1.4 for group A and mean baseline PASI score was 5.5 ±4.2 and after 8th week it was 2.5±1.4 for group B. There was statistically significant reduction in PASI score from base line after 8th week of treatment in both treatment groups ($p < 0.001$). After 8th week of treatment moderate response was 22(73.3%) in group A and 18(60%) in group B. Very good response was 4 (13.3%) in group A and 8 (26.7%) in group B and minimal response of treatment occurs equally 4 (13.3%) in group A and group B.

Conclusion: In the light of the findings of this study, topical Calcipotriol(0.005%) alone or combination with Betamethasone is individually effective for the treatment of plaque psoriasis but combination therapy is more effective than monotherapy. Therefore it may be recommended that monotherapy can be replaced by combination therapy in treating plaque psoriasis.

Key-words: Efficacy of calcipotriol in psoriasis, topical calcipotriol plus betamethasone in psoriasis. Psoriasis Area & Severity Index (PASI) score.

Introduction

Psoriasis is a chronic and incurable inflammatory skin disease, affecting 2 to 3 percent of the United States population, which may vary in severity from localized to diffuse[1,2]. Both genetic and environmental factors have been implicated in the pathophysiology of psoriasis[3]. About 35% of patients with psoriasis have a family history of the disease.

1. **Lt Col Md Shirajul Islam Khan**, MBBS, DDV, MCPS, FCPS (Dermatology & Venereology), Graded specialist in Dermatology and Venereology, AFMI, Dhaka Cantt; 2. **Maj Gen Md Nasir Uddin**, MBBS, MPH(HM), MPhil(PSM), Commandant, AFMC, Dhaka Cantt; 3. **Col Md Abdul Latif Khan**, MBBS, DDV, FCPS (Dermatology & Venereology), Classified Specialist in Dermatology and Venereology, CMH, Dhaka; 4. **Dr. Rowshan Ara**, MBBS, MPH(MCH & FP), MPhil(PSM), Asst Professor of Community Medicine, Dhaka Medical College, Dhaka; 5. **Dr. Lubna Khondker**, MBBS, MPH, DDV, MCPS, FCPS (Dermatology & Venereology), Assistant Professor, Dept of Dermatology and Venereology, BSMMU, Dhaka.

Treatment of psoriasis including, traditional therapeutic agents targeted abnormal keratinocyte proliferation and differentiation or induced general immunosuppression, resulting temporary improvement, partial response or rarely causing serious adverse effects. However, the vast majority of patients approximately 80-90% present with relatively mild disease and have only limited involvement of the skin which can be well-controlled with topical therapy[4,5]. Calcipotriol and Betamethasone Dipropionate both are widely used in the effective treatments for psoriasis. Vitamin D analogues and topical Corticosteroids have different mechanisms of action in the treatment of psoriasis[6,7]. At appropriate concentration Calcipotriol causes a decrease in the proliferation and an increase in the morphologic and biochemical differentiation of keratinocytes, hence regulate their proliferation and differentiation[8]. Calcipotriol ointment has been extensively evaluated for the treatment of chronic plaque-type psoriasis and has been shown to be effective in a number of short-term and long-term clinical trials[9,10].

For decades, topical corticosteroids have been the mainstay in the topical treatment of psoriasis. Psoriatic patients with thick plaques often require treatment with corticosteroids and observed multiple side effects with long term use[11]. Calcipotriol is generally considered to be effective in plaque psoriasis in some studies. Topical calcipotriol (0.005%) is found more effective than the conventional topical betamethasone dipropionate in some studies[12,13,14]. A new vehicle has been developed in order to contain both Calcipotriol and Betamethasone Dipropionate in an ointment form. By using Calcipotriol and a Corticosteroid together, greater efficacy may be achieved than by using either compound alone. Therefore the purpose of the present study was to compare the efficacy level of topical Calciprotriol (0.005%) and combination of topical Calcipotriol plus Betamethasone in plaque type psoriasis in Bangladesh.

Materials and Methods

A clinical trial was carried out in the department of Dermatology and Venereology, Combined Military Hospital- Dhaka and Jessore Cantonment and Bangabandhu sheikh Mujib Medical University, Dhaka Bangladesh. Sixty patients clinically and histopathologicaly diagnosed as chronic plaque type psoriasis were enrolled. Thirty patients were treated with topical Calcipotriol (0.005%) ointment (Group-A) and thirty patients with combination of topical Calcipotriol plus Betamethasone ointment (Group-B). Consequitive type of non-probability sampling method was followed in this study. Patients having serum calcium level within normal limit, age 18 years or above with both sexes and patients who were agreed to give the consent and willing to comply with the study procedure were included in the study. Acute guttate, pustular, severe or erythrodermic psoriasis, psoriasis which is predominantly located in the skin folds, face or scalp, patients with history of treatment for plaque type psoriasis with corticosteroid agents, vitamin D analogues or tacrolimus within the last 3 months, patients with history of systemic anti-psoriatic treatment or PUVA within 16 weeks period prior to visit, pregnant or lactating women, patients undergoing treatment with retinoids or antibiotics, patient with known or suspected renal / hepatic disease/ hematological disease and history of acute or chronic active infections were excluded from the study.

Procedure of Data Collection

Complete history, general physical and dermatological examinations were done for all enrolled patients. For women of reproductive age reproductive history, menstrual history, lactation and pregnancy plan were carefully judged. History and physical findings were recorded in a data sheet. Baseline investigations included complete blood count (total count, differential count of white blood cell), platelet count, Hb%, ESR, serum creatinine, serum alanine transaminase, random blood sugar, serum calcium level, serum albumin, serum total protein and pregnancy test (as required) were done. Finally those patients, who matched the selection criteria and willingly gave their informed consent, were selected for the study. Erythema, induration and scaling were recorded in term of PASI (Psoriasis Area and Severity Index) at baseline, after 4th weeks and 8th weeks of therapy as the tool of main outcome measure. Adverse effects of the drugs among all patients of two groups were noted.

Scoring of Psoriasis

Severity of psoriasis were scored by using Psoriasis area and Severity Index (PASI) formula, in which the body was divided into four areas Head (H), Upper limb (U), Trunk (T) and Lower limb (L). Erythema (E), Induration (I) and Desquamation (D) were measured for each area with a scale ranging zero (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe). Erythema and induration were measured as visual impression and palpation of the lesion in place of ideal chromometer and ultrasound respectively. Body surface was measured with palm of patients, taken as 1% total body surface area.

Head area: one palmar surface of hand = 10% of head area, Upper limb: two palmar surface of hand = 10% upper limb area, Trunk area: three palmar surface of hand = 10% trunk area, Lower limb: four palmar surface of hand = 10% lower limb area. PASI was calculated using the following formula: 0.1 (EH + IH + DH) A H + 0.2 (EU + IU + DU) AU + 0.3 (ET + IT + DT) AT + 0.4 (EL + IL + DL) AL[15].

Severity of plaque type psoriasis can be classified according to PASI score. Psoriasis can be defined as severe when PASI score >12, moderate when PASI score 7-12 and mild when PASI score <7. Percentage of PASI score reduction is used for assessment of the efficacy of drug and prognosis of plaque type psoriasis. The percentage of PASI score reduction can be describe as 4 grades. When PASI reduction <50% it can be defined as minimal response, 50%−<70% as moderate response, 70%−<90 % as very good response and >90% as excellent response.

Intervention

Group A were treated with Calcipotriol (0.005%) twice daily and group B were treated with combination of topical Calcipotriol plus Betamethasone once daily. They were treated for the period of 8 weeks. The results of the cases of both group A and group B were evaluated at the end of 8th week. Patients were examined at baseline, and after 4th week of treatment followed by re-examination at the end of 8th week. The severities of psoriasis were evaluated by a single investigator at the center, using the Psoriasis area and severity Index (PASI).

Laboratory parameters were measured before enrollment in the study and at the end of the follow-up period. Follow-up laboratory investigations were complete blood count (Total and differential count of white blood cell, hemoglobin and ESR, Platelet count, Serum alanine transaminase, serum creatinine, serum calcium level, random blood sugar and serum total protein and serum albumin level. Data analysis was performed by Statistical Package for Social Science (SPSS), version-16. Statistical analysis were done and level of significance were measured by using appropriate procedures like chi square test (χ^2), paired and unpaired t-test. Level of significance (p-value) was set at 0.05 and confidence interval at 95%.

Results

Table-I shows that the mean (±SD) age was 34.7±12.7 years and 34.5±15.8 years in group A and group B respectively. Male was found 14 (46.7%) in group A and 16 (53.3%) in group B. Family history of same disease was found 8(26.7%) in group A and 2(6.7%) in group B. Regarding the duration of illness, most of the patients suffered 1- 5 years in both groups, which were 16 (53.3%) and 20(66.7%) in group A and group B respectively. The mean duration of illness was 5.5±3.7 years in group A and 4.4±3.5 years in group B. There was no statistically significant difference between two groups in terms of age, sex, family history of same disease and duration of illness (p value >0.05).

Table-I: Distribution of patients by the age (n=30).

Age (in year)	N	%	N	%	Age (in year)	t-Value	p-value
≤20	2	6.7	6	20.0	≤20	0.05	0.960^{ns}
21-30	14	46.7	12	40.0	21-30		
31-40	6	20.0	2	6.7	31-40		
41-50	4	13.3	2	6.7	41-50		
>50	4	13.3	8	26.7			
Mean±SD	34.7	±12.7	34.5	±15.8	Mean±SD		

Group A: Calcipotriol, Group B: Combination of topical calcipotriol plus betamethasone.
Ns=Not significant, P value reached from unpaired t-test and chi square test.

Table-II: Distribution of patients by the sex (n=30).

Sex	Group- A (n=30)		Group-B (n=30)		Chi-square value	p-value
Male	14	46.7	16	53.3	0.13	0.715^{ns}
Female	16	53.3	14	46.7		

Group A: Calcipotriol, Group B: Combination of topical calcipotriol plus betamethasone.

Table-III: Distribution of patients by the family history of disease (n=30).

Family history of disease	Group-A (n=30)		Group-B (n=30)		Chi-square value	p-value
Yes	8	26.7	2	6.7	2.16	0.141^{ns}
No	22	73.3	28	93.3		

Group A: Calcipotriol, Group B: Combination of topical calcipotriol plus betamethasone.

Table-IV: Distribution of patients by the duration of illness (n=30).

Duration of illness (years)	Group-A (n=30)		Group-B (n=30)		t-value	p-value
1-5	16	53.3	20	66.7	0.78	0.443^{ns}
6-10	12	40.0	8	26.7		
>10	2	6.7	2	6.7		
Mean± SD	5.5	±3.7	4.4	±3.5		

Group A: Calcipotriol, Group B: Combination of topical Calcipotriol plus Betamethasone.
Ns=Not significant, P-value reached from unpaired t-test.

Mean Psoriasis Area and Severity Index (PASI) score of Group A and Group B at baseline was 6.7±4.5 and 5.5±4.2 respectively. The mean percentage of PASI reduction after 4th week of treatment was 39.4 and 35.4 in group A and group B (p value >0.05) and after 8th week of therapy it was 59.6 in-group A and 60.7 in-group B respectively. The mean different was not statistically significant (p value >0.05) between both groups.

Table-V: Comparison of Reduction of Psoriasis Area and Severity Index (PASI) in two groups.

	Group-A (n=30)		Group-B (n=30)		t-value	p-value
PASI	Mean	±SD	Mean	±SD		
Base line	6.7	±4.5	5.5	±4.2	1.39	0.174^{ns}
Reduction after 4th week (%)	39.4		35.4		1.46	0.155^{ns}
Reduction after 8th week (%)	59.6		60.7		-.20	0.802^{ns}

NS==Not significant, P-value reached from unpaired t-test.

Table-VI shows that after 8th week of treatment, moderate response is 22(73.3%) and 18(60%), very good response is 4(13.3%) and 8(26.7%) in group A and group B respectively.

Table-VI: Comparison of grading of PASI percentage reduction in two groups (n=30).

Grading of (%) PASI reduction	Group-A (n=30)		Group-B (n=30)		Chi value	p-value
	N	%	N	%		
Minimal response <50	4	13.3	4	13.3	0.867	0.648^{ns}
Moderate response 50 to <70	22	73.3	18	60.0		
Very good response 70 to <90	4	13.3	8	26.7		
Excellent response >90	0	0	0	0		

ns=Not significant, p value-0.648 reached from chi square test.

Table-VII shows that mean baseline PASI score was 6.7 ±4.5 and after 8th week, it was 2.0 ±1.4 for group A and mean baseline PASI score was 5.5 ±4.2 and after 8th week, it was 2.5 ±1.4 for group B. There was statistically significant reduction in PASI score from base line after 8th weeks of treatment in both treatment groups ($p < 0.001$).

Table-VII: Comparison of PASI scores before and after treatment in two groups.

Groups	Mean baseline PASI score with SD	Mean PASI score after 8th week with SD	*t*-value	p-value
Group A	6.7 ±4.5	2.0 ±1.4	12.94	<0.001*
Group B	5.5 ±4.2	2.5 ±1.4	7.37	<0.001*

*Paired t test was done to measure the level of significance.

Discussion

Our study showed statistically significant reduction in PASI score from base line to 8th week of treatment in both treatment groups ($p<0.001$). These findings were consistent with other studies[10,13,15,16,17]. A study was conducted by Dahri et al and 60 patients were divided into two groups, each having 30 patients, designated as group-A Calcipotriol ointment alone. While in the group-B they applied Calcipotriol plus Betamethasone combined therapy. The improvement in the parameter of PASI seen during the period of Day 0–90 and percentage change observed in group-A is 67.89% i.e. the mean change from 14.08±0.33 to 4.52±0.22. While improvement in the parameter of PASI seen during the period of day 0-day 90 and percentage change, observed in Group B (Calcipotriol plus Betamethasone) combination is more pronounced i.e. the change in mean from Day 0-90 is 12.81±0.35 to 2.37±0.36, with the percentage change of 81.495 ($p<0.001$). The results were highly significant i.e. ($p<0.001$) and showing great improvement in patient's symptoms. They conclude that Betamethasone plus Calcipotriol therapy is more efficacious than Calcipotriol alone[15].

Guenther et al conducted a study to compare the clinical efficacy of the combined ointment formulation (Calcipotriol and Betamethasone Dipropionate) used once daily with Calcipotriol Ointment used twice daily in psoriasis vulgaris.

There was no statistically significant difference in the mean percentage change in the Psoriasis Area and Severity Index (PASI) from baseline to end of treatment between the two groups, but the difference in PASI reduction was significantly higher in the combined formulation groups (68.6% once daily, 73.8% twice daily) than in the twice daily Calcipotriol group (58.8%). No statistically significant nor clinically relevant difference in efficacy was seen between the combined formulation used once daily and twice daily[13].

Papp et al compared the clinical efficacy of a fixed combination of Calcipotriene and Betamethasone Dipropionate in a new vehicle to Calcipotriene in the new vehicle and Betamethasone in the new vehicle. The mean percentage reduction in PASI from baseline to end of treatment was 73.2% in the combination group (n=301), 48.8% in the Calcipotriene group (n=308), and 63.1% in the Betamethasone Dipropionate group (n=312), (P < .001). The mean percentage reduction in PASI during the first week was 48.1%, 28.4%, and 41.4%, respectively (P < .001). They conclude that a combination product of Calcipotriene 50 mcg/g and Betamethasone Dipropionate 0.5 mg/g in the new vehicle shows superior efficacy with a more rapid onset of action than the new vehicle containing either constituent alone in the treatment of psoriasis vulgaris[16].

Kragballe conducted a study to investigate the efficacy of different treatment regimens with the two-compound product (Calcipotriol and Betamethasone Dipropionate) and Calcipotriol Ointment. In total, 972 patients with psoriasis vulgaris were randomized to one of three treatment regimens: group 1, the two-compound product once daily for 8 weeks followed by Calcipotriol Ointment once daily for 4 weeks; group 2, the two-compound product once daily for 4 weeks followed by 8 weeks of treatment with Calcipotriol Ointment once daily on weekdays and the two-compound product once daily at weekends; and group 3, Calcipotriol Ointment twice daily for 12 weeks. The efficacy was evaluated by Psoriasis Area and Severity Index (PASI) and investigators' global assessments of disease severity. The primary response criteria were percentage reduction in PASI and proportion of patients with absent/very mild disease according to the investigators' global assessments after 8 weeks of treatment. The mean reduction in PASI from baseline to the end of 8 weeks of treatment was 73.3% for group 1, 68.2% for group 2 and 64.1% for group 3. The proportion of patients with absent/very mild disease at the end of 8 weeks of treatment was 55.3% for group 1, 47.7% for group 2 and 40.7% for group 3. For both primary response criteria, group 1 was statistically superior to group 3 (P < 0.001), whereas group 2 did not differ significantly from group 3. The difference between group 1 and group 2 was statistically significant with regard to PASI but not regarding the proportion of patients with absent/very mild disease. Patients receiving initial therapy with the two-compound product achieved the fastest treatment response, and the maximum treatment effect for these patients was seen after 5 weeks. This effect was maintained with continued treatment with the two-compound product for up to 8 weeks. After 12 weeks of treatment, no significant differences were seen between the three groups with regard to reduction in PASI, whereas the proportion of patients with absent/very mild disease in group 2 was superior to that in group 3. Patients receiving therapy with the two-compound product experienced fewer lesional/perilesional adverse drug reactions than the Calcipotriol-treated patients (P<0.001): 10.9% in group 1,11.5% in group 2 and 22.3% in group 3.They concluded that two different short-term treatment regimens employing a recently developed two-compound product (Calcipotriol and Betamethasone Dipropionate) provided rapid and marked clinical efficacy and were shown to be safe therapies for psoriasis vulgaris[17]. Guenther et al observed that a fixed-dose combination product containing Betamethasone Dipropionate and Calcipotriene have greater efficacy and a faster speed of onset than the individual components of Calcitriol. Once daily and twice daily treatments have similar efficacy. Psoriasis Area and Severity Index reductions of approximately 40% after 1 week and 70% after 4 weeks of therapy were consistently noted in studies involving >6000 patients. Betamethasone dipropionate + Calcipotriene treatment is associated with approximately 75% less adverse cutaneous events as compared with Tacalcitol, 50% less compared with Calcipotriene, and a similar number as treatment with Betamethasone Dipropionate[10].

Conclusion

In the light of the findings of the study we conclude that the combination therapy of Calcipotriol(0.005%) and Betamethasone (0.1%) is more effective than monotherapy calcipotriol(0.005%), therefore it may be recommended that monotherapy can be replaced with once daily Calcipotriol and Betamethasone combination in treating plaque psoriasis. Study with a larger group of patients for longer period may result in superior outcome in clinical practice through improved compliance.

References

1. Kim GK.The Rationale Behind Topical Vitamin D Analogs in the Treatment of Psoriasis. J Clin Aesthet Dermatol. 2010; 3(8): 46–53.

2. Fenton C, Plosker G. Calcipotriol/Betamethasone dipropionate: A review. Am J Clin Dermatol. 2004;5:463–78.

3. Ashcroft DM, Li Wan PoA, Griffiths CE. Therapeutic strategies for psoriasis. J Clin Pharm Ther.2000;25:2–10.

4. Douglas WS, Poulin Y, Decroix J. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Derm Venereol. 2002;82:31–5.

5. Gelfand JM, Weinstein R, Porter SB. Prevalence and treatment of psoriasis in the United Kingdom. Arch Dermatol. 2005;141:1537–41.

6. Charakida A, Dadzie O, Teixeira F. Calcipotriol/Betamethasone dipropionate for the treatment of psoriasis. Expert Opin Pharmacother. 2006;7:597–606.

7. Kragballe K, van de Kerkhof PC. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. J Eur Acad Dermatol Venereol. 2006;20:39–44.

8. Kragballe K, van de Kerkhof PC. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. J Eur Acad Dermatol Venereol. 2006;20:39–44.

9. Koo JY. Current consensus and update on psoriasis therapy: a perspective from the U.S. J Dermatol. 1999;26:723–33.

10. Guenther L, Cambazard F, Van de Kerkhof PCM. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. Br J Dermatol 2002; 147(2):316–23.

11. Kaufmann R, Bibby AJ, Bissonnette R. A new calcipotriol/betamethasone dipropionate formujlation is an effective once daily treatment for psoriasis vulgaris. Dermatology. 2002 ;205:389–93.

12. Kragballe K, Gjertsen B, de Hoop D. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. Lancet. 1991;337:193–6.

13. GuentherLC. Calcipotriol Betamethasonedi-propionate: Daivobet/Dovobet. Therapy, 2005; 2: 343–48.

14. Cassano N, Miracapillo A, Coviello C, Loconsole F, Bellino M,& Vena GA. Treatment of psoriasis vulgaris with the two-compound product Calcipotriol -betamethasone dipropionate followed by different formulations of calcipotriol. Clin Drug Investig. 2006; 26(4): 227-33.

15. 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 Univ. Res. Jour. (Sci. Ser.) 2010; 42 (1):69-72.

16. Papp KA, Guenther L, Boyden B, Larsen FG, Harvima RJ, Guilhou JJ et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. J Am Acad Dermatol. 2003;48(1):48-54.

17. Kragballe K, Austad A. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product in the treatment of psoriasis. British Journal of Dermatology 2006; 6: 1155-60.