

Comparative efficacy and safety of the combination of betamethasone dipropionate and calcipotriene with topical betamethasone dipropionate and calcipotriene alone in the treatment of localized vitiligo

Mohd. Nurul Alam*, MA Wahab*, Lubna Khondker*, Md Shirajul Islam Khan**

* Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh

** Combined Military hospital (CMH), Dhaka cantonment, Dhaka, Bangladesh.

Abstract *Objective* To compare the efficacy and safety of topical calcipotriol ointment (0.005%) and betamethasone dipropionate (0.05%) cream, given alone and in combination, in treatment of localized vitiligo.

Methods It was a clinical trial conducted from January 2012 to August 2012. Patients of localized vitiligo attending outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka were the study population. In group A, 20 patients applied betamethasone dipropionate cream 0.05% in the morning and topical calcipotriene ointment (0.005%) in the evening, in group B, 20 patients applied betamethasone dipropionate cream 0.05% twice daily; In group C, 20 patients used calcipotriene ointment 0.005%.

Results in The vitiligo score in group A, B and C reduced from 26, 25 and 23, respectively to 3, 8 and 6 ($p < 0.05$). The side effects experienced by patients at 5th follow-up were: in group A, erythema (15%), dryness (15%), scaling (5%) and pruritus (5%); in group B, erythema (15%), scaling (5%), dryness (5%) and pruritus (5%); and in group C, erythema (10%) [$p = 0.005$].

Conclusion Both the drugs, calcipotriol and betamethasone dipropionate when used individually as monotherapy, were found to be equally effective in the treatment of vitiligo, but the combination of the two was found to be superior in efficacy. Regarding safety level, calcipotriene and betamethasone dipropionate when used individually, were found to be safer in the treatment of vitiligo, than the combination of the two.

Key words

Vitiligo, betamethasone dipropionate and calcipotriene.

Introduction

Vitiligo is an acquired skin disorder characterized by well-defined white patches that are often symmetrically distributed.¹ The cause is unknown but may involve genetic

factors, autoimmunity, toxic metabolites and/or a higher vulnerability of melanocytes.²⁻⁴

It affects 0.5–2% of the population worldwide.^{5,6} Vitiligo can be cosmetically disfiguring and is a stigmatizing condition leading to serious psychologic problems in daily life.^{7,8} Two of the major theories of the pathogenesis of vitiligo are the autoimmune theory and the autocytotoxicity theory.⁹ The autoimmune theory speculates that patients with vitiligo form autoantibodies against melanocytes. The existence of antimelanocyte

Address for correspondence

Dr. Lubna Khondker, Assistant Professor,
Dept of Dermatology and Venereology
Bangabandhu Sheikh Mujib Medical University
(BSMMU)
Dhaka, Bangladesh
Email: lubnaderma@gmail.com

surface antigen antibodies has been demonstrated, and the severity of vitiligo has been proven to be related to the amount of antibodies present.^{10,11}

Patients have numerous treatment options available, but none is universally effective. Even among patients who respond to treatment there is a high potential for relapse. Treatment of vitiligo is a challenge.¹² The most widely prescribed therapies are PUVA and topical corticosteroids. PUVA is not recommended for children because of concern over its long-term side effects, and prolonged use of topical steroids has the potential to cause cutaneous atrophy, including telangiectasis and perioral dermatitis.¹³

Calcipotriene is a synthetic analogue of vitamin D₃, calcitriol: 1, 25(OH)₂D₃ that has immunomodulating and immunosuppressive actions.¹⁴ Receptors for 1, 25(OH)₂D₃ the active form of vitamin D, have been demonstrated on keratinocytes, melanocytes and fibroblasts, and on immunologically active cells. Melanocytes and keratinocytes within vitiliginous lesions have shown defective calcium uptake. Based on this observation, recently investigators demonstrated that calcipotriene can be effective for vitiligo, both as monotherapy and in combination.^{15,16} We observed also the efficacy of a combination of calcipotriene 0.005% - betamethasone dipropionate 0.05% ointment in the repigmentation of vitiligo but the comparison of efficacy and safety of this drug alone or in combination has not been done in Bangladesh. We conducted a clinical trial to compare the efficacy and safety of this combination in localized vitiligo.

Methods

It was a clinical trial carried out from January 2012 to August 2012. Patients of localized vitiligo attending outpatient department of

Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka were the study population and purposive type of non-probability sampling method was followed in this study. Inclusion criteria were all localized vitiligo patients, aged more than 5 years of both sexes and willing to comply with the study procedure. The exclusion criteria were generalized vitiligo, previous skin malignancy, treatment for vitiligo with corticosteroid agents, vitamin D analogues, or tacrolimus within the last 3 months, pregnancy and lactation, renal or hepatic disease, lupus erythematosus, severely ill patients and patients or attendants unwilling to take part in the study.

Procedures of collecting data

A total of 60 patients suffering from localized vitiligo were primarily selected and complete history and general physical, dermatological and Wood's light examination were done and recorded. For women of reproductive age, reproductive history, menstrual history, lactation and pregnancy plan were carefully judged. Finally those patients, who matched the inclusion and exclusion criteria were randomized into three treatment groups. Blinding method was not applied in this study. In group A, 20 patients applied betamethasone dipropionate cream 0.05% in the morning and topical calcipotriene ointment (0.005%) in the evening; in group B, 20 patients were treated with betamethasone dipropionate cream 0.05% twice daily; and in group C, 20 patients used calcipotriene ointment 0.005% similarly. The respective medications were applied on each individual lesion treated daily for five months.

Clinical assessment for efficacy and safety was done at baseline and follow-up visits monthly for 5 months and photographs of all lesions were taken for subsequent assessment and further comparison. The repigmentation was labeled as marginal, perifollicular, diffuse or combined.

Safety of the medications of treatment was assessed by observing the side effects such as: itching, hyperaesthesia, erythema, irritation and burning, telangiectasia, atrophy of skin. Safety parameters (itching, erythema, irritation) were evaluated in the same way using 4-point score (categories: absent, mild, moderate, severe).

Efficacy was assessed by score of Vitiligo Area Scoring Index (VASI). The body was divided into 5 separate and mutually exclusive regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axillary and inguinal regions were included with the upper and lower extremities, respectively, while the buttocks were included with the lower extremities. The face and neck areas were assessed and treated for vitiligo if requested by the patient, but these areas were not included in the overall evaluation. One hand unit, which encompasses the palm plus the volar surface of all the digits, is approximately 1% of the total body surface area and was used as a guide to estimate the baseline percentage of vitiligo involvement of each body region..

At each follow-up assessment, any macular repigmentation was noted, and the extent of *residual depigmentation* within each affected patch that had been present at baseline was estimated to the nearest of 1 of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. Any new depigmented patches that developed during the study were also estimated using the hand unit method and were included in the VASI calculation.

Standardized assessment for estimating the degree of pigmentation to derive the Vitiligo Area Scoring Index: at 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at

25%, the pigmented area exceeds the depigmented area; and at 10%, only specks of depigmentation are present. For the second measurement method, total body photographs were taken at baseline and at each monthly follow-up visit as an aid to the global clinical scoring. These 35-mm slides were used by investigators for global assessments, which were done halfway through and at the end of the study.

For each body region, the VASI was determined by the product of the area of vitiligo in hand units (which were set at 1% per unit) and the extent of depigmentation within each hand unit—measured patch (possible values of 0, 10%, 25%, 50%, 75%, 90%, or 100%). The total body VASI was then calculated using the following formula by considering the contributions of all body regions (possible range, 0-100):

$$\text{VASI} = \sum \text{All body sites [Hand units]} \times \text{Residual depigmentation}$$

Data processing and analysis

All collected data were checked and rechecked for omissions, inconsistencies and improbabilities. Data analysis was performed by Statistical Package for Social Science (SPSS), version-12. Data was edited, coded and entered into the computer. Level of significance was measured by using appropriate procedures like chi square test (χ^2), relative risk (RR) measurement, t-test, and proportion (d) test and others where applicable. Level of significance (p value) was set at 0.05 and confidence interval at 95%.

Results

Table 1 shows the demographic and clinical features in group A, B and C. All three groups were well-matched in terms of pre-treatment features ($p>0.05$). Mean age of group A, B and C patients was 21.50 ± 3.32 , 21.55 ± 4.12 and

Table 1 Distribution of age and sex of the patients by groups.

	Group A (n=20)	Group B (n=20)	Group C (n=20)
<i>Age in years</i>			
13- 22	7 (35%)	8 (40%)	7 (35%)
23- 32	9 (45%)	6 (30%)	6 (30%)
>32	4 (20%)	6 (30%)	7 (35%)
Mean ± SD	21.50±3.32	21.55±4.12	22.25±4.67
<i>Sex</i>			
Male	8 (40%)	8 (40%)	9 (45%)
Female	12 (60%)	12 (60%)	11 (55%)
<i>Duration of lesions</i>			
< 1 year	9 (45%)	14 (70%)	13 (65%)
> 1 year	11 (55%)	6 (30%)	7 (35%)
<i>Distribution of lesions</i>			
Extremities	12 (60%)	14 (70%)	9 (45%)
Face	6 (30%)	4 (20%)	7 (35%)
Trunk	2 (10%)	2 (10%)	4 (20%)

* ANOVA test, $p>0.5$.

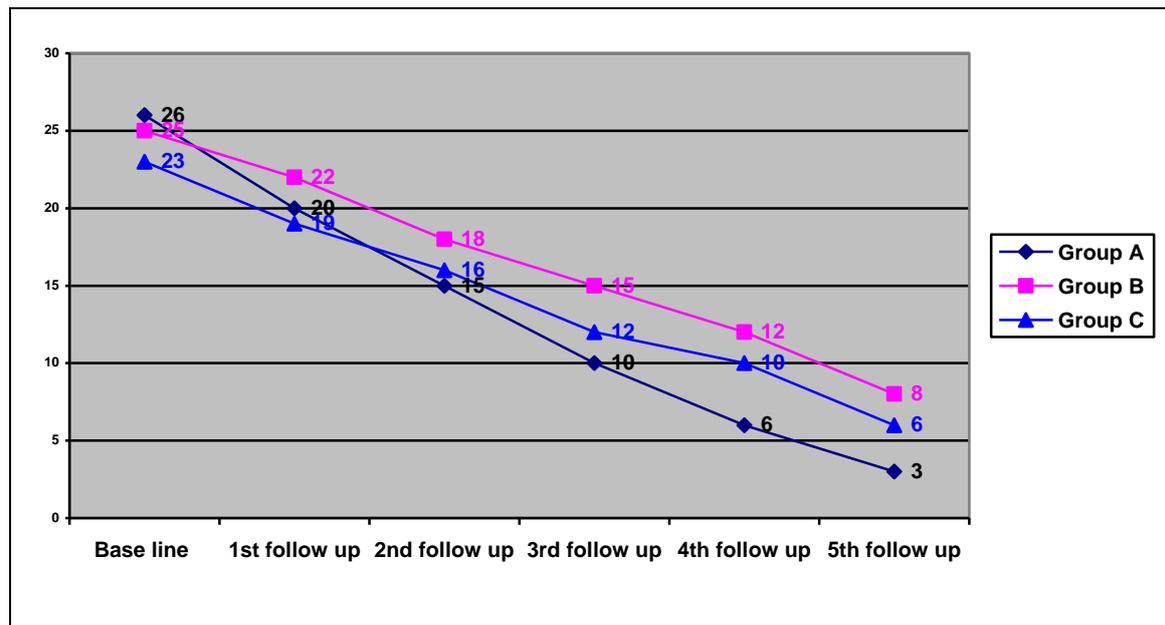


Figure 1 Total score of vitiligo at baseline and subsequent follow-ups in different groups.

Table 2 Side-effects of erythema, scaling, dryness, burning and pruritus at 1st and 5th follow-up.

<i>Side-effects</i>	Group A (n=20)		Group B (n=20)		Group C (n=20)	
	1 st follow-up	5 th follow-up	1 st follow-up	5 th follow-up	1 st follow-up	5 th follow-up*
Erythema	9 (45%)	3 (15%)	7 (35%)	3 (15%)	6 (30%)	2 (10%)
Scaling	2 (10%)	1 (5%)	5 (25%)	1 (5%)	5 (25%)	0 (0%)
Dryness	7 (35%)	3 (15%)	6 (30%)	1 (5%)	0 (0%)	0 (0%)
Pruritus	2 (10%)	1 (5%)	3 (15%)	1 (5%)	0 (0%)	0 (0%)
Burning	8 (40%)	0 (0%)	7 (35%)	0 (0%)	5 (25%)	0 (0%)

* p value=0.005

22.25±4.67 years, respectively. In group A and B 40% of the patient were male and 60% were female patient. In group C 45% were male patients and 55% were female patients. The common site of disease was extremities in all three groups with 60%, 70% and 45%

involvement, respectively. The duration of disease was less than 1 year in group A, B and C in 45%, 70% and 35% of patients, respectively. It was more than 1 year in 55%, 30% and 65%, respectively ($p>0.05$).

Figure 1 shows effect of treatment on the disease severity in three groups. At baseline the score of vitiligo in group A, B and C was 26, 25 and 23, respectively. At 1st follow-up, the respective score in group A, B and C reduced to 20, 22 and 19, and it further decreased to 15, 18 and 16 at 2nd follow-up. At 3rd follow-up, it was 10, 15 and 12 in group A, B and C, respectively and at 4th follow-up it became 6, 12 and 10, respectively. At final i.e. 5th follow-up, the respective final score was 3, 8 and 6 ($p < 0.05$).

The side effects experienced by patients of different groups at their first follow-up and final follow-up are shown in **Table 2**. In group A, erythema, scaling, dryness, burning and pruritus were present in 45%, 10%, 35%, 40% and 10% of patients, respectively. In group B, erythema, scaling, dryness, burning and pruritus were 35%, 25%, 30%, 35% and 15%, respectively. However, in group C dryness and pruritus were absent in all the patients and the erythema, scaling and burning were 30%, 25% and 25% respectively. At 5th follow-up visit, in group A, erythema, scaling, dryness and pruritus were present in 15%, 5%, 15%, and 5% of patients respectively, and burning was absent in group A. In group B erythema, scaling, dryness, and pruritus were 15%, 5%, 5% and 5% and burning was absent in group B. However in group C scaling, burning, dryness and pruritus were absent in all the patients and the erythema were present in 10% cases in 5th follow-up visit ($p < 0.005$).

Discussion

Our study observed that both the drugs, calcipotriol and betamethasone dipropionate when used individually as monotherapy, were equally effective in the treatment of vitiligo, but the combination of the two was found to be superior in efficacy. These findings were not consistent with that of Chiavérini *et al.*¹⁷ who evaluated the efficacy of topical

calcipotriol monotherapy in vitiligo. Twenty-four patients with localized or generalized vitiligo with symmetrical lesions were included. They concluded that topical calcipotriol as monotherapy is not an effective treatment of vitiligo.¹⁷

The results of present study were consistent with that of Yalçın *et al.*¹⁸, Cherif *et al.*¹⁹ and Parsad *et al.*²⁰, although the combination of drugs in our study was calcipotriol and betamethasone dipropionate, not calcipotriol and PUVA as in the studies of Yalçın *et al.*¹⁸, Cherif *et al.*¹⁹ and Parsad *et al.*²⁰ We compared our findings with theirs as all three used calcipotriol, which was the main drug in our study. Yalçın *et al.*¹⁸ conducted a study to determine whether the combination of topical calcipotriol and PUVA therapy increases the responsiveness of patients with vitiligo refractory to PUVA alone. Twenty-one patients with vitiligo refractory to previous PUVA therapy were studied. Patients received 60 sessions of PUVA 3 times a week and 0.005% topical calcipotriol twice daily. Patients were monitored for repigmentation overall and on the trunk, extremities, and acral regions. Some degree of repigmentation was observed in 71.5% of the patients. After treatment, cosmetically acceptable overall repigmentation was observed in 29% of patients; repigmentation of lesions on the trunk, extremities, and acral region was noted in 36%, 58%, and 0% of patients, respectively. They concluded that the combination of PUVA and calcipotriol may be effective therapy and should be further investigated for the treatment of vitiligo.¹⁸ Our study findings were also consistent with findings of Cherif *et al.*¹⁹ who evaluated the efficacy of the combination of calcipotriol and psoralen plus ultraviolet A (PUVA) in the treatment of vitiligo. Twenty-three patients with essentially bilateral symmetrical lesions of vitiligo were included. Calcipotriol (0.005 %) ointment was applied twice daily over the right side of the

body, with the other side left untreated. PUVA was performed three times per week. All patients received at least forty-five sessions of PUVA. At the forty-fifth session, 52% showed marked improvement on the calcipotriol side compared to 30% on the PUVA-only side ($p=0.13$), with more intense repigmentation on calcipotriol-treated areas. This combination was an effective treatment for vitiligo, especially in initiating repigmentation.¹⁹

Our study findings were also consistent with findings of Parsad *et al.*²⁰ They conducted a study to determine the efficacy of the combination of PUVASOL with topical calcipotriol in the treatment of vitiligo. Nineteen patients with essentially bilateral symmetrical lesions were enrolled in a randomized, double-blind, right/left comparative study of 18 months duration. An oral dose of 0.6 mg/kg 8-methoxypsoralen was given 2 h before exposure to sunlight thrice weekly to all patients. The patients were advised to apply calcipotriol (50 µg/g) on one side of the body and placebo ointment over the lesions on the other side twice daily. At the end of 6 months, 12 (70%) patients showed marked to complete improvement on calcipotriol-treated sides as compared to 6 (35%) patients showing similar improvement on placebo-treated sides ($p<0.05$). At the end of treatment, 13 (76%) patients showed marked improvement in calcipotriol-treated lesions whereas 9 (53%) patients showed moderate to marked improvement in placebo-treated lesions. The repigmentation of hands and feet was much better with the combination of PUVASOL and calcipotriol. They concluded that the combination of PUVASOL and calcipotriol is highly effective and works faster and may be used for shortening the therapy with PUVA in the treatment of vitiligo.²⁰

Our study findings also agreed with that of Pasricha *et al.*²¹ They tried a new approach

using mini-pulse therapy with betamethasone. Forty patients having extensive and/or fast-spreading vitiligo were given 5 mg betamethasone/dexamethasone as a single oral dose after breakfast on 2 consecutive days per week. Within 1-3 months, progression of the disease was arrested in 89% of the 36 patients having active disease, while 2 patients needed an increase in the dose to 7.5 mg per day to achieve complete arrest of lesions. Oral mini-pulse therapy with betamethasone seems to be an effective treatment modality to arrest the progression of vitiligo. It also induces spontaneous repigmentation.²¹

Different local side effects were experienced by patients of all groups at first follow-up of the study. Our findings were different from that of Kumaran *et al.*¹⁵ and Pasricha *et al.*²¹ A randomized trial conducted by Kumaran *et al.*¹⁵ observed atrophy and lesional burning sensations more common in group I (treated with betamethasone dipropionate [0.05%] cream twice daily) when compared with groups II (treated with calcipotriol ointment [0.005%] twice daily) and III (treated with betamethasone dipropionate [0.05%] in the morning and calcipotriol (0.005%) in the evening) [$p<0.05$].¹⁵ Pasricha *et al.*²¹ used mini-pulse therapy with betamethasone. The side effects included a weight gain of 5 and 7 kg in two patients, mild headache in two patients, transitory general weakness for 2 days after the pulse in two patients, and bad taste in the mouth in three patients; 23 patients, including six children, had no side effects.²¹

All the side effects observed in our study were minor in nature. No patients had to discontinue the drug therapy, due to severity of side effects and all side effects remitted spontaneously without any treatment during the follow-up period. These findings had a similarity with Yalçin *et al.*¹⁸ and Cherif *et al.*¹⁹ who observed that treatment was well tolerated, and no serious adverse effect was noted.¹⁹

Conclusion

Regarding efficacy and safety, calcipotriene and betamethasone dipropionate when used individually, were found to be safer in the treatment of vitiligo, than the combination of the two. Further multicenter, randomized, double-blind study should be conducted with large sample size.

References

1. Njoo MD, Westerhof W. Vitiligo. Pathogenesis and treatment. *Am J Clin Dermatol.* 2001;**2**:167-85.
2. Westerhof W. Vitiligo management update. *Skin Therapy Lett.* 2000;**5**:1-2,5.
3. Bleehe SS. Disorders of skin color. In: Champion RH, Burton JL, Burn DA, Breathnach SM eds. *Rook/Wilkinson/Ebling Textbook of Dermatology.* London Blackwell Science 1998; 1753-1815.
4. Kovacs SO. Vitiligo. *J Am Acad Dermatol.* 1998;**38**:647-66.
5. Halder RM, Taliaferro SJ. Vitiligo. In: Wolff K, Goldsmith LA, Katz SI *et al.*, editors. *Fitzpatrick's Dermatology in General Medicine.* New York: The McGraw- Hill Companies; 2008. p.616-8.
6. Habib A, Sheikh ZI, Khan QD, Rahman SB. Efficacy and safety of oral dexamethasone pulse treatment for vitiligo. *Pak Arm Forces Med J.* 2006;**2**:1-6.
7. Lebwohl M. Topical application of calcipriene and corticosteroid: combination regimens. *J Am Acad Dermatol.* 1997;**37**:55-8.
8. Travis LB, Silverberg NB. Calcipotrien and corticosteroid combination therapy for vitiligo. *Pediatr Dermatol.* 2004;**21**:495-8.
9. Kim SM, Lee HS, Hann SK. The efficacy of low-dose oral corticosteroids in the treatment of vitiligo patients. *Int J Dermatol.* 1999;**38**:546-50.
10. Pasricha JS, Khaitan BK. Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast spreading disease. *Int J Dermatol.* 1993;**32**:753-7.
11. Radakovic-Fijan S, Furnsinn-Friedl AM, Honigsmann H, Tanew A Oral dexamethasone pulse treatment for vitiligo. *J Am Acad Dermatol.* 2001;**44**:814-7.
12. Seister S, Ugruel S, Tilgen W, Reinhold U. Use of high dose methylprednisolone pulse therapy in patients with progressive and stable vitiligo. *Int J Dermatol.* 2000;**39**:624-7.
13. Majid I. Vitiligo management: An update. *BJMP.* 2010;**3**(3):a332.
14. Lisa BT, Nanette BS. Calcipotriene and Corticosteroid combination therapy for vitiligo. *Pediatr Dermatol.* 2004;**21**:495-8.
15. Kumaran MS, Kaur I, Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venereol.*, 2006;**20**:269-73.
16. Parsad D, Saini RDNB, Nagpal R. Calcipotriol in vitiligo: a preliminary study. *Pediatr Dermatol.* 1999;**16**:317-20.
17. Chiavérini C, Passeron T, Ortonne JP. Treatment of vitiligo by topical calcipotriol. *J Eur Acad Dermatol Venereol.* 2002;**16**:137-8.
18. Yalçın B, Sahin S, Bükülmez G *et al.* Experience with calcipotriol as adjunctive treatment for vitiligo in patients who do not respond to PUVA alone: a preliminary study. *J Am Acad Dermatol.* 2001;**44**:634-7.
19. Cherif F, Azaiz MI, Hamida AB, Dhari ABO. Calcipotriol and PUVA as treatment for vitiligo. *Dermatol Online J.* 2003;**9**(5):4.
20. Parsad D, Saini R, Verma N. Combination of PUVAsol and topical calcipotriol in vitiligo. *Dermatology.* 1998;**197**:167-70.
21. Pasricha JS, Khaitan BK. Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast spreading disease. *Int J Dermatol.* 1993;**32**:753-7.