COMPARISON OF EFFICACY OF TOPICAL CALCIPOTRIENE PLUS BETAMETHASONE WITH CALCIPOTRIENE ALONE IN LOCALIZED VITILIGO

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ABSTRACT

Objective: To evaluate the efficacy of topical calcipotriene in comparison with topical calcipotriene plus betamethasone dipropionate in the treatment of localized vitiligo.

Study Design: Randomized controlled trial.

Place and Duration of Study: Study was carried out at department of Dermatology, Pak Emirates Military Hospital (PEMH) Rawalpindi and Combined Military Hospital (CMH) Lahore from June 2015 to December 2015.

Material and Methods: Informed consent of the patients and approval of the hospital ethical committee were duly obtained. A total of 60 patients aged 15-40 years of either gender with localized vitiligo were included in the study. The disease was diagnosed on the basis of clinical features and wood's lamp examination. Patients were randomly allocated into two groups (30 patients in each group) by lottery method. Group A patients, were given topical 0.005% calcipotriene ointment twice daily. Group B patients were given combination of topical 0.05% betamethasone dipropionate and 0.005% calcipotriene ointment twice daily. For evaluation of comparative efficacy, patients of both groups were examined every 4 weeks and at the end of 12th week of treatment. Repigmentation greater than 75% of the affected area in any case was documented as effective response.

Results: Total 60 patients were inducted in the study, out of them treatment was effective in 35 (58.3%) patients whereas in 25 (41.7%) patients the treatment was ineffective. In-group A (calcipotriene), 13 (43.33%) patients had more than 75% repigmentation where as in group B (calcipotriene plus betamethasone), 22 (73.33%) patients had more than 75% repigmentation. Group B was numerically and statistically superior to group A in terms of effectiveness of drugs.

Conclusion: Based on our study combination of topical betamethasone dipropionate with calcipotriene was found to be more effective than topical calcipotriene used alone in the treatment of localized vitiligo.

Keywords: Betamethasone dipropionate, Calcipotriene, Vitiligo.

INTRODUCTION

Vitiligo is known as an acquired disorder of skin of an unknown etiology in which white macules of depigmentation are formed as a result of autoimmunity which destroys epidermal and sometimes hair follicle melanocytes resulting in loss of function of melanocytes[1]. Worldwide prevalence of vitiligo ranges from less than 0.1% to greater than 8%. In United States and Europe it is known to be around 1% that is every 1 in 100 individuals suffers from vitiligo in USA and UK[2]. Clinically vitiligo is characterized by well-defined but irregular shaped white patches that are often symmetrically distributed and may have a tendency to increase in size with time[3]. Vitiligo is classified into two main types which are localized and generalized. Localized vitiligo is defined as hypo pigmented macules limited to any one region or segment of the body and may be further sub classified into focal, segmental (SV) and mucosal types. Generalized vitiligo involves more than one region of the body and can be further sub classified into acrofacial, vulgaris, universal and mixed type's[2,4]. Depigmentation of more than 80% body surface area of skin is sub typed as universal vitiligo[5]. Although it can develop at any age but more than 50% of cases developed the disease before 20 years of age[2,3,6].

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In case of a late onset, possibilities of other autoimmune disease should be considered[2]. A female predominance has been recorded, probably because of a cosmetic concern[2]. Predominant symptoms of vitiligo are cosmetic disfigurement, burning/itching in white patches and increased tendency to burn in sunlight[7]. Besides being cosmetically disfiguring, early onset of the disease especially in females is associated with negative impact on self-confidence, self-esteem and self-image at a key time is social development, thus resulting in a reduced quality of life[8,9]. The exact etiopathogenesis of vitiligo is still not fully known[4,5,10]. There are various hypothesis and theories which explain pathogenesis of different types of vitiligo. Few of the widely accepted hypothesis are genetic predisposition, autoimmunity, neuro-hormonal, biochemical derangement, cytotoxicity, oxidative stress hypothesis and melanocytorrhagy[7,10,11]. Recently proposed ''convergence theory'' states that no single mechanism suffices to explain the pathogenesis, and vitiligo should be considered as a syndrome in which different starting events culminate in one common pathway of melanocyte loss and presenting with a common phenotype[1,4,5,10]. Recent studies have identified 36 loci with strong evidence supporting their role invitiligo susceptibility. They either contain or are located in near vicinity to the suspected biological candidate genes. Out of these loci, 90% loci contain genes for immunoregulatory proteins, whereas 10% encode melanocyte proteins that are likely to serve as auto antigens for the autoimmune response[12]. Low levels of vitamin D were found to be associated with development of vitiligo and VDR gene polymorphisms may affect[1] dihydroxy vitamin D3 levels thus increasing the risk for the development of vitiligo[13,14]. Keeping in view the pathogenesis of vitiligo, different treatment modalities have been suggested which include topical steroids, topical calcineurin inhibitors, topical vitamin D analogues, topical antioxidants, phototherapy, lasers, surgery and combination treatments[3,4]. Currently there is weak evidence to support superiority of any treatment over another[6]. A European evidence suggests that vitiligo of recent onset and in childhood should be treated with a combination of phototherapy and topical drugs including topical steroids, calcineurin inhibitors and vitamin D analogues[15]. The most widely prescribed therapies in all cases of vitiligo are topical corticosteroids and phototherapy including PUVA (psoralen combined with ultraviolet A) and NBUVB (narrow band ultraviolet B)[3]. Continuous use of topical steroids has the risk to cause local side effects like cutaneous atrophy, telangiectasia, acne and perioral dermatitis and PUVA cannot be used in cases of vitiligo in children because of its long term side effects[16]. Calcipotriene is a synthetic analogue of vitamin D3 (calcipotriol) and it has been shown to have immunosuppressive and immunomodulating properties. Keratinocytes, melanocytes, fibroblasts and immunologically active cells have receptors for 1, 25 dihydroxy vitamin D3, which is the active form of vitamin D. Defects in these receptors in melanocytes and keratinocytes within vitiliginous lesions have been identified resulting in defective calcium uptake[3]. Defect in this vitamin D receptor and reduced calcium uptake may have a role in etiopathogenesis of vitiligo. Furthermore, development of hyperpigmentation in indivi-duals treated with calcipotriene in patients of psoriasis has been observed[20]. Role of VDR (vitamin D receptor) gene polymorphism in vitiligo and development of hyperpigmentation after treatment with calcipotrienein patients of psoriasis provide strong basis for using calcipotriene in the treatment of vitiligo[13,14,17].

Based on these observations, Calcipotriene has been used to treat vitiligo, both as monotherapy as well as in combination with other established modalities like topical steroids and phototherapy[3]. The combination of topical steroid and calcipotriene has been shown to be more effective than calcipotriene used alone[3]. To date, limited no of comparative studies have been carried out in our country.

MATERIAL AND METHODS

This randomized controlled trial was carried out in department of Dermatology, Pak Emirates Military Hospital Rawalpindi and Combined Military Hospital Lahore from June 2015 to December 2015. Patients included in the study were those who had localized vitiligo for at least three months duration or more, belonged to both genders, had ages from 15 to 34 years, and were willing to comply with study procedures. The patients were diagnosed clinically and the diagnosis was further confirmed with wood's lamp examination. All those patients were excluded who had any kind of treatment for vitiligo in the last 30 days, any general medical condition, any other concomitant skin disease, pregnant or lactating females and those who were unwilling to take part in the study. Sample size was calculated using WHO sample size calculator taking level of significance 5% and power of test 80%. A total of sixty patients (60) who fulfilled the inclusion and exclusion criteria were enrolled through non-probability consecutive sampling.

Data Analysis

Patients from Dermatology Outpatient Department (OPD) of Pak Emirates Military Hospital (PEMH) Rawalpindi and Combined Military Hospital (CMH) Lahore fulfilling the inclusion criteria were selected after informed consent from patients and permission from Hospital Ethical Committee. OPD registration number, name, age, gender, weight, education status, marital status and residence were noted for each patient. A detailed and relevant history was taken including reproductive, menstrual and family history from females. Physical, dermatological and woods lamp examination were performed and recorded. Baseline blood complete picture, liver function tests, renal function tests, thyroid function tests, random blood glucose levels and urine for pregnancy tests were conducted to fulfill inclusion and exclusion criteria for induction of patients in the study. Patients were randomly allocated into two groups by lottery method. Group A patients, were advised to apply topical 0.005% calcipotriene ointment twice daily. Group B patients were advised to apply combination of topical 0.05% betamethasone dipropionate and 0.005% calcipotriene ointment in the evening. Patients were followed up every 4 weeks upto 12th week of treatment. Digital photographs of all lesions were taken at baseline and at each visit for record and comparative evaluation. Efficacy was assessed in terms of percentage improvement at the end of 12th week as compared to baseline. More than 75% repigmentation was considered as effective response and less than 75% repigmentation was considered as not effective. Patients in both groups were also inquired and examined for

Table-I: Gender, Mean age and duration of diseases in groups A & B.

Parameters		Groups	Total	*p*-value
Gender	Male	A	12 (20%)	0.397
		B	14 (23.3%)	
		Total	26 (43.3%)	
	Female	A	24.266 ± 5.105	
		B	21.500 ± 5.177	
		Total	22.883 ± 5.285	
Age (Mean & SD in Years)		A	24.266 ± 5.105	0.598
		B	21.500 ± 5.177	
		Total	22.883 ± 5.285	
Duration of Disease (Mean & SD in Years)		A	129.200 ± 23.439	0.416
		B	128.500 ± 22.278	
		Total	128.850 ± 22.674	

p-value of efficacy between groups A and B = 0.018, Group-A: Patients treated with topical 0.005% calcipotriene ointment, Group-B: Patients treated with combination of topical 0.05% betamethasone and 0.005% calcipotriene.

possible side effects like itching, burning, erythema, atrophy and telangiectasia.

Analysis of the data obtained was done using a computer software SPSS version 15. Mean and standard deviation (SD) were calculated for quantitative variables like age and duration of disease. Frequencies and percentages were presented for qualitative variables like gender and effectiveness of drug in both groups. Chi Square test was applied to compare the effectiveness between the two groups. *p*-value of ≤0.05 was taken as significant.

RESULTS:

A total of 60 patients were inducted in the study. Twenty six (43.3%) patients were males whereas thirty four (56.7%) patients were females (table-I). The age of patients ranged from 15 to 34 years, mean age was 22.88 ± 5.285 years. The mean age in group A was 24.26 ± 5.105 years while mean age in group B was 21.50 ± 5.177 years (table-I). Out of 60 patients recruited in the study, twenty nine (48.4%) patients were from age group 20-29 years and twenty (33.4%) patients were from age 15-19 years. It shows that more than 80% population which seeks medical advice for vitiligo is younger between 15-29 years. Individual suffering from localized vitiligo aged more than 34 years mostly had concomitant skin or medical disease rendering them ineligible for inclusion into the study. Duration of the disease ranged from 90 to 180 days, mean duration of the disease was 128.85 ± 22.674 days. The mean duration of disease in group A was 129.20 ± 23.439 days while mean duration of

Table-II: Relationship of efficacy between groups A and B with respect to Gender, Age and Duration of diseases.

Parameter		Groups	Efficacy		Total	*p*-value
			Yes	No		
Gender	Male	A	7	5	12	1
		B	6	5	14	
		Total	16	10	26	
	Female	A	6	12	18	0.007
		B	13	3	16	
		Total	19	15	34	
Age	15-19 Years	A	7	0	7	0.001
		B	13	0	13	
		Total	20	0	20	
	20-24 Years	A	6	3	9	0.124
		B	8	0	8	
		Total	14	3	17	
	25-29 Years	A	0	7	7	0.417
		B	1	4	5	
		Total	1	11	12	
	30-34 Years	A	0	7	7	-
		B	0	4	4	
		Total	0	11	11	
Duration of Disease	3-4 Months	A	7	6	13	0.249
		B	9	3	12	
		Total	16	9	25	
	4-5 Months	A	5	6	11	0.091
		B	9	2	11	
		Total	14	8	22	
	5-6 Months	A	1	5	6	0.179
		B	4	3	7	
		Total	5	8	13	

p-value of efficacy between groups A and B = 0.018, Group-A: Patients treated with topical 0.005% calcipotriene ointment, Group-B: Patients treated with combination of topical 0.05% betamethasone and 0.005% calcipotriene

disease in group B was 128.50 ± 22.278 days (table-I). There was no major difference in number of males & females (p=0.397), age (p=0.598) and duration of disease (p=0.416) between the two groups (table-I).

In group A, treatment was effective in thirteen (43.33%) patients and ineffective in seventeen (56.67%) patients. In group B treatment was effective in twenty two (73.33%) patients and ineffective in eight (26.67%) patients (fig-1). Group B was numerically (22 versus 13) and statistically superior in terms of efficacy (p=0.018). Although response was seen with both the drugs but more than 75% repigmentation was more in group B as compared to group A. Statistically significant relationship of efficacy (p-value ≤0.5) between the two groups was found in females (p-value=0.007) but not in males (p-value=1). Thus combination drug is more effective in females while both drugs are equally effective in males (table-II). Results were not statistically significant in different age groups and with duration of disease (p-values >0.05, as in table-II), but both the drugs are highly effective in young age group of 15-19 years, as ineffective response was not seen in any patient. Similarly both the drugs are least effective at higher ages, as efficacy was not seen in any patient (table-II). Both drugs have better efficacies in lesions of less than five months duration, as more number of patients showed response to both drugs in lesions of less than five months duration (table-II).

During follow up visits, patients were also inquired about common side effects of calcipotriene and betamethasone like burning, itching, erythema, thinning, striae, telangiectasia and acne. Twelve (40%) patients in group A and three (10%) patients in group B reported burning/ itching sensation, six (20%) patients in group A and none in group B developed erythema and only three (10%) patients in group B had atrophy while none in group A had any signs of thinning or atrophy after 12 weeks of treatment (table-III).

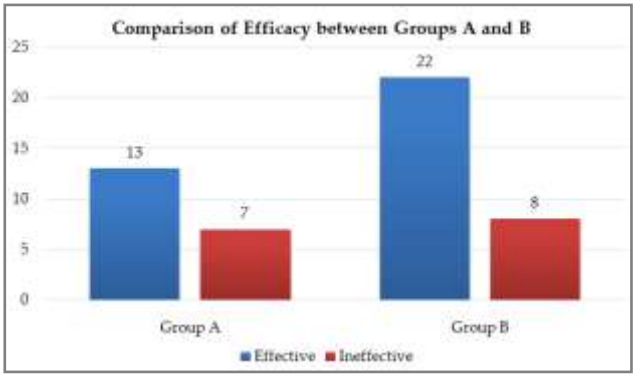

Figure-1: Frequency of efficacy in both groups.

p-value of efficacy between groups A and B = 0.018, Group A: Patients treated with topical 0.005% calcipotriene ointment, Group B: Patients treated with combination of topical 0.05% betamethasone and 0.005% calcipotriene.

Repigmentation is seen in both groups but group B has more patients than group A (22vs13) with >75% repigmentation which is the efficacy criterion.

Table-III: Side effect profile of drugs between groups A and B.

Side Effects	Status	Group		Total	p-value
		A	B		
Burning / Itching	Present	12	3	15	0.008
	Absent	18	27	45	
	Total	30	30	60	
Erythema	Present	6	0	6	0.012
	Absent	24	30	54	
	Total	30	30	60	
Atrophy	Present	0	3	3	0.119
	Absent	30	27	57	
	Total	30	30	60	
Acneiform eruption	-	-	-	-	-

Group-A: Patients treated with topical 0.005% calcipotriene ointment, Group-B: Patients treated with combination of topical 0.05% betamethasone and 0.005% calcipotriene

Significantly higher incidence of burning (*p*-value = 0.008) and erythema (*p*-value=0.012) was seen in group A while more atrophy (*p*-value=0.119) was observed in group B. Less incidence of burning and erythema in group B may be due to presence of betamethasone in combination regimen (table-III).

DISCUSSION

Vitiligo is the most commonly occurring disorder of hypopigmentation affecting both genders almost equally[14]. It is an autoimmune disease in which various types of auto-antibodies target individual's own melanocytes leading to depigmentation of skin and sometimes overlying hair. Its etiopathogenesis is still not completely understood[4,5,10], but studies have shown that both genetic factors as well as environmental triggers play a complex role finally culminating in one common pathogenesis and phenotype[1,4,5,10,18]. Vitiligo is thus a skin disorder which is acquired, idiopathic, progressive and clinically characterized by circumscribed hypopigmentation of the skin and hair, with total absence of melanocytes microscopically[3].

Various medical as well as surgical treatment modalities are being used for vitiligo[2,3]. Commonest of all is the use of potent topical corticosteroids which are considered effective in autoimmune diseases due to their immunosuppressive effects. Of these, 0.05% betamethasone dipropionate has been used frequently due to its high potency[2]. Side effects of long term potent topical corticosteroids are thinning of skin, striae, telangiectasia, acne, rosacea and atrophy of skin[2,16,18]. These adverse effects are time dependent and can be reduced if steroids are combined with another drug. Combination treatment decreases the effective dose and duration of treatment with either drug thus resulting in reduced adverse effect profile from each drug. The discovery of the role of VDR gene polymorphism in cases of vitiligo has led to the use of vitamin D analogues like calcipotriene for treating vitiligo[13,14]. Calcipotriene is a synthetic analogue of vitamin D3, having immunomodulating and immunosuppressive actions. Receptors for 1, 25 di-hydroxy vitamin D3 (theactive form of vitamin D) have been found on various types of cells located in skin like keratinocytes, melanocytes, fibroblasts, and immunologically active cells. Defective uptake of calcium in melanocytes and keratinocytes has been found within vitiliginous lesions[3]. 0.005% calcipotriene has been used as monotherapy as well as in combination with steroids for vitiligo but the combination is shown to be superior to monotherapy[3,20,21].

This study compared efficacy of topical 0.005% calcipotriene ointment against the combination of 0.005% calcipotriene with 0.05% betamethasone dipropionate in patients with localized vitiligo. Repigmentation was measured in terms of percentage improvement in size of the lesions. It was seen that improvement occurred in majority of patients with both the drugs but more than 75% improvement was seen in twenty two (73.33%) patients treated with combination of drugs as compared to thirteen (43.33%) patients treated with calcipotriene alone. Results in this study were concordant with those of Alam *et al*[3], Zahoor *et al*[20] and Kumaran *et al*[21]. Alam *et al*[3] compared combination of topical 0.05% betamethasone and 0.005% calcipotriene (group A) with topical 0.05% betamethasone (group B) and topical 0.005% calcipotriene (group-C). They conducted their study for five months and concluded that the combination drug was more effective than any one of the drugs used alone. A similar study was conducted by Zahoor *et al* in Mayo Hospital, Lahore and used Vitiligo Area Severity Index (VASI) to compare the efficacies of the three drugs[20]. They randomly divided patients into three groups, group A was given topical calcipotriene, group B topical betamethasone and group C was given combination of betamethasone and calcipotriene. After three months of treatment they concluded that all three drugs were efficacious and safe in the treatment of vitiligo, but out of the three drugs, the combination of calcipotriol and betamethasone was superior in efficacy. Kumaran *et al* evaluated

efficacies of calcipotriol and betamethasone used alone and in combination in treatment of localized vitiligo[31]. They divided patients into three groups, group 1 was advised to use topical betamethasone dipropionate (0.05%) cream twice daily, group II was advised to use calcipotriol ointment (0.005%) twice daily, and group III was advised to use betamethasone dipropionate (0.05%) in the morning and calcipotriol (0.005%) in the evening. Marked repigmentation (50% to 75%) was observed in 2 (13.3%), 1 (6.7%) and 4 (26.7%) patients in groups I, II and III, respectively and moderate repigmentation (25-50%) was observed in 7 (46.7%), 5 (33.3%) and 7 (46.7%) patients in groups I, II and III, respectively. According to them combined therapy gave significantly faster onset of repigmentation associated with better stability of the achieved pigmentation. Ha *et al* conducted an intra-individual right vs left sided comparative trial between CCB gel (combination of calcipotriol and betamethasone) and betamethasone dipropionate alone[22]. They advised patients to use CCB gel on vitiliginous lesions on one side and betamethasone cream on the other side. They assessed repigmentation by calculating VASI at 0, 4, 12, 24 and 48 weeks. The trial concluded that CCB gel was more effective and better tolerable than betamethasone cream used alone in vitiligo.

Efficacy of calcipotriene used in combination had also been supported in the past by Parsad *et al*[23]. They used topical calcipotriol in combination with sunlight in twenty-one patients having localized vitiligo and between ages 5 to 17 years. These patients were advised to use calcipotriol 50 ug/g inthe evening and expose themselves to sunlight the next day for 10 to 15 minutes. After 5-12 weeks, repigmentation was seen in majority of the patients with marked to complete repigmentation in 10 of 18 patients and 04 patients showed moderate improvement. In another study by Parsad *et al*[24], they compared PUVASOL (oral psoralen combined with ultraviolet A from sunlight) used alone with a combination of calcipotriol and PUVASOL in right vs left comparative trial. They recruited 19 patients with nearly bilateral symmetrical lesions and advised them to take 0.6mg/kg of 8-methoxypsoralen 2 hours before exposure to sunlight, three times in a week and apply 50ug/g calcipotriol to lesions on one side and placebo to lesions on the other side twice daily. In the end of the trial, 13 (76%) patients had marked improvement in calcipotriol -treated lesions whereas 9 (53%) patients had moderate to marked impro-vement in placebo treated lesions. They concluded that combination of calcipotriol with PUVASOL is more effective, fast and should be used to shorten treatment time with PUVA.

In this study, out of 60 patients enrolled, thirty four (56.7%) patients were females and twenty six (43.3%) patients were males. Predominance of females reporting for treatment has also been observed in studies of Alam *et al*[3] and Zahoor *et al*[20]. It may be due to the fact that females are more concerned about their physical appearance.

This study showed that more than 80% patient population who presented in outpatient seeking medical advice for localized vitiligo was younger with ages between 15-29 (mean age=22.88 ± 5.285 years), this finding concurs with those of Alam *et al*[3] with mean age of 22 years, 21 years and 21 years in their respective groups and Zahoor *et al*[20] with mean ages of 27.94 years (12-60), 28.37 years (12-55) and 22.47 years (12-61) in the respective groups.

In our study efficacy was maximum in patients having ages between 15 to 19 years. Efficacy was seen to decrease with increasing age and with increase in duration of the disease, as less number of patients responded to the drugs in high age group and in group with more duration of the lesion (table-II). Efficacy of calcipotriene in combination regimen in a younger age group was also observed in the results of a study conducted by Parsad *et al* who combined calcipotriol with phototherapy[23]. Zahoor *et al*[20] also compared efficacy of the combination drug with respect to the duration of disease and found

that the *p*-value was significant only in less than one-year group for all the drugs[20].

Statistically significant relationship of efficacy was seen with female gender (*p*-value 0.005) but not with male gender (*p*-value 1). Both drugs were equally effective in males but the combination of betamethasone with calcipotriene was more effective in females. This effect is not described previously in the literature and needs to further studied. All these studies support the fact that combination of vitamin D analogues with steroids is superior to vitamin D analogues alone. Results of our study are concordant with those found in international studies supporting superiority of combination over single drug treatment. In group A, thirteen (43.33%) patients showed more than 75% repigmentation, thus supporting the fact that vitamin D analogues if used alone can be effective in some patients. So in childhood cases of vitiligo, vitamin D analogues can be used alone.

CONCLUSION

Based on our study combination of topical betamethasone dipropionate with calcipotriene was found to be more effective than topical calcipotriene used alone in the treatment of localized vitiligo.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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