

# Efficacy and safety of 0.1% Tacrolimus ointment versus 0.05% Clobetasone butyrate ointment in childhood atopic dermatitis

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## ABSTRACT

**Introduction:** Atopic dermatitis (AD) is a chronic relapsing skin condition characterized by intense itching, dry skin, redness, inflammation and exudation with significant morbidity. It often requires long-term use of topical corticosteroids but, patients' adherence to corticosteroids may be limited by perceived risks and systemic adverse effects. Therefore, steroid-sparing topical agent is needed.

To compare the efficacy and safety of 0.1% tacrolimus ointment and 0.05% clobetasone butyrate ointment in patients with childhood AD.

**Materials and methods:** This monocentric prospective open-label comparative study was carried out in the Department of Dermatology and Venereology, Chittagong Medical College Hospital. Two hundred patients of 2–10 years of age with mild to moderate AD involving  $\leq 50\%$  of the total body surface area (BSA) were randomly assigned. The treatment duration was 4 weeks and was followed-up for 12 weeks. The eczema area and severity index (EASI) and the physician's global evaluation of clinical response were assessed and evaluated.

**Results:** Effective sample size was 176 as because 24 patients were dropped out during follow up. EASI score was significantly changed from baseline in follow up weeks and there was a statistically significant difference in the reduction of EASI of patients in Tacrolimus groups at the end of 2<sup>nd</sup> week, 4<sup>th</sup> week, 6<sup>th</sup> week than the other group ( $p < 0.05$ ). At the end of 4 weeks treatment, a median improvement of  $\geq 75\%$  in EASI was observed in 86% and 57% of patients in Tacrolimus and Clobetasone Group, respectively. At the end of the 12 week follow-up period, these improvements persist. Both the regimens were well tolerated.

**Conclusions:** The overall therapeutic effectiveness was in favour of topical Tacrolimus ointment (0.1%) over topical Clobetasone butyrate ointment (0.05%) for the treatment of AD in children.

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**Key words:** atopic dermatitis, ointment, tacrolimus, clobetasone butyrate

## INTRODUCTION

In 2004 the world Allergy Association suggested calling "Atopic eczema" an inflammatory condition determined by an IgE reaction, suggesting that the presence of eczema in an atopic patient could be associated with or herald the development of some allergic diseases such as rhinitis and asthma [1]. Atopic dermatitis (AD) usually manifests for the first time in infancy or childhood. Occasionally it appears for the first time in adulthood or rarely in elderly age [2]. The pathogenesis of AD involves a complex interaction of several factors. A combination of genetic, immune, neuroendocrine, infections, metabolic and endocrine factors mediate the development of AD [3].

There are multiple anti-inflammatory agents available for the treatment of AD. Topical Corticosteroids (TCS) are appropriate for the vast majority of patients and the potency

of TCS chosen should be individualized based on the severity of dermatitis, the location of the affected skin, the surface area of the affected skin and the age of the patient [4]. Thus mild to moderate potent TCS are generally recommended for treatment of children [5]. Clobetasone butyrate is a new TCS which has been formulated as a 0.05% cream and ointment for the treatment of inflammatory dermatosis. In animal studies, clobetasone butyrate has been shown to cause less thinning of epidermis than the steroids Flucinolone acetone and Triamcinolone acetone [6]. Even large doses of clobetasone butyrate do not seem to affect the HPA function. This corticosteroid seems, therefore, to offer effective topical anti-inflammatory activity with minimal risk for local or systemic side effects [7].

Tacrolimus ointment, formulated for the treatment of AD, is the first in a class of topical immunomodulators. Its

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mechanism of action is based on calcineurin inhibition [8]. Calcineurin inhibition can also decrease the production of the pro-inflammatory cytokines, tumour necrosis factor and granulocyte-macrophage colony-stimulating factor (GM-CSF), necessary for maturation of the dendritic cells [9]. A topical formulation of Tacrolimus is associated with an excellent safety profile, well-tolerated and was effective when applied twice daily for 4 weeks [10]. Similar to TCS it is associated with a reduction in staphylococcal skin colonization in AD lesion [11].

Bangladesh is a high burden of childhood AD. Adequate information concerning the safety, potency and appropriate use of topical drugs for this condition is essential for patients' careers and possibly for general practitioners also. The level of certainty and the class and the evidence of the recommendations regarding their use are low and their results have been non-conclusive. Most of the studies were often poorly designed. Nearly all studies were of > 4 week's duration. Moreover, there is a dearth of information in this field in Bangladesh. In this context the authors aim to conduct a study to assess the efficacy and safety of 0.1% Tacrolimus ointment with that of 0.5% clobetasone butyrate ointment in the treatment of childhood AD in this setting by addressing the limitation of previous studies.

## MATERIALS AND METHODS

This study was a monocentric, prospective, open-label, comparative study and was carried out in Chittagong Medical College Hospital (CMCH) between the periods September 2013 to October 2014. All patients of mild to moderate group of atopic dermatitis of 2–10 years of age were the study population.

### Inclusion criteria

- Patients who met the criteria of atopic dermatitis.
- Patients of both sexes.
- Age group 2 years to 10 years.
- Patients/Patients guardian who gave verbal/written consent and were willing to comply with the study process.
- Mild to a moderate group of patient with AD were included.

### Exclusion criteria

- Acute or chronic Liver disease and other systemic diseases which would contraindicate the use of Tacrolimus and Corticosteroids.
- Patients currently being treated with other modalities of treatment.

### Treatment protocol and evaluation

Patients of Tacrolimus group were advised to apply commercial preparation 0.1% Tacrolimus ointment twice daily

to areas for actively diseased skin for 4 weeks. All patients of Clobetasone group were advised to apply 0.05% Clobetasone butyrate ointment twice daily for 4 weeks. All other topical & systemic drugs used in AD were prohibited, only both oil and non medicated emollients were allowed. Inhaled or intranasal corticosteroids, if being used was limited to 1mg/day. No concurrent treatment was allowed during this study. Both Groups had a washed-out phase for 4 weeks.

Patients' baseline characteristics, such as age, sex, economic and educational level, disease-related variables, presenting features, baseline dermatological findings and baseline EASI along with baseline investigations were recorded. Patients in each group were evaluated by the Eczema Area and Severity Index (EASI) score as described below by the investigators.

Clinical evaluation was done two weekly intervals for twelve weeks. Safety was evaluated by repeating search for side effects at regular visits as well as by physical examination and assessment of adverse events. If any patient would come irregularly or completely absent from follow up visit after receiving treatment then he/she were considered as partially treated or dropped outpatient. A pre-designed data sheet was utilized to record each participant's information.

### Statistical analysis

All the data were checked and edited after collection. Continuous variables were reported as the means  $\pm$  SD. Means were compared using Student's t-test for two groups. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using chi-square or Fisher's exact test whichever was applicable. Baseline characteristics were compared by either Student's t-test for continuous variables and the  $\chi^2$  test or Fisher's exact test when the expected value is < 5 for categorical data. A binary logistic regression analysis was performed to control for baseline factors. Statistical significance was defined as  $p < 0.05$  and a confidence interval was set at 95% level. SPSS (Statistical Package for Social Science) for Windows version 23 software was used for the analyses.

## RESULTS

Sociodemographic characteristics of the patients concerning age, sex, place of residence and economic status of their parents were summarized in Table 1. Both groups were similar and comparable as there were no significant ( $p > 0.05$  in all variables) difference of the variables between two groups except the place of residence.

Table 2 summarized baseline disease-related characteristics of the patients like age of onset of the disease, duration of the disease, family history of atopy, history of bronchial asthma, allergic rhinitis and baseline EASI scores. Both groups were similar and comparable as there was no significant

**Table 1.** Sociodemographic characteristics of the patients

Characteristics	Tacrolimus		Clobetasone		Test statistics
	N	%	N	%	
Age [years]					
Range	2-10		2-10		p = 0.572*
Mean ± SD	5.97 ± 2.70		5.75 ± 2.79		
Sex					
Male	60	60	46	46	p = 0.567†
Female	40	40	54	54	
Socioeconomic status					
Lower class	12	12	17	17	p = 0.7†
Middle class	69	69	67	67	
Upper class	19	19	16	16	
Place of residence					
Urban	67	67	82	82	p = 0.015**
Rural	33	33	18	18	

\* Non-significant in Independent sample t-test; † Non-significant in Chi-square test; \*\* Significant in Chi-square test

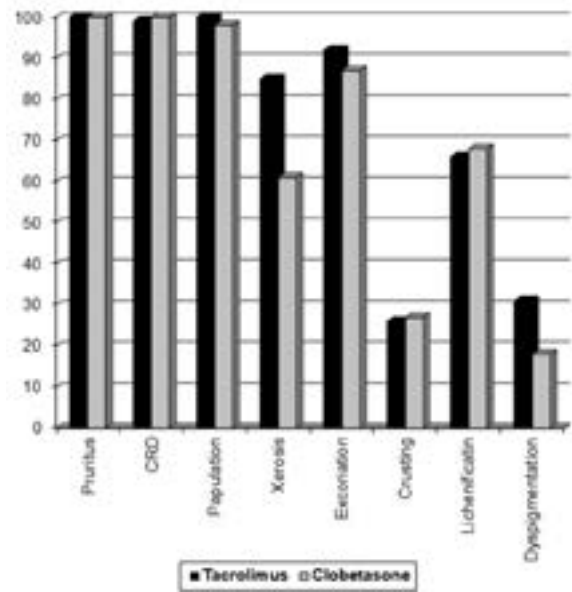
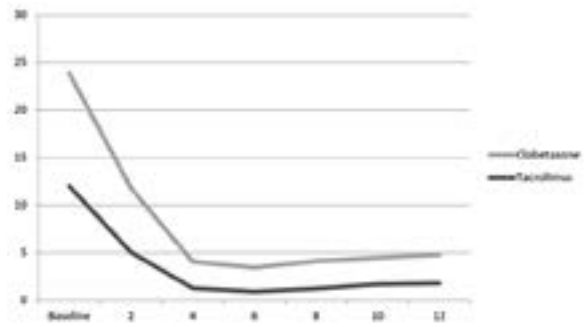
**Table 2.** Baseline disease-related features of the patients

Characteristics	Tacrolimus		Clobetasone		Test statistics
	N	%	N	%	
Age of onset [years]					
Mean ± SD	3.51 ± 2.20		3.56 ± 2.36		p = 0.87*
Duration of disease, in years					
Mean ± SD	2.68 ± 1.83		2.40 ± 1.54		p = 0.25*
Family H/O atopy					
Present	59	59	53	53	p = 0.393†
H/O allergic rhinitis					
Present	74	74	63	63	p = 0.094†
H/O bronchial asthma					
Present	44	44	30	30	p = 0.06†
Serum Ig E					
Above normal limit	86	86	83	83	p = 0.85†
Severity grading of the disease					
Mild	39	39	41	41	p = 0.89†
Moderate	61	61	59	59	
Baseline EASI score					
Mean ± SD	11.99 ± 4.99		11.87 ± 4.19		p = 0.85*

\* Non-significant in Independent sample t-test; † Non-significant in Chi-square test

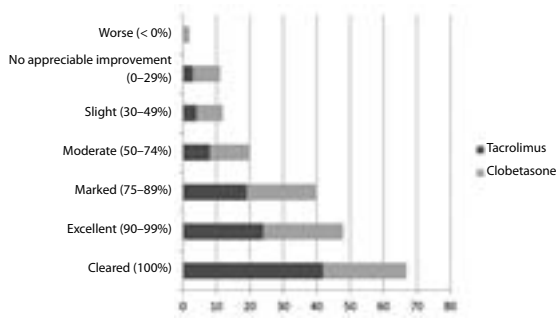
difference in the variables between two groups ( $p > 0.05$  in all variables).

Figure 1 showed the distribution of different presenting complaints in both groups. Most frequent complaints were pruritus (100%), chronic or chronically relapsing dermati-

**Figure 1.** Distribution of chief complaints of patients by groups**Figure 2.** Distribution of mean EASI score over time in both groups during 12 weeks treatment period

tis (CRD) (99.5%) and population (99%). Other complaints were xerosis (73.0%), excoriation (89%), crusting/oozing (26.5%), lichenification (67%) and dyspigmentation (24.5%). However, there was no statistically significant difference concerning the distribution of these variables between the two groups.

Dermatological examination revealed that 71.5% had flexural lichenification or linearity, 84% tended cutaneous infection, 34% had cheilitis with other variable findings. The EASI was measured at two weekly intervals until 12<sup>th</sup> week to evaluate the prognosis. Figure 2 showed the mean EASI score in two groups at different follow-ups. It revealed that indices were decreasing gradually in both groups but the rate of reduction was faster in Tacrolimus Group than in Clobetasone Group. During 4 weeks treatment period reduction of EASI score was significantly more in Tacrolimus Group than Clobetasone Group ( $p < 0.05$ ; calculated by independent t-test).



**Figure 3.** Physician's global evaluation of clinical response by groups

Overall treatment response was evaluated concerning the improvement of physician global evaluation score from baseline to 4<sup>th</sup> week (Fig. 3). There was a marked impro-

vement in percentage score between the two treatment groups; with greater improvement in Tacrolimus Group than in Clobetasone Group and the difference was statistically significant ( $p = 0.021$ , calculated by chi-square test) (Fig. 4 and 5).

Adverse events occurring at the application site as well as not occurring at the application site experienced by at least 4 patients in any treatment group are presented in Table 3. Skin burning was the only adverse event to show a significantly higher incidence in the Tacrolimus treatment group than the other group ( $p < 0.05$ ). Local pruritus was also common. Flu syndrome and headache were the most common non-applications site adverse events. Most cases of skin burning and pruritus due to local irritation were transient, decreasing in frequency over time.



**Figure 4.** Showing skin lesions of atopic dermatitis in a female child before and after treatment with 0.1% Tacrolimus ointment



**Figure 5.** Skin Lesions of Atopic Dermatitis in a child before and after treatment with 0.05% Clobetasone butyrate ointment

**Table 3.** Frequency of common adverse events by groups

Adverse events	Tacro- limus	Clobeta- sone	Test statistics
	%	%	
Adverse events at the application site			
Burning sensation	39	9	p = 0.02*
Increased localized pruritus	18	13	p = 0.08**
Skin infection	8	10	p = 0.67**
Allergic reaction	6	7	p = 0.85**
Atrophy/skin thinning	4	6	p = 0.86**
Dyspigmentation	3	5	p = 0.80**
Adverse events not at the application site			
Headache	8	10	p = 0.67**
Flue like symptoms	6	7	p = 0.85**
Skin burning	N (%)	N (%)	Total number
Week 2	39 (39)	9 (9)	48
Week 4	8 (8.16)	3 (3.09)	11
Week 6	0 (0)	0 (0)	00
Local pruritus			
Week 2	18 (18)	13 (13)	31
Week 4	10 (10.20)	9 (9.27)	19
Week 6	4 (4.21)	3 (3.15)	7

\* Significant in Chi-square test; \*\* Not significant in Chi-square test

A logistic regression analysis was conducted (Tab. 4) to predict whether the patients had achieved more than 50% improvement in physician global evaluation of clinical response or not using the age of the patients, duration of illness, age of onset, family history of disease, sex and treatment group as predictors. A test of a full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinct between achievement and failed to achieve > 50% improvement ( $X^2 = 40.08$ ,  $p < 0.001$ , with  $df = 2$ ).

The Wald criterion demonstrated that only the treatment group made a significant contribution to prediction ( $p = 0.001$ ). Other variables were not a significant predictor. AOR value indicates that the odds of achievement of > 50% improvement among patients treated with Tacrolimus was increased by 4.85 times than the patients treated by Clobetasone (AOR = 4.85, CI: 2.21–6.96).

## DISCUSSION

This study was conducted among the patient of childhood atopic dermatitis aged between 2–10 years, who came for treatment in the outpatient department of Dermatology and Venereology of CMCH from September 2013 to October 2014. The study was conducted to evaluating the efficacy and safety of 0.1% Tacrolimus ointment versus 0.05% clobetasone butyrate ointment in childhood atopic dermatitis. Compared with 0.05% clobetasone butyrate, 0.1%

**Table 4.** Adjusted effects (Adjusted Odds Ratio) of categorical predictive variables on treatment response

	B	AOR for attainment of > 50% improvement lower	95% CI for AOR		Test statistics
			Upper		
Age [years]	0.436	0.548	0.258	2.19	0.35
Duration of illness [years]	0.845	0.78	0.45	1.19	0.54
History of atopy (present vs. absent)	0.375	0.32	0.01	1.09	0.44
Family history (present vs. absent)	0.835	2.305	0.523	10.166	0.270
History of asthma (yes vs. no)	0.456	0.578	0.250	9.979	0.628
Sex (male vs. female)	0.274	1.315	0.284	6.086	0.726
Treatment group (tacrolimus vs. clobetasone)	3.08	4.85	2.21	6.96	0.001
Constant	-5.960	0.003			0.001

Tacrolimus ointment for 4 weeks was demonstrated to be effective in the treatment of mild to moderate AD in children 2 to 10 years of age. Improvement was apparent early in first follow up after two weeks of initiation of treatment. The greater efficacy of the tacrolimus ointment compared with the clobetasone butyrate ointment was apparent after two weeks of treatment. The quick onset of efficacy is consistency with the findings of Sikder et al. [12].

The age-specific cumulative AD cases at 2–6 years range were higher 117 (58.5%) than 7–10 years range 83 (41.5%). The male to female ratio was almost equal. This is a common scenario of age and sex distribution of the children presenting in the outpatient department of Bangladesh. These findings are also in accord with other studies [13, 14].

In this study regarding residence, patients more were from urban areas, economic status of patients revealed 36 (18%) were from the upper class, 136 (68%) were from the middle class and 28 (14%) were from lower-class families. There is a strong link of AD and socioeconomic advantages and also with smaller family size [8]. Regarding disease characteristics, 56.0% of patients had a history of atopy, 37.0% had a history of bronchial asthma and 68.5% cases had a history of allergic rhinitis. Family history provides clear evidence of the genetic basis of the disease. The highest risk was present when both parents were involved [15].

Regarding the presenting features, the patients were similar to the subjects of other studies. All had pruritus, 99.5% had chronic or chronically relapsing dermatitis, 73.0% had xerosis, 99% had papulation, 89% had excoriation, 26.5% had crusting/oozing, 67% had lichenification and 24.5% had dyspigmentation. This finding correlates with the findings with other previous studies [2]. 71.5% had flexural lichenification or linearity, 84% tended towards cutaneous infection, 34% had cheilitis with other variable findings were found in both groups.

Treatment response was analyzed by calculating the EASI score in both groups. EASI score in Group A and Group B before treatment were comparable ( $p < 0.05$ ). After initiation of treatment, in subsequent follow up after 2 weeks, statistically significant ( $p < 0.05$ ) difference was observed in favour of 0.1% tacrolimus ointment. A statistically significant score of EASI was also found in rest of the follow up at 4 weeks, 6 weeks, 8 weeks, 10 weeks and 12 weeks between Group A and Group B ( $p < 0.05$ ). It is also consonance with the study of Peller et al. [10].

In an open, randomized and comparative study, the efficacy and safety of 0.03% tacrolimus ointment, 0.05% clobetasone butyrate cream and their combination were evaluated in patients with AD [13]. The treatment duration was 4 weeks and was followed-up for 6 weeks. Only 13.3% patients who received 0.03% Tacrolimus ointment experienced excellent improvement and clearance by the end of the treatment compared with 66.7% patients who received 0.05% Clobetasone butyrate and 93.3% patients who received combination regimens. Marked to moderate improvement was observed for 73.3%, 66.7% and 6.7% of patients who received 0.03% Tacrolimus, 0.05% clobetasone butyrate and combination regimen respectively. At the end of follow-up, excellent improvement and clearance were observed in 6.7% of patients of 0.03% Tacrolimus group and 0.05% Clobetasone butyrate group respectively, and in 60.0% patients who received combination regimens. This study result was not in conformity with that study [12] as the authors have observed the result in favour of tacrolimus ointment. However, this difference might be due to the different concentration of Tacrolimus (0.1% vs. 0.03%) in the two studies.

A binary logistic regression was performed to ascertain the effect of the intervention, gender, age, family history of atopy on the likelihood that the patient showed improve-

ment in atopic dermatitis. To do so, the improvement of the score in physician's global evaluation of clinical response was dichotomized into two groups: Improved (30–100%) and not improved (0–29%). The statistically significant difference was found in symptom improvement among the Tacrolimus group.

The result of this study indicates that short term treatment (4 weeks) with 0.1% Tacrolimus ointment and 0.05% Clobetasone butyrate ointment in children (2–10 years of age) was safe. The only adverse event that showed a significantly higher incidence in tacrolimus treatment groups than the Clobetasone butyrate group was skin burning. The frequency of this adverse event was largely decreased by the 2<sup>nd</sup> week of treatment. Other studies have shown that the actual episode of skin burning lasts only about 10 minutes [10]. Next to which was localized pruritus, skin infection headache, flu like symptoms and allergic reactions. In a subsequent follow-up, side effects were reduced in both frequency and severity. During treatment period 2 of the 11 dropout cases reported skin burning, both of them were in 0.1% tacrolimus group but the reason for withdrawn was unknown. Otherwise, none had to discontinue treatment for these adverse events. Eighteen patients experienced headache, eight from 0.05% clobetasone butyrate group and ten from tacrolimus regimen group; this event did not suggest a relationship with treatment regimens. In another clinical trial, burning sensation of the skin was the most common side effect observed occurring 46 to 58% of patients treated with Tacrolimus [16]. Pruritus was reported in 46% of patients.

Data from clinical trials indicated a constant pattern of adverse effects mainly related to the site of administration of the ointment. These commonly include skin burning (adjusted incidence rate 45.6% and 57.7% for the 0.03% and 0.1% ointment) pruritus (46.1% for both strengths) and erythema (24.8 and 27.9% for the 0.03% and 0.1% ointment on short term use. These reactions especially skin burning is more severe during the first few days of therapy and decrease markedly thereafter as the skin heals. In the long term study skin burning, erythema and pruritus were common and incidence of skin burning was 45% on days one to four, 23% on day five to eight, 8% on days 23 to 30 and 2% in months 10 to 12. Other application site reactions with a lower incidence have included folliculitis, herpes simplex and maculopapular rash. The folliculitis and a maculopapular rash are possibly due to the occlusive nature of the ointment. It is also supported by another study [17]. Although the results of the present study showed better efficacy of 0.1% tacrolimus than 0.05% clobetasone butyrate in childhood AD, the authors must draw some limitations of this study. These should be kept in mind while deciding on the impli-

cation of the findings of the study. It was a single centre study with a relatively small sample size. It was an open-label trial, the researchers themselves were the investigators and evaluators and not blinded to the treatment received by the patients. It is not possible to make any comment about the persistency of the treatment effect, and the long term adverse effects as treatment was stopped after 4 weeks and follow up was stopped after 12 weeks.

## CONCLUSIONS

The present study demonstrates that Tacrolimus ointment (0.1%) is significantly more effective than clobetasone butyrate (0.05%) ointment for the treatment of AD in children. Other than transient skin irritation, the safety profiles of tacrolimus ointment and clobetasone butyrate ointment, over the 4-week treatment period, were similar.

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