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Comparison of Efficacy and Safety between Topical Tacrolimus (0.03%) and Fluticasone Propionate (0.005%) in Childhood Atopic Dermatitis

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ABSTRACT

Introduction: *Atopic dermatitis (AD) is an itchy, chronic or chronically relapsing inflammatory skin condition that often starts in early childhood, usually before 2 years of age. The burden of* atopic *dermatitis (AD) is substantial, as it can have a significant impact on individuals, families, and healthcare systems. In the context of Bangladesh, atopic dermatitis is also a prevalent dermatological condition. This study was aimed to compare the safety and efficacy of Tacrolimus 0.03% and Fluticasone propionate 0.005% in childhood AD.* ***Methods:*** *This randomized clinical trial was conducted in the Department of Pharmacology and Therapeutics of Sylhet MAG Osmani Medical College, Sylhet. A total of 70 patients were enrolled in this study attending in department of Dermatology and Venereology and department of Pediatrics in Sylhet MAG Osmani Medical College Hospital, Sylhet over a period of 12 months from July, 2022 to June, 2023. They were allocated in Group A and Group B equally using block randomization. Group A patients were treated with tacrolimus 0.03% ointment and Group B patients were treated with fluticasone propionate 0.005% ointment. Both groups of patients were treated twice daily (12 hourly) for 4 weeks. Data was collected at baseline and after the end of four weeks of treatment using pre-designed questionnaire.* ***Results:*** *Maximum patients were male and within five to ten years of age. After four weeks of treatment percentage of reduction of Eczema area and severity index (EASI) score was 95.23±2.15 in tacrolimus treated group and 85.29±1.66 in fluticasone treated group. Severity assessment showed, 54.8% tacrolimus treated participants cleared of AD whereas only 15.6% patients in fluticasone group showed similar response (p-0.002). Percentage of improvement of severity from baseline was 80.03±24.75 in tacrolimus treated group and 51.97±23.88 in fluticasone group (p-0.0001). Both the drugs showed no adverse effects.* ***Conclusion:*** *In this clinical trial, topical tacrolimus 0.03% showed better efficacy in contrast to fluticasone 0.005%. It was also proven to be safe and tolerable. So, it may be recommended for children with atopic dermatitis.*

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INTRODUCTION

The characteristic of atopic dermatitis (AD) are pruritus and chronic course of exacerbations with remission.[1] Atopy is an inherited tendency to produce immunoglobulin E (IgE) antibodies in response to minute amounts of common environmental proteins such as pollen, house dust, mites and food allergens. Dermatitis is derived from the Greek word "derma" for skin and "itis" for inflammation.[2] There are three stages of atopic dermatitis e.g. infantile atopic dermatitis (from two months to two years of age), childhood atopic dermatitis (from two years to 10 years) and adolescent/adult atopic dermatitis (after 10 years). It is common among all types of dermatitis globally, with varying prevalence rates across different populations. Recent studies shows, the global prevalence of AD ranges from 7% to 20%, depending on the geographical region and diagnostic criteria used.[3,4] Despite the lack of precise figures, AD is commonly observed in clinical settings and has been reported as a significant health problem in Bangladesh.[5,6] The prevalence of atopic dermatitis in Bangladesh has been on the rise, with a significant burden on healthcare systems and individuals affected. Though AD is sometimes seen as relatively harmless, but there is a detrimental impact on the quality of life of the patient, such as sleep disturbances, anxiety, social and psychological issues and decreased productivity at work or school. The family of the patient is also affected economically and emotionally. Keeping away from long, hot baths help prevent dry skin but an emollient should be applied after a bath. Corticosteroid (CS) creams are mainstay treatment[7] in medical care to manage eczema flares.[8,9] Although Corticoster-oids are safe in children but they are limited to use in different parts of the body in different age groups according to potency.[10,11] Moreover, there are only few available studies[12,13] comparing efficacy and safety of topical Tacrolimus and Fluticasone in AD. More studies required in search of a safer drug.

So, this study was conducted to compare the efficacy and safety of Tacrolimus (0.03%) and Fluticasone propionate (0.005%) in atopic dermatitis patients aged 2 to 10 years.

METHODS

This randomized clinical trial was conducted in the department of Pharmacology and Therapeutics, Sylhet MAG Osmani Medical College, Sylhet during the period July, 2022 to June, 2023. Study approval was taken from ethical committee of Sylhet MAG Osmani Medical College, Sylhet, Bangladesh. Memo no of ethical approval for this research is SOMC/2023/02. A total of 70 atopic dermatitis patients were selected purposively for this study from the outpatient department of dermatology and venereology and pediatrics in the Sylhet MAG Osmani Medical College Hospital, Sylhet. Sample size was calculated using mean±standard deviation formula for clinical trial with 5% significance level and 99.0% power. After calculation the total sample size was 6.74. As the minimum sample size for research purpose is 30, assuming 10% attrition, the calculated sample size was 33 for each group. So, the total sample size was 66 which was rounded to 70.Patients who met the selection criteria were included in this study. Selected 70 patients with atopic dermatitis was divided into two groups. Group-A received tacrolimus 0.03%(Ointment. Tacrolim 10gm, Incepta pharma) and Group-B received futicasone propionate 0.005% (Ointment. Lutisone 10gm, Incepta pharma). Drugs were allocated to the patients using block randomization (Figure 1). There were total 6 blocks and each sized 4 (2x2). The groups within a block were randomly generated in computer. One block was selected randomly every time and patients were assigned to a group according to the block.

1	2	3	4	5	6
A	B	B	A	A	B
B	A	A	A	B	A
A	A	B	B	B	B
B	B	A	B	A	A

Figure 1: Block randomization

All the patients of suspected AD were assessed by taking detailed history and physical examination. Informed written consent was taken from each patient or their parents after full explanation of study procedure. Clinical diagnosis was made and confirmed by clinicians using Hanifin and Rajka criteria.[14]Patientshaving at least 3 major criteria and 3 minor criteria were selected. Baseline and demographic data for the study such as name, age, gender, family history etc. were recorded for each patient. Serum IgE level and complete blood count (C.B.C) were done and recorded routinely for each clinically diagnosed patient. Both drugs were applied on the affected area twice daily (12 hourly) for four weeks. During this period the dosage was fixed and patients were allowed to use emollients/moisturizers and systemic antihistamine (Drop/Syrup. Alatrol, Square pharma). At the end of treatment patients of both groups were followed up (4 weeks after starting of treatment). During the follow up Eczema (Deramtitis) Area and Severity Index (EASI) score and any reported adverse effects were documented.

At the end of four weeks patients were reassessed and data were collected again. Both quantitative and qualitative data was documented in a predesigned data collection sheet which was constructed by reviewing literature and consulting experts. Determination of drugs efficacy was done based on change of EASI score, area involvement and percent of improvement of severity.[15] The presence or absence of adverse effects of drugs were used to determine safety of drug. Such as, skin burn, skin atrophy, local hirsutism, local depigmentation, stria, hypersensitivity etc. All data were edited meticulously through checking and rechecking. All omissions and inconsistencies were corrected and removed methodically. The results were collected, tabulated, and statistically analyzed by using windows based computer software device with a statistical package for social science (SPSS-25). Quantitative data were expressed as mean and standard deviation and comparison was done by using t-test. Qualitative data were expressed as frequency and percentage and comparison was done by using chi-square or fisher's exact test based on their applicability. A p-value of <0.05 was considered statistically significant in all statistical analysis

RESULTS

Maximum (100, 27.78%) patients were within 50 to 59 years of age group followed by >60 years (Table I). Out of 70 patients, 4 patients from Group-A (tacrolimus treated group) and 3 patients from Group-B (fluticas one treated group) were unable to complete the assigned treatment course. So, 31 patients in group A and 32 patients in group B, a total of 63 patients participated in the study's final analysis.

The ages of patients of both groups ranged from 2 to 10 years and the combined mean age was 5.81 ± 2.63 years. In Group-A the mean age was 5.16±2.72 years and mean age of patients in Group-B was 6.44±2.41 years individually. Most of the patients in Group-A were pre-school age (>2 - 5 years) which was 16 (51.6%) and in Group-B it was 24 (75.0%) who were school aged children (>5 - 10 years)

Table I: Age distribution between the study groups

Age groups	Study Group		Test value	*p*-value
	Group-A (n-31)	**Group-B (n-32)**		
Toddler (2 - 3 years)	3 (9.7%)	4 (12.5%)		
Pre-school (>3 - 5 years)	16 (51.6%)	4 (12.5%)	0.002	*p-0.002
School age (>5 - 10 years)	12 (38.7%)	24 (75.0%)		
Total	**31 (100%)**	**32 (100%)**		
Mean±SD	5.16 ± 2.72	6.44 ± 2.41	**t = 0.353	**p-0.73

SD: Standard deviation. *Fisher's Exact test and **unpaired't-test were employed to analyze the data
Group-A: Tacrolimus treated group, Group-B: Fluticasone treated group.

Majority of the patients were male in both groups. There was statistically similar gender distribution (t = 0.448; p-0.503) in both groups. (Figure 2)

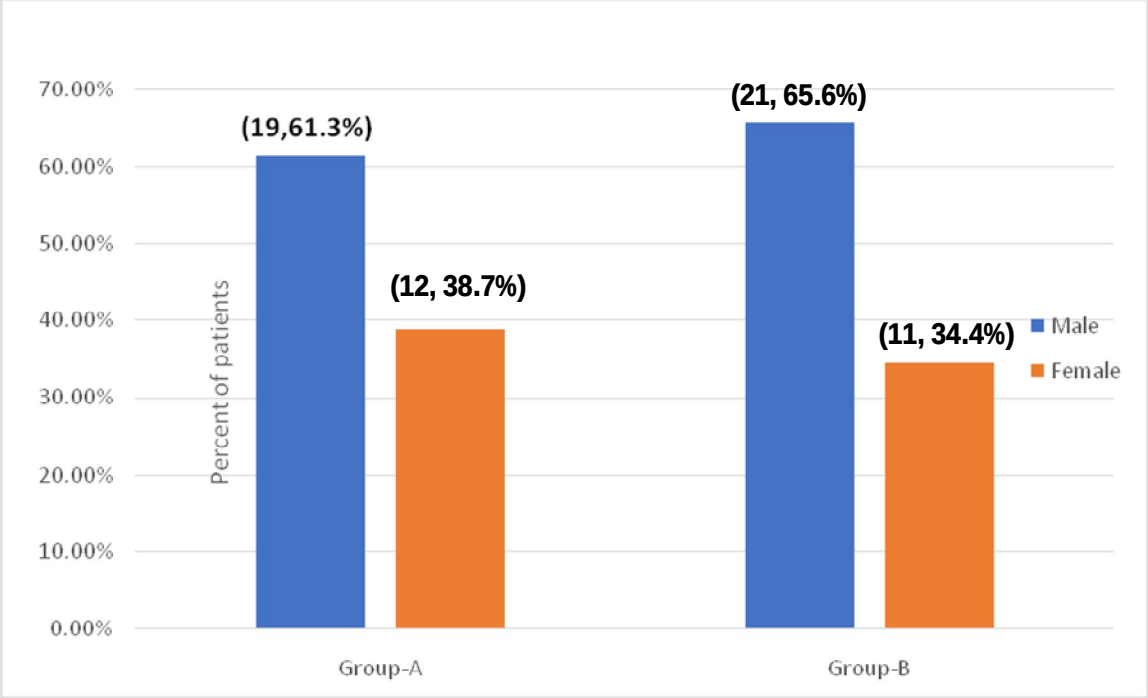

Figure 2: Gender distribution of patients

Table II showed the distribution of severity between study groups at baseline. In both groups maximum patients had moderate severity of Atopic Dermatitis. Very few cases are in very severe form of disease.

Table II: Distribution of severity between the study groups at baseline[15]

Level of Severity	Study Group		Test value	*p*-value
	Group-A (n-31)	**Group-B (n-32)**		
Mild	3 (9.7%)	5 (15.6%)		
Moderate	20 (64.5%)	22 (68.7%)	*χ^2 = 2.513	*p-0.473
Severe	7 (22.6%)	3 (9.4%)		
Very Severe	1 (3.2%)	2 (6.3%)		
Total	**31 (100%)**	**32 (100%)**		

*χ^2 (Chi-square) test was employed to analyze the data

The most numbers of improvement in Group-A was 17 (54.8%) patients whose EASI interpretation was clear and in Group-B it was 19 (59.4 %) patients whose EASI interpretation was mild. There was no severe and very severe form of dermatitis in both groups (Table III).

Table III: Outcome of Atopic dermatitis after four weeks of topical treatment[15]

Level of Severity	Study Group		Test value	p-value
	Group-A (n-31)	Group-B (n-32)		
Clear	17 (54.8%)	5 (15.6%)	*χ^2 = 14.359	*p-0.002
Almost Clear	7 (22.6%)	8 (25.0%)		
Mild	6 (19.4%)	19 (59.4 %)		
Moderate	1 (3.2%)	0 (0.0%)		
Total	**31 (100%)**	**32 (100%)**		

*χ^2 (Chi-square) test was employed to analyze the data

Significant improvement of severity of atopic dermatitis was observed in tacrolimus treated patient (Table IV).

Table IV: Comparison of mean percentage of improvement of severity between two groups

	Study Group		Test value	*p*-value
	Group-A (n-31) Mean ± SD	Group-B (n-32) Mean ± SD		
Mean of percentage of improvement severity	80.03± 24.75	51.97 ± 23.88	4.581	**p*-0.0001

*Unpaired t-test

Table V shows the comparison of the mean (±SD) of eczema area and severity index (EASI) grand total score of both groups. Tacrolimus treated group showed significant reduction of EASI score that meant tacrolimus is more efficacous than fluticasone.

Table V: Comparison of mean of grand total score of Atopic dermatitis[15]

Grand total	Group-A (n-31) Mean ± SD	Group-B (n-32) Mean ± SD	Test value	*p*-value
Baseline	16.36 ± 4.74	16.65 ± 4.38	*t = 0.045	**p*-0.964
After end of 4 weeks	0.78 ± 0.46	2.49 ± 0.39	*t = 2.842	**p*-0.006
Test value**	**t = 16.711	**t = 19.502		
p-value**	**p 0.001	**p0.001		
Mean reduction of Percentage	95.23 (± 2.15)	85.29 (± 1.66)	*t = 3.100	*p-0.003

*Unpaired t-test, **Paired t-test

None of the drugs showed any adverse effect during or at the end of the four weeks of treatment.

DISCUSSION

Atopic dermatitis is a growing prevalent skin disease among the pediatric population of Bangladesh. Steroids remain a cornerstone in the management of AD due to their potent anti-inflammatory properties, providing rapid relief during flare-ups. However, concerns over long-term use, such as skin thinning and systemic absorption, necessitate cautious application. Tacrolimus, a calcineurin inhibitor, offers a steroid-sparing alternative, particularly for sensitive areas like the face and neck, with a favorable safety profile.

In this study the range of age of patients allocated in both groups were 2 years to 10 years.

The mean (±SD) ages were 5.16 ± 2.72 and 6.44 ± 2.41 in Tacrolimus and Fluticasone treated groups respectively. The groups were statistically similar regarding the mean age difference (p-0.73), although the age distribution was not similar (p-0.003), which was due to the random allocation of patients in both groups using block randomization.

Most of the patients were within three to ten years of age. Sugiura et al.[16] showed 5 to 6 years old children had the highest (24%) prevalence of AD. Another study conducted by Weidinger et al.[6] showed prevalence rate of atopic dermatitis in similar age group of patients was 25%, which was the highest among the other age groups.

In both the groups male children were more but the difference was not statistically significant. Kanda[17] explained the reason behind this is probably due to low level gonadal hormone during childhood and dehydroepiandrosterone (DHEA) plays an important role regulating the immune response to allergy. Recent epidemiological study conducted by Lim et al.[18] similarly showed that male patients have higher chance of having atopic dermatitis compared to female. A unique analysis of this study was a comparison of improvement of severity of disease between different groups. No previous study was found at the time of this research that analyzed these parameters. These parameters are important in the sense of how fast the patient is responding to these treatments. Although at baseline there was no significant difference in severity scale between the groups (p-0.473), but after four weeks of treatment it showed better improvement in tacrolimus treated patients(p-0.0001). This may be due totacrolimus directly targets the immune cells involved in the inflammatory process, whereas fluticasone work through a broader mechanism that involves gene transcription and protein synthesis.Improvement (80.03%) of mean percentage of severity of atopic dermatitis in children was significantly (p-0.0001) highin tacrolimus treated patients. A study conducted in Bangladesh by Yazdi et al.[19] showed similar improvement (89.73%).

In this study the reduction of mean grand total score of EASI after end of four weeks in tacrolimus treated patients was statistically significant when compared with fluticasone treated patients and with baseline score. The difference between baseline and at the end of four weeks treatment both drugs individually showed very highly significant improvement of mean grand total score. One of the highlighting point of this study is after end of four weeks of treatment tacrolimus treated group showed better reduction in grand total score than fluticasone, which was also statistically significant (p-0.006).

The percentage of reduction of mean grand total score in tacrolimus treated patients from baseline was 95.23% and in tacrolimus treated Groupit was 85.29%, which was statistically significant (p-0.003). Study conducted by Kumar et al.[20] showed 83.70% reduction in tacrolimus treated patients and 79.10% reduction in fluticasone treated patients after four weeks and was also statistically significant (p-0.001) which is similar to current study. Actual cause of effectiveness of tacrolimus is unknown.

After safety analysis both drugs were found equally safe and well tolerated after four weeks of treatment. Patients of both groups did not report any adverse effect during and after the end of the treatment. Although some initial burning sensation was reported in Yazdi et al.[19] and Kumar et al.[20] but was concluded statistically not significant. The possible causes of non reporting of adverse effects are proper application, age group and under reporting.

Some limitations of this study includes single center study, short duration, single follow up and relatively short sample size.

CONCLUSION

Topical application of 0.03% tacrolimus ointment showed superior efficacy over 0.005% ointment of fluticasone propionate in childhood atopic dermatitis. Moreover, it is safe and tolerable. So, tacrolimus can be preferred during treatment of childhood atopic dermatitis.

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Conflict of interest: None

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