

Original Article

Efficacy of topical tacrolimus in atopic dermatitis

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Abstract **Background** Mainstay treatments for atopic dermatitis include cutaneous hydration, antihistamines and topical glucocorticoids. To avoid side effects associated with long term and higher potency topical corticosteroids, further topical immunosuppressive agents should be tried. Topical tacrolimus has been extensively studied and shows promise in treatment of inflammatory skin diseases such as atopic dermatitis.

Objective To determine the safety and efficacy of tacrolimus in atopic dermatitis.

Patients and method In this randomized, case-control study, out of 60 patients with atopic dermatitis (age ranging 2 to 45 years), 30 (case) were treated with tacrolimus (0.03%) ointment twice daily and 30 (control) were treated with vaseline twice daily for up to 3 weeks. Evaluation included per cent body durface area (%BSA) affected, individual signs of atopic dermatitis, the Severity Score of Atopic dermatitis (SCORAD), and the patient's assessment of pruritus.

Result The outcome variables like erythema, edema/papulation, oozing/crusting, excoriation, pruritus, body surface area involved and SCORAD in the case group improved significantly compared to those in the control group ($p < 0.001$, <0.001 , <0.001 , <0.005 , <0.001 , <0.001 and <0.001 , respectively). After 3 weeks of tacrolimus, all variables except lichenification score responded significantly. Significantly higher number complained of burning sensation in cases (20%) as compared to none in the control group.

Conclusion Topical 0.03% tacrolimus is more effective than the vehicle alone.

Key words

Atopic dermatitis, topical tacrolimus.

Introduction

Atopic dermatitis is a highly pruritic, recurring inflammatory skin disease with a

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personal or family history of atopy.¹ It is the most frequent type of chronic eczema and most common skin disease in children. Approximately 60% of atopic dermatitis patients develop this illness by the first year of life, and 85% manifest atopic dermatitis within first 5 years of age and is thought to affect 10-15% of the population.²

The prevalence of atopic dermatitis appears to be rising throughout the world. Genetic factors play a decisive role in the development of atopic dermatitis.³ Increased exposure to pollutants and indoor allergens and a decline in breast-feeding may contribute to this increase. There is a strong link between atopic dermatitis and socio-economic advantage (as measured by occupation of parents or household tenure) and also with smaller family size. These suggest that environmental factors correlated with a western lifestyle may account for a large part of the variation in the prevalence.⁴

Atopic dermatitis is a major public health problem worldwide. It has a profound effect on many aspects of patient's life and the lives of their family. Patients of atopic dermatitis suffer from sleep disorders, retardation of growth, secondary bacterial infections, viral infections and ophthalmologic problems.^{2,5,6}

The diagnosis of atopic dermatitis is usually clinical and based on Hanifin and Rajika criteria.⁷

Treatment should be designed according to individual needs, age, sex, social conditions, sites of involvement and severity. Initial treatments for atopic dermatitis include cutaneous hydration, topical glucocorticoids and antipruritics. Patients refractory to conventional form of therapy may necessitate alternative anti-inflammatory and immunomodulator agents.

Use of an effective emollient combined with hydration therapy helps to restore and preserve the stratum corneum barrier.⁸ Topical glucocorticoids as anti-inflammatory agents for eczematous skin

have systemic and local side effects.⁹ To avoid these side effects, many topical immunosuppressive agents like tacrolimus, pimecrolimus and sirolimus have been successfully used.¹⁰

Tacrolimus is a macrolide lactone produced by the soil fungus *Streptomyces tsukubaensis*.¹¹ Oral tacrolimus has been found useful in treatment of psoriasis but with potentially serious adverse effects. Topical tacrolimus has been extensively studied and shows promise in treatment of inflammatory skin diseases such as atopic dermatitis.¹²

Cyclosporin lacks efficacy in intact human skin due to higher molecular weight of 1202 D. The molecular weight of tacrolimus is 822.05 D because of which it can better permeate intact skin.¹³ Topically applied tacrolimus is safe and effective in treatment of skin diseases.¹⁴

Topical tacrolimus does not cause atrophy of the skin. It does not alter collagen synthesis.¹⁵ It has a special role in the treatment of facial dermatitis where corticosteroids cause atrophy.¹⁶ Tacrolimus when applied topically complexes with protein FKBP-12 found in T cells. This complex eventually binds to calcineurin, calmodulin and calcium and blocks the transcription of cytokines such as IL-2, IL-3, IL-4, IL-5, IFN- γ , TNF- α , GMCSF, all of which are involved in early stage of T cell activation and proliferation. This leads to decreased antigen recognition and inflammatory cascade.¹⁷ The effect of tacrolimus on pruritus may be related to inhibition of histamine release from skin mast cells and impairment of *de novo* mast cell prostaglandin D2 synthesis along with

diminished release of histamine from basophils.¹⁰

Several workers have reported successful treatment of atopic dermatitis with topical tacrolimus.^{14,15} To our knowledge no study has yet been done with tacrolimus in atopic dermatitis in Bangladesh. This encouraged us to undertake the present clinical study.

Patients and methods

Type of study

An open randomized control study.

Place and period of study

This study was carried out in the department of Dermatology and Venereology, BSMMU, Dhaka, Bangladesh for a total period of 15 months.

Study population

Out of 60 patients of atopic dermatitis, 30 were in the treatment group, treated with topical 0.03% tacrolimus (case) and 30 were in the control group, treated with vaseline (vehicle).

Method of sampling

Random sampling method was followed.

Inclusion criteria

- i) All patients fulfilled the Hanifin-Rajka criteria for diagnosis of AD
- ii) Either sex.
- iii) Aged 2 years and above.
- iv) At least 1 year of intermittent or persistent symptom of AD

- v) SCORAD \geq 30.

Exclusion criteria

- i) Pregnant women and nursing mothers.
- ii) Those known allergic to tacrolimus.
- iii) Acute or chronic liver disease.
- iv) Subjects unwilling to participate in the study.
- v) Patients currently being treated with systemic and topical steroids.
- vi) Age less than 2 yrs.

Ethical consideration

All the patients were explained the study protocol and informed consent was taken before entry into the study.

Investigations

- i) TLC, DLC including eosinophilic count, Hb%, and ESR.
- ii) Serum IgE
- III) Serum alanine transferase (SALT)
- IV) Serum creatinine

Methodology

A detailed history was taken from the patient. In case of females, special attention was given regarding menstrual history and use of contraceptives. A general physical examination and necessary investigations were done to rule out any systemic illness.

SCORAD Index system was assessed at baseline and 3 weeks after treatment. Weekly follow-up was done both for case and control groups. All information was recorded in a predesigned data sheet. Monitoring of adverse effects after 3 weeks

was done by query and physical examination.

Treatment regimen

Case group (n=30) received topical tacrolimus 0.03%, applied twice daily for three weeks. Control group (n=30) was treated with vaseline for three weeks. Both groups had a wash-out phase for 2 weeks and follow-up period for 6 weeks. Every week during the treatment phase, four 5gm tubes were dispensed to each patient. The patients were instructed to apply the ointment to the selected area twice daily with each application separated by about 12 hours. No concurrent treatment was allowed during the study.

Severity scoring of atopic dermatitis

The SCORAD Index (*SCORing Atopic Dermatitis*), a consistent and easy-to-use scoring index for measuring the severity of atopic dermatitis, was used for assessment.

The SCORAD Index is based on subscores

- i) A (extent score, sum of body surface area measured according to rule of 9)
- ii) B (intensity score, sum of scores of 6 clinical signs i.e. erythema, edema/papulation, oozing/crusting, excoriation, lichenification and dryness, each rated from 0-4)
- iii) C (subjective symptoms pruritus and sleep loss = score for pruritus from 0 to 10 + score for sleep loss from 0 to 10)
- iv) SCORAD INDEX = (A/5+ (7xB/2) +C)

Data analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences). The descriptive statistics were frequency, median and standard error of mean (SEM) and compared using Mann Whitney and Wilcoxon signed rank tests. Categorical data were expressed as percentage and evaluated using Fisher's exact probability test. *p* value <0.05 was considered significant. The summarized information was then presented in the form of tables and charts.

Results

A total of 60 patients of atopic dermatitis were grouped into two groups (case and control) of 30 subjects each, age ranging from 2 to 45 years. All the age categories were almost alike between the groups (*p*>0.05). The median ages of the case and control were 7.0 ± 1.83 and 8.5 ± 1.44 years, respectively. The minimum and maximum ages of case and control were 2-45 and 2-35 years, respectively. In the case group, 60% of the patients were males and 40% were females giving a male-female ratio of 3:2. In the control group half (50%) were male and half (50%) female giving a male-female ratio of 1:1. However, no statistical difference was observed between groups with respect sex (*p*>0.05).

The baseline characteristics of two groups, including erythema, edema/papulation, oozing/crusting, excoriation, lichenification, dryness, pruritus, body surface area involved and SCORAD were almost identical as evident by the *p*>0.05 in each group (**Table 1** and **2**).

All the variables except lichenification score responded significantly after 3 weeks of treatment with tacrolimus applied topically in twice daily doses. All but lichenification scores reduced by half after completion of treatment ($p<0.001$). Lichenification score remained as before ($p>0.05$) (**Table 1**). All the parameters except edema/papulation score, excoriation score and lichenification score responded well after 3 weeks of treatment with placebo in patients of the control group and did not experience any change in oedema/papulation, excoriation and lichenification ($p>0.05$) (**Table 2**).

The outcome variables like erythema, edema/papulation, oozing/crusting, excoriation, pruritus, body surface area involved and SCORAD in the case group improved significantly (as indicated by dramatic reduction of respective scores) compared to those in the control group ($p<0.001$, <0.001 , <0.001 , <0.005 , <0.001 , <0.001 and <0.001 , respectively). However, no sign of improvement was seen in case of lichenification and dryness features of atopic dermatitis ($p>0.05$) (**Table 3**).

Significant percentage of improvement was observed in all the outcome variables except lichenification and dryness of skin. Improvements in case of erythema, edema/papulation, oozing/crusting and excoriation in the case and control groups were 66.7% vs. 6.7%, $p<0.001$, 40% vs. 3.3%, $p<0.001$, 65.5% vs. 17.7%, $p<0.001$ and 41.1% vs. 7.3%, $p<0.005$, respectively. The improvements in pruritus, BSA(%) involved and SCORAD in cases and controls were 53% vs. 18.8% ($p<0.001$), 49.4% vs. 4.7% ($p<0.001$) and 50.2% vs. 15% ($p<0.001$), respectively.

Lichenification and dryness of skin did not improve appreciably ($p>0.05$).

Significantly higher number of patients complained of burning sensation in cases (20%) as compared to none in the control group ($p<0.05$). Increased localized pruritus, however, was not found to be significantly associated with either case or control group ($p>0.05$).

Discussion

Standard treatment of atopic dermatitis is often unsatisfactory, hence many newer agents have been under trial to search for effective and satisfactory treatment of atopic dermatitis. The present study was carried out to assess the efficacy and adverse effect of tacrolimus in atopic dermatitis. This study included 60 patients of atopic dermatitis. 30 patients were treated with 0.03% tacrolimus (case) for 3 weeks, another 30 patients (control) treated with vehicle (vaseline) for 3 weeks. Age distribution between the two groups categories were almost alike ($p>0.05$). However, no statistical difference was observed in sex distribution ($p>0.05$). All variables, the six signs of atopic dermatitis (erythema, edema/papulation, oozing/crusting, excoriation, lichenification and dryness), subjective symptom of pruritus, % body surface area involved and SCORAD were almost identically distributed in case and control group at baseline (before intervention). The outcome variables like erythema, edema/papulation, oozing/crusting, excoriation, pruritus, % body surface area involved and SCORAD in the case group improved significantly (as indicated by dramatic reduction of respective scores) as compared to those in

Table 1 Assessment of improvement in case (Tacrolimus) group after treatment.

Parameters of interest [#]	Case group		<i>p</i> values
	Before treatment (n = 30)	After treatment (n = 30)	
Erythema score	2.0 ± 0.12	1.0 ± 0.07	<0.001
Oedema/papulation score	2.0 ± 0.10	1.0 ± 0.08	<0.001
Oozing/crusting score	2.0 ± 0.13	1.0 ± 0.08	<0.001
Excoriation score	2.0 ± 0.09	1.0 ± 0.06	<0.001
Lichenification score	1.0 ± 0.15	1.0 ± 0.16	0.480 ^{NS}
Dryness score	2.0 ± 0.12	1.0 ± 0.08	<0.001
Pruritus score	6.0 ± 0.21	3.0 ± 0.15	<0.001
Body surface area involved (%)	19.0 ± 1.56	9.0 ± 0.97	<0.001
SCORAD	55.3 ± 1.93	26.85 ± 1.18	<0.001

All the variables are expressed as median ± SEM.

Table 2 Assessment of improvement in control group after treatment.

Parameters of interest [#]	Control group		<i>p</i> values
	Before treatment (n = 30)	After treatment (n = 30)	
Erythema score	2.1 ± 0.01	1.97 ± 0.10	0.046
Oedema/papulation score	2.0 ± 0.10	2.0 ± 0.08	0.083 ^{NS}
Oozing/crusting score	2.0 ± 0.12	1.0 ± 0.09	0.004
Excoriation score	1.5 ± 0.10	1.0 ± 0.12	0.257 ^{NS}
Lichenification score	0.57 ± 0.12	0.55 ± 0.13	0.317 ^{NS}
Dryness score	2.0 ± 0.13	1.0 ± 0.11	<0.001
Pruritus score	6.0 ± 0.24	5.0 ± 0.23	<0.001
Body surface area involved (%)	23.6 ± 2.13	22.2 ± 1.94	0.002
SCORAD	51.95 ± 1.73	43.9 ± 1.63	<0.001

All the variables are expressed as median ± SEM.

Table 3 Comparison of outcomes between case and control.

Outcome parameters [#]	Group		<i>P</i> values
	Case (n = 30)	Control (n = 30)	
Erythema score	1.0 ± 0.07	1.97 ± 0.10	<0.001
Oedema/papulation score	1.0 ± 0.08	2.0 ± 0.08	<0.001
Oozing/crusting score	1.0 ± 0.08	1.0 ± 0.09	<0.001
Excoriation score	1.0 ± 0.06	1.0 ± 0.12	0.002
Lichenification score	1.0 ± 0.16	0.55 ± 0.13	0.156 ^{NS}
Dryness score	1.0 ± 0.08	1.0 ± 0.11	0.116 ^{NS}
Pruritus score	3.0 ± 0.15	5.0 ± 0.23	<0.001
Body surface area involved (%)	9.0 ± 0.97	22.2 ± 1.94	<0.001
SCORAD	26.85 ± 1.18	43.9 ± 1.63	<0.001

All the variables are expressed as median ± SEM;

the control group ($p<0.001$, <0.001 , <0.001 , <0.005 , <0.001 , <0.001 and <0.001 , respectively). However, no sign of improvement was seen in case of lichenification features of atopic dermatitis ($p>0.05$). **Table 2** shows no improvement in lichenification features. SCORAD index

was calculated at baseline and 3 weeks after treatment. At 3 weeks treatment statistically significant SCORAD improvement was observed in tacrolimus group ($p<0.001$).

Improvement in efficacy parameters observed in the present study are consistent

with previous studies.¹⁶⁻²¹ All these testify that tacrolimus produced substantial clinical improvement and rapidly (generally during the first week of treatment) decreased the amount of affected body surface area while relieving such signs and symptoms as pruritus, edema, erythema, excoriation, lichenification, oozing and scaling. Three-week treatment with tacrolimus in the present study showed no significant improvement in lichenification score which probably might be due to short period of treatment time (3 weeks). Eichenfield *et al.*¹⁷ extended the treatment duration with 0.03% tacrolimus up to 12 weeks.

Results of the present study did not show any local and systemic side effects except burning sensation at the site of application that was statistically significant. Common adverse events with tacrolimus are the local irritation e.g. pruritus and the sensation of skin burning. Previous studies^{22,23,24} report that these events were short-lived, occurred early in treatment before skin condition improvement, and rarely required discontinuation of treatment. However, a statistical significant difference in the incidence of side effects was observed between vehicle and the 0.03% tacrolimus ointment. Side effects associated with long-term use of moderate to potent steroids e.g. skin atrophy and telangiectasia were not reported in this study that was consistent with previous data^{15,22,25} that tacrolimus ointment does not affect collagen synthesis. Moreover, Remitz *et al.*²⁴ suggested that tacrolimus has no inhibitory effect on bacteria, including *Staphylococcus aureus*. The reduction in *S. aureus* colonization suggests that the local activity of tacrolimus in the skin is not

immunosuppressive but immunomodulatory.

Although, blood concentrations were not done in the present study but Boguniewicz *et al.*²⁰ showed that absorbed concentration of drug was below an increased risk of toxicity. These findings are consistent with that topical tacrolimus is minimally absorbed through affected skin, and systemic absorption decreases as skin lesions heal. Kang *et al.*²² observed that no clinically meaningful changes occurred in hematology, hepatic and renal function, serum electrolytes, blood glucose and serum IgE at 6 and 12 months during their study. Nakagawa *et al.*¹⁹ observed that tacrolimus concentrations were detectable in blood in one third of patients ranging from 0.4-0.9 ng/ml for dermatitis without lichenification and from 0.09-0.7 ng/ml for dermatitis with lichenification. However, the whole blood concentrations were quite low. Laboratory results did not show any significant changes and no systemic side effects were seen. Though the histopathology was not done in the present study but histological findings observed by Nakagawa *et al.*¹⁹ on day three and seven revealed that T cell and eosinophil infiltration were markedly diminished. They suggested that the therapeutic effects of this agent might be due to inhibition of IL-4 and IL-5 gene transcription. However recent studies indicate that T cell activation in atopic dermatitis is biphasic with activation of the T_{H2}-like cytokines, IL-4, IL-5 and IL-13 during the acute phase of the eruption. In contrast, the chronic inflammatory response in atopic dermatitis skin lesions is associated with increased expression of the T_{H1}-cytokines interferon- γ and IL-12. Laboratory results did not show any significant change

and no systemic side effects were seen. Thus the capacity of tacrolimus to inhibit the activation of multiple cell types and different cytokines may account for its ability to effectively reduce skin inflammation in atopic dermatitis.

Though, the present study was not designed to assess relapse or rebound; however, the average condition of the patient at the follow up (up to 6 weeks) visit was better than recorded at base line. This suggests 0.03% tacrolimus ointment was more effective and safe for atopic dermatitis patients.

The present study was carried out with 0.03% tacrolimus ointment only. Ruzicka *et al.*¹² worked with 0.03% tacrolimus and 0.1% tacrolimus. They reported that no significant differences were observed between the two strength of ointment. Boguniewicz *et al.*²⁰ also worked with 0.03%, 0.1% and 0.3% ointment and found no statistical significant difference among the concentrations. However, no other strength was available in the local market.

So, in the present study it was established that 0.03% tacrolimus was more effective than the vehicle alone.

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Authors Declaration

Authors are requested to send a letter of undertaking signed by all authors along with the submitted manuscript that:

The material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *Journal of Pakistan Association of Dermatologists*.