Original Paper

COMPARISON OF EFFICACY AND SAFETY BETWEEN TACROLIMUS AND HYDROCORTISONE ACETATE IN 2-5 YEARS OLD CHILDREN WITH ATOPIC DERMATITIS

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Abstract

Introduction: Atopic dermatitis is a recurrent inflammatory skin disease with intense pruritus as its hallmark symptom. It often follows a chronic, relapsing course.

Objectives: This comparative study was done with an aim to find out the efficacy of Tacrolimus and Hydrocortisone acetate in 2-5 year old children with Atopic dermatitis.

Methods: This clinical trial was carried out on two equal groups of 60 patients. “Group A” was treated with topical tacrolimus ointment (0.03%) and “group B” with hydrocortisone acetate ointment (1%). Follow up was done at week 1, 2, 4, 8 and 12 of treatment for assessment of improvement and adverse event, which was measured by ‘overall clinical improvement in the physician's global evaluation of clinical response’. Data was collected in a predesigned data collection sheet, and analysis was performed by SPSS program (Version 12).

Results: Excellent, marked and moderate improvement were observed in 19 (63.3%), 9 (30.0%), and 2(6.7%) patients of tacrolimus group and 1(3.3%), 2(6.7%) and 27(90.0%) patients of hydrocortisone group respectively. Tacrolimus group had significantly better improvement than hydrocortisone group ($p<0.001$). Skins burning at application site were observed significantly more in tacrolimus group 8(26.7%) than in hydrocortisone group 2 (6.7%).

Conclusion: The study showed tacrolimus ointment is more effective than hydrocortisone acetate in the treatment of atopic dermatitis in paediatric patients.

Key-words: atopic dermatitis, tacrolimus, hydrocortisone acetate.

Introduction

Atopic Dermatitis (AD) or Atopic Eczema (AE) is a chronic relapsing, inflammatory skin disease[1]. It is characterized by typically distributed multiple skin lesions with erythema, episodes of intense pruritus, papules, excoriations, erosions accompanied by a serous exudate, lichenification and dry skin. Atopic patients are susceptible to develop cutaneous infections and a wide variety of cutaneous changes[1]. It frequently affects children. Symptoms develop in 65% of children before 1 year of age and in 90% by 5 years of age. Sixty percent of the atopic children remain symptomatic in adulthood with recurrent flares that may be severe and sometimes debilitating[2]. The prevalence of atopic dermatitis in industrialized countries is 15 to 30% in children and 2 to 10% in adults[3]. Several symptoms including sleep disturbances, changes in activity, irritability, and self-consciousness have been reported in children with AD[2]. The mainstay of therapy for AD, including mild to moderate disease, has been the liberal use of emollients and topical corticosteroids[4]. Avoidance of allergens and other triggering factors are necessary for prevention of flares.

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Severe cases may require systemic corticosteroids, phototherapy with ultraviolet light types A and B (UVA and UVB), and/or immuno-suppressant drugs. However, the adverse effects of stronger topical corticosteroids such as striae, atrophy, and telangiectasia limit the long-term use of these agents. When topical corticosteroids are applied to extensive body surface areas (BSAs), they can be absorbed systemically, and causes complications like Cushing's syndrome, adrenal suppression, and loss of bone density, hypertension, cataracts, and growth retardation in children[5]. The degree of systemic absorption of corticosteroids varies depending on the potency and amount of the drug applied, the nature and extent of affected skin etc. The drug penetration is more rapid and extensive in areas like face, eyelids, and genitals. For this reason, mid to high potency corticosteroids are not used routinely on these areas. Topical immune-modulators, anti-histamines, and antibiotics are now being used for the treatment of AD. Tacrolimus ointment (0.03% and 0.1%) has clinically shown to reduce the extent, severity and symptoms of moderate to severe AD in children. It has been considered to be safe and effective for long-term use for up to 4 years[6].

Materials & Methods

This is a prospective clinical trial, done in the Department of Dermatology and Venereology, CMH Dhaka from July 2012 to December 2012. Paediatric patients of both sexes aged 2 to 5 years suffering from atopic dermatitis were randomly selected for the study. A total of 60 children who fulfilled the inclusion and exclusion criteria were divided into two groups; Group A and Group B, each group consisting of 30 patients. . Group A was treated with tacrolimus ointment (0.03%) and group B was treated with 1% hydrocortisone acetate ointment.

At the screening visit (day-1), laboratory investigations, such as (a) blood for CBC, (b) serum IgE level, (c) total circulating eosinophil count, (d) urine R/M/E, and (f) X ray chest P/A view were performed.

Treatment consisted of a thin layer of ointment applied twice daily to areas of actively diseased skin. Advice was given to apply the medication on the healed lesion for seven more days after healing of the lesions. Prohibited therapies during the study were systemic antimicrobials, coal tar, topical nonsteroidal anti inflammatory drugs, nonsteroidal immunosuppressants, ultraviolet light treatments (UVA, UVB), hypnotics and sedatives and other investigational drugs. Bath oil and non-medicated emollients were allowed to apply on the lesions. Assessment of each individual patient were done at day 1 (baseline) and week 1, week 2, week 4, week 8 and week 12 of treatment. Erythema, oedema/induration/papulation, excoriations and lichenification were assessed on a scale of 0 to 3. Estimation of percentage of the total BSA affected by AD (0% to 100%) for five body regions (face, scalp, upper extremity, lower extremity and trunk) was done. Intensity of itch experienced during the previous 24 hours was assessed by the patients by using a 10 cm visual analogue scale with 0 cm to indicate 'no itch' and 10 cm to indicate 'worst itch imaginable'. These assessments were used to calculate the modified Eczema Area and Severity Index (mEASI). The mEASI is a variant of the Eczema Area and Severity Index (EASI) developed by Hanifin et al[7] (2001). The mEASI is identical to the EASI except that, in the latter, an assessment of itch is not included; which is considered a primary symptom of AD[8]. The EASI were summed with the itch score for a maximum EASI of 90 (the sum of 72 and 18). This system of scoring AD is similar to the SCORAD (for Scoring AD) index developed by the European Task Force on Atopic Dermatitis[9].

Data collection: Clinical, laboratory and follow up findings for each individual patient were collected in a predesigned data collection sheet.

Data analysis: Collected data were compiled and entered into computer based software, Statistical Package for Social Sciences (SPSS) for windows version 16. The continuous data were expressed as mean ± SD. The difference in mean between two groups was calculated by students't' test. The categorical data were expressed as frequency, proportion and percentage and the difference between groups was calculated by chi-square test. P value <0.05 was considered as minimum level of significance.

Result and Observation

The result was expressed as frequency, percentage, mean±SD and shown in tables and graphs. Analysis revealed that there was no significant difference between two groups in terms of presence of family history of atopic dermatitis (p=0.313), personal history of atopic dermatitis (p=0.153) and duration of sufferings (p=0.837).

Table-I: Distribution of patients by age group (n=60).

Age group of Patients	Group-A (n%)	Group-B (n%)	Total (%)
2-3 years	15(50.0%)	16(53.33%)	31(51.67%)
3-4 years	9 (30.0%)	9(30.0%)	18(30.0%)
4-5 years	6(20.0%)	5(16.67%)	11(18.33%)
Total	30(100.0%)	30(100.0%)	60(100.0%)

Group A = Tacrolimus group, Group B =Hydrocortisone group, p value derived from chi-square test.

Thirty one (51.67%) of total patients belonged to age group '2-3 years'; among them 15(50.0%) patients were in tacrolimus group and 16(53.33%) were in hydrocortisone group. Eighteen (30.0%) patients belonged to age group'3-4 years'; they were equally distributed in both the groups. Six (20.0%) patients of tacrolimus group and 5(16.67%) patients of hydrocortisone group belonged to age group '4-5 years' making a total of 11(18.33%) patients (Table-I).

Percentage improvement of lesion of face of two groups (n=60): After 1 week of treatment, the mean (±SD) percentage improvement of lesion of face from base was 11.39 (±2.87) % in tacrolimus group and 8.25(±1.07) % in hydrocortisone group. The tacrolimus group had highly significant improvement than hydrocortisone group (p< .001). Similarly highly significant improvement was observed in tacrolimus group than hydrocortisone group after 2, 4, 8 and 12 weeks' treatment ((p< .001 in each follow up)

Percentage improvement of lesion of scalp of two groups (n=60): After 1,2,4,8 and 12 weeks of treatment the mean (±SD) improvement of lesion of scalp from base were 11.87 ±3.72, 21.00±5.55, 38.75±10.9, 67.75±10.57, and 93.87±2.23% respectively in tacrolimus group and 8.72±1.01, 15.36±3.93, 27.09±7.13, 42.36±5.59, 66.09±3.53 % in hydrocortisone group. The tacrolimus group had significant improvement than hydrocortisone group after 1,2,and 4 weeks of treatment (p< .05) and highly significant improvement were observed in tacrolimus group than hydrocortisone group after 8 and 12 weeks treatment ((p< .001 in each follow up).

Percentage improvement of lesion of upper extremity of two groups (n=60): After 1,2,4,8 and 12 weeks of treatment, the mean ±SD improvement of lesions of upper extremity from base were 9.72±2.46, 18.58±5.17, 35.10±8.18, 65.62±8.37 and 89.13±2.94 % respectively in tacrolimus group and 6.75±1.52, 12.55±2.87, 23.69±5.43, 39.79±6.22, and 63.66±4.35 % respectively in hydrocortisone group. The tacrolimus group had highly significant improvement than hydrocortisone group at every follow up (p< .001 in each follow up).

Percentage improvement of lesion of lower extremity of two groups (n=60): After 1,2,4,8 and 12 weeks of treatment the mean (±SD) improvement of lesion of lower extremity from base were 9.47±2.59, 18.40±5.13, 34.17±8.44, 64.63±8.05, and 88.03±3.41% respectively in tacrolimus group and 6.60±1.54, 12.20±2.55, 22.50±6.80, 38.70±5.80, and 61.90±4.52 % in hydrocortisone group. The tacrolimus group had highly significant improvement than hydrocortisone group at all follow up (p< .001 in each follow up).

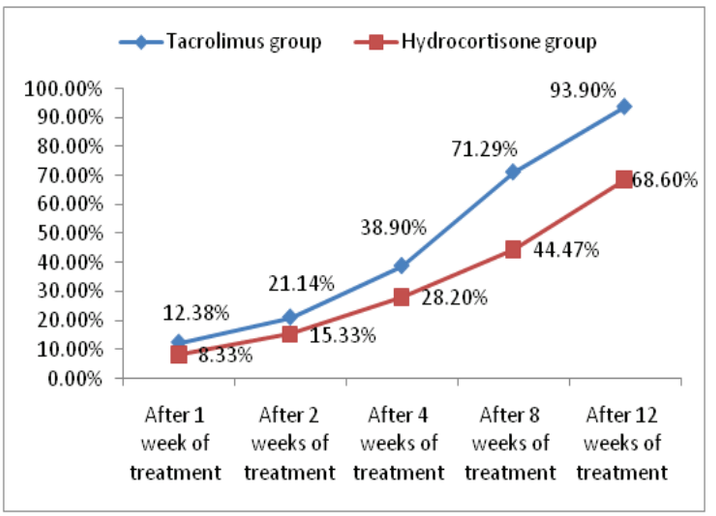

Fig-1: Mean plot of percentage improvement of lesion of trunk of two groups (n=60).

The mean (±SD) improvement of lesions of trunk from base after 1 week of treatment was 12.38±4.97 and 8.33±1.29% in tacrolimus and in hydrocortisone group respectively. The tacrolimus group had significant improvement than hydrocortisone group at follow up after 1 week (p< .05). The mean (±SD) improvement of lesions of trunk from base after 2, 4,8 and 12 weeks of treatment was 21.14±4.54, 38.90±7.03, 71.29±6.64, and 93.90±2.57% in tacrolimus group and 15.33±1.59, 28.20±4.06, 44.47±3.54 and 68.60±3.90 in hydrocortisone group respectively. The tacrolimus group had highly significant improvement than hydrocortisone group at all these follow up (p< .001) (Fig-1).

Table-II: Comparison of overall percentage improvement from base between two groups (n=60).

Overall percentage Improvement from base	Group-A (n=30)	Group-B (n=30)	P Value
Mean ±SD	89.73±4.77	66.20±6.05	0.000

Group A = Tacrolimus group, Group B =Hydrocortisone group, p value derived from Student't' test.

The mean ±SD overall percentage improvement from base was 89.73±4.77% in tacrolimus group and 66.20±6.05% in hydrocortisone group. The improvement was significantly high in tacrolimus group (p<0.001) than hydrocortisone group) (Table-II).

Improvement, p value derived from Chi-square test

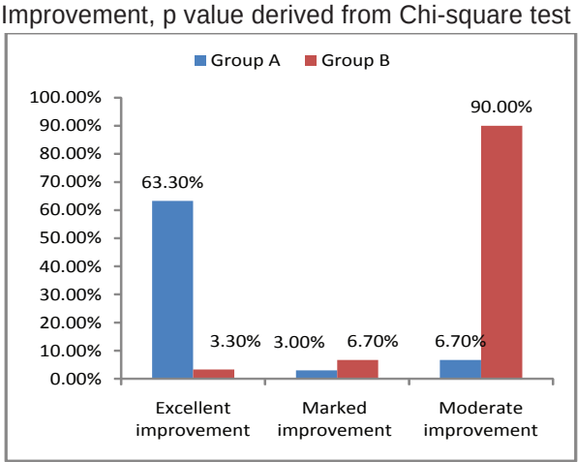

Fig-2: Bar diagram showing overall clinical improvement in the physician's global evaluation of clinical response (n=60).

Group A = Tacrolimus group, Group B = Hydrocortisone group, Excellent improvement = 90% - 99% improvement, Marked improvement = 75- 89% improvement, Moderate improvement = 50-74%.

Excellent, marked and moderate improvement were observed in 19(63.3%), 9(30.0%), and 2(6.7%) patients respectively in tacrolimus group. In hydrocortisone group excellent, marked and moderate improvement were observed in 1(3.3%), 2(6.7%) and 27(90.0%) patients respectively. Tacrolimus group had better improvement than hydrocortisone group (p<0.001).

Table-III: Distribution of patients by adverse effect like skin burning at application site (n=60).

Adverse effect	Group-A (n%)	Group-B (n%)	P Value
Application site adverse effects: skin burning at 1 week	8(26.7%)	2(6.7%)	0.038
Application site adverse effect: skin burning at 12 weeks	2(6.7%)	1(3.3%)	0.554
Non-application site adverse effect: Flu syndrome	1(3.3%)	0(0.0%)	0.640

Group A = Tacrolimus group, Group B = Hydrocortisone group, p value derived from chi-square test.

Adverse effects like skin burning at application site at 1 week were observed in 8(26.7%) patients of tacrolimus group and in 2(6.7%) patients of hydrocortisone group. Tacrolimus group had significantly more skin burning at 1 week at application site (p=0.038). Although, skin burning at application site at 12 weeks was observed in 2(6.7%) patients of tacrolimus group and 1(3.3%) of hydrocortisone group, this difference was not statistically significant (p=0.554). Flu syndrome as non-application site adverse effect was observed in 1(3.3%) patient of tacrolimus group and none of hydrocortisone group. This difference in flu syndrome between two groups was not statistically significant (p=0.313) (Table-III).

Discussion

When tacrolimus ointment is used to treat moderate to severe Atopic Dermatitis (AD), children generally respond to treatment within the first week with an improvement in signs and symptoms.

Transient burning and itching are present in first few days then decrease gradually. No increase in the incidence of infections or other adverse effects has been reported when used for long-term (up to 4 years). Because of the limitations of topical corticosteroid therapy, a non-steroidal treatment alternative is needed for children with mild to moderate AD.

In this study, we compared the efficacy and safety of tacrolimus ointment (0.03%) with hydrocortisone acetate among 60 patients with atopic dermatitis who were of 2-5 years of age. Among them 34 patients were male and 26 patients were female with a male-female ratio of 1.7:1.3. Thirty one (51.67%) patients belonged to age group '2-3 years'; 18(30.0%) patients to age group '3-4 years'; and 11(18.33%) patients to '4-5 years' group. The mean ±SD age of two groups had no difference (39.9±11.43 months vs 37.67±11.67 months, p=0.457). All of them came from middle class family. The mean ±SD duration of sufferings of the patients of tacrolimus group was 10.77±5.81 months and that of the hydrocortisone group was10.47±5.46 months.

There was no difference in duration of suffering between two groups (p=0.837). The face and scalp were affected in 70.0% and 30.0% patients respectively. Upper extremity, lower extremity and trunk were involved in 96.67%, 100.0% and 60.0% patients respectively. Assessment was done at 1,2,4,8 and 12 weeks of treatment. When the improvement of lesions after 12 week of treatment was compared between male and female of tacrolimus group, no significant difference was observed in the lesions of any regions of the body. Similarly, no difference was observed between male and female of hydrocortisone group. This result coincides with previous studies done by Reitamo et al (2002)[6] and Kang et al (2001)[10].

The mean ±SD overall percentage improvement from base was 89.73±4.77% in tacrolimus group and 66.20±6.05% in hydrocortisone group. The improvement was significantly high in tacrolimus group (p<0.001) than hydrocortisone group.

In the physician's global evaluation of clinical response, excellent, marked and moderate improvement was observed in 19(63.3%), 9(30.0%) and 2(6.7%) patients of tacrolimus group and 1(3.3%), 2(6.7%) and 27(90.0%) patients in hydrocortisone group respectively. Tacrolimus group had better improvement than hydrocortisone group (p<0.001). This result coincides with previous studies done by Alaiti et al (1998)[11]. Tacrolimus ointment, a topical immunomodulator, has been available since December 2000. It is indicated for short-term and intermittent long-term therapy of both adult and pediatric patients with moderate to severe AD. Tacrolimus acts through inhibition of calcineurin to suppress T-cell activation, inhibit inflammatory cytokine release, and reduce the stimulatory activity of antigen-presenting cells. Topical application of tacrolimus ointment results in minimal systemic absorption. It does not cause a decrease in collagen synthesis or skin thickness[12].

Conclusion

Tacrolimus ointment is more effective than hydrocortisone acetate in the treatment of atopic dermatitis in paediatric patients. It is also safe for long term use. Because tacrolimus ointment does not cause skin atrophy, it may be safely used for longer periods on all skin areas, including the face and intertriginous area.

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