

A Prospective Comparative Study of Tacrolimus and Corticosteroids in the Treatment of Atopic Dermatitis

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ABSTRACT

Background: Atopic dermatitis is a chronic inflammatory disease which can recur at adulthood particularly in people with genetic predisposition like asthma or other hypersensitivities. It has an adverse impact on the daily life of patients and hence, it is clear that appropriate treatment is necessary; hence the study was carried out to evaluate the efficacy of topical agents Tacrolimus and Corticosteroids. **Materials and Methods:** This Prospective Observational Study was carried out in 108 patients recruited from the Department of Dermatology, Cosmopolitan Hospital, Thiruvananthapuram for a period of 6 months. A written informed consent was taken. Out of the 108 patients, 54 patients received Topical Tacrolimus and the remaining 54 patients received Topical Corticosteroids. Eczema Area Severity Index (EASI) score analysis was performed at base line and after 2 weeks of drug therapy. **Results:** The result of the study was developed by comparing EASI scores of all the patients. Two statistical methods were used for developing the result. Independent 't' test for Between Group comparison and Paired 't' test for Within Group comparison. From the statistical evidences, it is deduced that both the drugs are effective for treatment of atopic dermatitis (P - value < 0.05). After comparing both the drugs, it was found that Corticosteroids are more effective than Tacrolimus (P - value < 0.05). **Conclusion:** From this study, it has been concluded that both the drugs Tacrolimus and Corticosteroids have a significant role in treatment of atopic dermatitis. But on comparison of both the agents, Corticosteroids are found to be more efficacious than Tacrolimus.

Key words: Atopic Dermatitis, EASI, Tacrolimus, Corticosteroids, Independent 't' test, Paired 't' test.

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory dermatological condition that extensively affects almost all parts of the body (upper extremities, lower extremities) with clear exemption of the groin and axillary regions. The pathogenesis of AD depends on environmental factors as a result there are wide variations in epidemiology from country to country.^{1,2} AD is a complex genetic disease with underlying epithelial barrier defect involving skin as well as mucosa hence is often accompanied by other atopic disorders such as allergic rhino conjunctivitis and asthma. Genetics, barrier dysfunction, defects in adaptive and immune response genes, immune dysregulation and microbial colonization are some of the mechanisms of pathogenesis.³

Hanifin and Rajka⁴ proposed major and minor diagnostic criteria based on their clinical experience.

Treatment mainly includes topical corticosteroids with emollients, topical calcineurin inhibitors and systemic therapy includes anti-histamines, antibiotics, cyclosporine, azathioprine, methotrexate, etc. Topical steroids are the predominant treatment for the atopic dermatitis and if not abused are very safe.⁵

The strength and mode of application of the topical steroids depends on the severity of the dermatitis. Less potent topical steroids should be used on the eyelids, the face, the axillae and the groins and inner thighs Less

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potent topical steroids are also usually employed in children who are less than 1 year old, because systemic absorption occurs, even with 1% hydrocortisone ointment, may be as effective as twice daily corticosteroid treatment. There appears no differences in efficacy or side effects between pulsed potent corticosteroid creams and the continuous use of mild topical corticosteroids in patients with mild to moderate disease.⁶

Low potency corticosteroids such as hydrocortisone 1% are suitable for the face and medium- potency corticosteroids such as betamethasone valerate 0.1% maybe used for the body.⁷ For longer duration maintenance therapy, low- potency corticosteroids are recommended.⁸ Mid strength and high potency CS should be used for short-term management of exacerbations.⁸ Ultra- high and high potency CS such as betamethasone Dipropionate 0.05 % or clobetasone propionate 0.05 % are typically reserved for short term treatment of lichenified areas in adults.⁹

Sedating anti- histamines are frequently used, especially at bedtime, to facilitate peaceful sleep. Because itch intensity often increases at night, the soporific effect of sedative formulations can quite be useful. Daytime use, however, is problematic, although some patients may acclimate to this effect. The development of non-sedating formulations (eg, loratidine) has led physicians to prescribe these agents in the hope of providing daytime relief.¹⁰ Exudation and pustule formation often indicates staphylococcal infection of the skin and oral antibiotics such as flucloxacillin or erythromycin are usually prescribed. Colonization of the skin by these bacteria may exacerbate the dermatitis, although *Staphylococcus aureus* colonization is effectively reduced by anti-inflammatory therapies.¹¹ In patients with recurrent flares of atopic dermatitis associated with infection, long-term antibiotic treatment - Topical steroid / antibiotic combination creams and measures to reduce staphylococcal colonization of the nose and perineum, could be considered.¹²

Topical tacrolimus has been shown *in vitro* to bind to specific receptors on T cells. This leads to an increase in intracellular calcium that, in turn, causes a series of reactions inhibiting the transcription of several genes, mainly the cytokines (IL-2, IL-4 and IL-5). Tacrolimus also acts to decrease the production of IL-8 receptor genes and inhibits the production of receptors for IgE molecules.^{13,14}

In this study, evaluation of efficacy of topical agents Tacrolimus and Corticosteroids in the treatment of atopic dermatitis was performed and its effect on patients was also compared.

MATERIALS AND METHODS

The study was conducted for duration of 6 months at the Dermatology Department of Cosmopolitan Hospital Private Ltd., Pattom, Thiruvananthapuram after getting clearance from Hospital Ethical Committee. 108 patients were enrolled in the study and written informed consent was obtained prior to enrollment. The total sample size (108 patients) was divided into two group having 54 patients in Tacrolimus group and 54 patients in Corticosteroids group. All information relevant to study was collected from case records and direct interview with patients and was recorded in a suitably designed proforma. For comparing the effect of Tacrolimus and Corticosteroids in Atopic Dermatitis, EASI scoring was done before and two weeks after prescribing the drugs. Eczema Area and Severity Index (EASI) is a validated scoring system that grades the physical signs of atopic dermatitis / eczema (erythema, oedema/population, excoriation, lichenification).^{15,16} It has been used after obtaining the permission from the copyright holder © Wiley.

At the end of the study all the parameters and scores were compared from baseline to end of the study.

Inclusion Criteria includes patients with Atopic Dermatitis willing for participation and those within 16-70 years of age with diagnosis of Atopic Dermatitis on the basis of Hanifin and Rajka criteria.

Exclusion Criteria includes patients with serious skin disorders or allergies other than AD, patients on topical and systemic corticosteroids, anti-inflammatory drugs, immunosuppressants, UVA and UVB therapy, sedatives and hypnotics and other investigational drugs and pregnant or lactating women.

Data entry was done on Microsoft Excel and changes in EASI scores were plotted using paired *t* test and independent *t* test.

RESULTS

Among the 108 patients, 54 patients were administered with Tacrolimus and another group of 54 patients with topical Corticosteroids. The result of the study was developed by comparing EASI score of patients at baseline and after a visit at two weeks of drug use. Two statistical methods are used for the result development - Independent '*t*' test for Between Group comparison and Paired '*t*' test for Within Group comparison.

Effectiveness of Drug within the group

From Table 1 and Figure 1,¹⁷ paired 't' test showed that the treatment has a significant effect on each group. The severity of disease got decreased after the treatment on each group. The treatment has significant effect on Tacrolimus group - ($t = 7.65, P < 0.05$). Before treatment, the EASI score was 7.3 ± 6.75 but after the treatment, the values changed to 2.64 ± 2.39 . In the case of corticosteroid group, the EASI score had a significant change from 15.08 ± 9.82 to 3.87 ± 2.75 after the treatment. ($t = 11.12, P < 0.05$). From the table, it is evident that treatment with Tacrolimus and Corticosteroids has a significant role in atopic dermatitis treatment to reduce the severity of disease on both groups.

Comparison of Effectiveness of Drug Therapy between Corticosteroid and Tacrolimus Groups.

From Table 2 and Figure 2,¹⁸ the independent 't' test shows that there exists a significant difference between Tacrolimus and Corticosteroid groups based on percentage scores on relief of disease ($t = 4.36, P < 0.05$). It is seen that Corticosteroid group reported

Table 1: The effectiveness of drug within the group was analysed by comparing EASI scores of two consecutive visits using a paired 't' test.

| Group | Mean \pm S.D | | t-value | P-value |
|----------------|------------------|-----------------|---------|---------|
| | Before treatment | After treatment | | |
| Tacrolimus | 7.30 \pm 6.75 | 2.46 \pm 2.39 | 7.65 | 0.000* |
| Corticosteroid | 15.08 \pm 9.82 | 3.87 \pm 2.75 | 11.12 | 0.000* |

Significant at $P < 0.05$

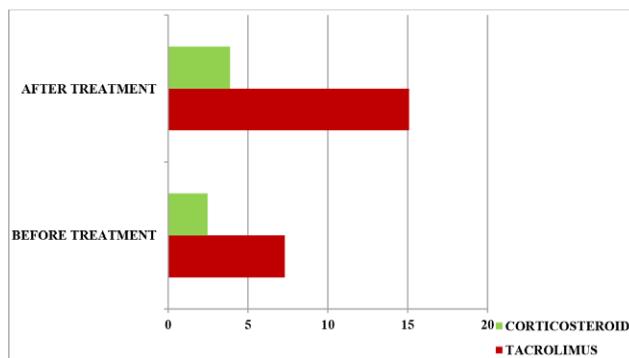


Figure 1: Effect of treatment on decrease in severity of symptoms in each group (paired 't' test).

Table 2: Comparison of effectiveness of drug therapy between Corticosteroid and Tacrolimus groups based on relief of disease (independent 't' test).

| Group | Mean \pm S.D | t-value | P-value |
|----------------|-------------------|---------|---------|
| Tacrolimus | 65.18 \pm 14.61 | 4.364 | 0.000* |
| Corticosteroid | 75.30 \pm 8.75 | | |

* Significant at $P < 0.05$

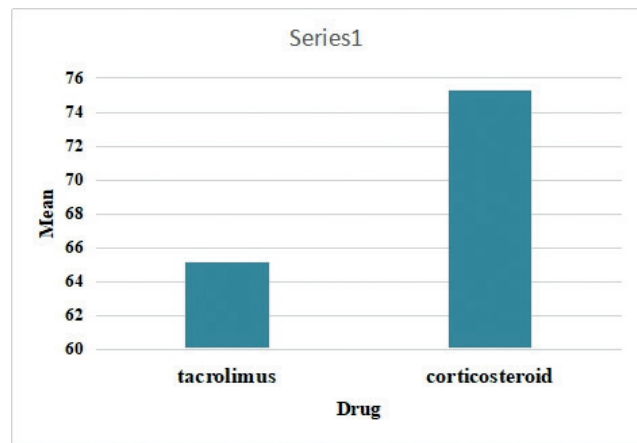


Figure 2: Comparison of drug effectiveness between groups (independent 't' test).

significantly higher level of disease relief as compared to Tacrolimus group. The Corticosteroid group has a mean of 75.3 ± 8.75 and Tacrolimus group have mean of 65.18 ± 8.75 (Here the mean is calculated from the gain score of drugs). This implies that when compared to tacrolimus, corticosteroid shows more effectiveness in reduction of symptoms.

DISCUSSION

In this study, it was observed that Tacrolimus and Corticosteroids have a key role. Improvement in the symptoms was analysed using the EASI scores collected before starting the treatment and then during the review after two weeks.

While comparing both of the EASI scores at the base line and after two weeks of drug therapy, both drugs proved to show a significant reduction in signs and symptoms and statistically significant results were obtained which implied the effectiveness of both agents in the therapy for atopic dermatitis. However, when comparisons of efficacy of agents were carried out individually, the statistical analysis revealed that Corticosteroids have superior efficacy over Tacrolimus.

In certain studies,¹⁹⁻²¹ Tacrolimus 0.03 % and Tacrolimus 0.1 % were compared with hydrocortisone 0.1 % and it was observed that 0.1 % hydrocortisone and 0.1% Tacrolimus were similarly effective than 0.03 % Tacrolimus.

In another study, by Johanna Mandelin *et al.*¹⁹ 0.1 % hydrocortisone was compared with 0.1 % tacrolimus, though Tacrolimus was found to have slight difference in efficacy, statistical significance wasn't evident and hence the conclusion was that both the drugs had same efficacy.

In a study by S. Reitamo *et al.*²² on long term treatment with 0.1% Tacrolimus ointment in adults, it was proved that Tacrolimus ointment is significantly more efficacious than a corticosteroid ointment regimen.

Study²³ related to comparison of 0.1 % methyl prednisolone aceponate ointment and tacrolimus 0.03 % published that both treatment groups showed similar efficacy results treatment and significant advantages were observed for EASI.

Nakagawa H²⁴ inferred statistically superior improvement with Tacrolimus over 0.1 % Aclometasone Dipropionate.

Svensson A *et al.*²⁵ concluded that Tacrolimus ointment showed similar efficacy to that of Corticosteroids.

In our study, we considered two groups – Tacrolimus group which includes both concentrations - Tacrolimus 0.1 % and Tacrolimus 0.03 % and Corticosteroids group consisting of drugs of different potency. Similar to previous studies, both the drugs are effective for therapy, but while comparing the efficacy of both the drugs, the Corticosteroids showed more effectiveness than the Tacrolimus.

CONCLUSION

Atopic dermatitis (AD) presents itself during childhood and may have a recurrence in adulthood provided there is genetic predisposition. A variety of treatment options are available for preventing the exacerbation of AD which includes topical calcineurin inhibitors like Tacrolimus, topical Corticosteroids, etc. This study depicts the effectiveness of Tacrolimus and Corticosteroids and is observed playing major roles in controlling the exacerbation of symptoms. However, on comparison, it has been inferred that Corticosteroids are more effective than Tacrolimus.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AD: Atopic dermatitis; **CS:** Corticosteroids, **EASI:** Eczema Area Severity Index; **UVA:** Ultraviolet A; **UVB:** Ultraviolet B; **S.D:** Standard deviation; **IgE:** Immunoglobulin E.

SUMMARY

Topical Corticosteroids are found to be more effective in the treatment of Atopic Dermatitis than Topical Tacrolimus.

REFERENCES

1. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups-variations in epidemiology, genetics, clinical presentation and treatment. *Exp Dermatol.* 2018;27(4):340-57.
2. Nutten S. Atopic dermatitis: Global epidemiology and risk factors. *Ann Nutr Metab.* 2015;66(Suppl):8-16.
3. Kabir S, Ananta K, Khushbu M, Anikhet B. Atopic Dermatitis, Chapter 9, Handbook of Eczema for Dermatologists. Second Edition. 2013.
4. Hanifin JM, Rajka RG. Diagnostic features of atopic dermatitis. *Acta Derm Venereol.* 1980;92(Suppl 144):44-7.
5. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol.* 2000;142(5):931-6.
6. Thomas KS, Armstrong S, Avery A, *et al.* Randomized controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild to moderate atopic eczema. *BMJ.* 2002;324(7340):768-71.
7. Lynde C, Barber K, Claveau J, Graton D, *et al.* Canadian Practical Guide for the Treatment and Management of Atopic Dermatitis. *Journal of Cutaneous Medicine and Surgery.* 2005;8(Suppl 5):1-9. <http://www.springerlink.com/content/r543200056r2748/fulltext.html>.
8. Leung DYM, Nicklas RA, Li JT, Bernstein L, *et al.* Disease management of atopic dermatitis: An updated practice parameter. *Change to: Ann Allergy Asthma Immunol.* 2004;93(9):S1-17.
9. Dipiro J, Robert L, Talbert GC, Lye G, Matzke R. Atopic Dermatitis, *Pharmacotherapy.* 8th Edition. 2008;1712.
10. Klein PA, Clark RA. An evidence-based review of the effectiveness of antihistamines in relieving pruritus in atopic dermatitis. *Arch Dermatol.* 1999;135(12):1522-5.
11. Hung SH, Lin YT, Chu CY, *et al.* *Staphylococcus* colonisation in atopic dermatitis treated with fluticasone or tacrolimus with or without antibiotics. *Ann Allergy Asthma Immunol.* 2007;98(1):51-6.
12. Breneman DL, Hanifin JM, Berge CA, *et al.* The effect of antibacterial soap with 1.5 % triclocarban on *Staphylococcus aureus* in patients with atopic dermatitis. *Cutis.* 2000;66(4):296-300.
13. Bieber T. Topical tacrolimus (FK506): A new milestone in the management of atopic dermatitis. *J Allergy Clin Immunol.* 1998;102(4):1555-7.
14. Ruzicka T, Assmann T, Homey B. Tacrolimus: The drug for the turn of the millennium?. *Arch Dermatol.* 1999;135(5):574-80.
15. Hanifin JM, *et al.* The eczema area and severity index (EASI): Assessment of reliability in atopic dermatitis. *Exp Dermatol.* 2001;10(1):11-8.
16. EASI User Guide. HOME- Harmonising Outcome Measures for Eczema website. <http://www.homecareeczema.org/documents/easi-user-guide-jan-2017-v3.pdf>.
17. Figure 24. Effectiveness of Tacrolimus and Corticosteroids within groups using paired 't' test.
18. Figure 25. Effectiveness of Tacrolimus and Corticosteroids in between groups using independent 't' test.
19. Mandelin J, Remitz A, Virtanen H, Reitamo S. One-year Treatment with 0.1% Tacrolimus Ointment versus a Corticosteroid Regimen in Adults with Moderate to Severe Atopic Dermatitis: A Randomized, Double-blind, Comparative Trial. *Acta Dermato-Venereologica.* 2010;90(2):170-4. <https://doi.org/10.2340/00015555-0803>
20. Reitamo S, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in adults with atopic dermatitis. *J Allergy Clin Immunol.* 2002;109(3):539-46.
21. Reitamo S, Wollenberg A, *et al.* Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group: *Arch Dermatol.* 2000;136(8):999-1006.
22. Reitamo S, *et al.* A multicentre, randomized, double blind, controlled study of long – term treatment with 0.1 % tacrolimus ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol.* 2005;152(6):1282-9.

23. Beiber T, Vick K, Folster-Holst R, Belloni- Fortina A, Stadler G, Wrm M, *et al.* Efficacy and safety of Methylprednisolone aceponate ointment 0.1 % compared to Tacrolimus 0.03 % in children and adolescents with an acute flare of severe atopic dermatitis. *Allergy*. 2007;62(2):184-9.
24. Nakagawa H. Comparison of the efficacy and safety of 0.1 % tacrolimus ointment with topical corticosteroids in adult patients with atopic dermatitis; review of randomized, double – blind clinical studies conducted in Japan. *Clin Drug Investig*. 2006;26(5):235-46.
25. Svensson AA. Systemic review of tacrolimus ointment compared with corticosteroid in the treatment of atopic dermatitis. *Curr Med Res Opin*. 2008;24(4):985-94. doi: 10.1185/030079908X280419. Epub 2008 Feb 18.