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Original Article

Comparative efficacy of topical calcipotriol and tacrolimus in alopecia areata: A prospective trial

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Abstract

Introduction Alopecia areata (AA) is a non-scarring, inflammatory type of hair loss, ranging in severity from patchy hair loss to alopecia totalis and universalis. Various treatment modalities are available for alopecia areata, including topical, intralesional, and systemic steroids, minoxidil, and systemic immunosuppressive. Multiple studies demonstrated the variable efficacy of vitamin D analogs in alopecia areata, but none have compared them with topical tacrolimus.

Methods It was a randomized control trial conducted at Tehsil Headquarters Hospital TakhtBhai, Mardan. A total of 80 patients were enrolled in the study, 40 in each group. Using the technique of a consecutive non-probability sampling, patients were separated into groups A and B. Group A received topical calcipotriol (0.005%), while group B patients were treated with tacrolimus (0.1%). Both drugs were used twice a day for 6 months. Lesions were examined every month, and at the end of 6 months, a final SALT score was calculated.

Results In our study, group A had 52% males and 48% females, while group B had 49% males and 51% females. The mean age was 32.6±6.7 and 31.5±7.4 in Group A and B respectively. The mean baseline SALT score in group A was 14.3±5.2 while in group B was13±5.1. On the other hand, the mean SALT score after 6 months was 6.2±2.3 in Group A and 8.5±5.6 in Group B. The efficacy in Group A came out to be 67%, while in group B, 33% efficacy was noted (p-value=0.0132).

Conclusion This study found that topical calcipotriol is superior to topical tacrolimus for hair growth in patients with alopecia areata. The difference was statistically significant.

Key words
Alopecia areata; Calcipotriol; SALT score; Tacrolimus.

Introduction

Alopecia areata is an inflammatory type of alopecia characterized by loss of hair from various body parts without any papules, pustules, scaling or scarring.[1] It can involve all areas of the body, with the scalp being the most commonly affected region. Whole scalps (alopecia totalis) and whole bodies (alopecia universalis) can be affected in severe cases.[2] The incidence rate and lifelong risk of AA are 0.1-0.2% and 1.7%, respectively, with a prevalence of 1% worldwide.[3] Both genders and all age groups can be affected, however, those between the ages of 20 and 40 are frequently involved; primarily male patients; although a few studies indicated a female predominance[4]. Since one inflammatory immune-mediated disease is usually associated with other autoimmune

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diseases, AA is also associated with type 1 diabetes, thyroiditis, celiac disease, pernicious anemia, etc.[5]

Multiple pathophysiologic mechanisms have been described for alopecia areata. The hallmark of an active lesion is the presence of peribulbar lymphocytes around the anagen hair follicle. Hair follicle-derived autoantigens are attacked by autoreactive CD8 and CD4 T cells, but the stem cell compartment is spared, that's why no scarring occurs and the possibility of hair regrowth persists.[6] Anagen is the most lengthy and active growth phase of hair follicles. The hair cycle is abnormal in early active AA, and the affected areas' hair follicles reach the telogen or late catagen stage prematurely.[7] Alopecia areata is a frequent clinical finding in individuals who have a vitamin D receptor (VDR) mutation, vitamin D-resistant rickets, or Vitamin D deficiency. Derivatives of vitamin D3 also regulate cytokine secretion, epidermal cell differentiation, and proliferation, among other biological and endocrine functions.[8] Vitamin D receptors (VDR) modulate the actions of vitamin D works. These have a high level of expression in the keratinocytes of hair follicles, and their mutation is linked to decreased epidermal development and hair follicle growth.[9] Furthermore, the basal layer of the epidermis and the matrix cells of hair follicles in the dermis both express 25-hydroxyvitamin D-1a-hydroxylase, indicating that keratinocytes in hair follicles produce and react to their own 1, 25(OH)2D3.[10] The innate and adaptive immune systems are both modulated by vitamin D, and for the most part, this results in the downregulation of immune reactions.[11] T and B cells respond differently to activation as a result of vitamin D's direct impact on them. It primarily inhibits the Th1 response by reducing the production of different interleukins and interferons.[12] The effectiveness of antigen presentation to T cells depends heavily on dendritic cell development. It has been demonstrated that 1,25(OH)2D3 is one of the most potent inhibitors of IL-12 and dendritic cell development. In vitro, 1,25(OH)2D3 prevents T cell-induced activation and dendritic cell differentiation in monocytes.[13] Furthermore, there is evidence that vit. D reduces oxidative stress in the cellular environment and restores the hair growth cycle via activation of Nrf2 pathways.[14]

Similar to cyclosporin, tacrolimus is a calcineurin inhibitor, but it is more effective than cyclosporine.[15] Tacrolimus down regulates the transcriptional activation of several lymphokine genes and prevents the activation and maturation of T cells.[16] Tacrolimus, unlike cyclosporin, inhibits calcineurin indirectly by binding to a protein called macrophilin. Calcineurin is involved in the activation and maturation of T lymphocytes by regulating interleukin (IL)-2 production, which is a potent stimulatory cytokine.[17] Topically applied tacrolimus appears to penetrate the skin sufficiently, and the immunosuppressive action of tacrolimus is demonstrated experimentally by inhibiting allergic contact dermatitis.[18]

Alopecia areata treatment options include topical, intralesional, and systemic steroids, topical vitamin D analogs, phototherapy (UVB), topical tacrolimus, systemic methotrexate, and cyclosporin, among others. All of these treatment modalities showed mixed results in various studies throughout the world. This study aimed to assess the efficacy of topical calcipotriol (0.005%) versus tacrolimus (0.1%) in AA. Calcipotriol is a topical vit. D analogue and various studies reported its efficacy in AA either alone or in combination, but there has been no study comparing head-to-head topical calcipotriol and tacrolimus on a local as well as international level. This makes our study using these drugs clinically relevant.

Material and methods

It was a randomized control trial consisting of 80 patients (40 in each group). After receiving approval from the hospital administration, patients were divided into groups based on non-probability consecutive sampling. Written consent was obtained from all patients along with presenting them with the full explanation of study procedure, possible drug adverse effects and complications. Group A received calcipotriol ointment (0.005%), while group B received tacrolimus ointment (0.1%), both on a twice-daily basis. Along with understudy drugs, patients in both groups used minoxidil spray as a first-line therapy regularly. Basic demographic data like age, gender, duration of disease, alopecia areata patterns, and previous therapies were collected. The SALT score at baseline and 6 months were calculated using a specific formula. Patients presented for monthly follow-ups, and study results were finalized at the sixth month's visit.

SALT score Scalp hair loss is assessed using the SALT (severity of alopecia areata assessment instrument), a quantitative and evaluative tool. Based on surface area, the complete scalp is divided into four quadrants: the vertex (40%), occipital region (24%), right temporal (18%), and left temporal (18%). The percentage of hair loss in each area is recorded separately and is multiplied by the percentage of the scalp covered in that area.[19]

Inclusion criteria All clinically and dermoscopically diagnosed patients of alopecia areata of any duration, with mild to moderate or patchy alopecia (i.e., less than 50% involvement of the complete scalp), and both sexes between the ages of 18 and 60.

Exclusion criteria Patients below the ages of 18 and above 60 years, who have severe AA (i.e., involvement of more than 50% of the total scalp, alopecia, totalis or alopecia universalis, other body parts involved by the disease, a clinical pattern suggesting a bad prognosis like ophiaisis, loss of eyebrows, or recurrent disease, and patients treated with any topical or systemic vitamin D analogs, topical, intralesional, or systemic/ pulsed steroids, cyclosporin, or other immunosuppressive drugs in the past three months. Pregnant and breastfeeding patients were also not included in the study. Similarly, patients with anemia, thyroiditis, and other autoimmune diseases were also excluded.

Data analysis The data was recorded and analyzed using social science statistical software (SPSS Version 25). Age, disease duration, and SALT score were computed as a mean±SD at baseline and six months after treatment. For gender and efficacy, frequencies and percentages were determined. To evaluate the effectiveness in the two groups, the chi-square test was used, using a two-sided P-value of ≤ 0.05 as significant. Both groups were compared by age, gender, duration of disease, and SALT score at baseline and at 6 months. Stratification was carried out by using a two-sided chi-square test to see the impact of these on the outcome. Efficacy was determined by a 50% reduction in the SALT score ($SALT_{50}$). To see the impact of baseline disease severity on the overall outcome, patients were divided into groups based on SALT 10 and >10.

Results

In this randomized control trial, a total of 80 patients participated, 40 in each group. The basic demographic data and clinical profiles of patients are in the **Table 1**, while efficacy and its stratification with respect to various variables are shown in **Table 2**. The mean age in the calcipotriol group was 32.6±6.7, while in the tacrolimus group, it was 31.5±7.4. The percentage of male and female patients in groups A and B was 52% and 48% and 49% and 51%, respectively. The status of the mean SALT score at baseline and at 3 monthly intervals is shown

Table 1 Basic and demographic data.

Parameter	*Calcipotriol (Group A)*			*Tacrolimus (Group B)*			*P value*
Number of patients	40			40			
Age (mean &SD)	32.6±6.7			31.5± 7.4			0.4879
Duration in months (mean±SD)	12±3.2			11.2± 2.8			0.237
Gender	Male 21		Female 19	Male 23		Female 17	
SALT Score (mean ±SD)	Baseline 14.3±5.2	3 months 10.2±3.9	6 months 6.2±2.3	Baseline 13±5.1	3 months 11.6±6.5	6 months 6.2±2.3	0.0204

Table2 Stratification of efficacy with respect to various variables.

Parameter	*Efficacy*				*P value*
	Yes		*No*		
	Group A	*Group B*	*Group A*	*Group B*	
No. of patients achieving $SALT_{50}$	27	15	13	25	0.0132
Gender					
Male	14	9	7	12	0.214
Female	13	6	8	11	0.1028
SALT score Viz. grouping					
≤10	10	7	8	14	0.28
>10	17	8	5	11	0.028

in **Figure 1** (p-value=0.0204). **Figure 2** shows that 67% of patients in Group A and 39% of patients in Group B achieved $SALT_{50}$ in 6 months (p -valve=0.0132). With the exception of baseline SALT score, there was no impact of other factors like gender, age, and disease duration on the efficacy of either drug **Figure 3**.

Discussion

AA is a common, autoimmune, disease characterized by loss of hair from body parts with variable intensity.[1] Several underlying mechanisms have been described in AA, including genetic, hormonal, and immune-related ones. Based on multiple pathogenetic mechanisms, various drugs and treatment modalities are utilized in AA to achieve hair regrowth. Steroids, various formulations of minoxidil, oral and topical Vitamin D analogs, anthralin, and immunosuppressant drugs such as cyclosporin, tacrolimus, and methotrexate are examples of these.[6] Steroids applied topically and administered intravenously are frequently used to treat alopecia areata, with generally positive outcomes but dermatitis, eczema, telangiectasia, folliculitis, and other conditions are the common side effects. Looking at the side effect profile of corticosteroids, the use of other immunomodulators with an acceptable side effect profile and better hair regrowth seems logical. Multiple studies have evaluated calcipotriol and topical tacrolimus in AA, but none have compared these drugs head-to-head in a single study. So, the aim of our study was to fill this gap in the research.

Our study showed an efficacy of 67% in the calcipotriol group and 39% in the tacrolimus

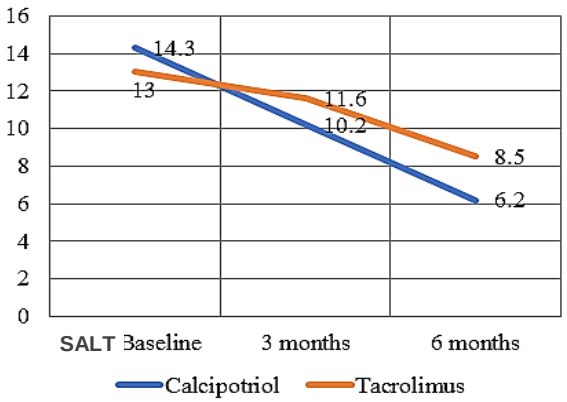

Figure 1 SALT score over time.

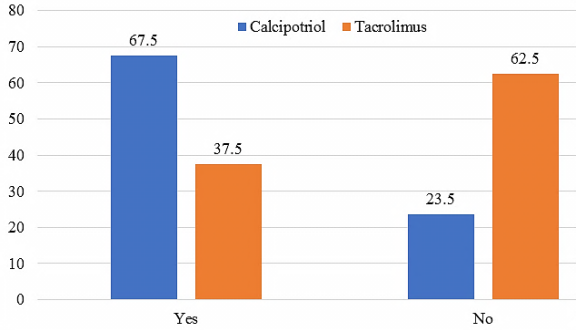

Figure 2 Efficacy of calcipotriol and tacrolimus.

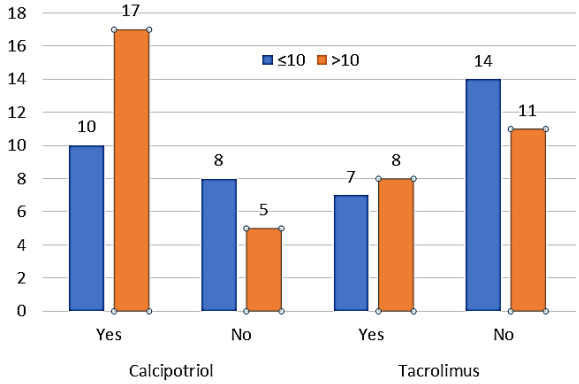

Figure 3 Comparison of both groups with respect to Baseline SALT score.

group based on a 50% reduction in the SALT score ($SALT_{50}$). The mean age, disease duration and gender status were comparable in both groups.

A retrospective study by Asl Aksu *et al*. showed significant improvement in hair regrowth compared to the baseline SALT score (p-value=0.001). All patients applied topical calcipotriol (0.005%) for 3 months on twice daily basis. Regrowth score (RGS) 3 (hair regrowth of 50%) was seen in 75% of the patients, RGS 4 (hair regrowth of 75% of patients) was seen in 62.5% of the patients, and the full regrowth (hair regrowth of 100%) was seen in 27.1 % of the patients.[20]

The efficacy of vitamin D analogs was evaluated in another study carried out by Tarun Narang *et al*; a total of 22 patients participated in this study. For three months, all patients used calcipotriol lotion at 0.005% concentration twice a day. Hair regrowth was seen in 59.1% of patients, with $SALT_{50}$ and $SALT_{100}$ achieved in 46.1% and 9% of patients, respectively.[21]

To compare the efficacy of calcipotriol and clobetasol, Elisa Molinelli *et al*. carried out a study based on an intrasubject design. 35 patients participated in this study, with a mean age of 32.3±8.1 and a male-to-female ratio of 53%:46%. All patients applied 0.005 calcipotriol and 0.05% clobetasol ointments twice a day on both hemispheres for 3 months. At the end of 3 months, hair regrowth (RGS4) was observed in 68.7 and 62.3 patients, respectively (p-value=0.08), with a lesser relapse rate and adverse effects on the calcipotriol side.[22]

Similarly, another study conducted in India by Mohan Lal Gupta confirmed the efficacy of calcipotriol. 60 patients were enrolled in the study; half of the patients applied 0.005% calcipotriol in combination with clobetasol, and the other half used 0.05% clobetasol ointment twice daily as monotherapy for 6 months. Both groups achieved statistically significant reductions in SALT score from the baseline (p=0.0001 and 0.0007, respectively), with better results in the combination group (P-value=0.02).[23]

A study conducted in Dhaka by Md. Shakhawat Hossaine *et al*. evaluated the efficacy of topical tacrolimus ointment. 30 patients (Group A) applied 0.1% tacrolimus ointment, while another group of 30 patients (Group B) applied 0.05% clobetasol twice a day for 3 months. Overall, 83.3% of patients in group A and 90% of patients in group B improved, with moderate responses (26–50% improvement) seen in 59.4% and 22.3%, respectively.[24]

Results comparable to our study were shown in a randomized control trial conducted by Farman Ullah *et al*. A total of 116 patients were divided into two groups, with 58 in each group. In both

groups, the male-to-female was 65.51% and 34.8%, respectively. One group applied 0.1% tacrolimus ointment twice a day, while another group applied 0.05% clobetasol ointment with the same frequency. At the end of 3 months, significant hair regrowth, defined as 51–75% improvement from the baseline, was achieved by 44.82% in the tacrolimus group and 79.31% in the clobetasol group (p = 0.00013).[25]

A study of 60 patients conducted in Karachi showed comparable results to our study. Patients were divided into three groups, each consisting of 20 patients. The mean age of the patients was 27; most were men. Groups A, B, and C applied betamethasone 0.1% ointment, 0.03% tacrolimus, and soft paraffin respectively, for 3 months, twice a day. 70% of group A, 45% of group B, and none of group C achieved an RGS of >3.[26]

Similarly, Amany Nassar *et al*. categorized 60 patients into 3 groups, each consisting of 20 patients. Group I patients applied tacrolimus 0.03%; group II patients used a topical mixture of calcium calcipotriol 0.005% and betamethasone 0.1%; and patients in group III used clobetasol dipropionate 0.05% ointment. Treatment was continued twice daily for 3 months. In the end, group 1, 2, and 3 patients showed 24.16%, 53.57%, and 48.57% reductions in SALT score from the baseline, with p values of 0.05 in all groups.[27]

Another Indian study compared the efficacy of 2.5% minoxidil (group A) and 0.1% tacrolimus ointment (group B). There were 35 and 34 patients in groups A and B, respectively. One group used 2% minoxidil, while the other group used 0.1% Tacrolimus ointment for 3 months. The frequency was two applications per day for both drugs. In the end, RGS > 3 was observed in 65.71% of minoxidil-treated patients, while tacrolimus group achieved this level of improvement in only 44.12% of patients (p-value=0.05).[28]

Similarly, many other studies did not show satisfactory results of topical tacrolimus in alopecia areata, which could be attributed to the smaller sample size, the selection of patients with severe disease, or poor penetration of the drug in the skin.[29-31]

Conclusion

Our study showed better efficacy for topical calcipotriol compared to tacrolimus, in the treatment of Alopecia Areata. Furthermore, tacrolimus should not be given priority when other alternatives are available.

Limitations of the study Firstly, our study lacks follow-up over many months or years to see the impact of understudied drugs on long-term remission and relapse of Alopecia Areata. Secondly the small sample size may limit the generalizability of the findings.

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