TO EVALUATE THE EFFICACY AND SAFETY OF TACROLIMUS OINTMENT AND FLUTICASONE PROPIONATE CREAM IN VITILIGO

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ABSTRACT

BACKGROUND

Vitiligo is an acquired chronic pigmentation disorder that causes depigmentation of the skin corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes. Histologically, it is characterised by degeneration and disappearance of melanocytes in the involved skin and not infrequently in the pigment epithelium of the eyes, leptomeninges and inner ear.

MATERIALS AND METHODS

The study was conducted on 46 patients of localised vitiligo attending outpatient department. The patients fulfilling the inclusion and exclusion criteria were divided into two groups alternately, 23 patients in each group. The assessment of effectiveness was done using VASI scale. The follow up of patients were done on 2nd, 4th and 6th week after initiation of treatment.

RESULTS

We observed 46 patients and they showed moderate response.

CONCLUSION

Both Tacrolimus ointment and fluticasone propionate were moderately effective in localised vitiligo. But, this did not show complete clearance of the patches in all patients.

KEYWORDS

Vitiligo, Tacrolimus, Fluticasone Propionate.

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BACKGROUND

The importance of skin is that it is literally the initial point of contact between internal and external environment.

Vitiligo is an acquired chronic pigmentation disorder that causes depigmentation of the skin corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes.[1] Histologically, it is characterised by degeneration and disappearance of melanocytes in the involved skin and not infrequently in the pigment epithelium of the eyes, leptomeninges and inner ear.[2]

In 'Vinay Pitah', the Buddhist sacred book (624-544 BC), white spot disease of the skin was mentioned as "Kilas." The white spots were also described in the Old Testament under the Hebrew word 'Zora'at.' This word was translated as 'lepra' in the Greek and English translation of the Bible. Thus, the confusion regarding vitiligo and leprosy, which is equally responsible for the social stigma attached to the white spots on the skin.[3]

Approximately, about 1-2% world's population is affected by vitiligo irrespective of age, sex or ethnic background.[4] In India, the incidence is 3-4%, although an incidence as high as 8.8% has also been reported.[5,6,7,8] The real incidence of vitiligo, however, remains unknown in the absence of any epidemiological survey.

Common sites of involvement include the extensor body surfaces such as the pretibial regions, sides of ankles, knees, elbows and skin overlying the digits, periorificial areas such as the periocular, circumoral and anogenital areas (glans penis, prepuce and vulva) and also the flexor aspect of the wrists, axillae, groins, lower back and loin, palms, soles, toe tips and fingertips and scalp. The pretibial region is the most commonly affected site in India.[9,10]

Although, vitiligo is difficult to treat, there are various modalities for treatment mentioned in the literature. They are psoralen compounds, UVA and UVB phototherapy, topical corticosteroids, topical tacrolimus and surgical treatment.

Tacrolimus is a macrolide immunomodulator that is produced by soil bacterium Streptomyces tsukubaensis is a novel treatment for vitiligo. It binds to cellular protein FK506-binding protein. This complex then binds to enzyme calcineurin, blocking its ability to dephosphorylase, the

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transcription factor NFAT (nuclear factor of activated T cells), thus blocking the action of calcineurin, preventing transcription of the gene encoding the cytokine Interleukin-2 (IL-2), blocking T-cell activation and proliferation and further cytokine production.[11] Tacrolimus is FDA approved drug indicated in treatment of vitiligo.[12,13] In recent years, tacrolimus has been used widely in localised vitiligo.

Fluticasone propionate is fluorinated corticosteroid. It is a medium potency steroid with high anti-inflammatory therapeutic efficacy. It has minimal potential to cause unwanted adverse effects. Based on favourable efficacy safety ratio, it can be used in long-term treatment of vitiligo.

This study was done to see safety and efficacy of topical tacrolimus and fluticasone propionate in localised vitiligo.

MATERIALS AND METHODS

The study was conducted on 46 patients of localised vitiligo who have attended the Outpatient Department of Dermatology at a tertiary care hospital.

Inclusion Criteria

- Patients willing for topical corticosteroids/topical tacrolimus therapy with their signed informed consent.
- Percentage of body surface area affected by vitiligo <20%.
- Patients of age group 10-60 years.
- Patients who did not have any vitiligo therapy for 2 months prior to the study.

Exclusion Criteria

- Cases of post inflammatory hypopigmentation.
- Lesions involving mucosal area.
- Pregnant and lactating women.
- Allergy or hypersensitivity to macrolides or steroids.
- Known history of malignancy, immunodeficiency, cardiovascular diseases, impaired renal and/or liver functions.
- Patients with signs of skin atrophy.

Approval from the institutional ethical committee was obtained before initiation of the study. Patient fulfilling the entire inclusion and exclusion criteria and those willing to complete to the follow up examinations were included in the study. A written consent was taken from all patients. Then, a detailed history was taken and recorded, including age, sex, duration, family history of vitiligo and other associated systemic diseases. Along with history, the detailed general, systemic and local examination was also recorded. The examination of vitiligo patch was done. Area of involvement of body surface was calculated by Wallace's rule of nines. Routine blood investigations including haemoglobin, TLC, DLC, T3, T4, TSH and LFT were advised to rule out any associated conditions.

After detailed history, clinical examination and diagnosis of vitiligo, patients were alternately assigned to 'Group A' and 'Group B.'

Total 50 patients were enrolled for the study, 25 in each group. Out of these patients, 2 patients in each group lost the follow up. Hence, 23 patients in each group have completed the study. The total duration of the study was 18 months.

The assessment of effectiveness was done with the help of "Vitiligo Area Scoring Index" (VASI) score, which was recorded at the baseline and at each follow up. Follow up of the patients were done at first visit, then at 2, 4, 6 months. Assessment of side effects was also done at each follow up.

Vitiligo Area Severity Index- The percentage of vitiligo involvement is calculated in terms of hand units. One hand unit (which encompasses the palm plus the volar surface of all digits) is approximately equivalent to 1% of the total body surface area. The degree of pigmentation is estimated to the nearest of one of the following percentages-

100% - Complete depigmentation, no pigment is present;
90% - Specks of pigment present;
75% - Depigmented area exceeds the pigmented area;
50% - Pigmented and depigmented areas are equal;
25% - Pigmented area exceeds depigmented area; and
10% - Only specks of depigmentation present.

The VASI for each body region is determined by the product of the area of vitiligo in hand units and the extent of depigmentation within each hand unit measured patch.

Total body VASI = Σ All body sites (hand units) x (residual depigmentation).

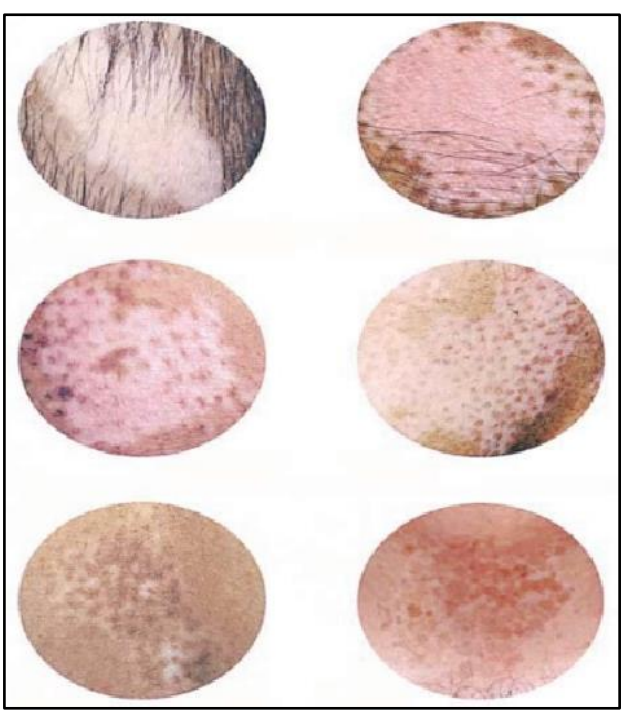

Figure 1

Figure 1. Standardised assessment for estimating the degree of pigmentation to derive the vitiligo area scoring index. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeds the depigmented area; and at 10%, only specks of depigmentation are present.

Categorisation of the Patients- All the patients taking topical therapy were divided into 4 categories depending upon the improvement in the VASI score.
Cat 0 - No improvement.
Cat I - <25% improvement in the VASI score.
Cat II - 25-75% improvement in the VASI score.
Cat III - >75% improvement in the VASI score.

Drugs Used in the Study
Group A- Topical 0.1% tacrolimus ointment twice daily application in morning and night.
Group B- Topical 0.05% fluticasone propionate cream once daily application in morning.
Ethics- This study was performed on human subjects, thus all patients were aware of presence of the study and they were fully informed about the drug and its side effects.

Group A-

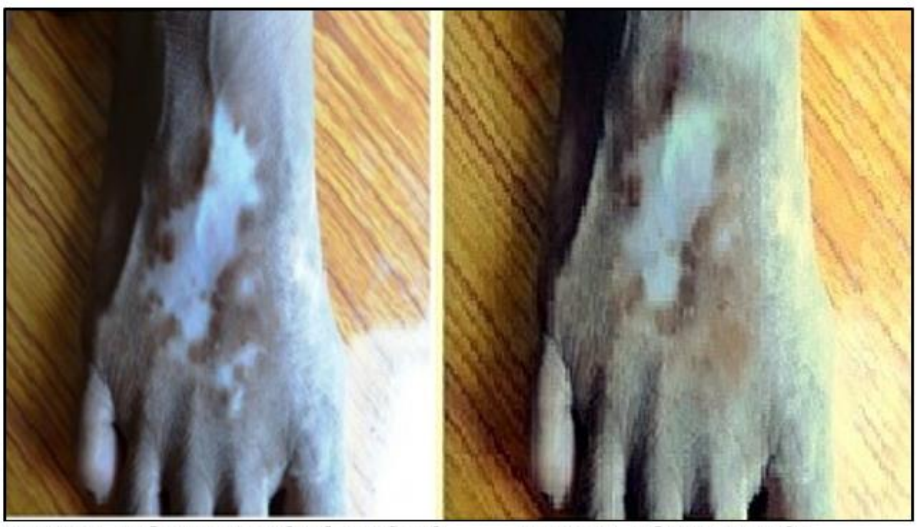

Figure 2. Before 6 Months (Baseline) *Figure 3. After 6 Months*

Group B-

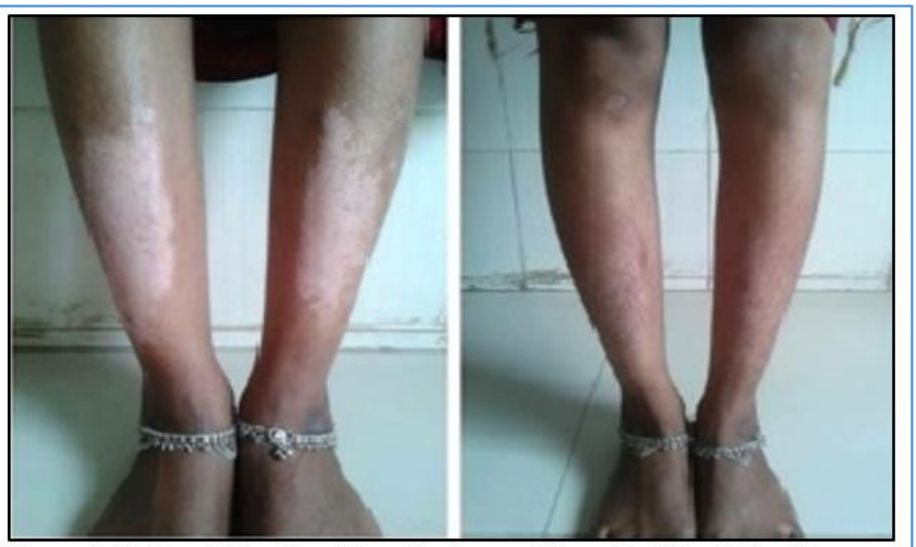

Figure 4. Before 6 Months (Baseline) *Figure 5. After 6 Months*

Age Group (Years)	Group A		Group B		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
10-20	8	34.98	4	17.39	12	27.08
21-30	5	21.73	8	34.98	13	28.26
31-40	4	17.39	5	21.73	9	19.56
41-50	3	13.04	4	17.39	7	15.21
51-60	3	13.04	2	8.69	5	10.86
Total	**23**	**100**	**23**	**100**	**46**	100
Mean	**30.48**		**31.43**		**30.96**	
SD	**15.56**		**12.69**		**14.05**	

Table 1. Age Distribution

Sl. No.	Duration (Months)	Group A		Group B		Total	
		Number	Percentage	Number	Percentage	Number	Percentage
1.	<1	14	60.87	13	56.53	27	58.69
2.	1-6	5	21.73	7	30.44	12	26.09
3.	6-12	4	17.40	2	8.69	6	13.05
4.	>12	0	0	1	4.34	1	2.17
Total		**23**	**100**	**23**	**100**	**46**	**100**

Table 2. Duration

Adverse Effects	Group A		Group B		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Erythema	1	4.35	2	8.70	3	6.52
Burning	1	4.35	0	0	1	2.18
Striae	0	0	0	0	0	0
Absent	21	91.30	21	91.30	42	91.30
Total	**23**	**100**	**23**	**100**	**46**	**100**

Table 3. Adverse Effects

Particulars	Baseline	2nd Month	% Diff.	4th Month	% Diff.	6th Month	% Diff.
Mean	8.51	7.32	1.20	6.48	2.03	5.27	3.24
SD	4.75	4.66		4.76		4.63	
't' value			4.90*		1.66		0.01

Table 4. Group A Comparison of Changes in VASI Scores (Tacrolimus)

*Significant at 0.05% level (fluticasone propionate).

Particulars	Baseline	2nd Month	% Diff.	4th Month	% Diff.	6th Month	% Diff.
Mean	9.58	7.55	2.02	5.32	4.26	3.60	5.98
SD	5.07	4.32		3.56		2.99	
't' value			2.01		6.48**		3.70*

Table 5. Group B Comparison of Changes in VASI Scores

*Significant at 0.05% level **Significant at 0.01% level.

Groups	Particulars	Baseline	6th week	Difference
Group A	Mean	8.51	5.27	3.21
	SD	4.75	4.63	0.12
	Paired t-test			1.18
Group B	Mean	9.58	3.60	5.98
	SD	5.07	2.99	2.08
	Paired t-test			2.33*

Table 6. Intergroup Comparison

*Significant at 0.05% level.

Category	Number of Patients Showing Response				Total
	0	I	II	III	
Group A	1	6	11	5	23
Group B	0	0	16	7	23

Table 7. Treatment Response in VASI

RESULTS

The above age distribution table showed maximum patients of localised vitiligo in group A is 34.98 percent between the age group of 10-20 years, and in group B, it is 34.98% between the age group of 21-30 years. The overall study showed maximum patients in the age group of 21-30 years that is 28.26%, followed by age group 10-20 years that is 27.08%. The least age group of presentation was 51-60 years (10.86%). The mean age of presentation was 30.96 years. The above table showed 60.87% patients had vitiligo for the duration less than one year in group A and 58.69% patients in group B. The maximum patients belonged to duration less than one month that is 58.69% and only 2.17% patients in duration more than 12 months. The above table of adverse effects showed 4.35% (1 patient) developed erythema in group A and 8.70% (2 patients) in group B. 4.35% (1 patient) of group A developed burning sensation. Overall, 8.70% developed adverse effects and 91.30% patients were devoid of any adverse effects. The above table of comparison of VASI score shows mean of VASI score at baseline and follow up after application of tacrolimus ointment. The mean VASI score at baseline was 8.51 ± 4.75

and it was reduced after 2nd, 4th and 6th month to 7.32, 6.48 and 5.27, respectively. The reduction of mean VASI score on first follow up was found to be statistically significant as compared to baseline, but on 2nd and 3rd follow up, it was not significant. The difference at 6th month follow up was 3.24. The above table of comparison of VASI score shows mean of VASI score at baseline and follow up after application of fluticasone propionate cream. The mean VASI score at baseline was 9.58 ± 5.07 and it was reduced after 2nd, 4th and 6th month to 7.55, 5.32 and 3.60, respectively. The reduction of mean VASI score on each follow up was found to be statistically significant as compared to baseline VASI score ($P<0.05$). The difference at 6th month was 5.98. After comparing both the groups, the difference in mean VASI score was 3.21 ± 0.12 in group A and 5.98 ± 2.08 in group B on completion of follow up on 6th month. The group B, i.e. fluticasone cream 0.05% was significant at 0.05% level. In group A, 5 patients and in group B 7 patients showed more than 75% response. Majority patients, i.e. 11 patients in group A and 16 patients in group B showed response between 25%-75%. Only 1 patient of group A showed no response to the treatment.

CONCLUSION

Both tacrolimus and fluticasone propionate were moderately effective in treatment if vitiligo lesions. On comparing with each other, fluticasone was more effective than tacrolimus. The cost of the drug becomes important in developing country. Tacrolimus ointment 0.1% costs almost about three times more than fluticasone propionate 0.05% cream. Tacrolimus is moderately effective in localised vitiligo. Also, as per the guidelines, tacrolimus is to be applied twice a day as compared to once daily application of fluticasone and so the cost also increases further.

Therefore, from the current study, we conclude that fluticasone propionate 0.05% is more effective than tacrolimus. Both can be used safely for 6 months without any side effects.

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