

Effectiveness and safety of topical tacrolimus in treatment of vitiligo

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J. Adv. Pharm. Technol. Res.

ABSTRACT

Vitiligo is one of the most primitive well-known dermatoid disorders with different suggested therapies. Therefore, this study investigated the efficiency and safety of topical tacrolimus in treatment of patients with vitiligo. This study was a clinical randomized designed study pre- post-test method, has been conducted on thirty cases with vitiligo who have referred to polyclinic and dermatology clinic. Participant's evaluated and demographic information recorded in designed checklist. In the next stage, the disease activity scored by vitiligo index disease activity system. Photography and depigmentation percent has recorded before treatment and further in 4th, 8th, 12th, 16th, 20th, and 24th weeks. Finally, gathered data compared through SPSS-20 software. The final sample comprised 30 persons including: 12 men (40%) and 18 women (60%). The average of patient's age in this study was 26/13 ± 18/20 (2–76-year-old). Eleven persons was ≤ 15 years old and rest was older than 15. Sixty-six lesions have funded in patients that maximum has accrued on face and neck (37/87%) and trunk (21/21%). In addition, minimum of lesions is related to genitalia (9/09%). In the in 4th, 8th, 12th, 16th weeks, improvement in face and neck had increased significantly, into the past weeks. In the 20th and 24th weeks, the improvement has increased although it was not significant enhancement. Also about trunk, in the 4th week the improvement does not have significant increasing in compare to the past week. In the eighth, 12th, 16th, 20th, and 24th weeks the improvement has been increased significantly in compare to the past weeks. Although in the case of limbs and genitalia, the improvement was lower. There was no significant difference between male and females and age. Although the improvement was, slow in older persons. Study results, has presented applying topical tacrolimus in vitiligo, particularly in face and neck, could be effective and does not seen any specified adverse effects during consumption of tacrolimus, it could be effective in decreasing effects in use of corticosteroid.

Key words: Safety, topical tacrolimus, vitiligo

INTRODUCTION

Vitiligo is characterized by achromatic spots related to the loss of melanocytes in the epidermis and the hair follicle.

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Access this article online

Quick Response Code:



Website:

www.japtr.org

DOI:

10.4103/2231-4040.197388

It happens at any age, affects both sexes and in some regions, affects up to 2% of the population. It influences considerably the quality of life of the patients. None of the therapeutic alternatives is fully satisfactory either because its improvement is unpredictable and the treatment is long or because of the side effects and operational difficulty of application of the medication.^[1]

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How to cite this article: Rokni GR, Golpour M, Gorji AH, Khalilian A, Ghasemi H. Effectiveness and safety of topical tacrolimus in treatment of vitiligo. *J Adv Pharm Technol Res* 2017;8:29-33.

Vitiligo is characterized by the progressive disappearance of melanocytes, resulting in depigmentation of the skin and/or hair. The etiology of vitiligo is unknown.^[2] Genetic studies support a non-Mendelian inheritance, suggesting that vitiligo is a multifactorial, polygenic disorder. The autoimmune theory remains the most widely accepted. Vitiligo has frequently been reported in association with autoimmune disorders such as thyroid disease, diabetes mellitus, and alopecia area.^[3] This disease is not a severe physical condition, but it leads to several complications in beauty while most of the clinicians neglects its impact on quality of life and self-esteem of patients.^[4] In one recent study, results showed that depression in vitiligo patients is related to the presence of lesions in a visible area, leading to poor body image and compromised self-esteem.^[5] They feel shame in communications,^[6] social isolation in some cases even results to suicide.^[7] Treatment of this disease is divided to medication and surgery. Medication also included two types of topical and systemic split. Topical treatments include topical steroids, intralesional steroids, tacrolimus, calcipotriol topical, topical psoralen ultraviolet A (PUVA). Systemic treatments include systemic steroids and systemic PUVA. None of the above therapies are not considered as first-line treatment method, but therapeutic approaches is depended to the condition of patient and therapist.^[7-9]

In a study aimed to the treatment of vitiligo Tamler *et al.* ten patients took part in the present study: six patients with lesions on the cephalic and cervical regions had more than 75% of re-pigmentation. As for extremities and trunk results varied from good to excellent in 27% of the cases.^[1] In a recent review, study conducted by Sisti *et al.* found 29 studies from 2002 to 2014. Overall, 709 patients were treated in 29 studies. Pooling the lesions, 50% re-pigmentation of vitiligo patches was never achieved before 2 months of treatment, with a peak after 6 months of therapy. The best results were obtained on lesions of the cephalic region, especially the face, with tacrolimus 0/1 ointment two times daily. The percentage of nonresponsive patients ranged from 0% to 14%. Treatment was generally well tolerated; only localized adverse effects were reported. In general, expensive, and time-consuming when done in the absence of some of the above treatment methods, it is possible that steroids systemic in stopping the spread of lesions and even re-pigmentation them effective.^[3]

Therefore, this study is aimed to investigated efficiency and safety of topical tacrolimus in the treatment of vitiligo patients during 4th, 8th, 12th, 16th, 20th, and 24th weeks of treatment.

METHODS

This was a clinical trial with pre- and post-test design method. The study has been conducted on vitiligo patients have referred to polyclinic and dermatology part of Bu Ali Sina Hospital, Sari, Mazandaran (2013–2014).

Sampling

A sample size of study selected by 95% confidence level and standard deviation of 16/9 according to previous study. The acceptable accuracy was six and final sample was 30 patients. The study population selected among patients referred to clinic according to inclusion and exclusion criteria: aged above 2 years, limited involved patients (lower than 20% of body) no systemic treatment indication, agreement to participate.

Exclusion criteria

light sensitivity family history, chronic systemic disease such as HIV and cancer pregnancy, systemic corticosteroid therapy and light therapy for at least 4 weeks before starting treatment with tacrolimus treatment with topical corticosteroids for at least 1 week ago, discontinuation of therapy to 1 month, patients with generalized form of the disease and more than 12% body surface involvement.

Design

In this study, the patients who examined, interviewed, and diagnosed as vitiligo patient by dermatologist included in the study. After sampling, the objectives of study and stages explained for them. The participants agreed to participate and signed a consent form. Then samples interviewed and examined by researchers of the present study. Demographic and clinical information such as age, gender, disease duration, extension, area, other disease, or illness. The information sintered in designed checklist.

Photography and depigmentation recorded before treatment, 4th, 8th, 12th, 16th, 20th and 24th weeks of therapy. The complications and signs compared in different periods. In patients who involved with pigments in different areas, every region categorized and compared. Therefore, in some patients more than one problem investigated.

Treatment

Therapy comprised tacrolimus 1% of ModuProc Company-Iran twice a day. To prevent sunlight interfere the patients asked to use sunscreen and hats during treatment.

Tools

Vitiligo disease activity score (vitiligo index disease activity)

Vitiligo disease activity score used to rate the activity level of disease: +4 (active in last 6 weeks); +3 (active in last 3 months); +2 (active in last 6 months); +1 (active in last year); 0 (no change in last 1 year); -1 (no change in last year and no new pigment).

Pigment measure

The pigments measured by ruler according mm: 0–25% (minimal); 26–50% (mild); 51–75% (moderate); 76–100 (excellent).

Pigment percentage = pigment areas/involved areas before therapy \times 100.

The results of therapy including improvement time, responses to therapy, complications, and information reported by patients recorded.

Statistics

The data entered to software and analyzed through IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY). Mean and standard deviation used to describe findings. Qualities data described by frequency and percentage and Chi-square, *t*-test and Fisher used to compare time frames difference in therapy. In all tests, 0/05 considered as the significance level.

Ethical issues

Proposal of study approved in committee of Mazandaran University of Medical Sciences. The samples participate voluntary, and they left study if they were not agree to continue. To keep confidence of samples, names does not record. The participants signed the consent form.

RESULTS

Demographic findings

The final samples included 30 patients 12 male (40%) and 18 females (60%). The mean age of participants were $26/13 \pm 18/20$ years, and age ranged 2–76. Eleven patients were below 15-year-old and rest were above 15. Of 30 patients 12 (40%) were married.

Clinical descriptive findings

The patient's disease duration was $3/77 \pm 0/74$ years. Of 30 patients 24 cases (80%) were under treatment already, 2 cases (6/7%) had a history of phototherapy and 5 (16/7%) had content disease history, i.e., anemia (2 cases) diabetes (1 case), migraine (1 case), and hypothyroidism (1 case).

Head and neck were the most involved areas (percentage 37/87), upper limb (18/18), lower limb (13/63), body (21/12%), and Genital area was only 9/9%. Sixty percent of pigments started first in head and neck, 20% in body and rest in lower limb and genital.

Distribution of pigments in 12 cases (40%) was focal, 17 cases (56/7%) vulgaris, and one case was segmental.

As shown in Table 1, treatment in the neck and head was significantly effective in 8th, 12th, 16th and 20th weeks ($P > 0/05$).

In body, therapy was significantly effective in 8th, 12th, 16th, 20th, and 24th weeks ($P > 0/05$).

In the treatment of upper limb, area therapy was significantly effective in 16th, and 20th weeks ($P > 0/05$).

In treatment of lower limb area therapy were significantly effective in 20th and 24th weeks ($P > 0/05$).

In treatment of genital area therapy were significantly effective only in the 24th week ($P > 0/05$).

In comparative study of the difference in therapy responses according to age and gender found there is no significant relationship between improvement with age or gender ($P > 0/05$).

DISCUSSION AND CONCLUSION

The findings showed the most involved area is head and neck and lowest was genitalia. The most prevalent start point also was in head and neck, and lowest was genitalia. In the present study, results indicated that in 4th, 8th, 12th, and 16th weeks after treatment the improvement was significant in head and neck area. The improvement was continued in 20th and 24th weeks also but the changes was not significant in 0/05 level. In body area in 4th week still there is no significant change in compared to before treatment but in 8th, 12th, 16th, 20th, and 24th weeks after treatment the improvement was significant ($P > 0/05$). In upper and lower limb and genitalia, improvement was less in compare to other body region.

In general, 90% of patients showed high improvement in head and neck and 30% reported good improvement in other body regions. This may be is related to environmental factors such as sunlight although we considered this point and tried to omit this factor. In Germany, Hartman *et al.* found 81% improvement after 12 months in head and neck and 80% in upper limb.^[10] This difference could be explained by treatment duration which was shorter in present study. In study conducted in New York by Travis and Silverberg also, 89% of head and neck and 63% of body and limbs pigments were responsive to Taklorimus ointment. In addition, segmental type vitiligo in the face was the most responsive type and region. Therefore, they concluded this ointment is an effective alternative during childhood especially in head and neck area.^[11] In Brazil, Tamler *et al.* reported 75% in head and neck and 27% in other regions responsive to this ointment.^[1] Udompataikul *et al.* in Thailand indicated 94%, 76 and 56% responsiveness of vulgaris – focalis, segmentalis, and acrofacialis pigments respectively.^[12] In more recent study in the USA, Mattox *et al.* in line with our findings introduced tacrolimus as an excellent alternative for optical corticosteroids.^[13] Therefore, according results and previous findings head and neck regions are more responsive to tacrolimus and in early weeks of disease it is more effective. Although in our study improvement, speed gets down by the time that can be explainable with the resistance of medication doses.

Table 1: Treatment results

	Weeks	Minimal (%)	Mild (%)	Moderate (%)	Excellent (%)	P
Head and neck	4	52	48	0	0	NS
	8	24	64	12	0	0/5*
	12	4	36	60	0	0/3*
	16	0	20	72	8	0/1*
	20	0	12	60	28	NS
	24	0	8	60	32	0/5*
Body	4	57.1	42.9	0	0	NS
	8	42.9	50	7.2	0	0/2*
	12	28.5	50	21.4	0	0/1*
	16	28.5	42.9	28.5	0	0/3*
	20	28.5	42.9	21.4	7.2	0/3*
	24	21.4	42.9	21.4	14.3	0/2*
Upper limb	4	41.7	58.3	0	0	NS
	8	33.3	58.3	8.3	0	NS
	12	25	58.3	16.7	0	NS
	16	16.7	58.3	25	0	0/3*
	20	8.3	66.7	16.7	8.3	0/2*
	24	8.3	66.7	16.7	8.3	NS
Lower limb	4	22.2	77.8	0	0	NS
	8	11.1	77.8	11.1	0	NS
	12	11.1	77.8	11.1	0	NS
	16	11.1	77.8	11.1	0	NS
	20	11.1	66.7	22.2	0	0/3*
	24	11.1	66.7	11.1	11.1	0/2*
Genital	4	33.3	66.7	0	0	NS
	8	16.7	66.7	16.7	0	NS
	12	16.7	66.7	16.7	0	NS
	16	16.7	66.7	16.7	0	NS
	20	16.7	66.7	16.7	0	NS
	24	16.7	50	33.3	0	0/4*

* $P > 0.05$. NS: Not significant

In the present study, complications or side effects do not seen except slight irritation in 3 cases which is in line with findings of Travis and Silverberg who reported slight irritation in 2 cases.^[11] This finding approves tacrolimus preference in compare to similar medications. As steroids are one of most common effective medicines in the treatment of vitiligo's through creating immunosuppressive and anti-inflammatory effect improves pigments. Although side effects of long steroids using, incorrect usage and high doses are not ignorable.^[14,15] While according our findings and other studies this ointment has minimum side effects. In some studies, effectiveness of tacrolimus and steroids was same. For example Vijayalakshmi *et al.* in India compared effectiveness of clobetasol 0/05 with tacrolimus 0/1 in the treatment of vitiligo. During 3 months in clobetasol group, 64% of cases and 76% of cases in tacrolimus group showed significant improvement.^[16] Lepe *et al.* also reported higher effectiveness of tacrolimus in compared to clobetasole.^[17]

Park *et al.* showed effectiveness of leister therapy increased in integration with tacrimulus ointment.^[18] Although in past

decades the patients who applied this ointment suggested to avoid ultraviolet (UV) ray. This decreased risk of cutaneous malignancies among transplant patients due to systemic treatment with tacrolimus. However, in vitiligo patients, this skin reaction is natural and penetrate of tacrolimus into the epidermis is very low. In addition, experimental studies revealed tacrolimus protects DNA from UV ray.^[19] Finally, it is recommended to combination these two methods with caution.

In this study 40% of patients were male and rest were female. There was not a significant difference between male and females in improvement. Although in last week's males improvement was higher. This disease prevalence is same in both gender, but females referee and proceed for treatment more frequently in compared to males. The age mean was about 26 years old. This a disease which appear frequently below 20 years old as in results also seen most of cases were below 15. Results also indicated no significant difference between improvement and age of participants. Although older cases improved later. In study conducted

by Udompataikul *et al.* also, age average of patients was 27.8 and children had 9 times more higher chance of improvement.^[12]

The mean of disease duration was about 4 years and 30% had treatment history. Hartman *et al.* also mentioned the patients who proceed early for treatment had higher chance.^[10] In study of Udompataikul *et al.* also higher therapy responsive has seen among patients with history lower than 5 years.^[12]

According to results of their study tacrolimus ointment is effective treatment especially in head and neck without serious side effect. The patients were satisfied with treatment. This is recommended to conduct the same study in compare to different medications and in a longer time. In addition, patient's satisfaction, commitment, and integration with other methods also recommended for future researchers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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