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Original Article

Effectiveness of topical tacrolimus treatment in vitiligo patients

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Abstract

Background: *Vitiligo is an acquired, pigmentary skin disorder that is disfiguring and difficult to treat. Phototherapy and the application of topical corticosteroids are most commonly prescribed. However, these therapies are often not effective and the use of corticosteroids on the face may lead to cutaneous atrophy, telangiectasia, and ocular complications.* ***Objective:*** *To evaluate the effectiveness of topical tacrolimus treatment in vitiligo patients.* ***Materials and methods:*** *This prospective, randomized control trial study was conducted among the patients who sought health care in the Dermatology and Venereology out patient department of KYAMC, Enayetpur, Sirajgonj from August 2021 to July 2022. The study was conducted with a view to evaluate the efficacy of topical tacrolimus in vitiligo and to see the adverse effects of topical tacrolimus in the treatment of vitiligo.* ***Results:*** *This study shows 70 patients were enrolled them 32 were male and 38 were female. The mean age was 28.52±10.98 years. Monthly evaluations were performed. Maximum 61 patients (87.1%) achieved varying levels of repigmentation. 28 patients (40.0%) had reported up to 50% repigmentation. Sign and symptoms of erythema (8.6%) and burning (7.1%) were minimal.* ***Conclusion:*** *This study revealed that tacrolimus ointment may be an effective and safe option for the treatment of vitiligo. The ease of topical self-administration with minimal side effects makes this novel immunomodulatory agent a promising addition to the therapeutic armamentarium for vitiligo.*

Keywords: *Vitigo, topical tacrolimus.*

Introduction: Vitiligo is an acquired pigmentary disorder of the skin, characterized by the loss of function of melanocytes in the epidermis and well-circumscribed, asymptomatic pearly white macules varying in size and shape which tend to extend and increase centrifugally with time in an unpredictable way.[1] Segmental vitiligo has depigmented macules arranged in a dermatomal or quasi-dermatomal distribution, which does not cross the midline and is usually unresponsive to medical treatment.[2] Tacrolimus and topical corticosteroids are effective in treating vitiligo,[3] but there are not many studies conducted on segmental vitiligo.

Vitiligo is characterized by the progressive disappearance of melanocytes, resulting in depigmentation of the skin and/or hair. The etiology of vitiligo is unknown.[4] 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 areata. Several studies have suggested that the presence of increased antimelanocyte antibodies and the imbalance of T-cell (CD4+/CD8+ and Tregs) subsets, along with their functional defects, may result in melanocyte destruction in vitiligo patients.[5] The disease affects both genders equally. It can appear at any age and the average age of onset is somewhat variable in different geographic regions. Vitiligo treatment remains a challenge. Therapeutic options for vitiligo include: topical and systemic corticosteroids, topical calcineurin inhibitors, calcipotriol, phototherapy, excimer laser, and surgical methods such as skin single-hair grafting,

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autologous cultured melanocyte or epidermal suspension transplantations. Topical corticosteroids are most commonly used drug to treat vitiligo but there are concerns over side effects due to long-term use. Steroid application causes skin atrophy, telangiectasia, hypertrichosis and acne. Tacrolimus and pimecrolimus are used as topical immunomodulators. They inhibit calcineurin action, thus preventing T-cell activation and the production of various inflammatory cytokines. Both have been used to treat other inflammatory and immunologic skin disorders, including vitiligo, with encouraging results.[6] Tacrolimus is a macrolide antibiotic produced by Streptomyces tsukubaensis with strong T-specific, immunosuppressant activity. The biological activity of tacrolimus takes effect after binding to the cytosolic 12- kd macrophilin FK506 binding protein (FK-BP). The tacrolimus/FK-BP complex inhibits calcineurin-mediated phosphorylation of the transcription factor, the nuclear factor of activated T-cells (NFAT). Hence, the expression of several inflammatory T-cell cytokines is inhibited.[6]

Vitiligo is an acquired depigmenting disorder characterized by loss of functional melanocytes. It is estimated that about 1-2% of population[7] suffers from vitiligo. The onset of vitiligo is usually in childhood or young adulthood. Men and woman are equally affected; all races are affected, in 50% of cases the age of onset fall within the first two decade of life. in Iraq the mean age of onset 17.9 years and in 60% of patients it develops before the age of 20 years, 25% of patients had family history of vitiligo.[8] Current treatment of vitiligo e.g. topical corticosteroid, topical tincture iodine 5%,[9] narrow band UVB[10] and PUVA are the most prescribed, corticosteroid applied to the face may lead to cutaneous atrophy, telangiectasia and ocular complication, narrow bad UVB requires expensive equipments and trained personnel and PUVA has been associated with risk of carcinogenesis, phototherapy and corticosteroid have limited effectiveness particularly on the face.[11] Immunomodulator such as Tacrolimus 0.1% and 0.03 %, and pimecrolimus cream 1 % are approved for treating atopic dermatitis in adult patients and pediatric patients over 2 years of age.(5) Tacrolimus (FK-506) is an immunosuppressive drug membered macrolide lactone discovered in 1984[12] from the fermentation broth of Japanese soil sample that contained the bacteria streptomyces tsukubaensis can be used as an alternative to topical steroids in many other forms of dermatitis. This ointment does not cause atrophy, telangectasiae or adverse ocular effects of topical corticosteroids which has limited application to the face and intertregnous areas.[11] Tacrolimus acts on T cells and mast cells inhibiting T cell activation and the production of proinflammatory cytokines such as tumor necrosis factor (TNF) whose level is higher in vitiligo lesional skin. Moreover, it prevents the release of proinflammatory mediators in mast cells by degranulation.[12]

MATERIALS AND METHODS

It was a prospective, randomized control trial study carried out in the Out Patient Department of Dermatology and Venereology, KYAMC, Enayetpur, Sirajgonj 2. Total 70 cases were included in this study from August 2021 to July 2021. Vitiligo was diagnosed by clinical assessment & wood's lamps examinations. Clinical assessment was done at baseline. Clinical assessment consists of examine all the treated lesions. Lesions of one palm sized area are considered as 1% of involvement. As the study was conducted by topical application of medicine, involvement less than 10% was included in the study. Disease activity was assess by taking history, disease was considered as active if the existing lesion increase in size or there is development of new lesions. History of spontaneously repigmenting vitiligo was excluded from the study. There is currently no quantitative tool for evaluating vitiligo treatment response using parametric methods.13 Repigmentation may starts on the hair follicle(typical perifollicular) or starts as homogenous pigmentation from the periphery of the lesions(perilesional).14 At the baseline repigmentation was considered as 0% means the lesion was completely depigmented or no pigmentary remnant. 1-25% pigmentation was considered as minimal, when only specks of pigment appeared. 26-50% pigmentation was considered as mild, when some pigmentation but depigmented area exceeded pigmented area. 51-75% pigmentation was considered as moderate, when there were some depigmentation but pigmented area exceeded depigmented areas. 76-100% pigmentation were considered as excellent, when the treated areas were either completely repigmented or there is only specks of repigmentation (Lepe et al 2003). Colored photographs of treated lesions were taken at the beginning of the study and subsequent monitoring of the efficacy of the treatment assess by comparing the treated lesions with baseline photograph.

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Topical tacrolimus 0.03% (Tacrol ointment) is applied twice daily for 24 weeks to the case group. The control group applied Vaseline only twice daily. Clinical assessment was done monthly for six months. The monthly assessment includes seeing the extent of repigmentation and depigmentation, and also monitoring the adverse effects such as pruritus, erythema, burning, stinging, anaphylactoid reaction. All data were checked and edited after collection. Then the data were entered into computer and analyzed with the help of SPSS windows version 25.

RESULTS

Table-1: Demographic characteristics of two groups (n=70)

Characteristic	Number of patients	Percentage (%)
Age in years		
≤20	7	10.0
21-30	33	47.1
31-40	18	25.7
41-50	12	17.1
Age (mean±SD)	28.52±10.98	
Sex		
Male	32	45.7
Female	38	54.3

Table 1 shows out of 70 patients maximum patients belong the age group 21-30 years 33 (47.1%), followed by age 31-40 years 18 (25.7%),41-50 years 12 (17.1%) and less than 20 years 7(10%). According to sex distribution female are more 38 (54.3 %) and male are 32 (45.7%).

Table-2: Koebner's sign between two groups (n=70)

	Number of patients	Percentage (%)
Present	19	27.1
Absent	51	72.9

Table 2 shows that Koebner's sign absent in maximum patients 51 (72.9%) and present only 19 (27.1%).

Table- 3: Distribution of side effects case (n=70)

Side effects	Frequency	Percent
Erythema	6	8.6
Burning	5	7.1
No side effects	59	84.3

Table 3 shows the pattern of side effects. The common side effects in most of the cases are erythema, 6 (8.6%), followed by burn 5 (7.1%). Maximum cases, 59 (84.3%) show no side effects.

Table- 4: Improvement of the body surface area before and after treatment of topical tacrolimus

	Mean±SD	P value
Before treatment (%)	6.84±2.91	0.001
After treatment (%)	4.25±2.13	

Table 4 shows the improvement of the body surface area before treatments are 6.84% and after treatment which is reduced to 4.25%.

Table-5: Percentage of repigmentation after tacrolimus use in case group and relationship with their site of lesion (n=70)

Percentage of repigmentation	Acral part No(%)	Non-acral part No(%)	Total No(%)
No Pigmentation	9(42.9)	0(00)	9(12.9)
1-25%	12(57.1)	5(10.2)	17(24.3)
26-50%	0(00)	28(57.1)	28(40.0)
51-75%	0(00)	14(28.6)	14(20.6)
76-100%	0(00)	2(4.1)	2(2.9)
Total	21(30.0	49(70)	100

Table 5 shows the percentage of repigmentation after use of tacrolimus. Among 70 patients 61 patients (87.1%) achieved varying levels of repigmentation and 9 patients (12.9) have no repigmentation.

DISCUSSION

Although medical and surgical options are available for the treatment of vitiligo, this condition remains one of the most daunting therapeutic challenges in dermatology. Sunscreens, cosmetics, topical

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and oral psoralens plus ultraviolet A, narrow-band ultraviolet B exposure and phenylalanine with heliotherapy are current medical approaches used to treat vitiligo. Surgical modalities include a variety of grafting and melanocyte transplant techniques. Each of this treatment options has achieved some success in the management of vitiligo. However, many patients are not successfully treated with the current therapeutic options due to a lack of efficacy, intolerance of side effects, concern about long-term effects or resistance of treatment.[15]

This study was conducted with a view to evaluate the efficacy of topical tacrolimus in vitiligo and to see the adverse effects of topical tacrolimus in the treatment of vitiligo. As there is no recorded study in this field, it happens to be the first time in Bangladesh. The present study findings were discussed and compared with previously published relevant studies.

This stud shows 70 patients were enrolled in this study as a case. Among them 32 were male and 38 were female. Mean age of this study group was 28.52±10.98 years which concurs with other similar studies.[1,16]

This study shows the mean involvement of the body surface area before treatment was 6.84%, which is reduce to 4.25% after treatment. It revealed that there is a strong association between tacrolimus use and repigmentation (P< 0.001). This is supported by many other studies.[16,17,18]

According to this study, 61 patients (87.1%) achieved varying levels of repigmentation. 28 patients (40.0%) had reported up to 50% repigmentation. This findings consistent with other studies accords the world.[1,5,6]

This study findings does not accord with the findings of Grimes et al where they found 41.3%.[14] and also differ from Silverberg et al findings of 61% for head/neck regions and 47% for trunk and/or extremities.[17] It is worthy mention that Grimes et al's study was performed by 0.1% tacrolimus upon the group of mean age 38.4 years with SD ± 10.26, and Silverberg et al.[17] study was performed upon children by 0.03 & 0.1% tacrolimus.

Excellent repigmentation was noted, 76-100%, in 2 (2.9%) patients. This result is largely differ other studies.[19,20] This result is also differ from Lepe et al, where they found tacrolimus produce more than 75% repigmentation, most of this on facial areas.[15,16,17] The probable causes of the difference is the concentration difference of tacrolimus 0.03% vs 0.1%.

The present study further documents the safety of tacrolimus for the repigmentation in vitiligo. Because of the need for an effective therapy with a positive benefit-risk profile, the results of the study are quite promising. Twice-daily tacrolimus 0.03% ointment therapy was well tolerated. Report of side effects from this study was only 20% & were transient and mild, no patient discontinue therapy due to adverse effects. 80% patient was free from any kind of side effects. Most common side effects were erythema and burning. This result is supported by various other studies.[12,16,14]

CONCLUSION

This study revealed that tacrolimus ointment may be effective and safe for the treatment of vitiligo. The ease of topical self-administration with minimal side effects makes this novel immunomodulatory agent promising to the therapeutic armamentarium for vitiligo.

Conflict of interest: None.

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Data availability statement
Data will be made available on request.

Ethical Approval
The ethical permission received from the ethics review committee of Khwaja Yunus Ali Medical College (KYAMC), Enayetpur, Sirajgonj, Bangladesh. Prior to data collection, patients were told about the project and consented, and anonymity was maintained throughout the study.

Consent for Publication: Not applicable

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