Original Article

Efficacy and Safety of Topical Tacrolimus (0.03%) in the Treatment Localized Vitiligo

Husain MA[1], Alam MN[2], Rahim R[3], Joarder Y[4], Wahidujjaman[5], Ferdous M[6]

Abstract

Vitiligo is an acquired, pigmentary skin disorder which is disfiguring and difficult to treat. Phototherapy and application of topical corticosteroids are most commonly prescribed. However, these therapies are often not effective and use of corticosteroids on the face may lead to cutaneous atrophy, telangiectasia, and ocular complications. This case control study was conducted among the patients who sought health care in the Dermatology and Venereology out patient department of Ibn Sina Medical College, Dhaka from January, 2014 to June, 2015. The study was conducted with a view to evaluate the efficacy of topical tacrolimus in localized vitiligo and to see the adverse effects of topical tacrolimus in the treatment of vitiligo. This study assessed the efficacy and safety of tacrolimus 0.03% ointment in patients with vitiligo compared with control. 60 patients were enrolled as case group, among them 22 were male and 38 were female. There mean age was 23.33 years with a standard deviation of ±11.43 years. Another 60 patients were enrolled as control group. Patients in case group were treated with tacrolimus 0.03% ointment applied twice daily. Monthly evaluations were performed. At six months, 50 patients (89%) achieved varying levels of repigmentation. There was a statistically significant decrease depigmentation & increase pigmentation at sixth month. Mean area of repigmentation was 33.33% with a standard deviation of ±23.90. 24 patients (40.0%) had reported up to 50% repigmentation. Sign and symptoms of erythema (10%) and burning (10%) were minimal. In conclusion, it is proposed that tacrolimus ointment may be a efficacious 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.

Key words: Localized vitiligo, Tacrolimus, Repigmentation.

1. Corresponding Author:
Dr. Md. Anwar Husain
Associate Professor & Head
Department of Dermatology & Venereology
Ibn Sina Medical College, Dhaka.
e-mail:anwarbd64@gmail.com

2. Dr. Mohd. Nurul Alam
Assistant Professor
Department of Dermatology & Venereology
Ibn Sina Medical College, Dhaka.

3. Dr. Rezaur Rahim
Assistant Professor
Department of Dermatology & Venereology
Rangpur Medical College, Rangpur.

4. Dr. Yasmin Joarder
Associate Professor & Head
Department of Dermatology & Venereology
Northern Medical College, Dhaka.

5. Dr. Wahidujjaman
Assistant Professor & Head
Department of Dermatology & Venereology
Khulna Medical College, Khulna.

6. Dr. Monalisa Ferdous
Registrar
Department of Dermatology & Venereology
National Medical College, Dhaka.

Introduction

Vitiligo is an acquired pigmentary disorder presenting as hypopigmented or depigmented macules and affects 0.5-2% of the population worldwide[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[2,3]. Tacrolimus and topical corticosteroids are effective in treating vitiligo,[4,5,6] 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[8]. 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[9]. 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. The mean onset age is reportedly 22 in the U.S. and India, 24 in Brazil and 25 in the UK[10]. 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, 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[11]. 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[11].

Vitiligo is an acquired depigmenting disorder characterized by loss of functional melanocytes. It is estimated that about 1-2% of population[13] 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[14]. Current treatment of vitiligo e.g. topical corticosteroid, topical tincture iodine 5%,[15] narrow band UVB[16] 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[17]. Immunomodulator such as Tacrolimus 0.1% and 0.03 %, and pimecrolimus cream 1 % are approved and pimecrolimus cream 1 % are approved for treating atopic dermatitis in adult patients and paediatric patients over 2 years of age.(5) Tacrolimus (FK-506) is an immunosuppressive drug membred macrolide lactone discovered in 1984[18] 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[17]. 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 are higher in vitiligo lesional skin. Moreover it prevents the release of proinflammatory mediators in mast cells by degranulation[18].

Materials and Methods

It was a prospective, randomized Case-control study carried out in the Out Patient Department of Dermatology and Venereology of Ibn Sina Medical College, Dhaka. Total 60 cases & 60 controls were included in this study from January, 2014 to June, 2015. 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 (Hamzavi et al 2004). Repigmentation may starts on the hair follicle(typical perifollicular) or starts as homogenous pigmentation from the periphery of the lesions (perilesional) (Baltas & Csoma 2002).

Repigmentation was assessed in a five point scale

At the baseline repigmentation was considered as 0% means the lesion was completely depigmented or no pigmentary remnant. 1-25% pigmentation were considered as minimal, when only specks of pigment appeared. 26-50% pigmentation were considered as mild, when some pigmentation but depigmented area exceeded pigmented area. 51-75% pigmentation were 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 depigmentation (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.

Consecutive 120 vitiligo patients were included in this study using lottery method of Random sampling. 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 win 12 software programme.

Results

The mean age of case and control groups are 23.33 years and 24.03 years respectively. Male and female percentage of cases are 36.7 and 63.3 respectively, where as that percentage of controls are 46.7 and 53.3 respectively (Table-I).

Table-I: Baseline characteristics of two groups

Characteristics	Case		Control	
	Frequency	Percent	Frequency	Percent
Age (Mean±SD)	23.33±11.43		24.03±11.24	
Sex				
Male	22	36.7	28	46.7
Female	38	63.3	32	53.3

Presence of family history was found in 23.3% of cases and 16.7% of control groups (Table-II) .

Table-II: Family history between two groups.

Family history	Case		Control	
	Frequency	Percent	Frequency	Percent
Present	14	23.3	10	16.7
Absent	46	76.7	50	83.3
Total	60	100.0	60	100.0

Koebner's phenomenon was present in 26.7% of cases and 30% of controls (Table-III).

Table-III: Koebner's sign between two groups

	Case		Control	
	Frequency	Percent	Frequency	Percent
Present	16	26.7	18	30.0
Absent	44	73.3	42	70.0
Total	60	100.0	60	100.0

Side effects (erythema, burning) were found in 12% of cases, where as in 80% cases there was no side effect (Table- IV).

Table- IV: Distribution of side effects case

Side effects	Frequency	Percent
Erythema	6	10.0
Burning	6	10.0
No side effects	48	80.0
Total	60	100

The mean involvement of the body surface area before treatment was 6.667%, which was reduced to 4.033% after treatment (Table-V).

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

	Mean±SD
Area of involvement before treatment (%)	6.67±2.73
Area of involvement after treatment (%)	4.03±2.27

The percentage of repigmentation after tacrolimus use was more in non acral part than acral part (Table-VI).

Table-VI: Percentage of repigmentation after tacrolimus use in case group and relationship with their site of lesion (n=60)

Percentage of repigmentation	Site of lesions		Total
	Acral part	Non acral part	
No Pigmentation	10	0	10
1-25%	8	4	12
26-50%	0	24	24
51-75%	0	12	12
76-100%	0	2	2
Total	18	42	60

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 corticosteroids, topical 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[21].

This case control study was conducted among the patients who sought health care in the Dermatology and Venereology out patient department of Ibn Sina Medical College, Dhaka from January 2015 to December, 2015. 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.

Sixty patients were enrolled in this study as a case. Among them 22 were male and 38 were female. Mean age of this study group was 23.33 years with a standard deviation ±11.433 years.

sixty control subjects were also included in this study. Among the control group 28 were male and 32 were female, mean age was 24.03 years with a standard deviation of ±11.245 years.

Present study revealed that there is a strong association between tacrolimus use and repigmentation ($P<0.001$). This is supported by many other studies[21,22,23].

According to this study, mean percentage of regimentation was 33.3333% with a standard deviation of ±23.90114%.

All patients are treated with 0.03% tacrolimus. This study findings does not accord with the findings of Grimes et al where they found 41.3%[24]. and also differ from Silverberg et al[22] findings of 61% for head/neck regions and 47% for trunk and/or extremities. It is worthy mention that Grimes et al's[24] study was performed by 0.1% tacrolimus upon the group of mean age 38.4 years with SD ±10.26, and Silverberg et al.[22] study was performed upon children by 0.03 & 0.1% tacrolimus.

From the present study it has been found that overall 83.3% of the patients responded positively to therapy. Silverberg et al support this result[22].

This result differ from Grimes et al[24] findings of (89%), Lepe et al.[25] findings (90%), Grimes et al findings of (100%),Tanghetti findings of (87%)patient's achieved repigmentation.

Of the 36 respondents in whom face and neck regions were treated, 34 patients (94.4%) responded to tacrolimus application. Of the 24 respondents with involvement of other than face and neck areas, 16(66.6%) patients responded to tacrolimus.

This result is different from Silverberg et al.[22] They studied three group of patients; one group had lesions on the head & neck area; one group had lesions on the trunk & extremities; one group had lesions head, neck, trunk & extremities. Furthermore they studied with two different strength of tacrolimus ointment.

Excellent repigmentation was noted, 76-100%, in 2 (3.3%) patient. This result is largely differ from Silverberg et al.[22] This result is also differ from Lepe et al.[25] where they found tacrolimus produce more than 75% repigmentation, most of this on facial areas. The probable causes of the difference is the concentration difference of tacrolimus 0.03% vs 0.1%.

Current study has revealed that 24(40%) patients experienced 26-50% repigmentation after medication with topical application of tacrolimus.

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[22,24].

In conclusion, the data presented by this study indicate that topical tacrolimus may represent a new effective treatment option of vitiligo, with convenient use and limited adverse effects.

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