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TACROLIMUS OINTMENT AS MONOTHERAPY IN MANAGEMENT OF MODERATE TO SEVEREREFRACTORY VERNAL KERATOCONJUNCTIVITIS.

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ABSTRACT

Introduction: In the modern era of industrialization and global seasonal change, human health has been adversely affected. One of its sequels is ocular allergy. **Objective:** To evaluate the efficacy and safety of (0.03%) tacrolimus skin ointment in patients with moderate to severe refractory vernal keratoconjunctivitis (VKC). **Study Design:** Prospective interventional study**. Setting & Duration:** Ophthalmology outpatient department (OPD) Peoples University of Medical and Health Sciences from 16 February 2019 to 16 August 2021. **Material &Methods:** 200 patients suffering from moderate to severe VKC were selected, based on TSSS (Total subjective scoring system) and TOSS total objective scoring system). The study participants were separated into 2 groups (100 each) withtreatment group receiving0.03% Tacrolimus ointment while the other receiving conventional therapy. To determine the effectiveness (measured by the change mostly in clinical condition), a randomised clinical investigation was carried out and safety (safe treatment from development of any complications or side effects) of Tacrolimus ointment in comparison with conventional therapy. **Result**: It was observed that 73% patients had tarsal form of VKC, 24% had limbal and 3% had mixed (both) types of disease. Every one of the patients had complete subjective symptom severity ratings (TSSS) and total objective ocular severity scores (TOSS) which ranged among 2 & 3. Treatment with either 0.03% Tacrolimus or conventional group was found to be effective in eradicating the symptoms of VKC measured by TSSS scores. **Conclusion**: Among the medical therapies used in this study it is found that, Tacrolimus ointment 0.03% was more nontoxic & actual in eradicating the severity of signs and symptoms of the vernal keratoconjunctivitis evident by the TSSS and TOSS scores. (ASM allergic systemic manifestations)rhinitis, asthma and eczema)

Keyword: Vernal keratoconjunctivitis, Tacrolimus,TSSS (total subjective scoring system), TOSS (total objective ocular scoring system) ASM (Associated Syestemic manifestation)

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INTRODUCTION

In the modern era of industrialization and global seasonal change, human health has been adversely affected. One of its sequels is ocular allergy. Seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), and other ocular allergy conditions that are frequently lumped together are all included in the category of ocular allergy. Giant papillary conjunctivitis (GPC), vernal keratoconjunctivitis (VKC), and atopic allergic keratoconjunctivitis (AKC) are all forms of allergic conjunctivitis that have a significant impact on the conjunctival tissue [1]. Vernal keratoconjunctivitis (VKC) is a severe inflammatory ocular illness that affects both eyes and has the Chronic ocular allergies known as vernal keratoconjunctivitis (VKC) can cause vision issues in children and adolescents in their adolescent years.[2, 3] VKC can result in a variety of ocular problems, including increase intraocular pressure, corneal scarring, punctate epithelial keratitis (PEK), shield ulcer, keratoconus, dry eyes, irregular astigmatism, and blindness[4]. Our knowledge of the epidemiology, pathogenesis, and treatment of vernal keratoconjunctivitis has significantly improved over the past two decades. Because VKC can cause irreversible vision loss if left untreated or ignored, it is important to get accurate treatment as soon as possible [5]. Patients with VKC often appear while they are in the early to late school years (between the ages of 5 and 15 years old) with predominantly visual symptoms [6]. The most common ocular symptoms that patients experience are itching, discharge, watering, irritation, redness of the eyes to a lesser extent, photophobia, and itchiness. Since some patients can have severe photophobia, they frequently wear sunglasses while working outside. [7]. Rhinitis and asthma can sometimes share symptoms, letting parents know that their child has an allergic reaction.[8] It's interesting to note that Bonini and Coassin's long-term follow-up of large case series [9], It was observed that the onset of eye symptoms preceded the onset of asthma. During an ocular examination, conjunctival hyperemia can be seen on the bulbar and tarsal conjunctiva. Large amounts of mucoid discharge frequently seen. It is crucial to consider the periodicity of illness while planning treatment. As an example, in children who have two or three incidents of a certain condition each year, a brief course of moderate steroids is perfectly safe. However, for children with chronic conditions for the entire year, giving chronic continuous steroid therapy would be too risky. When inflammation is completely absent at periods of two to three months, it is referred to as "intermittent illness phase." Chronic disease periodicity is characterized as time periods where the patient is medication-free and without experiencing inflammation. To say that the patient has constant continuing inflammation, which might occur while attempting to discontinue or taper therapy, implies that the patient has persistent inflammation. Majority of VKC patients do not experience glued eyes, in contrast to bacterial conjunctivitis, however, because of their acute photophobia and mucous secretion, they may have trouble opening their eyes in the morning [7, 10]. Pathognomonic papillae are more prevalent on the upper tarsal conjunctiva than on the lower tarsal conjunctiva in the palpebral/tarsal form of VKC [11]. On the upper eyelid's tarsal conjunctiva, papillae are frequently visible[12]. In routine practice, patients with ocular allergies frequently utilize variety of eye drops, which raises financial burden and reduces medication compliance. Macrolide antibiotic Tacrolimus (FK-506) has strong immunomodulatory properties [13]. cytokines

like interferon, IL-2, IL-3, and IL-5, as well as tumor necrosis factor (TNF) Tacrolimus (FK-506) mimics the activity of suppressing T-cell activation and mast cell and basophil IgE-dependent histamine release[14,15]. Tacrolimus ointment, with a concentration of 0.03% and 0.1%, is available for topical dermatological applications. [16]

Considering this, as well as the potential advantages of tacrolimus, we aimed to assess the safety and effectiveness of tacrolimus ointmenttopical monotherapy with conventional medication (olopatadine, sodium, cromoglycate flurometholone, dexamethasone, and prednisolone eye drops) in our two study groups for the treatment of VKC. Tacrolimus ointment 0.03% still not used as ophthalmic preparation in Pakistan, lot of burden for medicines cost patients facing for long duration, in spite of that patients present with complications of VKC.This study was conducted on skin ointment preparation eczymous 0.03% (Brook Pharma) to find out the efficacy and safety of tacrolimus ointment 0.03% in VKC.

MATERIAL& METHOD

This randomized control trial was carried out at ophthalmologyoutpatient department PUMHS Shaheed Benazirabad on200 patients suffering from moderate to severe VKC were taken based on TSSS and TOSS scores. Study participants were divided into 2 groups by probability sampling method (even and odd numbers 100 each group).One group received 0.03% Tacrolimus skin ointment while the other received conventional therapy. After the agreement of the participants through consent form, data was collected on the structured Performa.

Group A; 100 VKC patients who have to quit all the conventional therapy before starting tacrolimus therapy just kept on (0.03% tacrolimus dermatologic ointment (preservative free). First dose applied in front of researcher in OPD to check any immediate side effects followed for 15 minutes for any side and further guided to apply in lower fornix of both eyes twice daily, (not more than 5mm in length) and follow-up according to research protocol 1st visit ,4th week,8th week,12 week.

Group B; 100 VKC patients, advised to stop all other medicines on conventional therapy including 25 patients on Fluromethaloneacetate 0.1% least potent steroid, 25 patients onDexamethasone sodium phosphate0.1% medium potentsteroid, 25patients on Prednisoloneacetate 1% most potent steroid and 25 on (mast cell stabilizer) sodium chromoglycate 4% one drop 4 times a day and antihistamine (olopatidine) eye drop at bed time.

Inclusion criteria of this study

1. Patients (males and females) with moderate to severe VKC with score of 3& 4 according to TSSS & TOSS criteria
2. Patients with VKC from 3-16 years of age as mentioned in introduction its common ocular morbidity in this age group
3. Patients' refractory to the conventional therapy

Exclusion criteria of this study

1. Coexisting conjunctival disorders/pterygium/symblepharon
2. Ocular infections/uveitis/Trachoma
3. Ocular surface disorders (lid scaring, entropion, trichiasis/tumor)
4. Glaucoma, Cataract
5. Recent contact lenses use
6. Use of systemic non-steroidal anti-inflammatory drugs (NSAID's)/Steroid/Immunosuppres sive drugs
7. Ocular surgery in previous 3 months
8. Patients having supratarsalTriamicolone injection history with past one month

9. Non consenting patients

Statistical analysis Collected data was performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics was used to obtain the frequency and count of the variables discussed in this study. Test of independence was used to compare the baseline characteristics of the participants instead of a fisher's test due to a larger sample size. For follow-up, we used Friedman's non-parametric test was used. For all statist

Severity score of symptoms of VKC [11] Total subjective symptoms score (TSSS) [4]

Itching	0=no desire to scratch 1=intermittent desire to scratch 2=frequent desire to scratch 3=constant desire to scratch
Discomfort/foreign body sensation	0=no foreign body sensation 1=discrete similar to dust 2=mild similar to sand 3=sever constant similar to rock
Photophobia	0=o photophobia 1=mild squints in bright light 2=Moderate improve with use of sunglasses 3=sever improve with total eye occlusion
Tearing	0= absent 1=humid no epiphora 2=intermittent epiphora 3=constant epiphora

Severity score of signs of VKC[11] Total objective ocular sign score (TOSS) [4]

Conjunctival hyperemia	0= calm conjunctiva 1=mild increase in vessel diameter difficult to notice 2=moderate increase in diameter and number of vessels 3=diffuse and intense hyperemia
Upper tarsal papillae	0=no central tarsal vessel 1=central tarsal vessel present 2=some giant papillae 3=giant papillae predominant
Discharge	0=no discharge 1=little amount in fornix 2=moderate amount in fornix 3=sticky eyes in morning
Keratitis	0= no epitheliopathy 1=superficial punctate keratitis 2=confluent punctate keratitis

	3=shield ulcer
Shield ulcer	0= no evidence, 1= one quadrant 2= (two quadrants 3= (three or more quadrants)
Trantas dots	0=(no dots) , 1= (1 to 2 dots) 2= (3 to 4 dots),3= (more than 4 dots)
Limbus infiltration	0= no infiltration 1= < 90°of limbal infiltrate 2=< 180°but >90° 3=>180° of limbal infiltrate

Table 1.1: Qualitative socio demographic characteristics of participants of both groups

Variables	Categories	Treatment	Conventional
		Percentage	Percentage
Gender	Male	68	66
	Female	32	34
Family history of ocular	Yes	39	48
diseases	No	61	52
Any other ASM	Yes	12	8
	No	88	92

Table 1.2: Quantitative socio demographic characteristics of participants of bothgroups

Variables	Treatment		Conventional	
	Mean	SD	Mean	SD
Age (Years)	5.09	0.95	5.89	1.88
Duration of symptoms (Months)	8.14	5.05	9.68	6.72

Table 2:1**Sign and Symptoms at baseline**

Complaint	Treatment group (%)	Conventional group (%)
Itching	98	97
Discomfort	87	89
Photophobia	66	63
Tearing	82	81
Conjunctival hyperemia	100	91

Upper tarsal papillae	83	79
Discharge	81	82
Keratitis	63	64
Shield ulcer	4	3
Trantas dots	31	29
Limbus infiltration	27	28

Table 2:2 Total Subjective Symptom Score (TSSS) at different points in time

Time	Treatment Group			Conventional Group			Group A vs B (p-value)
	Mean	Change from baseline	p value	Mean	Change from baseline	p value	
Baseline	2.8 ± .12	-	-	2.93 ± .14	-	-	>0.05
4th week	.8 ± .48	2. ± .42	<0.01	1.86 ± .31	1.06 ± .35	<0.01	<0.01
8th week	.35 ± .27	2.46 ± .31	<0.01	1.36 ± .32	1.57 ± .35	<0.01	<0.01
12th week	.12 ± .21	2.68 ± .33	<0.01	1.23 ± .28	1.71 ± .3	>0.05	<0.01

TSSS score data presented in table 2.2 revealed a baseline score of 2.8 ± .12 for treatment group while 2.93 ± .14 for conventional group. Treatment group revealed highly significant decline throughout the treatment interval with mean scores .8 ± .48, .35 ± .27 and .12 ± .21 at 4th, 8th and 12th week, respectively. Conventional group showed some decline from the baseline score but it didn't fell below 1 which showed the presence of at least some symptoms in TSSS scores.

Table 2:3Total Objective Symptom Score (TOSS) at different points in time

Time	Treatment Group			Conventional Group			Group A vs B (p-value)
	Mean	Change from baseline	p value	Mean	Change from baseline	p value	
Baseline	2.56 ± .25	-	-	2.54 ± .28	-	-	>0.05
4th week	1.13 ± .52	1.42 ± .31	<0.01	1.92 ± .59	.62 ± .33	<0.01	<0.01
8th week	.66 ± .51	1.89 ± .31	<0.01	1.39 ± .76	1.14 ± .52	<0.01	<0.01
12th week	.23 ± .37	2.32 ± .25	<0.01	.81 ± .69	1.73 ± .46	<0.01	<0.01

TOSS score for baseline were 2.56 ± .25 for treatment group while 2.54 ± .28 for conventional group. Decline recorded throughout the weeks resulted in mean score 1.13 ± .52, .66 ± .51 and .23 ± .37 at 4th, 8th and 12th week for treatment group while 1.92 ± .59, 1.39 ± .76 and .81 ± .69 at 4th, 8th and 12th week for the conventional group. The decline was greater in treatment group which confirmed the efficacy of Tacrolimus against TOSS score as compared to the conventional treatment.

DISCUSSION

The socio-demographic information was recorded at the very first visit. a method for evaluating signs and symptoms objectively that has been adopted from clinical studies that used similar approaches. Following the initial approach and group task Conjunctival hyperemia, upper tarsal papillae, limbal inflammatory activity, keratitis, and discharge, as well as symptoms of tearing, photophobia, itching, and a feeling of a foreign body, were examined and rated on a scale of 0 to 3. According to Labcharoenwongs, Jirapongsananuruk[17] and Müller, Santos [18], moderate and severe VKC were evaluated subjectively by assessing patients on Total subjective symptoms score (TSSS) and Total objective ocular sign score (TOSS) criteria. There was no evidence for mild, moderate, or severe VKC, with higher scores indicating more severe symptoms (TISS and TOSS scoring). Tacrolimus' efficacy and safety were assessed both subjectively by observing the symptoms of the patient and objectively by noting an improvement in the clinical signs using the TSSS and TOSS scores. On subsequent follow-up visits, the improvement score dropped from 3 and 2 to 1 or 0 respectively. At each subsequent visit at the fourth, eighth, and 12th weeks, the severity scores of signs and symptoms were collected on a regular basis. Scores data was compared with in each group (Treatment and Conventional) and in between groups to identify the efficacy of treatment. Participants reported moderate to severe (2-3) ranges of TSSS severity scores for itching, discomfort, photophobia, tearing and also TOSS scores for conjunctival hyperemia, upper tarsal papillae, mucus discharge, keratitis, shield ulcer, trantas dots and limbal infiltration at the start of treatment. Descriptive analysis of the data showed that among 200 participants, 67% were male while 33% were female. 56.5% participants had no family history of ocular disease while 43.5% participants showed family history of ocular diseases. Only 10% reported to have other allergic systemic manifestation. Mean age was recorded as 5.49 ± 1.54/Years while mean duration of symptoms appearance was recorded as8.91 ± 5.93/Months. Socio demographic data from the participants subjected to 0.03% tacrolimus ointment treatment showed that most of the participants were males (68%), female 32%. Mean scores of age and duration of symptoms were recorded as 5.09 ± 0.95/Years and 8.14 ± 5.05/Months, respectively. Mean scores of age and duration of disease were 5.89 ± 1.88/Years and 9.68 ± 6.72/Months, respectively.

Data for the (TSSS) Total subjective symptoms score of the VKC vernal keratoconjunctivitis was recorded at the first visit. Analysis of this data was made to obtain the descriptive statistics of presented symptoms. VKC types recorded for the treatment group were 73% tarsal, 24% limbal and 3% mixed conventional group were 71% tarsal, 25% limbal and 4% mixed. Almost all of the participants from the treatment and conventional group had shown to have the symptoms of itching (98% for treatment group and 97% for conventional group). Discomfort data showed that, 87% of the respondents from the treatment group were having discomfort while 89% of the respondents reported discomfort from the conventional group. Photophobia was reported as 66% and 63% in treatment and conventional group, respectively. Statistical analysis of the data on the severity scores of discomfort revealed that, treatment group and conventional group showed a mean score between 2.87 ± 0.34 and 2.89 at baseline.

These values showed the existence of a moderate to severe condition of discomfort for both the groups. Statistical data recorded for photophobia showed a mean score of 2.66 ± 0.48 for the treatment group and 2.63 ± 0.49 for the conventional group. Difference recorded between the two groups was found to be non-significant at the baseline.

Treatment group treated with 0.03% Tacrolimus ointment showed a greater improvement at the end of study with lowering the severity score ranges (close to 0). Conventional group using Flurometha lone, Dexamethasone and Prednisolone also showed improvement in the TSSS and TOSS parameters but these changes were mild as compared to the changes reported by the participants in the treatment group. Another interesting feature of study was the intra ocular pressure (IOP) score for determining the possible side effects carried by each therapy. Tacrolimus group showed a score between 12-13 mmHg indicating a safer form of therapy while conventional group showed a rise in the IOP score throughout treatment and a mean score close to 20 mmHg was found which indicates a possibility of glaucoma in future, induced by conventional therapy. Tacrolimus 0.03% ointment was found to be safe and more effective in treating VKC as compared to Prednisolone acetate1% high potent topical steroid, Dexamethasone sodium phosphate 0.1% moderate potent topical steroid, Flurometha lone acetate 0.1% least potent topical steroid ,mast cell stabilizers and antihistamines(olopatidine 0.2%) eye drops .Prednisolone acetate and dexamethasone sodium phosphate shows increase efficacy but raised IOP during follow up period. While flurometha lone, mast cell stabilizers (sodium chromoglycate and antihistamine olopatidine sodium proved very low efficacy in improvement (TSSS) Total subjective score system (TOSS) total ocular sign score. IOP typically rises three to six weeks after topical steroid use in steroid-induced glaucoma, but it can happen earlier. The damage caused by prolonged steroid therapy is irreversible, but the increased IOP can be reversed. When steroids were stopped, intraocular pressure did not return to normal, requiring medical and surgical intervention. Antihistamines, mast cell stabilizers, and the occasional application of topical steroids are all components of the VKC topical ophthalmic preparation. Bycorticosteroids are abused for their high effectiveness and early symptom relief without being aware of their potential for vision-threatening complications, most notably cataract and glaucoma.[18]

CONCLUSION

In our study, we found that Tacrolimus ointment, 0.03 percent, was more effective and safer than the other medical treatments in reducing the disease's severity as measured by the TSSS and TOSS severity scores. In our rural areas due to poor temperature control and environmental conditions, VKC rate is higher especially in summer season. Management of vernal keratoconjunctivitis VKC is quite challenging step but this research proved that early diagnosis and improved management of VKC disease can prevent complications in early age. No side effects like burning or sensitivity to sunlight observed by tacrolimus use. Tacrolimus monotherapy is convenient to use, it relieve symptoms and also reduce financial burden and prevent patients from steroid induced hazards.

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Consent to participate: written and verbal consent was taken from subjects and next of kin

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