

Role of Tacrolimus Skin Ointment 0.03% in Severe Vernal Keratoconjunctivitis

Tacrolimus Skin Ointment 0.03% in Severe Vernal Keratoconjunctivitis

Attaullah Shah Bukhari¹, Sarmad Jamal Siddiqui², Vija Kumar Gemnani¹, Shahid Jamal Siddiqui¹, Mohammad Ali Shar¹ and Suhail Ahmed Shah¹

ABSTRACT

Objective: To determine the role of tacrolimus skin ointment (0.03%) in severe vernal keratoconjunctivitis.

Study Design: Interventional study

Place and Duration of Study: This study was conducted at the Department of Ophthalmology KMC Civil Hospital Khairpur Mir's, Al Ibrahim eye Hospital Malir Karachi PUMHS Nawabshah (SBA) from February, 2020 to February, 2021 for a period of one year.

Materials and Methods: After ERC approval and take informed consent, all sociodemographic variables were gathered from pts:/guardians. The best spectacle-corrected visual acuity was assessed, biomicroscopy, slit lamp was done, and conjunctival/corneal fluorescein staining was performed on all of them. Clinical signs like conjunctival Hyperemia, papillae, trans dots, and SPK were graded as no symptoms represent no any symptoms, mild, moderate, severe means grade 0,1,2 and 3.

Results: A total of 48 cases (48 eyes) were included in the study. The mean age was recorded as 10.75±4.19 years. After starting Tacrolimus skin ointment 0.03%, patients were followed for 1 month. All symptoms improved significantly; itching was the first symptom to be improved. By 1month of treatment, the symptom only included mild redness observed in 3 patients with 93.7% improvement and mild photophobia in 5 patients with 89.5% improvement. Conjunctival hyperemia improved in 40 patients (83.3%). In addition, papillae showed improvement in 39 eyes (81.25%). There was an improvement in Trantas dots in 34 cases 70.8%. SPK improved in 29 (60.4%) cases.

Conclusion: It was concluded that improvement in signs and symptoms was observed and recorded by use of topical tacrolimus skin ointment 0.03% from grade 3 to 1 and grade 2 to 0 within 1 month of therapy. No complications were observed during the 1month use of this medicine.

Key Words: Tacrolimus, Role, skin, severe, VKC.

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INTRODUCTION

Vernal keratoconjunctivitis is an inflammatory infection of conjunctiva and cornea which might be acute on chronic, mostly happens in 1st decade of life, more frequent in boys and more seemed in hot and dry region^[1] (Mediterranean basin, the mid-east, Africa and Indian subcontinent). In hot and dry season boys have usually affected.^[2]

Symptoms with itching, redness, photophobia along with watery discharge. Signs which can be seen on Slit

Lamp Microscope include Conjunctival Injection (hyperemia), Limbitis (Trantas Dots), Punctate Epithelial Keratopathy (superficial punctate keratitis SPK), and Giant Papillae (GPC).

There is a recurrence of about 95% of cases in adult teens.^[3] Patients usually are visually disturbed due to intense itching, redness, and watery discharge along with photophobia. Symptoms are aggravated by a hot and humid environment.

If properly not managed, VKC generally results in sight-threatening complications^[4] over some time like cataract glaucoma, corneal thinning, ectasia (keratoconus), and shield ulcer. Topical antiallergic, mast cell stabilizers, nonsteroids anti-inflammatory drugs, steroids, and immunomodulators are some of the treatment choices for Vernal keratoconjunctivitis.^[5]

Mainly steroids are used in the treatment of VKC, which causes serious side effects like glaucoma, cataract, and secondary infections.^[6] Certain immunomodulators are used to reduce the onset of steroid-induced problems in VKC patients.^[8] Two of these are cyclosporine and tacrolimus, the tacrolimus of them is a powerful, nonsteroidal macrolide

¹. Department of Ophthalmology, Khairpur Medical College Khairpur Mir's.

². Department of Community Medicine SMBBU, Larkana.

Correspondence: Dr. Vija Gemnani, Associate Prof. Faculty of Community Medicine, SMBBU, Larkana.

Contact No: 0335-3135679

Email: gemnanivijay@yahoo.com

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immunomodulator derived from *Streptomyces tsukubaensis* that is comparable to cyclosporine in terms of potency.^[9]

Tacrolimus ointment two times per day given good progress in symptoms of VKC, same as cyclosporine eye drop four times per day.^[7] Tacrolimus showed itching relief through mast cells (inhibit the release of histamine).^[8] FDA approved Tacrolimus, to apply in visceral transplantation (liver),^[9] and extended other body viscera and body parts. Skin problem such as vitiligo is broadly treated by Tacrolimus and are also so efficient and secure option in the management of vitiligo among children.^[10]

The present study is designed to evaluate improvement in signs and symptoms of VKC with Topical Ocular Tacrolimus use, so it can be utilized in the future to avoid long-term use of steroids, while simply anti-allergy eye drops (topical) are not enough to manage Vernal Keratoconjunctivitis. Tacrolimus topical Ocular ointment is not available in Pakistan, due to this Skin ointment is used in this study.

MATERIALS AND METHODS

Before the start of the study, approval was taken from the Ethical review committee from KMC Teaching Hospital Khairpur Mir's. Written consent was taken from all eligible patients and demographic information was taken including age, name, and sex was recorded descriptively. A total of 48 patients was included in the study. There were 10 new instances and 38 recurrent cases, all of which were resistant to earlier treatment with topical antihistamines, mast cell stabilizers, and steroids.

A questionnaire was given to all participants to evaluate the clinical symptoms grading such as Itching, redness, photophobia, etc on Likert like scale in grades 0,1,2,3 (no, mild, moderate, and severe symptoms)

Eye examinations were taken from all patients ie Spectacle-corrected visual acuity, slit-lamp biomicroscopy, and conjunctival/corneal fluorescent staining were performed on all of them.

Clinical signs like conjunctival Hyperemia, papillae, trans dots, and SPK were graded as in table No. 3 and described in the operational definition. The benefits and drawbacks of the treatment were thoroughly described to the patients or their guardians.

Tacrolimus 0.03 percent ointment was recommended for use in the inferior fornix in 02 times per day, whereas all other VKC management (antihistamines, mast cell stabilizers, and NSAIDS) were stopped, except for steroids, which were tapered down.

Prescription, TearcoolR (Lubricant eye drops) 02 times daily was applied to minimize irritation, seemed uncommon with tacrolimus ointment.

The success of the medication was determined both subjectively by the patient's symptoms and objectively

by improvements in clinical indicators observed with a slit lamp microscope.

Additional treatment should be recorded. Any therapeutic side effects, such as eye pain, were asked about, as well as any prospective problems, like a raise in ocular pressure, secondary bacterial infections, and lens opacification.

All these results were documented at the start of therapy as well as at all subsequent follow-ups of one week, two weeks, and one month.

During the follow-up period or after 3 months, notified all recurrence of symptoms or indications after quitting all therapies.

Statistical Analysis: Data analysis was analyzed by applying SPSS version 23.0. Mean and Standard deviation will be computed of quantitative variables. Frequency and percentages will be calculated for categorical variables. Pie Chart is used to define the gender distribution. Pre and Post-treatment frequencies will be noted to calculate improvement for each sign and symptom.

RESULTS

A total of 48 cases (48 eyes) were examined in the study, male (31) participation seemed doubled as compared to female (17) patients. Gender distribution is depicted in Figure-I. The mean age of the study participants was 10.75 ± 4.19 years. Itching and watering, as well as photophobia and redness, were the most prevalent symptoms. Table-I. Papilla was seen in all 48 cases (21 cases in Grade 2 and 27 cases in grade 3), Trans Dots were observed in patients as $n=23$ moderate cases and $n=25$ cases, SPK observed in patients as $n=21$ moderate cases and $n=27$ severe cases, conjunctival hyperemia observed in patients as $n=4$ mild cases, $n=23$ moderate cases and $n=21$ severe. Table-2.

After starting Tacrolimus skin ointment 0.03%, patients were followed for 1 month. All symptoms improved significantly; itching was the first symptom to be improved. By 1 month treatment, the residual symptom only included mild redness observed in 3 patients with 93.7% improvement and mild photophobia in 5 patients with 89.5% improvement, which disappeared after a further 1 month of therapy. Table-1

Noticeable progress was noted objectively. Conjunctival hyperemia was the primary sign to show progress in 2 weeks of therapy. Conjunctival hyperemia improved in 40 patients (83.3%), while it disappeared further 1 month of treatment in the remaining cases. In addition, papillae showed improvement in 39 eyes (81.25%). There was an improvement in Trantas dots in 34 cases 70.8%. SPK improved in 29 (60.4%) cases. Table-2.

The patients remained mostly asymptomatic during the treatment period, while 10 (20.83%) patients had recurrence after 1 month of treatment though in a

milder form. Table-3. Consequently, more than four weeks remained to continue and then slowly tapering within 04 weeks. No, additional treatment is needed such as topical antiallergic or steroids, while treating with tacrolimus.

There were only three cases of complaining of slight burning when applying the ointment; no complaint was observed in remained 45 cases. Figure-II In all cases intraocular pressure remained normal. In addition, no other complication was seen in the case while using tacrolimus skin ointment.

Table No.1: Symptoms before start of treatment and one month after treatment

Symptom	Grades prior to Rx				Grade After 1-month treatment				Improvement
	0	1	2	3	0	1	2	3	
Itching	0	0	n=25	n=23	n=48	0	0	0	100%
Redness	0	0	n=18	n=30	n=45	3			93.7%
Watery discharge	0	n=12	n=22	n=14	n=48	n=0	0	0	100%
Photophobia	0	n=3	n=20	n=24	n=43	5	0	0	89.5%

Table No.2: Signs before start of treatment and one month after the treatment

Signs	Grades prior to Rx				Grade After 1-month treatment				Improvement
	0	1	2	3	0	1	2	3	
Conjunctival Hyperemia	0	n=4	n=23	n=21	n=40	n=8	0	0	83.3%
Papillae	0	0	n=21	n=27	n=39	n=9			81.25%
Trantas Dots	0	0	n=23	n=25	n=34	n=14	0	0	70.8%
SPK	0	0	n=21	n=27	n=29	n=19	n=0		60.4%

Table No.3: Recurrence of Signs & Symptoms

Status	Frequency	Percent
None	38	79.1
Yes	10	20.83
Total	48	100

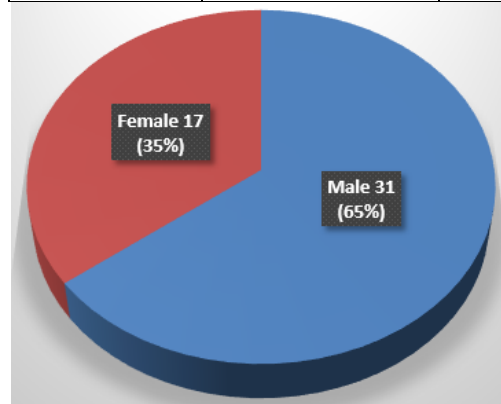


Figure No.1: Gender Distribution

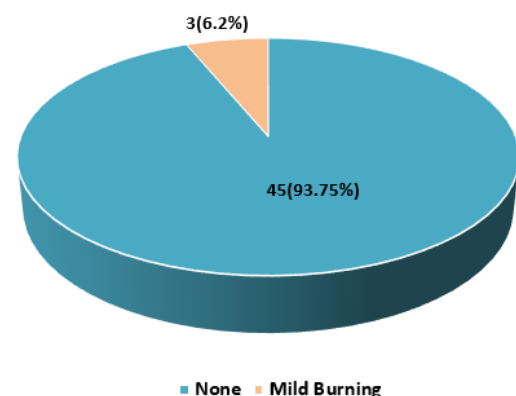


Figure No.2: Side Effects of Tacrolimus

DISCUSSION

Since, VKC is an immune-mediated illness with significant ocular morbidity, in moderate to severe instances, the use of an immunomodulation medicine to treat the debilitating symptoms of itching and watering in children becomes important. In most studies, the disease is recurrent after stopping therapy, hence treatment is used for a longer period. The preferred choice for VKC is Topical steroids in that cases, however, long-term usage can result in vision-threatening problems such as glaucoma, cataracts, corneal thinning, and corneal ectasia. As a result, Tacrolimus ointment has emerged as a highly safe and effective steroid-free alternative, inhibiting all immunological processes involved in VKC development.

The only drawback of this study was the off-label use of tacrolimus skin ointment 0.03% in the conjunctiva, though an ophthalmic preparation is not available in Pakistan. This study confirms that Tacrolimus skin cream (0.03%) in such a mild concentration is safe and effective in improving signs and symptoms of VKC and a safe alternative to topical steroids for VKC. The effectiveness of tacrolimus was also observed in other studies as we opted for this medicine after going through all this research. Tacrolimus 0.1% ‘skin’ cream applied to the skin of lower eyelid in previous studies^[11] had effectively controlled VKC. Sengoku et al used 0.01 – 1% eye drops in an animal study for ocular allergy while Ohashi et al used an 0.1% ophthalmic suspension in another clinical study.^[12,13] In the study, in all cases not only was there effective management of the patient's symptoms. (Table-I) Not only was there effective management of the patient's symptoms in all

cases (Table-I) but there was also a subjective improvement immediately after commencing the medication, according to our findings.

This study confirmed the improvement in signs and symptoms of VKC with Tacrolimus skin ointment 0.03%, which were refractory to conventional treatment. All signs and symptoms showed noticeable progress with no developing side effects. 03 patients showed burning (mild), however, it was subsided within 07 days. In their research population, it was also observed a minor transitory stinging sensation that lasted a few days.^[14]

The itching was the most prevalent symptom in our research, and it was also the earliest to go away. Incomparable research, it was found that 5 out of 20 patients had itching, with all instances improving within a week.^[15,16]

The commonest feature was papillary hypertrophy that was occurred in all 48 cases with n=21 moderate and n=27 severe which were also resolved with a success rate of 81.25% within one month of therapy. Conjunctival hyperemia resolved responded to treatment first and resolved within one month with an 83.3% success rate. Bardot et al. also reported conjunctival hyperemia to get resolved within 1 month in 60% of patients^[14]. Trantas dots, SPK, redness, photophobia, watery discharge all showed marked improvement.

In the current study, an attempt to stop Tacrolimus skin ointment 0.03% after 1month results in recurrence of a mild form of VKC in 10 cases 20.83% as depicted in table no. III, as a result, they were instructed to utilize it for at least 2– 3 weeks before progressively tapering it over the next month. Topical Tacrolimus was terminated after 4 weeks in VKC in previous investigations, and no recurrence was seen. No complication of tacrolimus ointment used in our study was observed. A study, in which topical Tacrolimus was used for up to 42 months in patients with AKC16, while it was used for up to seven months in another study in patients with AKC¹⁷⁻²² and no negative effects were recorded.

No extra drugs, such as antihistamines or mast cell stabilizers, were required in our trial. It can be applied as preventive medicine in less severe illnesses to stop aggravation during the hot, humid season of the year because long-term usage has been proved to be safe.

Tacrolimus creates a minor burning sensation when used for the first time in 3 out of 48 patients which also resolved after 2 weeks spontaneously. This mild burning sensation with tacrolimus was also observed in other studies.^[15]

CONCLUSION

We highlighted that using 0.03 percent Tacrolimus skin cream two times per day in the lower conjunctival fornix seemed significant improvement in VKC; all

patients experienced effective remission of their symptoms after four weeks of treatment. During the research, no extra drugs such as antihistamines or steroids were required. As a result, it was an alternative for steroid responders to reduce the risk of steroid-induced problems.

Author's Contribution:

Concept & Design of Study: Attaullah Shah Bukhari
Drafting: Sarmad Jamal Siddiqui,

Data Analysis:

Vijia Kumar Gemnani
Shahid Jamal Siddiqui,
Mohammad Ali Shar,
Suhail Ahmed Shah

Revisiting Critically:

Attaullah Shah Bukhari,
Sarmad Jamal Siddiqui

Final Approval of version:

Attaullah Shah Bukhari

Conflict of Interest: The study has no conflict of interest to declare by any author.

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