International Journal of Medical Ophthalmology

E-ISSN: 2663-8274
P-ISSN: 2663-8266
www.ophthalmoljournal.com
IJMO 2021; 3(2): 128-132
Received: 18-11-2021
Accepted: 23-12-2021

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A clinical study examining the effectiveness of topical tacrolimus 0.03% eye ointment for vernal keratoconjunctivitis

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DOI: https://doi.org/10.33545/26638266.2021.v3.i2b.180

Abstract
Background: Recurrent bilateral allergic inflammation of the conjunctiva and cornea is known as vernal keratoconjunctivitis (VKC). In hot, arid climates like the Indian subcontinent, it is more common. Mast cell stabilizers and antihistaminics are the first line treatments for VKC. Corticosteroids are used in severe situations. Nevertheless, immunomodulators have been utilized in place of corticosteroids due to the significant adverse effects of steroids. Determining the topical 0.03% tacrolimus's clinical effectiveness as the only treatment for VKC is the goal of this investigation.
Material and Methods: Fifty VKC patients were chosen and split into two smaller groups.
Group A: Where by tear drops were used as a placebo and 0.03% tacrolimus ointment was given twice daily.
Group B: Where by 0.03% tacrolimus ointment and 0.1% olapatadine ophthalmic solution were used twice a day. Before starting treatment, each patient was checked under a slit lamp, and their symptoms and signs were assessed on a scale of 0 to 3 on days 7, 30, and 90. The outcomes between the two groups were compared using the student's T-test for independent sample.
Results: On days 7, 30, and 90, there is a notable decrease in the group's signs (Conjunctival hyperaemia, tarsal papillary response, punctuate epithelial keratitis, limbal gelatinous infilterate) and symptoms (Itching, tearing, foreign body feeling, photophobia, discharge). ($p<0.05$)
Conclusion: When treating VKC patients who are not responding to traditional medication, both the solo use of tacrolimus and the combination of tacrolimus and olopatadine had comparable effectiveness in lowering clinical symptoms and signs.

Keywords: Opatatedine, tacrolimus, immunomodulators, and vernal keratoconjunctivitis

Introduction

It has been thought that one of the most frequent ocular conditions seen in clinical practice is allergic eye illness. Vernal keratoconjunctivitis (VKC) is an allergic inflammation of the conjunctiva that is recurring, bilateral, interstitial, self-limiting, and has a seasonal occurrence. It eventually damages the cornea. The majority of the continents have recorded cases of VKC worldwide. There is a sizable Indian population that has VKC [1, 2]. The frequency, severity, duration, and responsiveness to therapy of the condition vary widely, according to reports. This disorder is more common in hot, dry climate zones, according to many studies [2].

Being a Th2 lymphocyte-mediated illness, VKC is distinct from both seasonal and perennial allergic conjunctivitis. Nevertheless, little is known about the specific functions of mast cells, eosinophils, fibroblasts, and their cytokines in the remodelling of conjunctival tissue and the inflammatory process [3-5].

First-line therapy for VKC consists of topical application of antihistamines, mast cell stabilizers (MCSs), and, more recently, dual-action drugs (DADs), which are medications having both actions. Corticosteroids are utilized for a brief length of time to stimulate the remission of the allergic crisis in the more severe kinds. Nonetheless, several distinctive characteristics of VKC will be examined in the department of ophthalmology at the Fathima Institute of Medical Sciences, A.p., Kadapa, India. Because this area is heated, there are situations when stopping the corticosteroid without a clinical deterioration is not an option. As a result, patients are more vulnerable to the hazards associated with long-term use of these medications, including cataract, glaucoma, and corneal problems. Immunomodulators have been utilized to treat asymptomatic VKC patients and manage allergy crises in place of corticosteroids over the last 20 years [6]. Tacrolimus is a macrolide that is obtained from Streptomyces tsukubaensis.

It is a powerful immunomodulator that can reduce T lymphocytes' production of inflammatory mediators by inhibiting calcineurin, an intracytoplasmic protein that is necessary for the transcription of IL-2 and IL-4 [7, 8]. Tacrolimus has been effectively used in several studies to treat autoimmune illnesses of the ocular surface, including atopic keratitis, scleritis, dry eye, Mooren ulcer, cicatricial conjunctivitis, and VKC [9-13]. Tacrolimus and other immunosuppressive medications, such corticosteroids, have also been shown in recent clinical studies to be similarly effective in controlling allergy crises and providing maintenance treatment for patients with VKC, with a low frequency of adverse effects [14-16].

The purpose of this research is to evaluate the effectiveness of tacrolimus as the only treatment for VKC. This group of patients has a greater incidence of VKC due to the windy and dry climate.

Materials and Methods

All VKC patients who were resistant to standard treatment and who came into the outpatient department of a tertiary eye hospital made up the research group. In this case, "refractory" indicated that there was a recurrence after topical corticosteroid removal or that the clinical state was maintained or worse throughout treatment. Fifty patients were chosen at random and split into two subgroups, A and B, each with twenty-five members.

Group A (Experimental Group): Tear drops were used as a placebo in conjunction with 0.03% tacrolimus ointment, administered twice daily.

Group B (Control Group): 0.03% tacrolimus ointment and 0.1% olapatadine ophthalmic solution were used twice daily in this group.

Together with the ointment, the patients received identical flasks containing both eye drops. The eye drop flasks were numbered and devoid of any medication identification in order to facilitate double masking of the trial. Only after the data gathering period concluded was the contents of the flasks disclosed. The block system was used to carry out the randomization.

After a slit lamp examination of each patient, each symptom and sign was scored from 0 to 3 (Tables 1 and 2). The signs and symptoms were evaluated before to starting treatment, thirty days later, and ninety days later.

Using an objective 0-3 scale, the clinical perception of each case's development as well as the patient's self-evaluation will be recorded. Itching, burning, intraocular pressure, lens opacification, secondary infections, or other potential consequences were evaluated in order to evaluate the treatment's safety and adverse effects.

After receiving clearance from the Institutional Ethics Committee, the study's data gathering process began. For independent samples, the Student's T test was used. The Student T test for paired samples was used to compare the outcomes for each group's two assessment periods. We employed the Fisher exact test and the chi-square test to compare the two groups with respect to the qualitative factors. Significant P-values were those that were less than 0.05. The data was analysed using statistical software, statistical product and service solutions (SPSS 15.0), and graphs, tables, and other graphics were created using Microsoft Word and Excel.

Results

Patients in the research group ranged in age from 6 to 20 years. Most of the patients were discovered to be between the ages of 6 and 15. Nineteen (18.0%) were female and 41 (82.0%) were male out of 50. youngsters at school (82.0%), preschoolers (12%), and youngsters working outside with their parents (6%), made up the majority of patients. Eighty percent of the patients were from rural areas. The majority of patients (46.0%) had the bulbar type of VKC, followed by the palpebral (34.0%) and mixed (20%) varieties. Eleven out of fifty patients (22%) had corneal involvement in total; of them, twenty-three cases (13.44%) had bulbar form, seventeen cases (23.52%) had palpebral form, and ten cases (40.00%) had mixed type of corneal involvement. Four instances had epithelial scarring, while seven cases had superficial punctate keratitis. A higher incidence of corneal involvement was seen in individuals with palpebral or mixed disease types.

Result of therapeutic trial with drugs

Two groups of fifty patients each had their symptoms and signs evaluated on day 0 (Base line), day 7, day 30, and day 90. Tables 3 and 4 summarise the means for the signs and symptoms (Conjunctival hyperemia, tarsal papillary reaction, punctuate epithelial keratitis, limbal gelatinous infilate, tearing, foreign body sensation, photophobia, discharge), as well as how they compare between the two groups with a p-value. On days 7, 30, and 90, there is a notable decrease in the group's indications and symptoms. At day 90 of the trial, it was discovered that the severity of signs and symptoms had decreased in groups A (Tacrolimus plus placebo) and B (Tacrolimus plus olopatadine). (Figure 1).

Table 1: Shows slit lamp examination of each patient, each symptom and sign was scored from 0 to 3 (Tables 1 and 2).

	0	1	2	3
Itching	**Absent**	**Occasional desire to rub or scratch**	**Frequent need to scratch or rub the eye**	**Constant need to rub or scratch the eye**
Tearing	Normal tear production	Positive sensation of fullness of the conjunctival sac without tears spilling over the lid margin	Intermittent, infrequent spilling of tears over the lid margin	Constant, or nearly constant, spilling of tears over the lid margins
Foreign body Sensation	Absent	Mild	Moderate	Severe
Photophobia	Absent	Mild difficulty with light	Moderate difficulty, necessitating dark glasses	Extreme photophobia, cannot stand natural light even with dark glasses
Discharge	Absent	Mild, occasionally discharge accumulates	Moderate, noted in the lower cul-de-sac	Severe, eyelids tightly matted together upon awakening

Table 2: Shows slit lamp examination of each patient, each symptom and sign was scored from 0 to 3 (Tables 1 and 2).

	0	1	2	3
Conjunctival hyperaemia	**Absent**	**Minimal redness**	**Diffuse redness**	**Very marked diffuse redness**
Tarsal papillary reaction	Absent	Mild mosaic flat appearance	Elevated papillae	Cobble stone appearance of papillae
Punctuate epithelial keratitis	Absent	Up to one quadrant	Up to two quadrants	three or more quadrants
Limbal gelatinous infiltrate	Absent	Up to one quadrant	Up to two quadrants	three or more quadrants

Table 3: Summarise the means for the signs and symptoms (Tables 3 and 4)

Symptoms	Group	Day 0 mean score (Base line)	Day 30 mean score	Day 90 mean score
Itching	Group A	2.76	1.04 $p<0.05$	0.16 $p<0.05$
	Group B	2.72	0.84 $p<0.05$	0.12 $p<0.05$
	P Value	0.753 (p>0.05)	0.231($p>0.05$)	0.691 ($p>0.05$)
Tearing	Group A	2.80	1.08 $p<0.05$	0.44 $p<0.05$
	Group B	2.88	1.00 $p<0.05$	0.20 $p<0.05$
	P Value	0.451 ($p>0.05$)	0.645 ($p>0.05$)	0.07 ($p>0.05$)
Foreign body sensation	Group A	2.76	1.08 $p<0.05$	0.48 $p<0.05$
	Group B	2.96	0.88 $p<0.05$	0.44 $p<0.05$
	P Value	0.042 ($p>0.05$)	0.060 ($p>0.05$)	0.782 ($p>0.05$)
Photophobia	Group A	2.76	1.00 $p<0.05$	0.44 $p<0.05$
	Group B	2.84	1.00 $p<0.05$	0.42 $p<0.05$
	P Value	0.49 ($p>0.05$)	1 ($p>0.05$)	0.98 ($p>0.05$)
Discharge	Group A	2.32	0.84 $p<0.05$	0.24 $p<0.05$
	Group B	2.40	0.68 $p<0.05$	0.24 $p<0.05$
	P Value	0.565 ($p>0.05$)	0.485 ($p>0.05$)	1 ($p>0.05$)

Table 4: Summarise the means for the signs and symptoms (Tables 3 and 4)

Signs	Group	Day 0 mean score (Base line)	Day 30 mean score	Day 90 mean score
Conjunctival Hyperemia	Group A	2.44	0.56 $p<0.05$	0.08 $p<0.05$
	Group B	2.48	0.60 $p<0.05$	0.08 $p<0.05$
	P value*	0.837 ($p>0.05$)	0.780 ($p>0.05$)	1 ($p>0.05$)
Tarsal Papillary Reaction	Group A	2.28	0.48 $p<0.05$	0.08 $p<0.05$
	Group B	1.88	0.36 $p<0.05$	0.04 $p<0.05$
	P value*	0.226 ($p<0.05$)	0.40 ($p<0.05$)	0.307 ($p<0.05$)
Punctate Epithelial Keratitis	Group A	0.52	0.04 $p<0.05$	0.00 $p<0.05$
	Group B	0.84	0.08 $p<0.05$	0.00 $p<0.05$
	P value*	0.876	0.801	1
Limbal Gelatinous Infiltrates	Group A	2.04	0.44 $p<0.05$	0.12 $p<0.05$
	Group B	2.28	0.52 $p<0.05$	0.12 $p<0.05$
	P value*	0.565 ($p>0.05$)	0.485 ($p>0.05$)	1 ($p>0.05$)

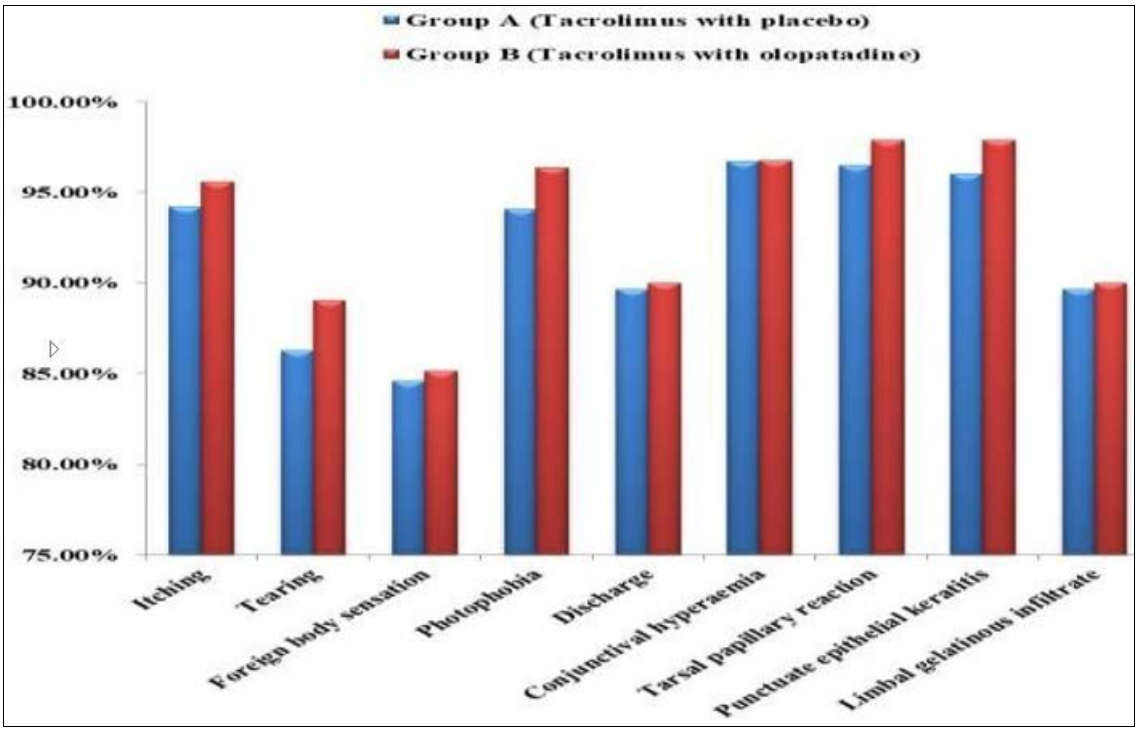

Fig 1: A (Tacrolimus with placebo) and group B (Tacrolimus with olopatadine) severity of signs and symptoms were found to be reduced at day 90.

Discussion

Treating refractory VKC is a challenging condition. Effectively relieving signs and symptoms, steroids are known to have major adverse effects when used over an extended period of time. We compared infants as early as five months old in this research [17-19]. After puberty, typically 4- 10 years after beginning, it resolves [20, 21]. Labcharoenwongs P *et al*. included 24 participants in prospective double-masked comparative research. They were 9.61 years old on average [16]. In their research, Pucci N *et al*. found that the mean age was 9.05 ± 2.12 years [22]. Of the 50 patients in the current research, 41 (82%) were between the ages of 6 and 15.

Although there is a greater impact on men than on women, this difference decreases with age [23]. In their investigation, Harada N *et al*. found 24 males and 6 women with VKC [24]. In their research, Marey HM *et al*. found that the male-to-female ratio in the school-age group was 2.3:1. 49 male and 13 female patients with VKC were included in research by Shoughy SS *et al*. [26]. Of the 50 participants in the current research, 41 (82.0%) were men and 09 (18.0%) were women.

It is hypothesised that greater levels of pollution from pollens and other allergens are the secondary cause of the increased occurrence in warmer locations [20]. The incidence of VKC varies greatly depending on location and climate [27]. The incidence of VKC is greater in Adhara Pradesh, Kadapa, India because of the area's hot, windy, and dry climate. In this research, 10 out of 50 patients (20%) were from metropolitan areas, while 40 out of 50 patients (80%) were from rural areas. Despite the term "vernal," which implies a seasonal, springtime occurrence, this allergy illness sometimes lasts all year long and often becomes worse in warmer temperatures [28, 29]. Since April through July are regarded to be the hottest months in Andhra Pradesh, Kadapa, India, the majority of patients (82%) in the current research reported during these months.

Known to be among the most severe types of ocular allergies, VKC carries the risk of irreversible corneal damage and blindness. Patients with VKC who have corneal involvement or more than one recurrence year are at higher risk of irreversible vision loss, according to Sacchetti *et al*. [29]. In the current research, corneal involvement affected 11 out of 50 individuals, or 22%.

VKC is often a benign, self-limiting condition that goes away with age or arises on its own throughout adolescence. However, treatment is required to manage symptoms since this condition may be incapacitating at times when it is active [17, 18]. The purpose of this research is to evaluate the efficacy of presently offered treatment options, with a focus on newer medications that, when used alone, are successful in treating VKC instances that do not respond to traditional therapy, such as tacrolimus ointment for the eyes.

Topical tacrolimus has been deemed an efficient and secure substitute in several trials for managing allergic crises and sustaining symptoms of VKC [15, 29, 30]. Ohashi *et al*. [14] found that the tacrolimus-using group significantly outperformed the placebo group in a randomized clinical study.

In their comparison of 0.1% tacrolimus and 2% cyclosporine, Labcharoenwongs *et al*. [16] found no appreciable difference in clinical improvement between the two medications in either group. Nevertheless, tacrolimus 0.03% eye drops' absorption was shown by Moscovici *et al*. [9] to be much lower than the point at which systemic administration of the medication resulted in adverse consequences.

In this trial, at day 90, the intensity of signs and symptoms was observed to have decreased in groups A (Tacrolimus plus placebo) and B (Tacrolimus plus olopatadine). The subjects in group A experienced a 94.20% decrease in itching, 86.28% in tearing, 82.60% in foreign body sensation, 84.06% in photophobia, 89.65% in discharge, 96.72% in conjunctival hyperemia, 96.49% in tarsal papillary reaction, 96.00% in punctuate epithelial keratitis, and 89.65% in limbal gelatinous infiltrate. Group B experienced 95.59%, 89.05%, 85.13%, 96.37%, 90.00%, 96.77%, 97.87%, 97.87%, and 90% in the corresponding reductions in these conditions. Refractory VKC symptoms were observed to have promptly and significantly improved in both groups A and B. After seven days of therapy, itching has been seen to be mostly improved in all patients. Most of the symptoms have subsided. Objective indicators showed significant improvement over time, including: better conjunctival papillary hypertrophy and giant papillae after 7 days; improved limbal hypertrophy and corneal signs within a month; and reduced hyperaemia within 7 days. According to the results of the current trial, group B (Tacrolimus plus olopatadine) and group A (Tacrolimus plus placebo) both effectively reduce VKC symptoms and signs with the least amount of pain. Fifty patients (100%) showed an improvement in the clinical picture, while twenty cases (40%) complained of burning in their eyes after using tacrolimus ointment.

Therefore, the primary complaint was burning that occurred when tacrolimus was being applied. There was no discernible change in intraocular pressure, lens opacification, secondary infections, or other variables over the research period. Furthermore, no significant side effects related to tacrolimus (Ointment or drops) ocular usage have been reported in the literature. In one investigation, just one incidence of herpes keratitis and one case of throat discomfort were reported [14].

The tiny sample size of this research had limitations. We used tear drops as a placebo, which somewhat reduces the symptoms and indications of VKC. This research lacked the capacity to determine if tacrolimus's systemic absorption results in any negative effects.

Conclusion

When treating patients with VKC who are not responding to traditional medication, both the solo use of tacrolimus and the combination of tacrolimus and olopatadine show comparable success in lowering clinical symptoms and signs.

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