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Original Research Article

A Randomized Controlled Study of Antihistamines, Cyclosporine and Tacrolimus in Vernal Keratoconjunctivitis in Tertiary Eye Care Centre, Hyderabad

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Abstract

Background: Ocular allergies can affect various parts of the ocular surface, including the eyelids, lid margins, conjunctiva, and lacrimal system. The condition can range from mild to severe, potentially impacting quality of life and visual function. This study was done to determine the efficacy of Antihistamines Cyclosporine and Tacrolimus in Vernal Keratoconjunctivitis in the Tertiary Eye Care Centre.

Methods: This cross-sectional study was done in the Department of Ophthalmology, Sarojini Devi Eye Hospital, Hyderabad. After receiving informed consent from the participants, or from their parents or legal guardians, patients with Vernal Kerato-conjunctivitis who were visiting our hospital's ophthalmology outpatient department were evaluated for inclusion and exclusion criteria and included in the study. Each patient underwent a thorough ocular examination. Vernal keratoconjunctivitis symptoms and signs were assessed.

Results: 60 patients were divided equally into three groups with 20 cases each. Significant improvement in redness was observed after 7 days of treatment in all groups. Cyclosporine showed the most significant reduction in symptoms, including itching, discharge, and photophobia, across follow-ups, with p-values less than 0.05. Olopatadine and tacrolimus also improved itching, redness, and photophobia, though cyclosporine was superior for discharge reduction. Tacrolimus was less effective in controlling discharge but effective for H.T.S and PGTn. Cyclosporine showed consistent improvement in all signs, making it the most effective treatment.

Conclusion: Within the limitations of the current study, we found Olopatadine 0.1% eye drops had faster onset of action observable at 1 week. The maximum effect was seen by the end of 4 weeks, after this the effect seem to plateau off. Cyclosporine 0.05%, Tacrolimus 0.03% eye ointment had a maximum effect by the end of 3 months. The analysis of total showed that olopatadine has a faster onset of action demonstrated by lower scores in the first 2 weeks, later three drugs olopatadine, cyclosporine and tacrolimus had a similar efficacy.

Keywords: Cyclosporine, Tacrolimus, Olopatadine, Vernal Kerato-conjunctivitis (VKC).

Introduction

All parts of the ocular surface, including the lid, lid margin, conjunctiva, and lacrimal system, might be affected by ocular allergies. The severity of this illness ranges from mild to severe types, which can affect quality of life and perhaps compromise visual function. Allergic conjunctivitis can be classified as seasonal and perennial allergic conjunctivitis, Vernal Kerato-conjunctivitis (VKC), Atopic Kerato Conjunctivitis (AKC), giant papillary conjunctivitis, and contact or drug-induced dermato-conjunctivitis [1]. Corneal involvement is typically restricted to the two more severe forms of ocular allergy, Vernal Kerato-conjunctivitis (VKC), and Atopic Kerato Conjunctivitis (AKC). The condition has a larger gender inclination for boys (Male: Female ratio - 2:1), an early onset with remission by the late teens, a preference for warm climes over cold ones, a familial history of atopic disease, and other characteristics. Commonly when puberty begins. VKC is difficult to treat because the pathophysiology is unknown and anti-allergic treatment frequently fails [2]. The conjunctival allergic reaction in VKC, a Type 1 and Type 4 hypersensitivity condition, is characterized by eosinophil, lymphocyte, and structural cell activation. Therefore, histamine receptor antagonists or interventions aimed at stabilizing mast cells alone are typically ineffective in

reducing conjunctival inflammation and the frequent involvement of the cornea [3].

The intricate immunological process that starts and feeds the allergic ocular surface inflammation cannot be stopped by the medications that are now on the market; they are only palliative [4]. Only mild to moderate instances benefit from topical mast cell stabilizers, antihistamines, and leukotriene antagonists. Topical steroids are utilized in severe cases or situations with abrupt exacerbations [5]. The most effective drug for treating VKC" when given topically is corticosteroids, which also reduce phagocyte response and have a broad-reaching anti-inflammatory and immunosuppressive impact [2]. However, corticosteroids are known to cause severe adverse effects, including an increase in intraocular pressure, a posterior subcapsular cataract, a higher risk of infection, and a delayed rate of wound healing. Corticosteroids, therefore, cannot be utilized as a long-term treatment [6]. The class of medications known as calcineurin inhibitors includes the immunosuppressant cyclosporine. Helper T-lymphocyte proliferation and interleukin-2 production are inhibited by cyclosporine. Additionally, human mast cells and basophils are prevented from releasing histamine by cyclosporine. Cyclosporine does not cause serious ocular side effects such as lens alterations or an increase in intraocular pressure, unlike corticosteroids. In certain clinical trials on Vernal Kerato-conjunctivitis, topical cyclosporine has been tested as the first line of treatment. It is efficacious in both the palpebral and limbal types of Vernal Kerato-conjunctivitis [2, 6]. In contrast to topical steroids, not much research has been conducted on the effectiveness of cyclosporine in VKC. Therefore, the goal of this study is to determine if cyclosporine can replace steroids as a safe and effective treatment for vernal kerato-conjunctivitis. The current study aimed to evaluate and compare the safety of topical antihistamines, topical Cyclosporine, and topical tacrolimus in the treatment of vernal keratoconjunctivitis.

Material and Methods

This Randomized controlled study was done in the Department of Ophthalmology, Sarojini Devi Eye Hospital, Hyderabad. After receiving informed consent from the participants, or from their parents or legal guardians, patients with Vernal Kerato-conjunctivitis who were visiting our hospital's ophthalmology outpatient department were evaluated for inclusion and exclusion criteria and included in the study. Each patient underwent a thorough ocular examination. Vernal keratoconjunctivitis symptoms and signs were assessed by annexure III [7] documented in the proforma.

Symptoms – Itching, tearing, photophobia, and feelings of a foreign body. Signs -Tranata dots, Punctate keratitis, Hyperemia, and Papillae A rebound tonometer was used to measure intraocular pressure (I Care; Tiolat Oy, Helsinki, Finland) Before the trial, it was made sure that there were no targeted treatments for vernal keratoconjunctivitis for a week. A comprehensive ocular examination was performed on each subject. Vernal kerato-conjunctivitis symptoms and signs were evaluated according to Annexure III documented in the proforma. Enrollment (wash out Period). Patients were allocated at random after the washout period to the following groups.

Group A (n=20) received Olopatadine Hydrochloride 0.1% 4 times per day for 3 months.

Group B (n=20) received Cyclosporine 0.05% 4 times per day for 3 months.

Group C (n=20) received Tacrolimus 0.03% 4 times per day for 3 months.

The patients were followed, and Vernal Kerato-conjunctivitis symptoms, signs, and intraocular pressure were recorded on day 7^{th}, 14^{th}, and 30^{th} day. The drops were then stopped, and patients were reviewed after 3 months i.e. 180 days and their signs symptoms, and IOP were recorded.

Statistical Analysis: All the available data was refined and uploaded to an MS Excel spreadsheet and analyzed by SPSS version 22 in Windows format. The continuous variables were represented as mean, standard deviation, and percentages. The categorical variables were analyzed by ANOVA for differences between the groups. The values of p (<0.05) were considered as significant.

Results

A total of 60 cases were equally allotted to three groups. The mean age of our cohort was 11 years. There was a clustering of cases in the 05 - 20 years age group Table 1 depicts the age-wise distribution pattern in study participants. With regard to gender 33(55%) of the total subjects were male and 27(45%) of the total subjects were females.

Table 1: Age distribution among study participants (N= 60)

Age	Frequency	Percentage
5-10 years	21	40
11-15 years	30	50
16-20 years	9	10
Mean age ± SD	12.55 ± 4.1	

Symptoms: Itching and tearing were the most frequent complaints in all three groups. The baseline scores were statistically similar between the three groups except for itching, discharge which was more in the cyclosporine group, and tacrolimus group when compared to the olopatadine group (P value 0.005). The baseline mean scores are depicted in Table 2. The baseline scores indicate that all three groups experienced similar levels of itching and photophobia at the beginning of the study.

Table 2: Baseline symptom scores of (N= 60)

Group	Itching	Redness	Discharge	Photophobia
Olopatadine	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
Cyclosporine	2.00 ± 0.00	1.60 ± 0.50	1.80 ± 0.41	1.60 ± 0.50
Tacrolimus	1.70 ± 0.47	1.80 ± 0.41	1.70 ± 0.47	1.70 ± 0.47
P value	0.1	0.6	0.34	0.71

1st Follow-up (7th day): Scores at the first follow-up were significantly lower in the cyclosporine group when compared to the tacrolimus group and olopatadine group. *Reduced Redness*: All three groups experienced a significant reduction in redness after 7 days of treatment. *Mixed Results for Other Symptoms*: For itching, discharge, and photophobia, there were no significant differences between the groups. The substantial reduction in redness across all groups suggests that all three medications are effective in addressing this symptom. The lack of substantial differences in itching, discharge, and photophobia indicates that the choice of medication may not have a substantial impact on these symptoms after 7 days of treatment.

Table 3: 1st follow up symptom scores of (N= 60)

Group	Itching	Redness	Discharge	Photophobia
Olopatadine	1.60 ± 0.50	2.00 ± 0.00	1.80 ± 0.41	1.40 ± 0.50
Cyclosporine	1.40 ± 0.50	1.60 ± 0.50	1.80 ± 0.41	1.60 ± 0.50
Tacrolimus	1.50 ± 0.51	1.20 ± 0.41	1.60 ± 0.50	1.50 ± 0.51
P value	0.463	< 0.001*	0.266	0.463

*Significant

Table 4 presents the symptom scores for three groups after a 2nd follow-up. All three groups showed further improvement in symptoms at the 2nd follow-up compared to the baseline and 1st follow-up. Cyclosporine demonstrated the most significant improvement in all symptoms, with p-values less than 0.05 for all four categories. Both Olopatadine and Tacrolimus showed significant improvement in itching, photophobia, and redness. However, Tacrolimus was less effective in reducing discharge compared to Cyclosporine. Both Olopatadine and Tacrolimus are effective in reducing itching, photophobia, and redness, but Cyclosporine may offer a more significant benefit. While all medications showed improvement in discharge, Cyclosporine was more effective than Olopatadine and Tacrolimus.

Table 4: 2nd follow up symptom scores of (N= 60)

Group	Itching	Redness	Discharge	Photophobia
Olopatadine	1.40 ± 0.50	1.20 ± 0.41	1.20 ± 0.41	2.00 ± 0.00
Cyclosporine	0.80 ± 0.41	1.20 ± 0.77	0.80 ± 0.77	0.80 ± 0.41
Tacrolimus	1.00 ± 0.00	1.00 ± 0.50	1.00 ± 0.00	0.70 ± 0.47
p-value	< 0.001*	0.034*	0.050	< 0.001*

*Significant

Table 5 shows the 3rd Follow-up Symptom Scores. All three groups showed further improvement in symptoms at the 3rd follow-up compared to previous assessments. Cyclosporine demonstrated the most significant improvement in all symptoms, with p-values less than 0.05 for all four categories. Both Olopatadine and Tacrolimus showed significant improvement in itching, redness, and photophobia.

Table 5: 3rd follow up symptom scores of (N= 60)

Group	Itching	Redness	Discharge	Photophobia
Olopatadine	1.20 ± 0.41	1.40 ± 0.50	1.00 ± 0.00	1.20 ± 0.41
Cyclosporine	0.80 ± 0.50	1.00 ± 0.00	0.60 ± 0.50	0.60 ± 0.50
Tacrolimus	0.80 ± 0.47	0.80 ± 0.47	0.20 ± 0.41	0.30 ± 0.47
p-value	0.041*	0.016*	< 0.001*	< 0.001*

*Significant

Table 6 presents the sign scores for three groups of patients (Olopatadine, Cyclosporine, and Tacrolimus) after the 1st follow-up. The signs evaluated include papillae, hyperemia, H.T.S, infiltration, and PGTn. All three groups showed minimal changes in papillae, hyperemia, and PGTn at the 1st follow-up. Significant Improvement in H.T.S.

Table 6: 1st Follow up sign scores of (N= 60)

Group	Papillae	Hyperaemia	H.T.S	Infiltration	PGTn
Olopatadine	2.60± 0.50	2.60± 0.50	3.00± 0.00	2.80± 0.41	2.40± 0.50
Cyclosporine	2.60± 0.50	2.40± 0.50	2.60 ± 0.50	2.80 ± 0.41	2.60 ± 0.50
Tacrolimus	2.50± 0.51	2.50 ± 0.51	2.20± 0.41	2.60 ± 0.50	2.50 ± 0.51
p-value	0.260	0.463	< 0.001*	0.266	0.467

*Significant

Table 7 presents the sign scores for three groups of patients (Olopatadine, Cyclosporine, and Tacrolimus) after a 2nd follow-up. All three groups showed further improvement in signs at the 2nd follow-up compared to the 1st follow-up. Cyclosporine demonstrated significant improvement in all signs, with p-values less than 0.05 for all categories. Both Olopatadine and Tacrolimus showed significant improvement in most signs, with Tacrolimus being particularly effective in reducing H.T.S and PGTn.

Table 7: 2nd Follow up sign scores of (N= 60)

Group	Papillae	Congestion	H.T.S	Infiltration	PGTn
Olopatadine	2.60± 0.50	2.40± 0.50	2.20± 0.41	2.20± 0.41	3.00± 0.00
Cyclosporine	2.00± 0.00	1.80± 0.41	2.20± 0.77	1.80 ± 0.77	1.80 ± 0.41
Tacrolimus	2.00± 0.00	2.00± 0.00	1.00± 0.00	2.00 ± 0.00	1.70 ± 0.47
p-value	< 0.001	<0.001	<0.001	0.050	<0.001

*Significant

Table 8 presents the sign scores for three groups of patients (Olopatadine, Cyclosporine, and Tacrolimus) after a 3rd follow-up. All three groups showed further improvement in signs at the 3rd follow-up compared to previous assessments. Both Olopatadine and Tacrolimus showed significant improvement in most signs, with Tacrolimus being particularly effective in reducing H.T.S and PGTn.

Table 8: 3rd Follow up sign scores of (N= 60)

Group	Papillae	Congestion	H.T.S	Infiltration	PGTn
Olopatadine	2.00 ± 0.00	2.00 ± 0.00	2.40 ± 0.50	2.00 ± 0.00	2.20 ± 0.41
Cyclosporine	1.60 ± 0.50	1.40 ± 0.50	2.00 ± 0.00	1.60 ± 0.50	1.60 ± 0.50
Tacrolimus	0.70 ± 0.47	0.50 ± 0.51	0.80 ± 0.41	1.20 ± 0.41	1.10 ± 0.72
p-value	< 0.001	<0.001	<0.001	<0.001	< 0.001

*Significant

Intraocular Pressure: The baseline IOP in the cyclosporine group was 14.24 mm of Hg and tacrolimus in the group was 13.89 mm of Hg. The difference in IOP at baseline and on the 7th day was not statistically significant, but was statistically significant on the 14th, and 30th day. The change in IOP in the cyclosporine group from baseline to the last follow-up was not statistically different but in the tacrolimus group, it increased from13.89 mm of Hg to 18.40 mm of Hg on the 90th day and 15.27 on the 180th day which was statistically significant (ANOVA test P value < 0.05).

Discussion

The incidence of Vernal Keratoconjunctivitis in this study was found to be more common in males as compared to females (55 percent vs. 45 percent). Our cohort included an age range from 5 – 20 years. However, cases tended to cluster in the age range of 6 to 10 years in earlier studies. In a similar study by Sruthi et al. [8] in a cohort of 50 cases with vernal keratoconjunctivitis following 8 weeks of follow-up the mean reduction in the scoring of symptoms and signs with olopatadine was 60% compared with the results of this study which stood at 72% reduction of Toxic Anterior Segment Syndrome (TASS) and Total Ocular Symptom Score (TOSS) in 40 eyes of vernal keratoconjunctivitis following 12 weeks of treatment. McCabe et al.[9] compared the efficacy of bepotastine besilate 1.5% ophthalmic solution versus olopatadine hydrochloride 0.2% ophthalmic solution found olopatadine group had a significant reduction in ocular itching, a similar result showed in our study during initial follow-ups on 7 and 14 days. Saha et al. [10] in a similar study found that Tacrolimus versus Cyclosporine showed a 52% reduction in TASS and TOSS compared to our study's 49% reduction in the scoring system. Maharana et al. [11] in their study of vernal keratoconjunctivitis found the mean total subjective score at presentation was 13 ± 1.4, which reduced

to 11.2 ± 1.3 at 2 weeks of topical cyclosporine therapy. The mean total objective score at presentation was 9.4 ± 1.4 reduced to 8.0 ± 1.3 at 2 weeks of topical Cyclosporine therapy, similar results in our study mean TASS and TOSS are 15 ± 1.2 and 8.4 ± 2.0 reduced to 11.2 ± 0.5 and 10.2 ± 0.6 and 3 weeks.

Kheirkhah et al. [12] used topical tacrolimus ointment in 20 eyes of 10 patients Mean age of patients was 13±0.4 years, and symptoms showed dramatic relief. In addition, there was an improvement in objective signs including conjunctival hyperemia, conjunctival papillary hypertrophy, giant papillae, limbal hypertrophy, corneal punctate epithelial erosions, and corneal pannus; conjunctival hyperemia was the first sign to show improvement in 6 Months. Our study with a mean age of 10±0.4 years in 20 patients of 40 eyes showed improvement of TASS and TOSS after a period of 3 months. Kiliç A et al. [13] showed that topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis, in 20 patients of 20 eyes found a statistically significant decrease was observed in both sign and symptom scores ($p < 0.001$, for both) of eyes that received cyclosporine A, similar results observed in our study of 20 patients of 40 eyes for a period of 12 weeks.

Benaim et al. [14] used tacrolimus ointment for the management of VKC in 18 patients and the first follow-up visit occurred after an average of 40.3±10.3 days after initiation of treatment, score improved significantly for seven of the sub-scores ($P<0.05$) in our study of 40 eyes with mean age 10 ± 0.8 years in due of 30 days scores improved ($P<0.001$). Chatterjee et al. [15] in a prospective, comparative, placebo-controlled study carried out on 68 VKC patients, with 34 patients treated with topical Cyclosporine A 0.05% group significantly showed more reduction in symptom ($P < 0.0001$ in all follow-up visits) and sign ($P <0.0001$ in all follow-up visits), similar to observations of this study. Subedi et al. [16] Efficacy of Topical Cyclosporine 0.05% the Treatment of Vernal Keratoconjunctivitis Fifty patients of moderate, severe to very severe vernal keratoconjunctivitis were selected for the study in follow-up with symptom score reduction from median of mean of 2.4 to 0.6 ($p=0.00$) and a similar sign score reduction from 1.75 to 0.625 ($p=0.00$). There was gradually more improvement as therapy continued and the beneficial effects were maintained till the end point of the study at three months where a median mean symptom score was 0.4 ($p=0.00$) and a similar sign score of 0.375 ($p<0.002$) in our study. We saw that the 0.05 percent cyclosporine eye drops started working sooner after one week since the patients in that group were experiencing fewer symptoms. Between the second and fourth weeks, there was the greatest decline in overall scores. At the end of the first week, the conjunctival hyperemia also dramatically decreased when compared to the olopatadine group. The maximum decrease in the cumulative scores was observed by the end of 4 weeks or 30 days. Cyclosporine inhibits antigen-dependent T-cell activation. It also has a direct inhibitory action on eosinophils and mast cell activation, it reduces the eosinophil recruitment in conjunctiva by reducing IL 5 levels.

When compared to the cyclosporine, and tacrolimus group, patients on olopatadine experienced fewer foreign bodies, perhaps because of its positive effects on tear film. According to impression cytology results from research, cyclosporine has been reported to enhance goblet cell density. However, the patients using cyclosporine experienced more itching at days 14 and 30 than the individuals taking olopatadine, most likely as a result of the latter's stronger antihistaminic action. The most common side effect reported by the research population was a burning or stinging feeling after receiving the medication, however, it was not severe enough to cause the medication to be discontinued. There was no effect on intraocular pressure in patients taking Cyclosporine eye drops, contrary to what has been seen in numerous other trials. The baseline intraocular pressure was 14.24 mm Hg, while the intraocular pressure was 14.41 mm Hg even after three months of use. We saw that Olopatadine had a maximal reduction in symptoms between the second and fourth weeks. Throughout the research period, no recurrences were discovered. The analysis of all indicators revealed that, up until the second week of follow-up, the eyes receiving olopatadine consistently scored much higher than those in the cyclosporine, tacrolimus group. The scores between the two groups were equivalent starting in the fourth week. In our investigation, the effects of both medicines were comparable after three months of treatment. All these three groups were also treated along with mast cell inhibitors (sodium cromoglycate), as a common drug in this trial.

Conclusion

Within the limitations of the current study, we found Olopatadine 0.1% eye drops had faster onset of action observable at 1 week. The maximum effect was seen by the end of 4 weeks, after this the effect seem to plateau off. Cyclosporine 0.05%, tacrolimus 0.03% eye ointment had a maximum effect by the end of 3 months. The analysis of total showed that olopatadine has a faster onset of action demonstrated by lower scores in the first 2 weeks, later three drugs Olopatadine, Cyclosporine and Tacrolimus had a similar efficacy. Our study suggests that olopatadine has greater efficacy,

safety can be used as first line of drug when compare with tacrolimus and cyclosporine. Tacrolimus and cyclosporine have equal potentials to be used as second line drugs in vernal keratoconjunctivitis.

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