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Study of Cost-effectiveness and Safety of 0.2% Olopatadine in Comparison with Combination of 0.1% Olopatadine and 0.4% Ketorolac Eye Drops in Vernal Keratoconjunctivitis among Rural Population

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Abstract

The study aimed to compare the cost-effectiveness and safety of 0.2% Olopatadine with a combination of 0.1% Olopatadine and 0.4% Ketorolac eye drops in Vernal keratoconjunctivitis (VKC) among the rural population. This was a randomized, open-label, prospective study conducted on 129 patients who were diagnosed with VKC. All the patients were randomly allotted to 2 treatment groups. Group 1 received 0.2% Olopatadine eye drops/single drops/three times a day. Group 2 treated with a combination of 0.1% Olopatadine and 0.4% Ketorolac eye drops/single drops/two times a day for four weeks. The patients were advised to follow up during the study period in the second and fourth weeks. During the follow-ups, post-intervention cure rate, adverse drug reactions (ADR) monitoring, and cost-effectiveness of both the drugs were evaluated. A statistically significant ($p<0.05$) reduction of clinical symptoms was observed in both groups after four weeks of treatment. In 0.2% Olopatadine intervention, 9 cases of ADR were reported out of the 62 patients. Furthermore, treatment with a combination of 0.1% Olopatadine and 0.4% Ketorolac has shown 12 cases from 58 having ADR. Our study revealed that the 0.2% Olopatadine eye drops were a comparatively affordable choice since the cost was less. Therefore, 0.2% Olopatadine is considered a better drug choice in the given scenario of the rural population regarding their safety and cost-effectiveness.

Keywords: Vernal Keratoconjunctivitis; Olopatadine; Ketorolac

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Introduction

Vernal keratoconjunctivitis (VKC) is a bilateral allergic inflammation of the conjunctiva, which is interstitial and recurrent in occurrence and is self-limiting. It has a seasonal incidence, which is referred to as spring cataracts.[1] Incidence is more common in the ages 5 to 25 years, with an onset between 10-12 years. It is mainly observed in geographical locations with hot, arid environments, such as the Mediterranean basin, West Africa, and the Indian subcontinent.[2]

The pathogenesis of VKC is that it is a Type 1 Immunoglobulin-E (IgE)-mediated hypersensitivity reaction involving infiltration of the conjunctival epithelium and corneal stroma with mast cells, eosinophils, lymphocytes, dendritic cells, basophils, and macrophages.[3] The characteristic symptoms of VKC are severe itching, photophobia, foreign body sensation, mucous discharge, blepharospasm, and blurring of vision. The important features of VKC are the appearance of papillary hypertrophy of the palpebral and the limbal conjunctiva, horner Trantas dots, limbal thickening, bulbar conjunctival pigmentation, and mucous discharge.[4]

Currently, there is no defined gold-standard treatment algorithm for VKC, but many other treatment options are available.[5] The first-line pharmacotherapy for VKC is a topical treatment, and there is considerable therapeutic overlap with other forms of allergic conjunctivitis.[6] Treatment should be tailored to the individual, which is done by considering the duration and frequency of symptoms along with the severity of corneal involvement.[7]

In mild to moderate forms of VKC, mast cell stabilizers and antihistamines have been proven to be effective for the treatment. Furthermore, topical steroids have been considered the medication of choice for reducing conjunctival and corneal inflammation in severe cases.[8] Vasoconstrictors, antihistamines, mast cell stabilizers, 'dual-acting' agents (with antihistaminic and mast cell stabilizing properties), non-steroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive drugs are the currently available group of drugs for the treatment of VKC.[9]

Olopatadine is a histamine H1 receptor antagonist with broad pharmacological effects and is widely used in allergic conditions of the eye.[10] It inhibits tachykinin release, chemical mediators, and eosinophil infiltration suppressor properties.[11] Ketorolac, an anti-inflammatory drug, helps convert arachidonic acid to prostaglandins by blocking the cyclo-oxygenase enzyme that catalyzes the reaction. Hence, the mechanism of action is to stop the release of substances that cause allergic symptoms and inflammation.[12] It is also a drug of choice for various other ocular inflammatory conditions and has also been effective in controlling postoperative inflammation following cataract surgery.[13]

Although the drugs like Olopatadine and Ketorolac have been preferred for treating VKC, none of the studies have compared the affordability and side effects. We have explored the cost of the treatment, which plays an important role at an individual level, and the health care system of India. Therefore, the present study was designed to compare the cost-effectiveness, safety, and efficacy of 0.2% Olopatadine and combination medication of 0.1% Olopatadine and 0.4% Ketorolac in treating VKC.

Methods

A prospective, open-label, randomized, comparative study was performed on VKC patients. The permission and approval from the Institutional Ethics Committee were taken

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before the start of the study. The study was conducted from 1st June to 31st July 2021. The patients who visited the Out Patient Department (OPD) of Ophthalmology, RVM Institute of Medical Sciences and Research Center, Laxmakkapally Village, Mulugu Mandal, Siddipet District in Telangana State, India, and were diagnosed with VKC were enrolled in the study.

A total of 129 patients (86 male and 43 female) who were clinically diagnosed with VKC were incorporated into the study, and they were randomly assigned to 2 treated groups. Group 1 were treated with 0.2% Olopatadine single eye drop three times a day for four weeks. Group 2 were treated with a combination of 0.1% Olopatadine and 0.4% Ketorolac single eye drops two times a day for four weeks. After the initial treatment, patients were advised to follow up during the second and fourth weeks of the study period.

Inclusion Criteria

1. Patients within the age group of 5 to 60 years of either sex who were clinically diagnosed with Grade 0 to grade 3 VKC.
2. Patients who had submitted a written informed consent form and were willing to participate.

Exclusion Criteria

1. Patients who have corneal ulcers or who have grade 4 of VKC
2. Have history of diabetic retinopathy
3. Have history of ocular herpes infection or any other ocular infection
4. Undergone ocular surgery within 8 weeks before commencing study
5. Currently or earlier use of systemic or topical steroids, anticholinergics, immunosuppressants, antihistamines, and NSAIDs.
6. Pregnant and lactating women

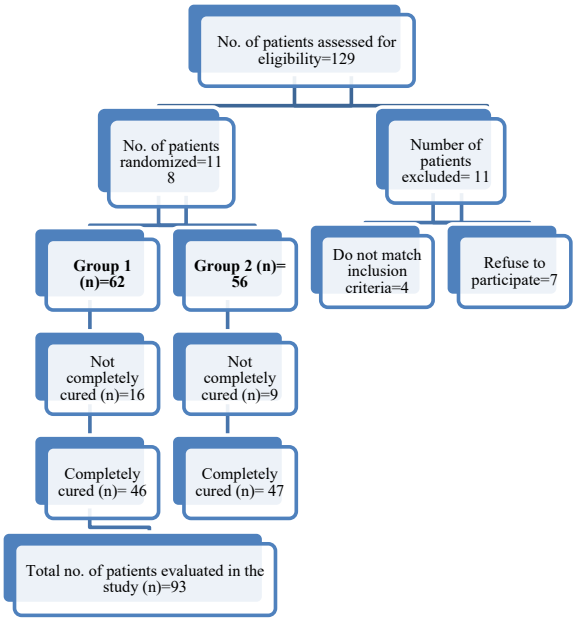

Figure 1. Study Design

Interventions

1. 0.2% Olopatadine eye drops /single drops/ three times a day for 4 weeks. The cost of eye drops containing 5 mL is INR 140.
2. Combination of 0.1% Olopatadine and 0.4% Ketorolac eye drops/single drop/two times in a day for 4 weeks. The cost of eye drops containing 5 mL is INR 198.

Clinical Grading of VKC[7]

The severity of lesions is clinically graded on a scale of 0 to 4

- Quiescent (Grade 0): Absence of Symptoms
- Mild (Grade1): Presence of Symptoms with no corneal involvement
- Moderate (Grade 2): Presence of Symptoms + Photophobia with no corneal involvement
- Severe (Grade 3): Presence of symptoms + Photophobia, Mild to moderate superficial punctate keratopathy / corneal involvement
- Very severe (Grade 4): Presence of symptoms + Photophobia + Diffuse superficial punctuate keratopathy/ corneal ulcer

Table 1. Clinical Grading of VKC

Clinical Grade of VKC	Number of Cases	Percentage (%)
Quiescent (Grade 0) Absence of Symptoms	18	13.95
Mild (Grade 1) Presence of Symptoms with no corneal involvement	24	18.60
Moderate (Grade 2) Presence of Symptoms + Photophobia with no corneal involvement	75	58.14
Severe (Grade 3) Presence of symptoms + photophobia, Mild to moderate superficial punctate keratopathy / corneal involvement	12	9.30
Very Severe (Grade 4) Presence of symptoms + photophobia + diffuse superficial punctate keratopathy/ corneal ulcer	0	0

Patients Assesment

All patients were assessed based on their clinical signs and symptoms, which are classified into four grades, i.e., grade 0, 1, 2 and 3. Following the grading, group 1 involved 62 patients treated by 0.2% Olopatadine, and 56 patients treated by combined medication of 0.1% Olopatadine and 0.4% Ketorolac eye drops. All patients were advised to revisit the hospital at 2 and 4 weeks for a follow-up, to evaluate the signs and symptoms, and to record the medication's ADR if any. Few patients got cured by the end of 2nd week, while the others who still have symptoms must continue the medication until they are assessed again in the 4th week.

Statistical Analysis

The results were analyzed by using the Chi-square test. The Statistical Package for the Social Sciences (SPPS) statistics 20 software was used for the statistical analysis. The significance level was assumed as $p<0.05$.

Results and Discussion

In the present study, 129 patients were included as participants and randomly assigned into two treatment groups. However, 11 patients dropped out before the start of the study. Most of the patient's ages ranged from 21 to 60 years (53.49%), and the following were 16 to 20 years (42.64%), 6 to 11 years (3 patients), and 11 to 15 years (2 patients). Moreover, all patients were clinically graded based on the symptoms of VKC. The grading of VKC is shown in Table 1.

In assessment of clinical symptoms, the ocular symptoms like itching, discomfort, foreign body sensation, stinging, photophobia, and watering were examined by taking the help of an ophthalmologist. All patients have

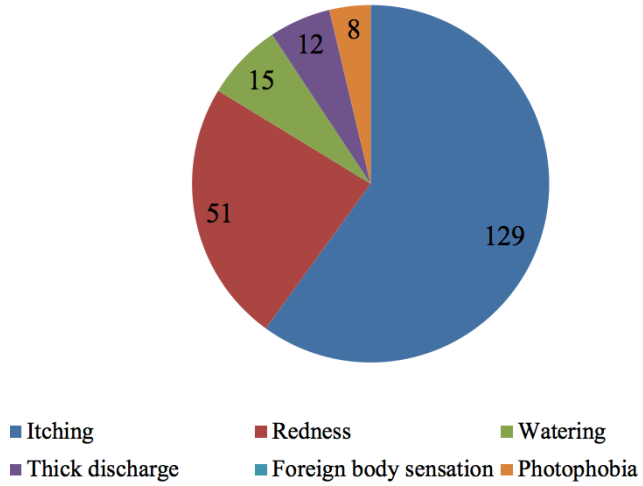

Figure 1. Scoring of VKC Symptoms

reported itching (100%), whereas 39.5% (51) complained of redness, 11.63% (15) of watering, 9.52% (12) with thick discharge, and 6.20% (8) with photophobia. None of the patients reported foreign body sensations in the eye (Figure 1).

All the patients in treatment groups were assessed during each follow-up for the ocular signs and symptoms at various time intervals, such as visit 1 (at baseline), visit 2 (2nd week), and visit 3 (4th week). The ocular signs of VKC were conjunctival congestion, chemosis, and lid edema examined using a Slit lamp biomicroscope that was graded according to the severity (grade 0-absent, grade1-mild, grade 2-moderate, grade 3 severe) (Table 2).

At the end of the 2nd week, group 1 showed improvement in clinical symptoms in patients (grade 0= 4 patients; grade 1= 4 patients; grade 2= 9 patients). Meanwhile, two weeks of treatment was inadequate to treat the grade 3 of VKC completely; hence it requires continuation of therapy beyond this duration. Similarly, group 2 also showed reduced clinical symptoms (grade 0= 5 patients; grade 1= 4 patients; grade 2= 10 patients). In contrast, none of the patients with grade 3 improved.

At the end of the 4th week, most patients appeared to be completely treated in both groups. Group 1 showed a number of patients that were cured; grade 0 (6 patients), grade 1 (7 patients), grade 2 (14 patients), and only 2 patients with grade 3 of VKC have shown to be free from the signs and symptoms. Furthermore, the number of patients shown to be cured with 0.1% Olopatadine and 0.4% Ketorolac eye drops is shown in Table 3.

The present study findings revealed that the drugs used were equally effective in treating VKC in the rural population. A statistically significant ($p<0.05$) reduction of clinical symptoms was observed in both groups after four weeks of treatment.[14] Patients were examined for the assessment of clinical symptoms during each visit. Most patients have shown clinical improvement at the end of 4th week. No significant difference was observed between the two treatment groups regarding the efficacy. However, they needed to continue the medication beyond four weeks to cure the disease completely.[15]

In 0.2% olopatadine intervention, 9 cases of ADR were reported. Among these, 6 had mild burning sensation while the other had mild

Table 2. Number of Patients Improvement in Clinical grades of VKC at Each Revisit

Clinical grades of VKC	Group-1 0.2% Olopatadine			Group-2 0.1% Olopatadine and 0.4% Ketorolac		
	Baseline	2nd week	4th week	Baseline	2nd week	4th week
Grade 0	10	04	06	11	05	06
Grade 1	11	04	07	12	04	05
Grade 2	36	09	14	27	10	14
Grade 3	05	00	02	06	00	03

Note: Each resulting value indicates number of patients

Table 3. Assessment of Improvement in the Treatment

Treatment Groups	Cured	Not Cured	Chi- Square	p value*
Group 1 (62)	46	16		
			1.67	0.1963_{NS}
Group 2 (56)	47	9		

* P<0.05 there is an insignificant association between group 1 and group 2.
NS: Non-significant | S: Significant
Note: Each resulting value indicates number of patients

Table 4.Adverse Effects Reported during the Study

Treatment Groups	Group 1	Group 2	Chi- Square	p value*
Burning	6	8		
			0.06	0.8058_{NS}
Mild Eye Pain	3	5		

eye pain (3 patients). However, these adverse effects subsided within 4-5 minutes without medication to treat side effects. In contrast, other studies have reported blurring of vision and dryness of the eye upon administering olopatadine eye drops.[16] (Table 4)

Furthermore, the other group treated with a combination medication of 0.1% Olopatadine and 0.4% Ketorolac has shown 12 cases from a population of 58 having adverse drug effects. Out of these 12 cases, 8 patients suffered from mild burning sensation while the rest 5 had mild eye pain after administering the eye drops. Although a previous study of the combination of Olopatadine and Ketorolac did not exhibit any side effects, our findings revealed milder side effects.[17] Like the other treatment group, the intensity of side effects had reduced within 6-8 minutes. ADR in 0.2% Olopatadine were slightly less compared to combination medication of 0.1% Olopatadine and 0.4% Ketorolac. (Table 4)

Our study showed that patients receiving 0.2% Olopatadine eye drops was a comparatively affordable choice since the 556 pricer was less.[21] However, patients in group 2 receiving

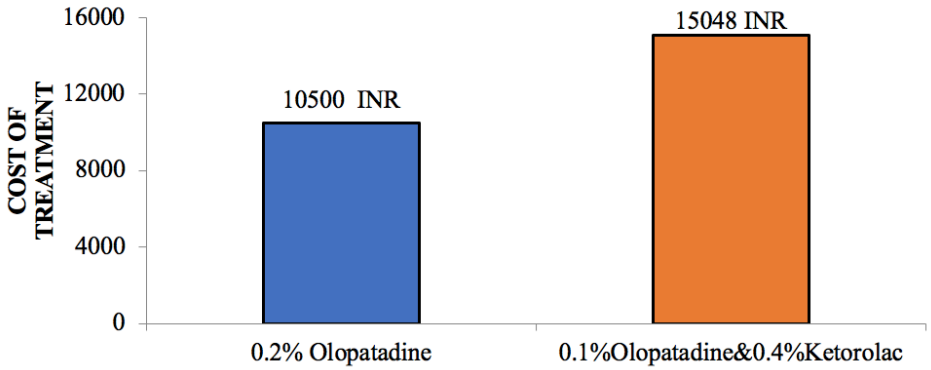

Figure 2. Cost-effective Analysis of the Total Treatment of VKC

combined medication of 0.1% Olopatadine and 0.4% Ketorolac eye drops were expensive compared to group 1 treatment. The cost of a 5 mL container of 0.2% Olopatadine eye drops was INR 140; the cost of combined medication, i.e., 0.1% Olopatadine and 4% Ketorolac eye drops, was INR 198 for a 5 mL container. These medications were continued for two weeks and four weeks. (Figure 2)

The total expenditure for group 1, patients were found to be INR 10,500, whereas for group 2 expenditure was INR 15,048. There were 11 dropouts (7 from group 1 and 4 from group 2) during the study period. Out of the 7 patients, 2 patients had discontinued due to the cost factor in group 1. At the same time, it was noticed that there were 3 dropouts out of 4 patients due to the financial constraints in group 2. To conclude, the ratio of dropouts in group 2 was comparatively high compared to group 1 patients regarding economic reasons. This study did not analyze the gender-wise differences in treatment groups.

This present study addressed the cost-effective analysis in which only direct medication cost was considered. It has been done by calculating the total expenditure incurred on medications for the treatment of VKC till cured. Socioeconomic reasons are the main drawback to acquiring effective therapy in a poor-income rural population.[18,19] Our study also focused on knowing the patients' financial burden in both treatment groups. It reveals direct medical expenditure and indirect costs resulting from their multimorbidity.[20]

Conclusion

Although 0.2% Olopatadine was as effective as a combination of 0.1% Olopatadine and 0.4% Ketorolac, 0.2% Olopatadine eye drops medication is considered a better drug choice in the treatment of VKC in rural population about their safety and cost-effectiveness.

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Conflict of Interest
None declared

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