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To compare the safety and efficacy of Azelastine hydrochloride 0.05% ophthalmic solution with olopatadine 0.1% ophthalmic solution in patients with vernal keratoconjunctivitis in a tertiary care hospital

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Abstract:
INTRODUCTION*: Vernal conjunctivitis comprises 0.5% of allergic eye diseases. The study is made to collate the effectiveness of drugs by following the patient to observe the reduction in signs and symptoms.*
OBJECTIVES*: The objective of the study is to compare the effectiveness and safety of olopatadine 0.1% ophthalmic drops with azelastine hydrochloride 0.05% ophthalmic drops in patients with vernal keratoconjunctivitis (VKC).*
MATERIALS AND METHODS*: A randomized, comparative study conducted in patients attending the OPD of Viswabharathi medical college,Penchikalapadu, kurnool,Andhra Pradesh.The study included 50 patients who has attended our OPD diagnosed with VKC, of which odd number to Group A and even numbers to Group B with 25 each were given olopatadine 0.1% ophthalmic drops and azelastine hydrochloride 0.05% ophthalmic drops, respectively, two times a day for 8 weeks. The reduction in signs and symptoms in both groups was compared. Absolute eosinophil count was evaluated for all the patients before and after .The observations and results were tabulated accordingly, and data were analyzed using the SPSS version. The unpaired t-test is used as the test of significance in between the two groups. P value is statistically significant when it is < 0.05.*
RESULTS*: Overall, 50 cases were included in the study, 72% of total patients were in the age group of 5–10 years, and 28% were in the age group of 11–15 years. There were 39 males and 11 females. After 8 weeks of follow-up, the mean reduction in making the scores of symptoms and signs provided better and quicker relief of watering, ocular discomfort, and conjunctival hyperemia with azelastine hydrochloride 0.05% eye drops. Olopatadine 0.1% eye drops provided faster improvement in papillary hypertrophy. Both drugs were equally effective in reducing itching. Laboratory findings of absolute eosinophil count had no statistical significance in between the two groups.*
CONCLUSIONS: *In this study, based on the evaluation of therapeutic performance, azelastine eye drops proved quicker relief to the symptoms and signs compared to olopatadine eye drops but this was not statistically significant.*
KEYWORDS: *Azelastine, olopatadine, Absolute eosinophil count, Allergy, Vernal keratoconjunctivitis.*

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I. Introduction

Allergies are the fifth leading cause of the world's chronic illnesses, affecting 40% of the population [1]Globally in the last 10years there is a drastic increase of allergic diseases. The occurrence of allergic diseases among children is rising moderately in between 0.3% and 20.5%.The incidence of allergic conjunctivitis is more in kurnool district compared to other districts in AP because of the fine dust particles.

There are so many causative factors such as genetics, pets, air pollution, and early childhood exposure being the reasons for this increase.[2] Among the causes of ocular morbidity in India, allergic conjunctivitis is at the second position and involves about 15%–20% of people attending ophthalmology clinic. School absenteeism in children is common because of its distressing symptoms.[3] Allergic conjunctivitis includes persistent allergic conjunctivitis, seasonal allergic conjunctivitis (SAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis. SAC is about 25%–50% of cases.[4] VKC constitutes 0.5% of allergic diseases in eye.[5] VKC occurs most frequently in the male population belongs to warm, dry, subtropical areas such as Japan, India, Thailand, South America, Mediterranean, Central, Middle East, and Western Africa. Most

common VKC seen in dark-skinned African and Indian population is limbal form. The prevalence for Western Europe was 3.2 in 10,000, whereas a higher prevalence ranging from 2.4 to 27.8 in 10,000 was seen in Italy, a country with a Mediterranean climate.[6] VKC is a persistent, bilateral, occasionally asymmetric, cyclically worsened, allergic ocular surface inflammation that includes bulbar and/or tarsal conjunctiva.

VKC is characterized by giant papillae seen in both upper tarsal conjunctiva or at the limbus.[7] It is an IgE- and T cell-mediated condition, progressing to a chronic inflammatory conjunctival allergic response involving eosinophil,lymphocyte, and structural cell activation. New antihistamines that combine stabilizing properties of the mast cells with antagonism to histamine receptors such as olopatadine, bepotastine, alcaftadine, azelastine, epinastine, and ketotifen are currently available.

Olopatadine hydrochloride is a second-generation antihistamine (as well as anticholinergic and mast cell stabilizer) that exerts comprehensive pharmacological actions such as histamine H1 receptor antagonism, chemical mediator suppression, tachykinin release inhibitory action, and eosinophil infiltrative suppression.[8,9] During 1996 and 2002, olopatadine ophthalmic solution was approved for the treatment of SAC and chronic allergic conjunctivitis in the USA and the European Union, respectively. In India, olopatadine 0.1% ophthalmic drops with the trade name of Pataday or Olopat, which is used for once or twice-daily regimen in severe cases of allergic conjunctival diseases.[10] In animal studies and clinical trials, olopatadine ophthalmic solution proved to be a safe and efficacious medicament in SAC and perennial allergic conjunctivitis.
Drug successfully alleviates itching, redness, edema, watering, and nasal allergic symptoms.[11]

SIDE EFFECTS:
Blurred vision
Burning ,dryness, stinging of the eye Eye redness, irritation or pain Swelling of eyelids ,lips, face or feet Trouble breathing .
In rats and rabbits, olopatadine was established to be not having any teratogenic potential. This drug should be used in pregnant women cautiously, considering risk–benefit ratio, as there are no abundant and controlled trials in pregnant women. Olopatadine was detected after oral administration in nursing rat milk. There is no evidence for sufficient systemic absorption with topical ocular administration, so caution should be exercised. In patients below the age of 2 years, safety and efficacy have not yet been established.
Azelastine is primarily a selective antagonist of histamine H1-receptors, with a lesser affinity for H2-receptors, used for the symptomatic treatment of allergies[12]. Histamine H1-receptors are G-protein-coupled receptors with 7 transmembrane spanning domains[13]that are found on nerve endings, smooth muscle cells, and glandular cells.Following allergen exposure in sensitized individuals, IgE-receptor cross-linking on mast cells results in the release of histamine, which binds to H1-receptors and contributes to typical allergic symptoms such as itching, sneezing, and congestion[14]. Though its primary mode of action is thought to be via H1-receptor antagonism, azelastine (like other second-generation antihistamines) appears to affect other mediators of allergic symptomatology. Azelastine has mast cell-stabilizing properties that prevent the release of interleukin-6, tryptase, histamine, and TNF-alpha from mast cells, and has been shown to reduce mediators of mast cell degranulation such as leukotrienes in the nasal lavage of patients with rhinitis,as well as inhibiting their production and release from eosinophils (potentially via inhibition of phospholipase A2 and leukotriene C4 synthase). Additionally, patients using oral azelastine were observed to have significantly reduced concentrations of substance P and bradykinin in nasal secretions2, both of which may play a role in nasal itching and sneezing in patients with allergic rhinitis.

Azelastine side effects
- fever.
- bitter taste in your mouth.
- nose pain or discomfort.
- nosebleeds.
- headache.
- sneezing.
- drowsiness.
- upper respiratory tract infection.

Being a chronic condition, prudent use of medicament is needed because drug treatment is prolonged and frequent. There were only minimal research studies done in VKC by comparing efficacy and safety of 0.1% olopatadine and Azelastine 0.05% in India. Our study is intended to compare the effectiveness and safety of olopatadine 0.1% ophthalmic drops and Azelastine 0.05% ophthalmic drops with BD administration to relieve the symptoms of VKC.

II. Materials and Methods

The study was done in the Outpatient Department of Ophthalmology in Viswabharathi medical college,Penchikalapadu, Andhra Pradesh for duration of 6months from March 2021 to August 2021. Institutional ethics committee approved the study . For participants above 18 years of age, written informed consent was taken in an authorized format in local language after describing all study procedures and course of action. For participants less than 18 years of age, their parents or guardians were explained the procedures, and written informed consent was attained. For illiterate people, left thumb mark was taken. After acquiring informed consent from all participants, the analytical details of 59 patients including past and present history and clinical and slit-lamp examination of eyes performed were entered. Following the screening of 59 patients, 50 patients were enlisted in the study who fit into inclusion and exclusion criteria by dividing odd numbers into GROUP A and even numbers GROUP B with 25 patients each.Absolute Eosinophil Count was evaluated for all the patients before and after the study.

Inclusion criteria 1. Patients with the age group of 5–25 years attending our OPD. 2. Patients who can adherent to follow-up schedule.

Exclusion criteria 1. Age less than 5 years 2. Contact lens wearer during the period of study 3. Patients with active ocular infections and pathological conditions 4. Patients with ocular disorders such as pterygium, dry eyes, and ophthalmic conditions such as uveitis or glaucoma 5. History of ocular surgery in 3 months.

By simple randomization (odd/even number) method, registered patients were grouped into A and B. Group A and GroupB were given olopatadine 0.1% ophthalmic drops and Azelastine 0.05% ophthalmic drops, respectively, administered one drop in the affected eye twice daily for 8 weeks. The ocular signs such as conjunctival hyperemia and papillary hypertrophy were evaluated. The gradings were given according to the severity of signs (absence of signs as grade 0, mild signs as grade 1, moderate signs as grade 2, and severe signs as grade 3). Ocular symptoms such as itching, discomfort, and watering were estimated by discussing with the patients, and grading was given depending on severity (absence of signs as grade 0, mild signs as grade 1, moderate signs as grade 2, and severe signs as grade 3). During the study, none of the patients were lost to follow-up.

Statistical analysis

The observations and results were tabulated accordingly and data were analyzed using the SPSS Version 16. The unpaired t-test is used as the test of significance in between two groups. P value is statistically significant when it is less than 0.05.

III. Results

The age and gender distribution of the study population is shown in Figure 1.

Among 50 patients, 36 patients (72%) are in the range of 5–10 years, and 14 patients (28%) are in the range of 11–15 years. Of 50 patients included in the study, 39 (78%) patients were male and 11 (22%) patients were female.

Table 1 shows mean itching scores during each visit. The itching scores among the treatment groups with all follow-ups compared with baseline are not statistically significant ($P > 0.05$). Table 2 shows the mean ocular discomfort scores during each visit. At the 1st, 2nd, and 3rd follow-up, there is statistical significance in ocular discomfort scores with Group B ($P < 0.05$). Table 3 shows the mean watering scores during each visit. In Group B, during the 2nd, 3rd, and 4th follow-ups, there is statistical significance in watering scores ($P < 0.05$).

Table 4 shows the mean conjunctival hyperemia scores during each visit. During 1st, 2nd, and 3rd follow-ups, there is statistical significance in conjunctival hyperemia scores with Group B ($P < 0.05$).

Table 5 shows the mean papillary hypertrophy scores during each visit. During the 2nd, 3rd, and 4th visits, there is statistical significance in papillary hypertrophy scores with Group A ($P < 0.05$).

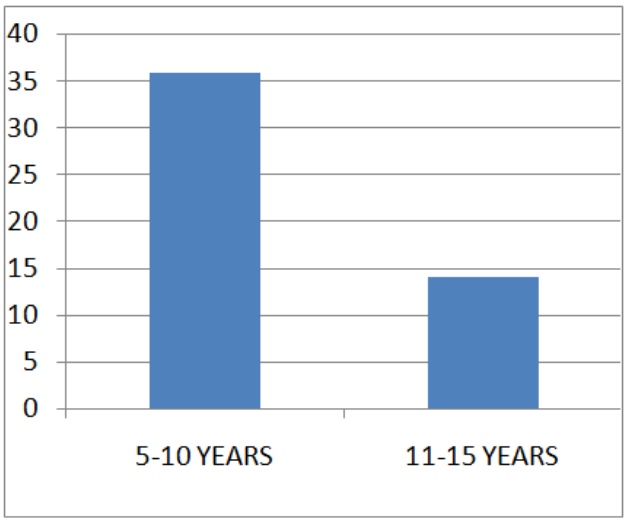
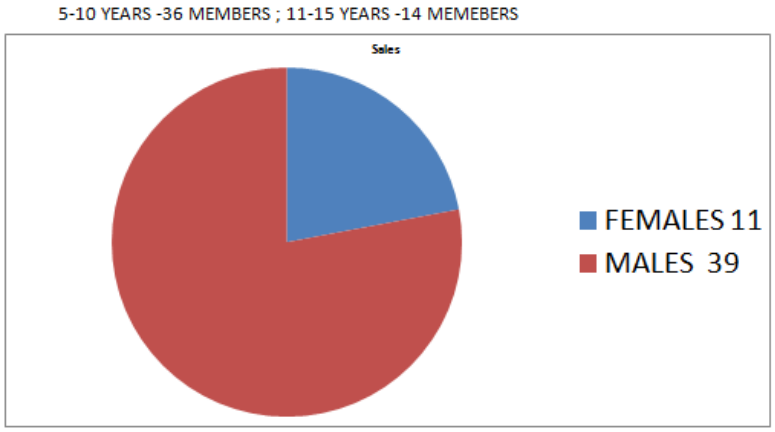


FIG 1: AGE AND GENDER DISTRIBUTION



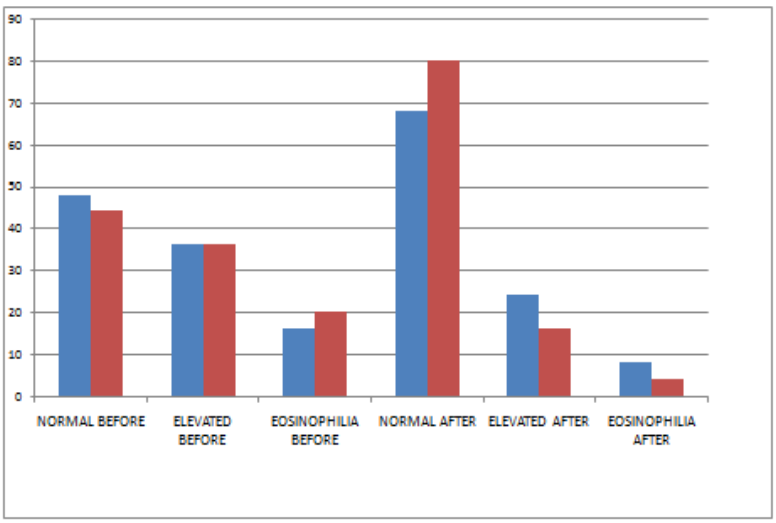


Figure 2 shows the absolute eosinophil count (AEC) levels between treatment groups.

Before and after the treatment, there is no statistical significance in reduction of AEC levels. Very minimal patients complained of adverse events during the study. In Group A, two patients had headache, and in Group B, three patients encountered headache and one had sinusitis.

Table 1: Mean itching scores during each visit Itching scores

Itching scores	Group A Olopatadine μ SD		Group B Azelastine μ SD		Unpaired t-test significance level
Preintervention	2.88	0.332	2.88	0.332	1.000
1st week (1st visit)	2.84	0.374	2.84	0.374	1.000
3rd week (2nd visit)	2.08	0.4	2.00	0.289	0.421
5th week (3rd visit)	1.16	0.374	1.08	0.277	0.394
8th week (4th visit)	0.32	0.690	0.12	0.332	0.198

SD=Standard deviation

Table 2: Mean ocular discomfort scores during each visit

Ocular discomfort scores	Group A Olopatadine μ	SD	Group B Azelastine μ	SD	Unpairedt-test significance
Preintervention	2.88	0.332	2.92	0.277	0.646
1st week (1st visit)	2.76	0.436	2.08	0.277	0.000*
3rd week (2nd visit)	2.00	0.408	1.20	0.408	0.000*
5th week (3rd visit)	1.20	0.408	0.40	0.500	0.000*
8th week (4th visit)	0.32	0.476	0.12	0.332	0.091 *

Significant if P<0.05. SD=Standard deviation

Table 3: Mean watering scores during each visit

Watering scores	Group A Olopatadine μ	SD	Group B Azelastine μ SD		Unpairedt-test significance
Preintervention	2.92	0.277	2.92	0.277	1.000
1st week (1st visit)	2.80	0.408	2.00	0.000	0.000*
3rd week (2nd visit)	2.00	0.000	1.04	0.200	0.000*
5th week (3rd visit)	1.08	0.277	0.28	0.458	0.000*
8th week (4th visit)	0.36	0.490	0.08	0.277	0.016*

Significant if P<0.05. SD=Standard deviation

Table 4: Mean conjunctival hyperaemia scores during each visit

Conjunctival hyperaemia scores	Group A Olopatadine μ	SD	Group B Azelastine μ	SD	Unpairedt-test significance
Preintervention	2.96	0.200	2.96	0.200	1.000
1st week (1st visit)	2.76	0.436	1.96	0.200	0.000*
3rd week (2nd visit)	2.00	0.500	1.08	0.277	0.000*
5th week (3rd visit)	1.04	0.539	0.28	0.542	0.000*
8th week (4th visit)	0.24	0.436	0.16	0.374	0.490 *

Significant if P<0.05. SD=Standard deviation

Table 5: Mean papillary hypertrophy scores during each visit

Papillary hypertrophy scores	Group A Olopatadine μ	SD	Group B Azelastine μ	SD	Unpaired t-test significance
Preintervention	2.68	0.476	2.60	0.500	0.565
1st week (1st visit)	2.44	0.507	2.60	0.500	0.267
3rd week (2nd visit)	1.08	0.277	1.64	0.490	0.000*
5th week (3rd visit)	0.08	0.277	1.08	0.277	0.000*
8th week (4th visit)	0.00	0.000	0.40	0.500	0.000*

*Significant if P<0.05. SD=Standard deviation

IV. Discussion

VKC is a bilateral, long-term, cyclical allergic ocular inflammation which affects bulbar or tarsal conjunctiva. Children and young adults with an atopic history are more prone to VKC.[15] It commonly affects people with history of allergic conditions such as seasonal allergy, bronchial asthma, or eczema.[16] VKC has a wide geographic distribution. Young males are primarily affected in the dry and hot climates.[17] It is prevailing in Mediterranean temperate zones, Western Africa, Middle East, Japan, Indian subcontinent, and South America.[18] 49% of VKC patients show familial history of allergic conditions such as asthma, rhinitis, eczema, urticaria, and multiple atopic diseases.[19] Among them, asthma is the most frequently seen allergic disorder in VKC.[20] Other inflammatory diseases, such as psoriasis and thyroiditis, may be associated with a family history.[21,22] It has a major impact on day-to-day life and performance in school-going children. The present research was conducted in an attempt to determine which agent would help regulate the symptoms of VKC in our patient population. It is very important to understand the fundamental mechanisms in allergy and selection of the right medication. Olopatadine found to be effective in VKC.[23,24] Azelastine is a less commonly used drug.[25] In this review, we seek to assess the two medications and evaluate their effectiveness in treating Spring Catarrh. For this study, different signs and symptoms of VKC were used as criteria for assessment.[26] This is a randomized study in which the patients diagnosed with VKC who attended ophthalmic outpatient department divided into Group A and Group B. Group A patients were given olopatadine 0.1% twice a day for 8 weeks, and Group B patients were given Azelastine hydrochloride twice a day for 8 weeks. Olopatadine which is commonly used compared with Azelastine for efficacy, safety, and tolerability. In the present study, out of 59 patients who were screened, 50 patients were included in the study, randomized to Group A and Group B, each including 25. During the study period, none of the patients have not missed their follow-ups. A study between 0.1% olopatadine, 0.05% Azelastine , and 0.25% alcaftadine worked similarly in relief of mild-to-moderate allergic conjunctivitis symptoms, after 1 week of treatment.

For allergic conjunctivitis, 0.2% olopatadine and 0.05% Azelastine eye drops are safe and well-tolerated topical medications.[27,28] In a study done by Hida et al., a comparison between 0.1% olopatadine hydrochloride and 0.025% ketotifen fumarate in VKC between the baseline and the 2nd visit, olopatadine treatment resulted in decreased burning, but ketotifen was slightly better after 4th visit.

Papillae and Horner-trans dots in both classes were not significantly different. In our study, during initial follow-ups on days 7, 21, and 35. Azelastine showed significant reduction in symptoms such as ocular discomfort, watering, and capillary hyperemia, suggesting the faster onset of action. Olopatadine showed marked reduction in papillary hypertrophy. After 8 weeks of treatment, both drugs were uniformly efficacious in reducing signs and symptoms of VKC. Studies with different attributes such as larger sample size, double masking, and patient preference and studies at different geographical locations and during different seasons of the year are needed for better definition of therapy in VKC.

V. Conclusions

In this study, although azelastine altered the natural course with quicker onset of action at the end of the 8th week, both drugs are equally effective in reducing the signs and symptoms.

Azelastine proved quicker to relieve watering, ocular discomfort, and conjunctival hyperemia. Olopatadine provided faster improvement in papillary hypertrophy. Laboratory findings had no statistical significance between 0.1% olopatadine and 0.05% Azelastine in improving the AEC of the VKC patients. Being more commonly prescribed of the two drugs, olopatadine is readily available at the pharmacy store. Azelastine, on the other hand, was available at a few selected retail stores and comparatively as it is a cheaper drug it can be prescribed for poor people often. Researches with above-mentioned attributes can be done in the future.

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