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Manisha Rathi
Profesor, Regional Institute of Ophthalmology Pt Bd Sharma PGIMS, Rohtak, Haryana, India

Dr. Rajesh Garg
Regional Institute of Ophthalmology Pt Bd Sharma PGIMS, Rohtak, Haryana, India

Dr. Jitender Phogat
Regional Institute of Ophthalmology Pt Bd Sharma PGIMS, Rohtak, Haryana, India

Sumit Sachdeva
Profesor, Regional Institute of Ophthalmology Pt Bd Sharma PGIMS, Rohtak, Haryana, India

Dr. Dixit Soni
Regional Institute of Ophthalmology Pt Bd Sharma PGIMS, Rohtak, Haryana, India

Corresponding Author:
Manisha Rathi
Profesor, Regional Institute of Ophthalmology Pt Bd Sharma PGIMS, Rohtak, Haryana, India

Comparison and evaluation of ketorolac tromethamine 0.5%, ketotifen fumarate 0.05% and azelastine hydrochloride in patients of seasonal allergic conjunctivitis

Manisha Rathi, Dr. Rajesh Garg, Dr. Jitender Phogat, Sumit Sachdeva and Dr. Dixit Soni

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Abstract
Ocular allergy in the form of Seasonal Allergic Conjunctivitis is one of the most common conditions that ophthalmologists deal with. The signs and symptoms can be distressing and debilitating. The search is still on for the perfect topical drug with maximum efficacy and minimum side effects. We decided to undertake a study to compare and evaluate the efficacy of 3 commonly used drugs, topical Ketorolac tromethamine 0.5%, Ketotifen fumarate 0.05% and Azelastine hydrochloride in patients of Seasonal Allergic Conjunctivitis. 150 patients of Seasonal Allergic Conjunctivitis of both sexes in the age group of 15- 55 years were included. Patients included in the study had bilateral signs and symptoms of Seasonal Allergic Conjunctivitis. Group A patients were given Ketorolac tromethamine 0.5% to be instilled four times a day; Group B patients were given Ketotifen fumarate 0.05% to be instilled two times a day, and Group C patients were given Azelastine hydrochloride 0.05% to be instilled two times a day. The drops were dispensed in identical containers labeled A to C so that the patient did not know the type of drug administered. Informed consent was taken from all the patients. Patients were given the drugs on day 0 and the responses were assessed at 30 minutes (day 0), day 2, day 7, day 14, day 28 and 3 months. The drugs were instilled in both the eyes but the efficacy variables were studied in the eye with greater sign and symptoms. If both eyes had same grades of signs and symptoms, left eye of the patient was assessed. All 3 groups were age and sex matched. On each visit, the patient's signs and symptoms were graded by the investigator and the total score was noted. During the course of the study, patients were asked regarding any side effects pertaining to the drugs being instilled. Drug A (Ketorolac) had a statistically significant difference as compared to Drug B (Ketotifen) at all follow-up intervals ($p< 0.05$), except at three month follow up, when there was no significant difference between them ($p = 0.07$). Also, Drug A had a statistically significant difference as compared to Drug C (Azelastine) throughout the study period ($p< 0.05$). On comparing Drug B and Drug C, we observed a significant difference from the seventh day onwards. All three drugs had a statistically significant improvement in the total score over baseline from the 30 minute period ($p< 0.001$).

Keywords: Comparison, evaluation, tromethamine, ketotifen, conjunctivitis

Introduction
Ocular allergy has always been and continues to be one of the most common ocular conditions encountered by an ophthalmologist. There are multiple factors which are believed to be responsible for allergic conjunctivitis including genetics, air pollution in urban areas, pets, and early childhood exposure [1]. Topical and systemic treatment are generally used to diminish the allergic response and provide relief to patients. There are several drugs used for relief of allergic conjunctivitis, which may have to be used for long periods of time. The ideal treatment is one which would provide maximum relief with minimum side-effects.
Several studies have demonstrated that ketorolac effectively treats allergic conjunctivitis [2]. Through inhibition of chemotaxis, ketotifen is postulated to limit the number of eosinophils at the inflammation site during allergic reaction, which can lead to relief in allergy, including allergic conjunctivitis [3]. Topical azelastine has been shown to improved itching and conjunctival redness allergic conjunctivitis patients Rapid relief was attributed to H(1)-receptor antagonist action [4].

We undertook a study to compare and evaluate topical Ketorolac tromethamine 0.5%, Ketotifen fumarate 0.05% and Azelastine hydrochloride in patients of Seasonal Allergic Conjunctivitis.

Material and Methods

The present study was carried out in the Department of Ophthalmology, Pt. B.D. Sharma, PGIMS, Rohtak, Haryana. 150 patients of Seasonal Allergic Conjunctivitis of both sexes in the age group of 15- 55 years were included. Patients included in the study had bilateral signs and symptoms of Seasonal Allergic Conjunctivitis. On day 0, patients were enrolled in the study if their eyes were moderately red (score of 2 on a 0-3, four point scale) and on questioning their eyes were severely itchy (score of 3 on a 0-3, four point scale), according to the following grading system:

Signs

1. Lid Edema	0 - None, 1- Mild, 2 -Moderate, 3 - Severe
2. Conjunctival chemosis	0 No chemosis, 1 Minimal chemosis,
3 Focal areas of chemosis	3 Obvious chemosis
4. Conjunctival injection	0 No Redness, 1- Minimal Redness
	2. Obvious, but not diffuse Redness
	3 Diffuse Redness
5. Conjunctival mucus	0 No mucus strands
	1 Few mucus strands
	2 Easily detectable mucus strands
	3 Many mucus strands

Symptoms

1. Swollen Eyes	0 Absent
	1 Lids feel full in morning
	2 Lids feel full all day
	3 Interpalpebral fissure decreased
2. Burning/Stinging	0 Absent
	1 Occasional
	2 Daily with occasional eye Closing
	Close eye daily
3. Discharge/Tearing	0 Absent
	1 Occasionally wipe eye
	2 Wipe eyes daily
	3 Wipe eye several times daily
4. Foreign Body Sensation	0 Absent
	1 Occasionally feels sandy
	2 Feels sandy daily
	3 Occasionally looks for Foreign body
5. Photophobia	0 Absent
	1 Occasional
	2 Daily and occasionally Squints eye
	3 Occasionally closes eye
6. Itching	0 Absent
	1 Occasionally feels like rubbing eye
	2 Occasionally rub eye
	3 Rub eye daily

Exclusion Criteria

1. Ocular diseases or disorders other than Seasonal Allergic Conjunctivitis.
2. Known hypersensitivity to any component of test medication.
3. Ocular surgery within last 3 months.
4. Patients receiving concomitant medications that could influence the therapeutic response (corticosteroids, other NSAIDs, Aspirin, anticholinergics, immunosuppressants, other mast cell stabilizers, and other antihistamines) will be ineligible for study unless the medications are discontinued for at least one week before enrolment and for the duration of study.
5. Those patients who wish to use contact lenses during the course of study.
6. Pregnant / breast feeding females.
7. Patients with serious medical illnesses like Diabetes Mellitus and Congestive Heart Failure. Informed consent was taken from all the patients.

A detailed systemic and ocular examination was done. Patients were randomly allocated into 3 study groups (A, B and C) of 50 each. Group A patients were given Ketorolac tromethamine 0.5% to be instilled four times a day; Group B patients were given Ketotifen fumarate 0.05% to be instilled two times a day, and Group C patients were given Azelastine hydrochloride 0.05% to be instilled two times a day. All the drugs given were the ones available as commercial preparations.

The drops were dispensed in identical containers labeled A to C so that the patient did not know the type of drug administered.

Patients were given the drugs on day 0 and the responses were assessed at 30 minutes (day 0), day 2, day 7, day 14, day 28 and 3 months.

The drugs were instilled in both the eyes but the efficacy variables were studied in the eye with greater sign and symptoms. If both eyes had same grades of signs and symptoms, left eye of the patient was assessed.

On each visit, the patient's signs and symptoms were graded by the investigator and the total score was noted. During the course of the study, patients were asked regarding any side effects pertaining to the drugs being instilled. On each visit slit lamp examination, applanation tonometry, visual status assessment and fundoscopy was done.

At the completion of the study, the assessment of responses of the patients to the particular drug was done. It was based on the individual scores of the various signs and symptoms and the net score was also analyzed.

The individual t-test was done between the three groups to look for any statistical difference in the results. Also, paired t-test was done within the three groups to look for statistical improvement with each drug. A significance level of 0.05 was used for all analysis.

Results

The mean age in Group A was 30.74 (±8.98), in Group B was 32.04(±8.85) and in Group C was 31.98 (±9.14). There was no statistically significant difference in the mean age of patients in all the three study groups ($p > 0.05$).

Patients are equally distributed in the three groups on the basis of sex. All the drugs, Drug A (Ketorolac), Drug B (Ketotifen) and Drug C (Azelastine) showed a decrease in mean value from the second day onwards, but statistically significant improvement was observed from 28th day onwards for Ketorolac and on the third month follow up for Ketotifen and Azelastine. ($p>0.05$) Ketorolac and Ketotifen proved effective in suppressing chemosis from seventh day onwards ($p = 0.01$ and 0.04 respectively). Azelastine was effective from the 14th day onwards ($p = 0.04$)

Table 1: P values between three groups Conjunctival injection

Groups	Day 0	30 minutes	Day 2	Day 7	Day 14	Day 28	3 months
A vs B	0.40	0.26	0.29	0.21	0.21	0.27	0.27
A vs C	0.50	0.10	0.04	0.05	0.05	0.05	0.05
B vs C	0.40	0.26	0.15	0.20	0.21	0.16	0.16

There was a statistically significant difference ($p< 0.05$) between Drug A (Ketorolac) and Drug C (Azelastine) from the second day onwards (p = 0.04, 0.05, 0.05, 0.05 and 0.05).
Ketorolac was found to be superior to Azelastine in controlling the sign of conjunctival injection. All the three drugs had a statistically significant effect from 30 minutes of administration.

Conjunctival Mucus
Conjunctival mucus was found to be statistically significantly reduced from 14th day in Ketorolac group (p =0.04) and from 28th day onwards in Ketotifen and Azelastine groups (p =0.04).

Swollen Eyes
Ketorolac and Ketotifen had significant effect on the second day and Azelastine had a significant effect from the seventh day onwards.

Burning/ Stinging
All drugs were comparable in treating the symptom of burning/stinging. All the three drugs were highly statistically significant for the relief of burning/stinging ($p<0.001$).

Discharge
The present study showed no drug to be superior to the other in treating the symptom of discharge. All the three drugs were highly statistically significant for the relief of discharge ($p< 0.001$)

Foreign Body Sensation
The present study showed no drug to be superior to the other in treating the symptom of foreign body sensation. All the three drugs were highly effective for the relief of foreign body sensation ($p< 0.001$).

Photophobia
The present study showed no drug to be superior to the other in treating the symptom of photophobia. Drugs Ketorolac and Ketotifen had a significant improvement on the second day itself, while Azelastine had a significant effect on day 7.

Itching
The present study demonstrated the superiority of Ketorolac in controlling itching compared to Ketotifen and Azelastine within 30 minute interval. Also, Ketotifen was statistically significant in reducing itching as compared to Azelastine. All the three drugs showed statistical significance over the baseline readings demonstrating their efficacy in controlling itching.

Total Score

Table 2: Comparison of Mean of Total Scores

Groups	Day 0	30 minutes	Day 2	Day 7	Day 14	Day 28	3 months
A	14.58	9.70	8.86	6.96	5.88	5.06	4.36
B	14.54	10.44	9.74	7.76	6.54	5.68	4.78
C	14.52	10.72	10.12	8.40	7.02	6.24	5.42

Table 3: P values between the three groups (Total Scores)

Groups	Day 0	30 minutes	Day 2	Day 7	Day 14	Day 28	3 months
A vs B	0.46	0.04	0.01	0.01	0.02	0.03	0.07
A vs C	0.44	0.005	‹0.001	‹0.001	‹0.001	‹0.001	‹ 0.001
B vs C	0.48	0.24	0.15	0.03	0.05	0.03	0.01

Table 4: P values within the three groups (Total Scores)

Groups	Day 0-30 minutes	Day 0-Day 2	Day 0-Day 7	Day 0-Day 14	Day 0-Day 28	Day 0-Day 3 months
A	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001
B	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001
C	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001	‹ 0.001

Mean scores at baseline (14.58, 14.54, and 14.52) were comparable ($p> 0.05$). Drug A (Ketorolac) had a statistically significant better efficacy as compared to Drug B (Ketotifen) at all follow-up intervals ($p< 0.05$), except at three month follow up, when there was no significant difference between them (p = 0.07). Drug A also had a statistically significant difference as compared to Drug C (Azelastine) throughout the study period ($p< 0.05$). On comparing Drug B and Drug C, we observed a significant difference from the seventh day onwards. All three drugs had a statistically significant improvement in the total score over baseline from the 30 minute period ($p<0.001$).

Table 5: Side Effects

Side - effects	Group A Ketorolac	Group B Ketotifen	Group C Azelastine
Headache	—	—	—
Ocular stinging	5 (10%)	4 (8%)	—
Conjunctival Injection	—	—	—
Bitter taste	—	—	5 (10%)

Transient stinging on instillation was noted by five patients (10%) in the Ketorolac study group and in four patients (8%) of the Ketotifen study group. Bitter taste was observed in five patients (10%) in the Azelastine study group.

Discussion
With an estimated prevalence of 15-20%, Seasonal Allergic Conjunctivitis is the most common form of ocular allergy, affecting adults and children alike.[5] Although serious sequelae as a result of corneal involvement are rare, the distressing signs and symptoms may cause extreme discomfort [6].
The present study demonstrated the effectiveness of all three drugs in the relief of signs and symptoms of Seasonal Allergic Conjunctivitis. All three drugs showed highly statistically significant differences ($p< 0.001$) from baseline scores.

Ketorolac showed a statistical significant advantage over both Ketotifen and Azelastine from the 30 minute interval. Ketotifen showed a statistically significant difference over Azelastine from the seventh day.

There was no change in the best corrected visual activity in any patient in the post treatment follow up as compared to the pre-treatment status. Taste perversion was noticed in five patients (10%) in the Azelastine group. Transient stinging on instillation was noted by five patients (10%) in the Ketorolac study group and in four (8%) patients of the Ketotifen study group. These results did not appear to exert any negative effect on the overall therapeutic response.

No significant adverse event was noted during the study so as to preclude the instillation of any of the drugs. No individual discontinued treatment prematurely because of any adverse events. Thus all these 3 topical drugs were effective and well tolerated in the treatment of Seasonal Allergic Conjunctivitis, with Ketorolac being more effective than the other 2 drugs.

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