A comparative study of Olopatadine and Ketorolac eye drop with Ketorolac eye drop alone in seasonal allergic conjunctivitis

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Abstract

Background: Seasonal allergic conjunctivitis is the most common allergic disorder seen in eyes. The aim of study was to compare the clinical efficacy of combination of 0.4% ketorolac and 0.1% olopatadine with 0.4% ketorolac alone in seasonal allergic conjunctivitis. Material and Method: The study was prospective, double blind parallel group comparative. Two hundred cases enrolled in the study. All the subjects were randomly divided in two groups, 100 in each. Group 1 patients received 0.4% ketorolac eye drop in both eyes 2 times a day and group 2 patients received combination of 0.1% olopatadine and 0.4% ketorolac in both eyes 2 times a day. Observations were collected at baseline and on day 3, 7, 15 and analyzed statistically regarding improvement in sign and symptoms. Result: In group 1, 50-60% patients had no sign and symptoms on day 15 whereas in group 2 more than 95% patients showed improvement in clinical picture. p value was significant (p<0.0001) at day 15 in all sign and symptoms and on day 3 in itching and on day 7 in watering. Overall group 2 patients had better and earlier response regarding symptoms of itching at day 3. Conclusion: The combination of 0.1% olopatadine and 0.4% ketorolac was more effective than 0.4% ketorolac alone in seasonal allergic conjunctivitis patients.

Key words: Seasonal allergic conjunctivitis, Combination, Ketorolac, Olopatadine, Comparison

Introduction

Seasonal allergic conjunctivitis affects most of the people during their lifespan [1]. Main sign and symptom are itching, redness, watering and photophobia, some patients present with chemosis [1-6]. Severity of allergic conjunctivitis also depends upon allergen and immune system of the patient itself. It is the result of reaction between allergen and mast cell of our body [5,7,8,9]. Mast cells play very important role in pathogenesis of allergic conjunctivitis [10-14].

The best option to reduce its occurrence is to identify responsible substances for it and avoid its exposure but practically this thing is impossible [15]. Variety of drugs available in market for allergic conjunctivitis [2,16,17], but the drugs which have been used mostly are steroids but due to some adverse effects and serious complication now a days we switch on some other non steroidal drugs like ketorolac, ketotifen, sodium chromoglycate, olopatadine etc. but in some severe cases these eye drops alone are not so effective in alleviating the sign and symptoms of seasonal allergic conjunctivitis.

So now the preparations which are coming in market are of combination of two or more molecules. Olopatadine have dual action mode as mast cell stabilizer and antihistaminic with safety profile, many studies have done on it [18-22].

Ketorolac is a NSAIDs which acts by inhibiting the prostaglandins and very effective in relieving the symptoms of itching.

In this study our aim was to compare the effectiveness of combination of 0.4% ketorolac and 0.1% Olopatadine eye drop with 0.4% Ketorolac alone in seasonal allergic conjunctivitis.
Material and Methods

**Study design:** Prospective, randomized, double-blind, single-centre, parallel group comparative study.

**Setting:** The study was conducted in the department of ophthalmology at Jhalawar medical college (raj.)

**Inclusion criteria:** All the Patients coming in the outpatient department with complaining of itching, redness, watering and photophobia were selected to participate in the study and diagnosed as a case of seasonal allergic conjunctivitis on the basis of sign (hyperemia) at slit lamp and symptoms (itching, watering, photophobia). No other methods of diagnosis were considered besides clinical signs and symptoms. For example, skin testing may have been useful to provide more accurate diagnosis but we chose to use signs and symptoms rather than skin testing mainly to reduce cost as the study was not externally funded.

**Exclusion criteria:** Patients were excluded if they had
1. Uveitis, conjunctivitis and other ocular pathology.
2. Bronchial asthma, eczema.
3. History of dry eye, blepharitis, using contact lens.
4. Receiving topical or systemic medication
5. History of sensitivity to any constituents of the eye drops.

**Participants:** 200 OPD patients diagnosed on the basis of sign and symptoms of allergic conjunctivitis were participated in the study.

**Variables:** The studied demographic variables included age, sex, rural, urban and occupation.

Questions pertaining severity of sign and symptoms of allergic conjunctivitis were asked. The study was conducted from April 2017 to June 2017 after obtaining permission from the ethical committee of our institute. This period was selected because most of the allergic patients came across during this period due to season of crop harvesting and change in temperature of atmosphere.

**Data Source:** The sign and symptoms of patients on clinical examination after scoring of these sign and symptoms.

**Bias:** No bias.

**Study Size:** 200 patients of allergic conjunctivitis.

**Quantitative variables:** No quantitative variables seen in our study.

**Statistical Methods:** Analysis was performed using chi-square test, p-value <0.0001 was considered significant

**Methodology**- After obtaining written informed consent and detail explanation of the study Patients who were found to be eligible according to selection criteria were recruited in to one of the treatment groups according to a stratified randomization list based on age and sex 100 patients in each.

Group 1 (0.4% ketorolac group) both eye of each of these patients received 0.4% ketorolac twice daily.

Group 2 (0.4% ketorolac and 0.1% olopatadine combination group) received combination of 0.4%ketorolac and 0.1% olopatadine in both eye two times a day.

Detailed history and clinical examination were performed in a prescribed data collection form Study medications were provided in identical containers so that both patients and investigators were remained blinded. follow up was done at day 0,3,7,15 regarding improvement in number of patients for Itching, Hyperemia, watering and photophobia by using four point scale method. During the study period if any patient complained regarding any side effect of eye drop we instruct them to contact immediately in OPD to chief investigator.

**Results**

Total 200 patients participated in this study. Data were collected and arranged in tables. Table no.1 showed the demographic profile of patients, age, sex and occupation which showed that range of age was 18-50 years. Mean age of group1 patients was 30.24 where as in group 2 mean age was 33.52. Most of the patients in both groups
are of male and by occupation they are field workers females those were affecting were of housewives. All these data showed no significant difference in between two groups.

Table No.-1: Scoring of sign and symptom of allergic conjunctivitis.

| Sign and symptoms | Scoring of Sign and symptoms of allergic conjunctivitis |
|-------------------|--------------------------------------------------------|
|                   | Score 0 (absent) | Score 1 (mild) | Score 2 (moderate) | Score 3 (severe) |
| Itching           | Absent          | occasionally   | frequently         | continuously     |
| Hyperemia         | Absent          | Slightly dilated blood vessels | Moderate vasodilatation | Obviously dilated blood vessels deep red in colour |
| Watering          | Absent          | occasionally   | frequently         | Persistent       |
| Photophobia       | Absent          | occasionally   | continuous         | Eye responds to lepharospasm on exposure to light |

Table No.-2: Distribution of cases according to age and sex

|                      | Group 1 | Group 2 |
|----------------------|---------|---------|
| Mean age             | 30.24   | 33.52   |
| Male                 | 58      | 68      |
| Female               | 42      | 32      |
| Total                | 100     | 100     |

Table No.-3: Scoring of itching on different day

|                      | 0 (none) | 1 (mild) | 2 (moderate) | 3(severe) | Total | Chi square | P value |
|----------------------|----------|----------|--------------|-----------|-------|------------|---------|
| Baseline             |          |          |              |           |       |            |         |
| Group1               | 00       | 20       | 40           | 40        | 100   | 2.667      | 0.2635  |
| Group2               | 00       | 30       | 35           | 35        | 100   |            |         |
| Day 3                |          |          |              |           |       |            |         |
| Group1               | 30       | 40       | 20           | 10        | 100   | 18.333     | 0.0003  |
| Group2               | 50       | 20       | 10           | 20        | 100   |            |         |
| Day 7                |          |          |              |           |       |            |         |
| Group1               | 40       | 45       | 10           | 05        | 100   | 12.00      | 0.0074  |
| Group2               | 60       | 30       | 10           | 00        | 100   |            |         |
| Day 15               |          |          |              |           |       |            |         |
| Group1               | 50       | 40       | 05           | 05        | 100   | 51.188     | <0.0001*|
| Group2               | 95       | 05       | 00           | 00        | 100   |            |         |

Table No.-4: Scoring of hyperemia on different day

|                      | 0 (none) | 1 (mild) | 2 (moderate) | 3(severe) | Total | Chi square | P value |
|----------------------|----------|----------|--------------|-----------|-------|------------|---------|
| Baseline             |          |          |              |           |       |            |         |
| Group1               | 00       | 15       | 45           | 40        | 100   | 5.794      | 0.0552  |
| Group2               | 00       | 25       | 30           | 45        | 100   |            |         |
| Day 3                |          |          |              |           |       |            |         |
| Group1               | 25       | 45       | 20           | 10        | 100   | 26.408     | <0.0001*|
| Group2               | 60       | 20       | 15           | 05        | 100   |            |         |
| Day 7                |          |          |              |           |       |            |         |
| Group1               | 50       | 37       | 10           | 03        | 100   | 9.559      | 0.02271 |
| Group2               | 68       | 22       | 10           | 00        | 100   |            |         |
| Day 15               |          |          |              |           |       |            |         |
| Group1               | 60       | 30       | 08           | 02        | 100   | 35.76      | <0.0001*|
| Group2               | 95       | 05       | 00           | 00        | 100   |            |         |
Table No.-5: Scoring of Watering on different day.

|          | 0 (none) | 1 (mild) | 2 (moderate) | 3 (severe) | Total | chisquare | P value |
|----------|----------|----------|--------------|------------|-------|-----------|---------|
| Baseline |          |          |              |            |       |           |         |
| Group 1  | 00       | 40       | 40           | 20         | 100   | 5.853     | 0.0536  |
| Group 2  | 00       | 30       | 35           | 35         | 100   |           |         |
| Day 3    |          |          |              |            |       |           |         |
| Group 1  | 30       | 40       | 15           | 15         | 100   | 13.262    | <0.0041 |
| Group 2  | 53       | 32       | 10           | 05         | 100   |           |         |
| Day 7    |          |          |              |            |       |           |         |
| Group 1  | 38       | 42       | 08           | 12         | 100   | 21.77     | <0.0001*|
| Group 2  | 65       | 30       | 05           | 00         | 100   |           |         |
| Day 15   |          |          |              |            |       |           |         |
| Group 1  | 50       | 42       | 05           | 03         | 100   | 59.391    | <0.0001*|
| Group 2  | 98       | 02       | 00           | 00         | 100   |           |         |

Table No.-6: Scoring of photophobia on different day

|          | 0 (none) | 1 (mild) | 2 (moderate) | 3 (severe) | Total | chisquare | P value |
|----------|----------|----------|--------------|------------|-------|-----------|---------|
| Baseline |          |          |              |            |       |           |         |
| Group 1  | 00       | 58       | 32           | 10         | 100   | 0.098     | 0.9522  |
| Group 2  | 00       | 60       | 30           | 10         | 100   |           |         |
| Day 3    |          |          |              |            |       |           |         |
| Group 1  | 38       | 43       | 15           | 04         | 100   | 10.78     | 0.0129  |
| Group 2  | 58       | 32       | 10           | 00         | 100   |           |         |
| Day 7    |          |          |              |            |       |           |         |
| Group 1  | 42       | 47       | 10           | 01         | 100   | 11.364    | 0.0099  |
| Group 2  | 65       | 30       | 05           | 00         | 100   |           |         |
| Day 15   |          |          |              |            |       |           |         |
| Group 1  | 53       | 44       | 01           | 02         | 100   | 58.01     | <0.0001*|
| Group 2  | 99       | 01       | 00           | 00         | 100   |           |         |

Table no.2 showed that in group 1 patients had improvement in itching on day 3 and 7 which is not so significant (p >0.0001) whereas group 2 patients had significant improvement at day 15(p<0.0001).

Table no. 3 has data of hyperemia which reflect that group 1 patients also have good response in this sign although not significant

Table no. 4 depict that group 2 patients had better response in symptom of watering (p<0.0001)

Table no. 5 & 6 also depict that group 2 patients had good results in comparison of group 1 if considering watering of eye and photophobia. (p<0.0001)

Discussion

Allergic conjunctivitis is a common ocular problem. It is rarely associated with vision-threatening complication but can hamper the quality of life for patients due to its recurrent nature. To improve quality of life it is important to get early relief from signs and symptoms of allergic conjunctivitis. There are three types of simple allergic conjunctivitis acute, seasonal and perennial. Allergic conjunctivitis affects 10% to 30% of the general population [23]. In most of the cases younger age group patients suffers more in comparison to older people [24, 25]. The pathogenesis of allergic conjunctivitis is predominantly an IgE-mediated hypersensitivity reaction in which allergens interact with IgE bound to sensitized mast cells resulting in increased tear levels of histamine, tryptase, prostaglandins and leukotrienes [26,27].

The diagnosis is made clinically by taking history and ocular examination. Laboratory investigation is generally not required although skin prick test or serum allergy testing can be helpful identifying the offending allergens so that they can be avoided if possible. Variety of treatment available for allergic conjunctivitis very first we should educate the patients about the disease, the trigger factors, and the importance of avoiding exposure to the allergens.
patients about general care of eye that they should not rub their eyes which causes worsening of symptoms. Advice them to use artificial tear and cool compresses frequently. When all these measure become fail pharmacologic treatment should applied topically to diminish the allergic response. The mainstay of the management of ocular allergy involves the use of anti-allergic therapeutic agents such as antihistamine, vasoconstrictor, and mast cell stabilizer. Topical antihistamines block histamine receptors and relieve itching and redness but only for a short time which necessitates frequent dosing of up to 4 times per day [28].

Combination of decongestants with antihistamines have been shown to be more effective and are administered to the eye as drops up to 4 times daily [29]. Decongestants are effective in reducing hyperemia but still side effects of burning and stinging on instillation, mydriasis, and rebound hyperemia with chronic use [29]. Therefore these drugs are suitable only for short period.

Mast cell stabilizer’s mechanism is not clear. They may increase calcium influx into the cell which prevents changes in membrane or they may reduce membrane fluidity prior to mast cell degranulation which results in decrease of degranulation of mast cells, that prevents the release of histamine and other chemotactic factors which are present in the preformed and newly formed state. Mast cell stabilizers don’t relieve existing symptoms and they can be used only for prophylaxis.

They require a loading period during which they must be applied before the antigen exposure. Therefore, poor compliance should be taken as a possible drawback of Mast cell stabilizers. In recent years many other drugs have been introduced with multiple anti-allergic action such as olopatadine, ketotifen, azelastine and epinastine that exert multiple anti allergic effects such as histamine receptor antagonist action, stabilization of mast-cell degranulation and suppression of activation and infiltration of eosinophils [30].

Olopatadine is a new topical ocular dibenzoxepin derivative [22]. It inhibits the release of preformed and newly synthesized inflammatory mediators from mast cells and also has antihistaminic properties towards H1 receptors. Its dual activity is an advantage and the drug may be used both as a therapeutic and prophylactic agent. The dual action also renders the drug superior in terms of clinical effectiveness, rapid onset and length of duration of action [19,20].

Non-steroidal anti-inflammatory drug (NSAIDs) such as Ketorolac works through the inhibition of cyclooxygenase, which produces prostaglandins. Prostaglandin D2 is among the newly synthesized mediators released by mast cells following antigen stimulation, and inhibition of the production of this mediator can decrease the signs and symptoms of allergic conjunctivitis. It is used as additive drugs to reduce the conjunctival hyperemia and itching related to prostaglandin D2 and prostaglandin E2 [31].

Topical Corticosteroids also used in more severe variants of ocular allergy [32-36]. Corticosteroids possess immunosuppressive and anti-proliferative properties but they have some limitations like including elevated intraocular pressure, and formation of cataract. These agents are therefore appropriate for short courses (up to 2 weeks); however, if needed for longer durations, an eye examination should be carried out, including baseline assessment of cataracts and intraocular pressure measurement [37,38].

In previous studies, olopatadine hydrochloride demonstrated significantly greater efficacy than placebo, mast cell stabilizers, NSAIDs and some other drugs Spangler et al.2001[48] Yaylali et al. 2003[39] Leonardi & Zafirakis 2004[13].

We designed a single centre double-masked randomized trial, to compare the efficacy of combination of 0.4% ketorolac and 0.1% olopatadine with 0.4% ketorolac eye drop in allergic conjunctivitis patients.

Yaylali et al [39] conducted a study on 40 patients of allergic conjunctivitis, 21 were male and 19 were female. Their average age was 19 years (range 15–25 years). When the mean scores of olopatadine treated eyes were compared to the scores of ketorolac treated eyes, the mean scores of hyperemia were found to be lower in the olopatadine group, indicating better therapeutic effectiveness, although the difference did not reach statistical significance (p 0.154, 0.9, 0.65, 0.79,
0.79, for baseline, 30 minutes, 2, 7 and 15 days scores, respectively) the results were favor of our study.

Chaudhary et al [44] conducted a study on 92 patients of allergic conjunctivitis out of which 42-45% are male patients mean age was 28 ± 12 and 28 ± 11 years. The baseline/pretreatment mean scores (SD) of hyperemia, tearing, itching and photophobia were 1.93 ± 0.258, 1.07 ± 0.258, 2.40 ± 0.495 and 1.35 ± 0.573, respectively, in the KF group. After 2 weeks of treatment with 0.025% KF reduced the mean scores of hyperemia, tearing, itching and photophobia by 64, 63, 55 and 81%, respectively. On the other hand, the baseline mean scores (SD) of hyperemia, tearing, itching and photophobia were 1.90 ± 0.304, 1.13 ± 0.607, 2.45 ± 0.677 and 1.27 ± 0.452, respectively, in the OHCL group. After 2 weeks of treatment with 0.1% OHCL reduced the mean scores of hyperemia, tearing, itching and photophobia to 96, 97, 88 and 96%, similarly in our mean age of group 1 patients was 30.24 where as in group 2 mean age was 33.52, group 2 patients mean score of itching, hyperemia watering and photophobia were 95, 95, 98, 99% respectively which strongly prove that olopatadine in combination with ketorolac is very effective and safe.

We observed male predominance in both the groups (group 1 58%, group 2 68%) similar observation found in study of Pallasaho et al[40] where males were at higher risks for presenting allergic symptoms than females, Raukas- Kivioja et. Al [41] in their study demonstrated that the prevalence of allergic conjunctivitis was 34.50% and inversely related with the age.

Most of the patients in our trial are outdoor worker which gives the idea that allergic conjunctivitis was more in field worker especially young patients although could not prove statistically.

The mean scores for itching were found to be lower in the olopatadine and ketorolac group than in the ketorolac group in our study. At day 15, 95% of patients had no complaint of itching in group 2 (p value<0.0001) table no.1 indicating that olopatadine and ketorolac in combination was superior to ketorolac in inhibiting ocular pruritus. The higher clinical effectiveness of olopatadine compared to ketorolac in alleviation of signs and symptoms allergic conjunctivitis, particularly of itching, may be explained by the dual action of this drug [3,19, 47-51].

According to Deschenes et al [47] Ketorolac, unlike olopatadine, does not inhibit mast cell degranulation and does not possess antihistamine activity. Although ketorolac inhibits pruritogenic prostaglandin synthesis, and thus has antipruritogenic effectiveness in the treatment of allergic conjunctivitis, the resultant anti-itching effect is less than that of olopatadine, which is a potent antihistaminic agent.

The authors explained ketorolac’s lack of effectiveness in the inhibition of allergic response in the human conjunctiva on the basis that either prostaglandin D2, which is important in guinea pig allergic conjunctivitis, might have a limited role to play in human allergic conjunctivitis. But this explanation contradicts other studies which have clinically demonstrated the effectiveness of ketorolac in the treatment of allergic conjunctivitis patients [43,45,46]. In these studies ketorolac was used four times daily for 1 week, in a similar manner to our study we prescribed ketorolac two times a day.

Katelaris et al (2002)[42] conducted a 6-week, multicenter, randomized controlled study to compare the effects of olopatadine hydrochloride 0.1% ophthalmic solution and disodium cromoglycate 2% ophthalmic solution on itching and hyperemia in 185 patients with allergic conjunctivitis which showed better efficacy for hyperemia that results were also consistent with our study hyperemia score in group 2 reduced to 95%, p<0.0001 on day 3 and 15 group 1 patients have less response for hyperemia because ketorolac itself causes hyperemia on instillation.

Combination of olopatadine and ketorolac also showed effectiveness in reducing the watering and photophobia both the result of that are consistent with Deschenes et al. 1999 [47].

Overall the result of our study were in favor of combination of olopatadine and ketorolac eye drop use for allergic conjunctivitis as Castilo M etal [1] which also proved that olopatadine had summative role when given in combination with 0.4% ketorolac.
Significant effectiveness was observed in reducing the signs and symptoms of itching, hyperemia and photophobia the reduction of photophobia was more than 46% higher in the group 2 than group1.

**Conclusion**

1. 0.1% Olopatadine and 0.4% Ketorolac eyedrop is more effective and safer than 0.4% Ketorolac alone in the management of seasonal allergic conjunctivitis.
2. Patients who received combination of olopatadine and ketorolac have faster recovery in hyperemia and itching without any side effect and thus this offers a promising new strategy for the management of allergic conjunctivitis.
3. Frequency of dose is very less.
4. low cost of olopatadine and ketorolac in combination have improved patient Compliance.
5. Patients feel significantly less discomfort upon instillation.

So we can conclude that the combination of olopatadine(0.1%) and ketorolac(0.4%) eye drop is more beneficial for seasonal allergic conjunctivitis

**Benefit of study in future-** This is the one of unique study in terms of that we used combination of olopatadine and ketorolac in treatment of allergic conjunctivitis which have better efficacy and results rather than single drug so it will be beneficial in future for patients as well as doctor

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