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Original Research Article.

A Comparative Study of Olopatadine and Ketorolac Eye Drop vs Ketorolac Eye Drop Alone in Seasonal Allergic Conjunctivitis

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ABSTRACT

Aim: To compare the clinical efficacy of combination of 0.4% ketorolac and 0.1% olopatadine with 0.4% ketorolac alone in seasonal allergic conjunctivitis.

Materials and Methods: The study was prospective, double blind parallel group comparative with 200 cases attending the OPD of RIO, RIMS were included in the study. All the patients 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 and 15 and analyzed statistically regarding improvement in sign and symptoms.

Results: 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 i.e 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.

Keywords: Seasonal Allergic Conjunctivitis, Combination, Ketorolac, Olopatadine.

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INTRODUCTION

Seasonal allergic conjunctivitis affects most of the people during their lifespan.[1] Main signs and symptoms 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.[5,7-9] Mast cells play a key role in pathogenesis of allergic conjunctivitis.[10- 14] The best option to reduce its occurrence is to identify substances responsible for it and avoid its exposure but practically it is impossible.[15] Variety of drugs are available in market for allergic conjunctivitis[2,16,17] and the drugs which have been used mostly are steroids but due to its adverse effects and serious complications, now a days we have switched over to some other non-steroidal drugs like ketorolac, ketotifen, sodium chromoglycate, olopatadine etc. However, 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 combination of two or more molecules. Olopatadine has dual action mode as mast cell stabilizer and antihistaminic with safety profile, many studies have been done on it.[18-22] Ketorolac is a NSAID which acts by inhibiting the synthesis of prostaglandins and is 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.

MATERIALS AND METHODS

Study Design

Prospective, randomized, double-blind, single-centre, parallel group comparative study.

Inclusion Criteria

200 Patients coming in the outpatient department of RIO, RIMS with complaint of itching, redness, watering and photophobia were selected to participate in the study and were diagnosed as a case of seasonal allergic conjunctivitis on the basis of sign (hyperemia) at slit lamp and symptoms (itching, watering, photophobia).

Exclusion Criteria

1. Uveitis, conjunctivitis and other ocular pathology.
2. Bronchial asthma, eczema.
3. History of dry eye, blepharitis, use of contact lens.
4. Receiving topical or systemic medication
5. History of sensitivity to any constituents of the eye drops.

The studied demographic variables included age, sex, rural, urban and occupation. Questions pertaining to severity of sign and symptoms of allergic conjunctivitis were asked. The study was conducted from April 2018 to June 2018 in same year.

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 into 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 medication were provided in identical containers so that both patients and investigators 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.

RESULTS

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

Table 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 3 has data of hyperemia which reflect that group 1 patients also have good response in this sign although not significant.

Table 4 depict that group 2 patients had better response in symptom of watering (p<0.0001)

Table 5 & 6 also depict that group 2 patients had good results in comparison to group 1 if considering watering of eye and photophobia. (p<0.0001)

Table 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 blepharospasm on exposure to light

Table 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 3: Scoring of itching on different day

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

Table 4: Scoring of hyperemia on different day

		0 (none)	1 (mild)	2 (moderate)	3 (severe)	Total	Chi square	P value
Baseline	**Group 1**	00	15	45	40	100	5.794	0.0552
	Group 2	00	25	30	45	100		
Day 3	**Group 1**	25	45	20	10	100	26.408	<0.0001*
	Group 2	60	20	15	05	100		
Day 7	**Group 1**	50	37	10	03	100	9.559	0.02271
	Group 2	68	22	10	00	100		
Day 15	**Group 1**	60	30	08	02	100	35.76	<0.0001*
	Group 2	95	05	00	00	100		

Table 5: Scoring of Watering on different day

		0 (none)	1 (mild)	2 (moderate)	3 (severe)	Total	Chi square	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 6: Scoring of photophobia on different day

		0 (none)	1 (mild)	2 (moderate)	3(severe)	Total	Chi square	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		

DISCUSSION

Allergic conjunctivitis is a common ocular problem. It is rarely associated with vision-threatening complication but can hamper the quality of life of 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 suffer 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 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 in identifying the offending allergens so that they can be avoided if possible. Variety of treatment options are available for allergic conjunctivitis but firstly we should educate the patients about general care of eye that they should not rub their eyes which causes worsening of symptoms, advice them to use artificial tears and apply cold compresses frequently. When all these measures fail, pharmacological treatment should be initiated 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 antihistaminics 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 antihistaminics has 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 like burning and stinging sensation on instillation, mydriasis, and rebound hyperemia with chronic use have been reported.[29] Therefore these drugs are suitable only for short period.

Mast cell stabilizer's mechanism of action 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 decreased 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 action is beneficial 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 add-on therapy to reduce the conjunctival hyperemia and itching related to prostaglandin D2 and prostaglandin E2.[31]

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

In previous studies like Spangler et al.2001[39], Yaylali et al. 2003[40], Leonardi & Zafirakis 2004[13], olopatadine hydrochloride has been demonstrated to have significantly greater efficacy than placebo, mast cell stabilizers, NSAIDs and some other drugs.

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.[40] 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 in favour of our study.

We observed male predominance in both the groups (group 1 58%, group 2 68%) similar observation was found in study of Pallasaho et al.[41] where males were at higher risks of presenting allergic symptoms than females. Raukas- Kivioja et al.[42] in their study demonstrated that the prevalence of allergic conjunctivitis was 34.50% and was inversely related with the age.

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, 39,48-51]

Katelaris et al (2002)[43] 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.

Combination of olopatadine and ketorolac also showed effectiveness in reducing the watering and photophobia; the result is consistent with Deschenes et al. 1999.[48]

Overall, the result of our study was in favor of combination of olopatadine and ketorolac eye drop use for allergic conjunctivitis as Castilo M et al.[1] which also proved that olopatadine had summative role when given in combination with 0.4% ketorolac.

Significant effectiveness was observed in reduction of 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. Combination of 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 had 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 dosing 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.

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