Olopatidine and Ketorolac Vs Olopatidine Alone in Treatment of Seasonal Allergic Conjunctivitis [Combination Vs Single Drug Therapy Study]

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Abstract

Purpose: To compare the therapeutic effects of combination of Olopatidine and Ketorolac vs Olopatidine alone (0.1% Olopatidine hydrochloride and 0.5% Ketorolac tromethamine) in seasonal allergic conjunctivitis (SAC).

Methods: 200 patients with the signs and symptoms of SAC (i.e. hyperaemia, itching, mucus discharge, tearing) were included in this study. In group 1 (100 patients) each patient was treated with “olopatadine and Ketorolac” and group 2 patients were treated with Olopatidine alone. The principle signs and symptoms of SAC (hyperaemia, itching, watering and photophobia) were evaluated at day 0, day 7, day 15 and day 21 by using a 4 point scale. Mean scores of each of the parameters were calculated using paired t test.

Results: When the mean scores of Group 1 (Olopatidine plus Ketorolac) were compared to the scores of Group 2 (Olopatidine only) the mean scores of hyperaemia, itching and watering were found to be lower in Group 1, indicating better therapeutic effectiveness with a significant difference statistically ($p<0.05\%$) on day 7,day 15 and on day 21.

Conclusions: Olopatadine and Ketorolac combination therapy is an effective treatment for seasonal allergic conjunctivitis when compared to Olopatidine alone.

Introduction

Seasonal allergic conjunctivitis (SAC) is a type 1 hypersensitivity reaction mediated by IgE in response to these environmental antigens such as pollen grains, weeds and animal dander.1 Itching, conjunctival hyperaemia, tearing, mucus discharge, chemosis and lid oedema are the tale tell clinical features of the disease. [1] The key pathophysiological step in the disease include degranulation of the mast cells. When specific allergens bind to sensitized mast cells in the conjunctiva, degranulation of mast cells, and release of preformed (histamine, eosinophil chemotactic factor, tryptase) and newly synthesized mediators (prostaglandins, leukotrines) occur. Hence, typical signs and symptoms of SAC appear. Histamine is the predominant mediator. [2] On the other hand, prostaglandin D2 which is produced by the arachidonic acid pathway has a role in the pathogenesis of SAC. Prostaglandin D2 induces conjunctival hyperemia, oedema and mucus.[3] Currently available topical drugs include H1 antihistamines such as Olopatidine, H1 antihistamine, vasoconstrictor combinations such as antazoline-naphazoline, mast cell stabilizors such as cromolyn sodium and lodoxamide, and non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin synthesis, such as Ketorolac tromethamine. Inhibition of prostaglandin synthesis, including prostaglandins D2 and E2, may play a role in the treatment of SAC. Ketorolac works by inhibiting the prostaglandins hence the pruritogenic effects on the conjunctiva. A new topical drug, Olopatidine, has been shown to have a dual action, in terms of both mast cell degranulation inhibition and histamine H1 receptor blockage. [4][5][6][7] This agent has a rapid onset due to antihistamine activity and prolonged duration of action due to mast cell stabilization, which allows for a

twice daily dosage. The aim of the current study was to compare the therapeutic effectiveness of combination of two ophthalmic solutions of Olopatidine and Ketorolac vs Olopatidine alone in SAC. Despite SAC being one of the commonly treated disease not many combination vs single drug therapy studies have been done. Some studies however have evaluated the effectiveness of Olopatidine and Ketorolac comparing them with placebo

Methodology

This study is a Prospective, randomized, single-center, parallel group comparative study conducted in Reyukai Eiko Masunaga eye hospital from April 2020 to July 2020. This period was selected because most of the allergic patients came across during this period. Patients who presented with itching, redness, watering and photophobia and diagnosed as a case of seasonal allergic infective conjunctivitis were involved in the study. Patients were excluded if they had conjunctivitis, history of Bronchial asthma, eczema, blepharitis, contact lens wearer, or had allergy to any constituents of the eye drops. Patients who could not comply with the treatment or who were lost at regular follow-ups were also excluded from the study.200 OPD patients diagnosed on the basis of signs and symptoms of seasonal allergic conjunctivitis were included in the study. Analysis was performed using paired t test. A P-value < 0.005(confidence interval 95%) was considered significant. Every third patient with seasonal allergic conjunctivitis were included in the study to avoid selection bias. A written informed consent was taken. Patients who were found to be eligible according to selection criteria were recruited in to one of the treatment groups. Group 1(0.4% Ketorolac group + 0.1% Olopatidine) received 0.1% Olopatadine twice daily and 0.4% Ketorolac TID whereas Group 2 (0.1% Olopatadine alone group) received 0.1% Olopatadine in both eye two times a day. No other eye drops were prescribed. Detailed history and clinical examination were performed on day 0, day 7, day 15 and day 21.On each examination patients were evaluated for Itching, Hyperemia, watering and photophobia by using four point scale method.(Table 1) This scoring system was taken from a study conducted by Meena et al.[8]

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	Blepharospasm on exposure light

Results

Total 200 patients participated in this study with 100 in each group. Mean age in group 1 was 29.05 years and in group 2 was 23.39 years.

Table no 2 : Demographic profile of the study groups

	Group 1	Group 2
Mean Age $\bar{x}$ ±SD (Range)	29.05 ± 0.60 years (18–46 years)	31.39 ± 0.48 years (2–49 years)
Male	60	48
Female	40	52
Total	100	100

The mean scores of the clinical parameters were computed for each examination as depicted in table 3. The baseline scores were found to be similar in both groups ($p > 0.05$) for all 4 parameters (itching, hyperemia, watering and photophobia).None of the patients had chemosis or lid edema. When the mean scores of Group 1 (Olopatidine plus Ketorolac) were compared to the scores of Group 2 (Olopatidine only) the mean scores of hyperaemia, itching and watering were found to be lower in Group 1, indicating better therapeutic effectiveness with a significant difference statistically ($p < 0.05\%$) on day 7,day 15 and on day 21.(Table 2). However mean scores for photophobia, although was seen to be lowered with treatment there was no statistically significant difference between two groups. Adverse reactions were reported in 15% of patients who had received Ketorolac. All of them reported to have a stinging sensation with the drug for which lubricating eye drops were prescribed once the study was completed.

Table number 3: Mean scores of parameters at baseline and consecutive follow-ups

	Baseline	7th day	15th day	21st day
Itching				
Group 1	1.82+-0.65	1.28+-0.80	0.85+-0.77	0.61+-0.84
Group 2	1.89+-0.61	1.38+-0.86	1+-0.80	0.79+-0.88
P* value	0.052	0.012	0.001	0.01
Hyperemia				
Group 1	2.26+-0.76	1.66+-1.01	0.93+-0.47	0.46+-0.59
Group 2	2.33+-0.72	1.76+-0.98	1.01+-0.50	0.54+-0.61
P* value	0.052	0.032	0.011	0.011
Watering				
Group 1	1.29+-0.98	1.06+-0.82	0.53+-0.50	0.45+-0.50
Group 2	1.34+-1.01	1.10+-0.79	0.58+-0.49	0.56+-0.49
P* value	0.096	0.045	0.025	0.001
Photophobia				
Group 1	0.68+-0.80	0.21+-0.40	0.08+-0.30	0.05+-0.21
Group 2	0.72+-0.84	0.20+-0.40	0.10+-0.33	0.07+-0.25
P* value	0.28	0.65	0.15	0.15

Discussion:

This study compared the use of “Olopatidine and Ketorolac” combination therapy vs Olopatidine alone single therapy for treatment of seasonal allergic conjuncitivitis. The results showed that combined treatment with Olopatidine and Ketorolac ophthalmic solutions were more effective in alleviating the clinical signs and symptoms of SAC with combination therapy achieving greater response than Olopatidine alone as single drug therapy.

The mean scores for hyperemia were found to be lower in the Olopatidine plus Ketorolac group than in the Olopatidine alone group in our study. As for ocular itching, the difference reached statistical significance, indicating that Olopatidine plus Ketorolac combination was superior to Olopatidine alone in inhibiting ocular pruritus. The higher clinical effectiveness of Olopatidine plus Ketorolac compared to Olopatidine alone in alleviation of signs and symptoms of SAC, particularly of itching, may be explained by the dual action of this combination. Watering had also improved significantly in the patients who had

received combination treatment. However with respect to photophobia there was no any significant difference in either of the group. This study compliments and extends the work by Albeson. They had conducted a placebo-controlled, randomized studies which demonstrated the effectiveness of Olopatidine in the treatment of allergic conjunctivitis. [9] Olopatadine is a dibenzoxepin derivative that inhibits the release of preformed and newly synthesized inflammatory mediators from mast cells upon allergen challenge, and also has antihistaminic properties towards H1 receptors. [5] [9] [7] On the other hand, Ketorolac is an NSAID; it works through the inhibition of cyclooxygenase, which produces prostaglandins.[3] Antipruritogenic and antihyperaemic actions of Ketorolac in the treatment of SAC can be explained by inhibition of prostaglandin synthesis, particularly prostaglandins D2 and E2. [3] Olopatidine was found to be significantly more effective than Ketorolac in the alleviation of the clinical parameters studied.[7] According to Deschenes et al. (1999), Ketorolac did not significantly reduce itching and increased the hyperaemia compared to placebo. [7] The authors explained Ketorolac's lack of effectiveness in the inhibition of allergic response in the human conjuctiva 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, The first explanation contradicts our as well as other studies which have clinically demonstrated the effectiveness of Ketorolac in the treatment of SAC. [10] [11] In these studies, Ketorolac was used three times daily, in a similar manner to our study. One limitation to our study is that this study included patients who had SAC under natural conditions, implying that they might have been exposed to varying amounts of allergen during the study. In order to minimize a large fluctuation of pollens, all subjects were evaluated within the same month.

Conclusion:

In conclusion, combination therapy with "Olopatidine and Ketorolac ophthalmic solutions" were found to be effective in alleviating the clinical signs and symptoms of SAC achieving greater response than Olopatidine single drug therapy.

Declarations

Ethical clearance: Not required

Consent to participation: written informed consent

Consent for publication: Transferred by the author

Competing interests: None

Funding: None

Authors' contributions: Sanket Parajuli carried out the main study and drafted the manuscript, Ruchi Shrestha made sure the patients were on follow-up on time and examined the patients on followup,

Senny chapagain and Prerana singh made sure 100 patients were taken on each group and sampling was done accurately. Every coauthor has given a significant contribution for making ready this article.

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