International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 15, Issue 10, 2023

Original Article

A COMPARATIVE STUDY OF OLOPATADINE 0.01% COMBINED FLUOROMETHOLONE 0.1% TREATMENT VERSUS OLOPATADINE 0.01% COMBINED KETOROLAC 0.4% TREATMENT IN ALLERGIC CONJUNCTIVITIS IN SAROJINI DEVI EYE HOSPITAL

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Received: 03 Feb 2023, Revised and Accepted: 28 Aug 2023

ABSTRACT

Objective: Comparative study of the efficacy of olopatadine 0.01% combined fluorometholone 0.1% treatment versus olopatadine 0.01% combined ketorolac 0.4% in the treatment of Allergic Conjuctivitis.

Methods: This was a randomized control trial done on 80 subjects with 40 subjects in each group. The clinical signs (chemosis, mucus secretion, eyelid edema) and symptoms (itching, redness, watery eyes, burning) of the patients were evaluated by summing up the scores using a 3-point scale at baseline, 1st and 7th d of initiation of treatment. Results were analyzed by Student's Independent t-test to assess the significant difference of means between the groups. p-value less than 0.05 was considered significant.

Results: The mean age of the study subjects was 29.8±13.5 in Group A and 32.6±8.8 in Group B. Majority were females in both group A and group B with 52.5% and 62.5%, respectively. The reduction was high for chemosis (87.7%) followed by mucous secretion (87.5%) in group A. Highest reduction was seen with itching (59.9%) followed by burning (52.5%) in group B. Significant difference between the groups was noticed with itching (p=0.04), mucous secretion(p=<0.001), chemosis (p=0.01) and eyelid oedema (p=0.009). No significant difference was observed between the two groups (p=0.15) regarding adverse events.

Conclusion: Olopatadine 0.01% combined fluorometholone 0.1% had better efficacy than olopatadine 0.01% combined ketorolac 0.4%.

Keywords: Allergic conjunctivitis, Olapatadine, Fluorometholone, Ketorolac

DOI: https://dx.doi.org/10.22159/ijpps.2023v15i10.47483. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

Allergic conjunctivitis is an ocular disease involving the eyelid, conjunctiva, and cornea with common etiopathogenesis [1]. These diseases affect 15–20% of the population [2]. Three types of Allergic conjunctivitis were identified and they include acute allergic conjunctivitis, Seasonal allergic conjunctivitis (SAC) and Perennial allergic conjunctivitis (PAC). Three differ in clinical characteristics with acute allergic conjunctivitis being severe and resolving within 24 h, Seasonal allergic conjunctivitis is mild and has less dramatic onset, although it can be chronic relating to seasonal allergens. Perennial allergic conjunctivitis (PAC) is a mild, chronic, and related to environmental exposure to perennial, usually indoor, allergens such as dust, animal danders, and molds [3]. Most common was Seasonal allergic conjunctivitis among the three.

Although the condition doesn't threaten vision it can cause significant suffering [4]. It is a type 1 hypersensitivity reaction mediated by IgE antibodies in response to allergens like pollen, grass, dust, etc [5]. Symptoms include itching, tearing, mucosal discharge, lid edema, chemosis, and conjunctivalhyperemia [6].

Mast cells play a pivotal role in the pathophysiology of allergic conjunctivitis. When specific allergens bind to mast cells in the conjunctiva, sensitized mast cells degranulate with the help of calcium and release histamine, tryptase, arachidonic acid, Phospholipase A etc. The reaction of arachidonic acid with cyclooxygenase and lipoxygenase enzymes produces prostaglandins, leukotrienes, thromboxane and platelet-activating factor (PAF). This leads to the manifestation of signs and symptoms [7].

First step of the treatment is keeping away from allergens. Cold compression, irrigation with saline solutions or lubrication with artificial tear drops [8]. When symptoms are severe, pharmacological treatment with H 1 receptor antagonists, mast cell stabilizers, corticosteroids or immunotherapy may beconsidered. H1 receptor antagonists block the action of histamine by competitive binding to the H1 receptor [9]. Mast cell stabilizers such as nedocromil sodium and cromolyn sodium affect on the mucous membranes of the eye by blocking the calcium channels and inhibiting the release of mediators [10]. They also deactivate substance-P and other neuropeptide secretion from the nerve endings. Olopatadineis also H1 receptor blocker and mast cell stabilizer which also inhibits eosinophil degranulation and eosinophil chemotaxis activated by interleukin [11]. Corticosteroids like fluorometholone cause inhibition of transcription proteins and supress phospholipase A and further reduce mast cells in mucosa but long-term usage was implicated in cataract, glaucoma and even exacerbates the condition [12]. Non-steroidal anti-inflammatory agents like ketorolac were an alternative to avoid side effects of corticosteroids [13].

This article evaluates the therapeutic efficacy of low-effective steroid fluorometholone 0.1% and non-steroidal anti-inflammatory ketorolac 0.4% when concurrently used with olopatadine 0.01% in relieving clinical signs and symptoms of allergic conjunctivitis.

The objective of our study was to compare the efficacy of olopatadine 0.01% combined flurometholone 0.1% treatment versus olopatadine 0.01% combined ketorolac 0.4% treatment in patients of allergic conjunctivitis and study to the adverse events among both the groups.

MATERIALS AND METHODS

Study type: Randomised control study

Study population and setting patients diagnosed to have allergic conjunctivitis by Ophthalmologist at a Sarojini Devi Eye Hospital in Hyderabad.

Study period: 12 mo

Sample size: Sample size was calculated using the below formula,

$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\delta_0} \right)^2 \times p \times (1-p)$$

p= Response Rate Of Standard Treatment Group

Z1-β = It is the desired power (0.84 for 80% power)

z1-α/2 = Critical value and a standard value for the corresponding level of confidence. (At 95% CI or 5% type I error it is 1.96) and

δ is margin of error

By review of the literature [14], p=25 and error was considered as 10%. With that, the estimated sample size was calculated to be 75, which is approximated to 80.

Inclusion criteria

We included patients who were clinically diagnosed with allergic conjunctivitis by an ophthalmologist and were willing to give consent. We included patients of both genders in the age group of 8-70 y.

Exclusion criteria

Patients who were contact lens users or had any other ocular abnormalities like dry eye syndrome, blepharitis, uveitis, ocular trauma, or history of any ocular surgery in the last 3 mo were excluded from the study.

Pregnant, lactating mothers and patients who were not willing to give informed consent were excluded from the study.

Ethical consideration

Ethical approval was taken from an institutional ethics committee, Osmania medical College, koti, Hyderabad, bearing reference no: IEC/OMC/2022/M. No.(7)/Acad-62.

Data collection

This is a randomised controlled trial on 80 subjects who were randomly allocated into Group A and Group B with 40 subjects in each group after written informed consent. Group A included subjects whose treatment was with olopatadine 0.01% and fluorometholone 0.1%, while Group B with olopatadine 0.01% and ketorolac 0.4%, with a double blinding technique. Olapatidine 0.01% was instilled 2 times per day and fluorometholone and ketorolac was instilled 4 times per day for 7 d. Data included a detail history including present, past, family, diet and drug history. Findings from a thorough general physical examination and systemic examination were also included. Evaluation of clinical signs i. e; chemosis, mucus secretion, eyelid edema and symptoms i. e; itching, redness, burning and tearing were done on a 3-point scale questionnaire. 0 point–absent, 1 point–mild, 2 points–moderate, 3 points–severe. Signs and symptoms were noted at baseline, on the first day and the seventh day of treatment. Adverse events reported include headache, runny nose, blurring of vision etc.

Statistical analysis

Data analysis was done using Epi-info 7.2.6.6 and Med Calc software. Quantitative variables were represented with mean and SD. Qualitative variables were represented with tables and percentages. Chi-square test was used to test the significance. Student Independent t-test was used to test the significant difference between means of two groups.

RESULTS

The mean age of the study subjects was 29.8±13.5 in Group A and 32.6±8.8 in Group B. No significant difference was noticed (p=0.27, 95% C. I-2.3-7.9). Majority were females in both group A and group B with 52.5% and 62.5%, respectively. There was no significant difference (p=0.73).

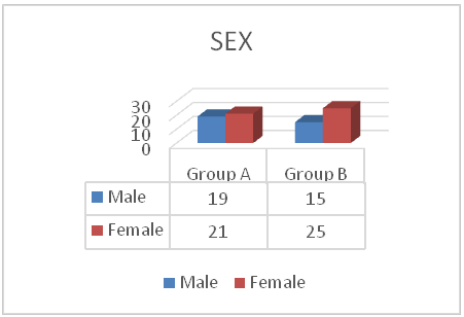

Fig. 1: Sex distribution

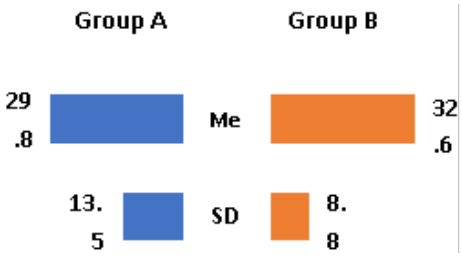

Fig. 2: Mean Age

Table 1: Mean scores of group a (olopatadine-fluorometholone)

Parameter	Baseline	1st d	7th d
Redness	2.41	2.29	0.89
Itching	1.88	1.81	0.70
Burning	2.1	1.99	0.99
Mucous secretion	0.88	0.81	0.11
Watery eyes	1.72	1.65	0.82
Chemosis	0.65	0.60	0.08
Eyelid oedema	0.45	0.41	0.10

Table 2: Mean scores of group B (olopatadine-Ketorolac)

Parameter	Baseline	1st d	7th d
Redness	2.31	2.26	1.21
Itching	1.99	1.92	0.8
Burning	1.94	1.8	0.92
Mucous secretion	0.89	0.81	0.48
Watery eyes	1.66	1.61	0.99
Chemosis	0.71	0.65	0.45
Eyelid oedema	0.49	0.44	0.31

Table 1 illustrates the signs and symptoms in group a on 1st d and 7th d of initiation of treatment. Maximum score was observed with redness and less with eyelid oedema before initiation of treatment. All parameters were improved from baseline to 7th d. Reduction was high for chemosis (87.7%) followed by mucous secretion (87.5%), eyelid oedema (77.7%), redness (63.1%), itching (62.7%), burning (52.8%) and watery eyes (52.3%).

Table 2 shows the signs and symptoms in group B on 1st d and 7th d of initiation of treatment. Redness and itching were more common in this group. Similar reduction of score was observed in group B as well. Highest reduction was seen with itching (59.9%) followed by burning (52.5%), redness (47.6%), mucous secretion (46.1%) watery eyes (40.4%), eyelid oedema (36.7%), chemosis (36.6%).

Table 3: Comparison of mean reduction in scores on 7th d after initiation of treatment

Parameter	Group A (Mean reduction in score)	Group B (Mean reduction in score)	p-value
Redness	1.52±0.46	1.1±0.92	0.05
Itching	1.18±0.11	1.13±0.15	0.04
Burning	1.11±0.21	1.02±0.23	0.15
Mucous secretion	0.77±0.05	0.41±0.15	<0.001
Watery eyes	0.9±0.41	0.67±0.43	0.07
Chemosis	0.57±0.07	0.26±0.9	0.01
Eyelid oedema	0.35±0.2	0.05±0.33	0.009

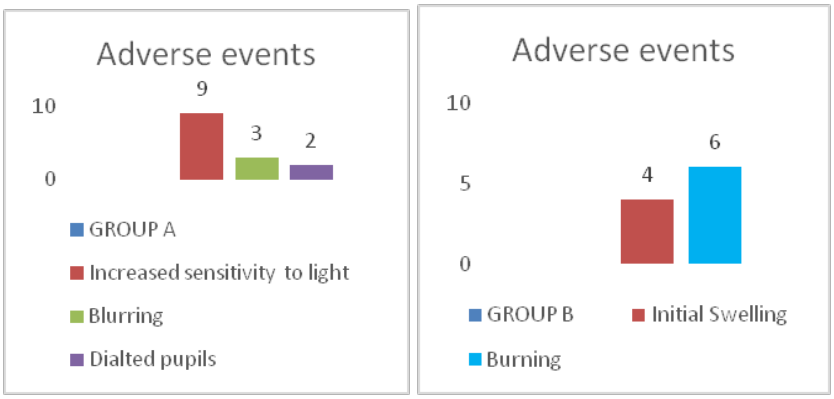

Fig. 3: Adverse events

Table 3 compares the mean reduction of signs and symptom scores of the two groups assessed on 7th d after initiation of treatment. Highest reduction was seen with group A compared to group B. The mean reduction for redness was 1.52±0.46 in group A and 1.1±0.92 in group B. For itching, it was 1.18±0.11 in group A and 1.13±0.15 in group B. Other symptoms like burning showed a reduction of 1.11±0.21 and 1.02±0.23 group A and group B, respectively. Mean reduction score for watery eyes was 0.9±0.41 in group A and 0.67±0.43 in group B and for eyelid oedema it was 0.35±0.2 and 0.05±0.33 in each group.

Most common noticed signs were mucous secretion and chemosis. Mean reduction for mucous secretion was 0.77±0.05 and 0.41±0.15 in group A and group B, respectively. The sign chemosis showed mean reduction of 0.57±0.07 and 0.26±0.9 in group A and group B, respectively, were also reduced. Significant difference was noticed with itching (p=0.04), mucous secretion (p=<0.001), chemosis (p=0.01) and eyelid oedema (p=0.009).

Fig. 3: shows the adverse events noticed in the two groups. Majority (n=9, 22.5%) had increased sensitivity to light in group A and burning was more common in group B (n=6, 15%). No significant difference was observed between the two groups (p=0.15).

DISCUSSION

Total 80 subjects were divided into two groups, with group A receiving treatment with olopatadine 0.01% and fluorometholone 0.1%, while Group B receiving treatment with olopatadine 0.01% and ketorolac 0.4%.

The detrimental effects of allergic conjunctivitis can be mitigated by effective therapeutic medications. Traditional steroids like prednisolone, which were effective, can cause potential adverse events like glaucoma, cataract and even delays wound healing. Modified corticosteroids were introduced, which have better safety profile as they gets metabolized much faster than traditional steroids [15, 16].

These modified corticosteroid scan still increase intraocular pressure and leads to cataract on long-term use. Modified corticosteroid fluorometholone has low intraocular absorption and was found to be highly effective in reducing itching, tearing and conjunctival hyperaemia and did not exhibit any statistically significant changes in intraocular pressure [17].

Olopatadine is a topical ocular dibenzoxepin derivative and acts by inhibiting the release of inflammatory mediators from mast cells and also had antihistaminic properties. This dual activity makes it suitable for both therapeutic and prophylactic action. Concomitant usage had added beneficial effect. Olopatadine hydrochloride is shown to be significantly more efficacious than NSAIDs, mast cell stabilizers, and placebo [18-20].

Considering the adverse effects of steroids, the importance of NSAIDs was emphasized in therapeutic management. They act by blocking cyclooxygenase and the subsequent release of prostaglandins, which is a key inflammatory mediator in IgE-related diseases such as AC. Thus, it aids in relieving the associated itching and redness in Allergic Conjunctivitis with minimal side effect [21-23].

In the present study majority were females in both the groups (52.5% and 62.5%, respectively) and the mean age was mean age was 29.8±13.5 in Group A and 32.6±8.8. In a similar study by Cevik *et al.*, considering gender distribution, females were 61.5% and 62.9% in respective groups. The mean age of the first group was 30.1 y (range, 15–48) and the mean age of the second group was 32.3 y (range 17–44). There was no significant difference (p=0.82) between the two groups, which is similar to the present study (p=0.73).

The signs and symptoms were compared in both groups. There is noticeable reduction in scores among both the groups from baseline to 7th d of initiation of treatment.

Maximum score was associated with redness in both groups (2.41 and 2.31, respectively). In Cevik *et al.* study, maximum scores were associated with redness (2.26) in group A and burning (1.07) in group B.

Reduction was high for chemosis (87.7%) followed by mucous secretion (87.5%) in group A, while in group B, the highest reduction was associated with itching (59.9%) followed by burning (52.5%). In Saeed *et al.* study, patients who received sodium cromoglycate-fluorometholone eye drops experienced significant improvements in their itching score (mean difference [MD]: 1.14) and conjunctival redness score (MD: 1.18) [24]. In Rajeev *et al.* study, the mean itching scores was lower in the olopatadine with ketorolac group compared to ketorolac group. At day 15, 95% of patients had no complaint of itching in group 2 (p value<0.0001), indicating that the combination of olopatadine with ketorolac as superior to ketorolacalone in inhibiting ocular itching.

In the present study, a significant difference was seen with itching (p=0.04), mucous secretion (p=<0.001), chemosis (p=0.01) and eyelid oedema (p=0.009), with group a (olopatadine with fluorometholone) showing better reduction than group B (olopatadine with ketorolac). There is no difference with respect to redness (p=0.05), burning (p=0.15) and watery eyes (p=0.07). Castilo M *et al.* proved olopatadine has cumulative role when administered in combination with 0.4% ketorolac [25].

In Cevic *et al.* study, both drugs were similar in alleviating the symptoms of itching, burning and tearing (p = 0.074 for itching, p = 0.064 for burning, p = 0.072 for tearing). On the other hand, fluorometholone was superior to ketorolac in reducing redness, mucus secretion, chemosis and eyelid oedema (p = 0.032 for redness, p = 0.028 for mucus secretion, p = 0.030 for chemosis, p = 0.042 for eyelid oedema).

In Rajeev *et al.* study, they compared olopatadine with ketorolac. 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. According to Ravindra *et al.* study, the combination of 0.1% olopatadine and 0.4% ketorolac was more effective than 0.4% ketorolac alone in seasonal allergic conjunctivitis patients [26].

Olopatadine 0.01% combined fluorometholone 0.1% is more efficacious than olopatadine 0.01% combined with ketorolac 0.4% in the present study. The combination of 0.1% olopatadine and 0.4% ketorolac was more effective than 0.4% ketorolac alone in seasonal allergic conjunctivitis patients in Ravinder *et al.* study [26].

The side effects in group A included increased sensitivity to light (n=9), burning (n=3) and dilated pupils (n=2), while in group B swelling of eyes (n=4) and burning (n-6) In Li *et al.* study, the intraocular pressure increased by 0.7 mm Hg in the fluorometholone group while in Solomon *et al.* study, transient stinging and burning on instillation of ketorolac tromethamine 0.5% was reported by 40% of subjects participating in clinical trials [27].

CONCLUSION

The present study concluded that, Olopatadine 0.01% combined fluorometholone 0.1% had better efficacy than olopatadine 0.01% combined ketorolac 0.4%. Very less studies were present comparing steroids with NSAIDs in treating allergic conjunctivitis.

Further research is necessary to contribute to literature and choosing a better drug combination in acute seasonal allergic conjunctivitis considering the side effects of steroids on long term use.

ACKNOWLEDGEMENT

Authors would like to thank the Staff of Ophthalmology department at Sarojini Devi Eye hospital and the Staff members of Department of Pharmacology Osmania Medical College for their constant support and encouragement and would like to express our sincere gratitude to all the patients for the generosity shown by them and having consented to take part.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Special thanks to all the authors having made significant contributions in writing, reviewing and submitting the manuscript

CONFLICTS OF INTERESTS

Declared none

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