

## Comparison of Symptomatic Relief of VKC between Topical 0.025% Ketotifen Fumarate and topical 4% Cromolyn Sodium

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### ABSTRACT

**Aim:** To compare the relief of symptoms of vernal keratoconjunctivitis after use of ketotifen fumarate 0.025% and cromolyn sodium 4%.

**Methods:** This was a comparative study and was conducted at Department of Ophthalmology, King Fahad Armed Forces Hospital, Jeddah from February March 2013 to September 2013. Total 600 hundred patients suffering with VKC symptoms were included in this study.

**Results:** In Group A and Group B mean age was 17.01±5.13 years and 16.72±5.02 years. Symptomatic relief of VKC was seen in 215(71.67%) patients treated with Ketotifen Fumarate as compare to 162 (54%) patients treated with Cromolyn Sodium. More symptomatic relief of VKC was observed in male as compare to female.

**Conclusion:** Symptomatic relief of VKC symptoms with ketotifen fumarate 0.025% is significantly better than the use of cromolyn sodium 4%. Better symptomatic relief of VKC was seen in male as compare to female. So it can be taken as first line drug for the symptomatic relief of VKC symptoms.

**Keywords:** Keratoconjunctivitis, ketotifen fumarate, cromolyn sodium

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### INTRODUCTION

Ocular allergies are the most common conditions affecting the external ocular adnexa throughout the world<sup>1</sup>. These allergies are type 1 hypersensitivity reactions which are mediated by Ig-E antibody in response to various environmental allergens such as pollens, mites, molds, dust, grass, weeds and animals dander<sup>2,3</sup>.

Vernal Keratoconjunctivitis (VKC) is a bilateral, recurrent disorder in which Ig-E and cell mediated immune mechanism play key role<sup>2</sup>. It initially affects the body and usually found in first decade of life (mean age 7 years); about 95% cases remit by the late teens and the remainder develops atopic keratoconjunctivitis<sup>2</sup> it usually occurs at the onset of hot weather and subsides during winter<sup>2</sup>. In temperate regions about 1/3 of patients have associated atopy and 2/3 have a family history of atopy<sup>2</sup>. Symptoms are intense itching associated with lacrimation, a foreign body sensation, photophobia, burning and thick mucoid discharge<sup>2</sup>.

Mast cells play a major role in pathogenesis of vernal keratoconjunctivitis<sup>2</sup>. When a specific allergen binds to the sensitized mast cell in conjunctiva it causes degranulation of mast cells and inflammatory mediators are released i.e., histamine, prostaglandins, leukotrienes, PAF of all, histamine is

responsible for symptoms of vernal keratoconjunctivitis predominantly<sup>3</sup>. Most common agents for symptomatic relief of vernal keratoconjunctivitis are mast cell stabilizers, antihistamine, steroids and ciclosporins<sup>4</sup>.

Commonly used topical agents in vernal keratoconjunctivitis include antihistamines, mast cell stabilizers, immunosuppressive drugs and corticosteroids<sup>5</sup>. Newer, more selective therapeutic strategies like leukotriene receptor antagonists, antichemokine receptor antibodies and specific macrobiomolecules are under evaluation<sup>5</sup>.

In literature, there is a variation in comparing symptomatic relief of VKC symptoms after the use of ketotifen fumarate 0.025% and cromolyn sodium 4%. So a study was planned to evaluate the symptomatic relief of VKC with the use of ketotifen fumarate 0.025% and cromolyn sodium 4%. Results of this study will guide us, which one drug has better safety and efficacy profile.

### MATERIAL AND METHODS

This comparative study was consisted on 600 patients with VKC symptoms and was conducted at Department of Ophthalmology, King Fahad Armed Forces Hospital, Jeddah from February March 2013 to September 2013. An approval was taken from institutional review committee and verbal consent was taken from every patients. Patients with symptoms of intense itching, pain, redness, lacrimation, photophobia, foreign body sensation and with signs; conjunctival chemosis, hypertrophy,

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hyperemia, papillae, mucous deposition on papillae, punctate epithelial erosion on slit lamp examination were considered as a case of vernal keratoconjunctivitis. Symptoms were graded as present or absent according to history and after complete slit lamp examination. The absence or presence of symptoms was used as a mean of determination.

Patients having age 8 to 25 years either male or female and were not using any topical medicine for VKC (mast cell stabilizers antihistamines and steroids) were excluded from this study. Patients with glaucoma, diabetic retinopathy, corneal ulcer and ocular hypertension were excluded from the study. All the patients were divided into two groups A and B randomly.

Ketotifen fumarate was advised to the patients of Group A 1 drop BD and cromolyn sodium was advised to the patients of Group B Q.I.D. Weekly follow-up of the patients was done and final outcome was determined at 28<sup>th</sup>. Efficacy of the both drugs was noted in pre-designed proforma in terms of present or absent of VKC symptoms. The disappearance of the symptoms of the disease was considered as resolution of the disease. Demographic data of all the patients were also noted in the proforma.

All the collected data was entered in SPSS version 16 and analyzed. Mean and SD was calculated for age and frequencies were calculated for categorical data. Chi-square test was used as test of significance to compare the proportion of relief of symptoms between the two groups. P. value  $\leq$  0.05 was considered as significant.

## RESULTS

This study consisted of 600 patients with symptoms of VKC. Mean age of patients in Group A was 17.01 $\pm$ 5.13 years and mean age of the patients in group B was 16.72 $\pm$ 5.02 years. At the end of 4<sup>th</sup> week (day 28<sup>th</sup>), out of 300 patients of Group A, symptomatic relief of VKC was seen in 215(71.67%) patients and in group B symptomatic relief of VKC symptoms was seen in 162(54%) patients. Significantly higher proportion of symptomatic relief of VKC in Group A was seen as compared to group B. P. value 0.001 (Table 1)

Among the 300 patients of Group A, male patients were 184(61.33%) and female patients were 116(38.67%). Symptomatic relief of VKC was seen in 153(83.15%) male patients and 62 (53.45%) female patients. Significant association was observed between relief of VKC symptoms and gender, P. value 0.001 (Table 2).

Patients of Group A were divided into two age groups, 8-16 years and 17-25 years. There were

146(48.67%) patients in age group 8-16 years and symptomatic relief of VKC symptoms were observed in 97(64.44%). Age group 17-25 years consisted of 154(51.33%) patients and symptomatic relief of VKC was seen in 118(76.62%) patients. Significant association was seen between symptomatic relief of VKC and age of the patients, P. value 0.034 (Table 3).

Table 1: Comparison of symptomatic relief of VKC between two groups

Groups	Present	Absent	Total
Group A	85(28.33%)	215(71.67%)	300(50%)
Group B	138(46%)	162(54%)	300(50%)
Total	223(37.17%)	377(62.83%)	600(100%)

P value: 0.001

Table 2: Relation of symptomatic relief of VKC with gender

Gender	Present	Absent	Total
Male	31(16.85%)	153(83.15%)	184(61.33%)
Female	54(46.55%)	62(53.45%)	116(38.67%)
Total	85(28.33%)	215(71.67%)	300(100%)

P value 0.001

Table 3: Relation of symptomatic relief of VKC with age

Age group	Present	Absent	Total
8-16 yrs	49(33.56%)	97(64.44%)	146(48.67%)
17-25yrs	36(23.34%)	118(76.62%)	154(51.33%)
Total	85(28.33%)	215(71.67%)	300(100%)

P value: 0.034

## DISCUSSION

VKC is a most common, preventable and clinically significant IgE mediated hypersensitivity response. VKC is an immunopathological disease in which the number of mast cells in substantia propria increase. Activation of mast cells by IgE bound receptor crosslinking by allergen promotes the release of many mediators like histamine, cytokinase and prostaglandins, all of which contribute to the symptoms of VKC. The mast cell played an important role in producing symptoms of VKC<sup>6</sup>. Current therapy of VKC focuses on modulation of the immune system and pharmacologic inhibition of the chemical mediators involved in the immune response. Antihistamines and mast cell stabilizers are frequently used groups of therapeutic agents. They stabilize the mast cell membranes by preventing calcium influx across the mast cell membranes, thereby preventing mast cell degranulation and mediator release. The new antihistamines have been capable to be capable of affecting several phenomena of the allergic inflammation including mediator release<sup>6</sup>.

Among these drugs, new multiple - action agents like Ketotifen fumarate is histamine H1-receptor antagonist, as well as mast cell stabilizer.

Additionally, in vitro and animal studies have demonstrated that Ketotifen fumarate inhibits the activation and chemotaxis of eosinophils into the conjunctiva, which is an important step in the late phase of the immune response<sup>6</sup>.

Cromolyn sodium, as a mast cell stabilizer is effective and safe in the treatment of VKC, but topical steroids which are often required, increase the chance of bacterial keratitis, cataract, and glaucoma, so we decided to perform this study in order to investigate and compare the effect of the topical Ketotifen fumarate with Cromolyn sodium in moderate VKC.

In the present study main VKC symptoms decreased significantly by day 28. As shown in table 1, the control of VKC symptom with Ketotifen fumarate 215 (71.67%) is better as compare to cromolyn sodium 162 (54%). In a study Shoja et al<sup>6</sup> reported symptomatic relief of VKC with Ketotifen fumarate as 61.5% which is comparable with my study. Another study of Australia<sup>7</sup> reported better control of VKC symptoms as 49.5% which is lower than my study. Ganz et al also<sup>8</sup> documented a higher cure rate of ketotifen fumerate. Clinical trials demonstrated that ketotifen eye drop was safe and effective, providing a rapid onset and long duration of action.<sup>9</sup> Leonardi's<sup>10</sup> study showed that investigators assessment of response rates for Ketotifen fumerate was superior to Cromolyn which is similar to our study. A study by Andren et al<sup>11</sup> reported response rate 91.2% for Ketotifen fumerate and 83.5% for Cromolyn treatment groups that were close to our study. Ketotifen was found to have a faster onset of action than Cromolyn.

Although the effectiveness of ketotifen fumarate in seasonal allergic conjunctivitis (SAC) has already been shown. The findings of our study confirm effectiveness of Ketotifen in VKC. Ketotifen fumerate, two times daily was significantly more effective than sodium Cromolyn three times daily in alleviating symptoms and signs of moderate VKC.<sup>6</sup> The faster onset of action (within 15 minutes) and better symptoms relief observed with Ketotifen during the initial 2 hours, along with favourably safety and tolerability profile make Ketotifen fumerate a new valuable therapy for patients with moderate VKC<sup>6</sup>. In contrast to our study, a study at Canada Ketotifen reported to be slightly discomfort (mild burning) after installation as compared to other anti allergic drugs, but even then its efficacy is not in doubt<sup>12</sup>.

In one study it was concluded that ketotifen was effective and safe for the reduction of ocular itching, hyperemia associated with allergic conjunctivitis; it

has a rapid onset within 15 min and extended duration (at least 8 hours)<sup>13</sup>. Ketotifen also was superior to cromoglycate Na in controlling itching, tearing and redness when used as a single dose vs. four times daily use of the later for 2 weeks in conjunctival allergy challenge model<sup>14</sup>.

## CONCLUSION

Symptomatic relief of VKC symptoms with ketotifen fumarate 0.025% is significantly better than the use of cromolyn sodium 4%. Better symptomatic relief of VKC was seen in male as compare to female. So it can be taken as first line drug for the symptomatic relief of VKC symptoms.

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