ORIGINAL ARTICLE

Safety and efficacy of Lodoxamide 1% and sodium chromoglycate 4% in patients with vernal keratoconjunctivitis

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Abstract

Objective: To compare the severity of the disease after seven days treatment with Lodoxamide 0.1% ophthalmic solution eye drops with cromolyn sodium 4% eye drops in patients with bilateral VKC with each follow up till 12 weeks. (90 days). To compare the type and severity of complications after the two drugs 12 weeks follow ups.

Study Design: Quasi experimental , Interventional

Setting : This study was carried out in the outpatient department at Jinnah Medical College Hospital, Karachi from February 2007 to April 2009.

Subjects : Non Probability purposive

Intervention : This comparative study was 12 weeks (three months) with each follow up after two weeks.

Results: 60 patients between 5 to 18 years examined and selected for study. The patients were randomly divided into equal groups (30 patients in each group) with A and B. Group A received topical Lodoxamide ophthalmic solution 0.1% (LOS): Group B prescribed topical cromylin sodium ophthalmic solution 4% (CSO) in dose of two drops four times daily.

Conclusions: From our study it can be concluded that vernal conjunctivitis is a disease of unknown etiology and is self limiting upto age of 18 years in majority of cases. No treatment is curative but we can make the patients symptom free as much as possible and can prevent its complications.

Keywords : Lodoxamide, Sodium Chromoglycate, Vernal Keratoconjunctivitis

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Introduction:

Vernal conjunctivitis is an allergic inflammatory condition with characteristic giant papillae, usually on the upper tarsal conjunctiva and less commonly limbus.

It is probably a combination of Type I and type IV hypersensitivity reaction. This is associated with mucous discharge usually containing eosinophils. It has seasonal incident commonly at the beginning of summer and is self limited. Its etiology is not known. It occurs on both sexes predominantly males. There is usually a personal or family history of other atopic reaction.

The predominant symptoms are ocular itching with associated tearing, burning, mucous production and light sensitivity. The giant papillae on upper tarsal conjunctiva may have the appearance of cobblestone and are the probable cause of a diffuse superficial punctuate keratitis or ulceration.

A morphologic shield ulcer may develop which is persistent and can lead to microbial infection or corneal scarring. There may be accumulation of inflammatory cells mainly eosinophils near limbus called Horner Tranta's dots upto 27% of patients may have permanent visual loss as a result of vernal kerato conjunctivitis.

Material and methods:

This was a comparative study which was conducted in outpatient department at Jinnah Med-

ical College Hospital, Karachi. The selection of the patients were between the age of 5 to 18 years. A printed Proforma was given to each patient and was enrolled according to the criteria of our study. The diagnosis of VKC was based on history of symptoms (redness, itching, tearing etc) and signs of junction conjunctival papillary hypertrophy and hyperemia, gelatinous infiltration of the limbus known as trantas dots and superficial punctuate keratitis. Complications such as shield ulcers. The patient was an OPD subject using the drugs at home with strict compliance. Follow up was of fifteen days in OPD. The parents/guardians of patients were ensure the compliance of drugs used by the patient. The study was conducted between February 2010 to April 2010 in Jinnah Medical College Hospital OPD.

Results:

A total of 60 eyes of 60 patients were analyzed. There were 40 (66.7%) males and 20 (33.3%) females in the study with 1:2 male to female ratio (Figure-1). Average age of the patients was 12.60 ± 3.53 (ranging from 6 to 18) years. Age distribution is given in figure-2. Mean age in the patients who underwent LOS-0.1% is observed 12.07 ± 1.70 (ranging from 5 to 18) years. Insignificant difference was observed (p = 0.28) between the average age of both groups (Table-1)

Systemic diseases were evaluated as asthma (n = 8, 13.3%), vasomotor rhinitis and chronic tonsillitis were equally noticed (n = 5, 8.3%) (Table-2).

Level of patients comfort at different follow up visits was observed. At first follow up after 2 weeks, 60% patients of group-A and 33.3% patients of group-B were found comfortable, proportion of comfortable patients was significantly higher (p = 0.038) in group-A. The same pattern of higher proportion of comfortable patients was observed at every visit in group-A patients than group-B. At final follow up the trend consistent with 93.3% vs. 70% (p = 0.001) (Table-3).

Average severity score was computed according

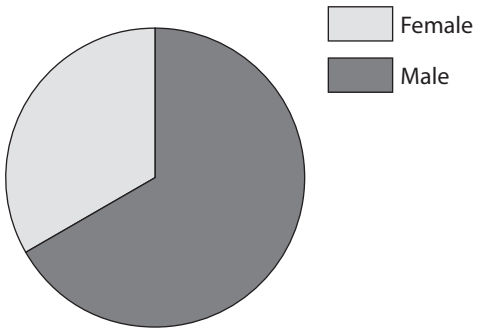

Figure 1: *Sex distribution (n=60)*

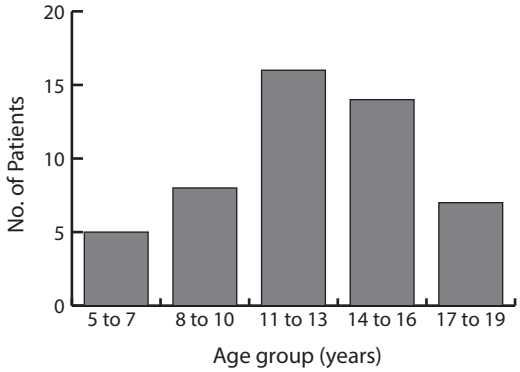

Figure 2: *Age distribution (n=60)*

to patients compliance. Average severity of signs and symptoms in group-A was computed 2.15 ± 0.27 comparing with group-B 2.12 ± 0.35, the mean severity of group-A was significantly less than that of group-B (p = 0.001). A uniform trend of reduction of severity was observed in group-A at every successive follow ups (p = 0.001). At final follow up after 12 weeks, average severity score (0.74 ± 1.25) of group-A was significantly less than (1.02 ± 2.70) of group-B (p = 0.001) as shown in table-4.

Symptoms of itching at baseline examination was not statistically significant between two group-A and group-B (80% vs. 86.7%) respectively (p = 0.49). After two weeks at first follow up visit a significant difference in reduction of symptoms was observed between group-A and group-B (63.3% vs. 83.3%) respectively (p = 0.045). The same pattern of reduction of itching was observed at all follow up visits. At final follow up after 12 weeks, the trend was found maintained in group-A than group-B (16.7% vs. 40%) (p = 0.045) as shown in table-5.

Table 1: *Comparison of mean between two groups with dys*

Variable	0.1% (LOS) n = 30	4% (COS) n = 30	Significance
Age (in years)	12.7 ± 1.70 (5 – 18)	13.23 ± 1.12 (5 – 18)	t = 1.31 p = 0.28

Key: Given values in column-3 is Mean ± Standard deviation (Range)
Insignificant difference of means between two groups at p < 0.05

Table 2: *Systemic Disease (n = 60)*

Systemic disease	Number of patients	Percentage
Asthma	8	13.3
Vasomotor rhinitis	5	8.33
Chronic tonsillitis	5	8.33

Table 3: *Outcome at different follow up visits*

Follow up Visits	No.of patients Comfortable		Significance	
	0.1% (LOS) n = 30	4 % (CSO) n = 30	X^2 - value	p - value
2 weeks	18 (60%)	10 (33.3%)	4.27	0.038*
4 weeks	21 (70%)	12 (40%)	5.46	0.020*
6 weeks	22 (73.3%)	14 (46.7%)	4.44	0.035*
8 weeks	25 (83.3%)	17 (56.7%)	0.0	0.0001*
10 weeks	26 (93.3%)	19 (70%)	0.22	0.65
12 weeks	28 (93.3%)	21 (70%)	17.0	0.0001*

*Key: *Showed statistical significance at p < 0.05.*
LOS: Lodoxamide 0.1% ophthalmic solution
CSO: Cromolyn sodium 4% ophthalmic solution

Table 4: *Comparison of mean severity between two groups:*

Follow up Visits	0.1% LOS)	4% (CSO)	Significance
2 weeks	2.15 ± 0.27	2.33 ± 0.17	p = 0.001
4 weeks	1.96 ± 0.35	2.25 ± 0.19	p = 0.001
6 weeks	1.85 ± 0.45	2.12 ± 0.35	p = 0.005
8 weeks	1.55 ± 0.40	1.98 ± 0.42	p = 0.001
10 weeks	1.22 ± 0.56	1.65 ± 0.34	p = 0.001
12 weeks	0.74 ± 1.25	1.02 ± 2.70	p = 0.001

Key: Given values in column-3 is mean ± standard deviation (Range)
**Significance difference of means between two groups at p < 0.05*
LOS: Lodoxamide 0.1% ophthalmic solution
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Reduction of symptoms of redness was insignificant between group-A and group-B (50% vs. 73.3%, p = 0.06) until second follow up (after 4 weeks). A significant reduction in group-A than group-B (40% vs. 66.7%, p = 0.001) was found at third follow up visit (after 6 weeks). The successive visits were also showed same pattern (Table-6).

Signs of gelatinous infiltration of limbus, hyperemia and trantos dots were compared between two groups at successive follow up visits. A less proportion of patients with these signs was observed in group-A than group-B however this difference was not significant (Table7, 8 and 9).

Discussion:

Vernal keratoconjunctivitis is a chronic inflammatory disorder in which both IgE and cellular mechanism are recognized as pathogenic factors. The typical clinical signs of vernal conjunctivitis are presence of papillae on tarsal conjunctiva and presence of Horner Tranta's dots on limbus. There is itching, photophobia, lacrimation and Foreign body sensations.

The typical histological features of vernal conjunctivitis are the conjunctival infiltration of eosinophils and basophiles, a constant increased number of mast cells and a connective tissue hyperplasia with an increased deposition of collagen.[1,2]

An accumulation of TH2 like helper T cells, producing interleukin 3,4 and 5 has also been shown to occur in VKC, accounting for the frequent occurrence of high levels of tear immunoglobulin E, mast cells proliferation and the abundant presence of eosinophils.[3]

Activated consinophils are known to release toxic factors, such as currently studies ECP (eosinophil catonic proteins) in addition to major basic protein, eosinophil peroxidase, eisonophil derived neurotoxin/ eosinophil protein X.

Eosinophil major basic protein has already been shown to play a role in the pathogenesis of epithelial erosions observed in VKC, indicating the importance of eosinophil activication in severe forms of this disease.[5]

Higher levels of serum ECP were also shown indicating that VKC should be considered a systemic disorder with circulating activated eosinophils.65 The toxic effect of ECP on corneal epithelial cells has been shown in vitro.[6]

The barrier properties of in vitro human corneal epithelial model are not altered by eosinophil major basic protein or eosinophil catonic pro-

Table 5: *Symptoms of itching at different follow up*

Follow up Visits	No.of patients		Significance	
	0.1% (LOS) n = 30	4 % (CSO) n = 30	X^2 - value	p - value
Baseline	24 (80%)	26 (86.7%)	0.48	0.049*
1st visit (2 weeks)	18 (63.3%)	25 (83.3%)	4.02	0.045*
2nd visit (4 weeks)	15 (50.0%)	23 (76.7%)	4.59	0.032*
3rd visit (6 weeks)	12 (40.0%)	20 (66.7%)	4.29	0.038*
4th visit (8 weeks)	10 (33.3%)	18 (60%)	4.29	0.038*
5th visit (10 weeks)	08 (26.7%)	17 (56.7%)	5.55	0.018*
6th visit (12 weeks)	05 (16.7%)	12 (40.0%)	4.02	0.045*

*Key: *Showed statistical significance at p < 0.05.*
LOS: Lodoxamide 0.1% ophthalmic solution
CSO: Cromolyn sodium 4% ophthalmic solution

Table 6: *Symptoms of redness at different follow ups*

Follow up Visits	No.of patients		Significance	
	0.1% (LOS) n = 30	4 % (CSO) n = 30	X^2 - value	p - value
Baseline	24 (80%)	23 (76.7%)	0.10	0.75
1st visit (2 weeks)	18 (60.0%)	22 (73.3%)	1.20	0.27
2nd visit (4 weeks)	15 (50.0%)	22 (73.7%)	3.45	0.06
3rd visit (6 weeks)	12 (40.0%)	20 (66.7%)	17.0	0.001*
4th visit (8 weeks)	10 (33.3%)	18 (60%)	4.29	0.038*
5th visit (10 weeks)	08 (26.7%)	16 (53.3%)	4.44	0.035*
6th visit (12 weeks)	04 (13.3%)	11 (36.7%)	4.36	0.037*

*Key: *Showed statistical significance at p < 0.05.*
LOS: Lodoxamide 0.1% ophthalmic solution
CSO: Cromolyn sodium 4% ophthalmic solution

Table 7*: Signs of gelatious infiltration of limbus at different follow ups*

Follow up Visits	No.of patients		Significance	
	0.1% (LOS) n = 30	4 % (CSO) n = 30	X^2 - value	p – value*
Baseline	26 (86.7%)	24 (80.0%)	0.48	0.49
1st visit (2 weeks)	22 (73.3%)	22 (73.3%)	0.00	0.99
2nd visit (4 weeks)	20 (66.7%)	21 (70.0%)	0.08	0.78
3rd visit (6 weeks)	17 (56.7%)	20 (66.7%)	0.64	0.43
4th visit (8 weeks)	14 (46.7%)	18 (60%)	1.07	0.30
5th visit (10 weeks)	13 (43.3%)	15 (50.0%)	0.27	0.61
6th visit (12 weeks)	11 (36.7%)	14 (46.7%)	0.62	0.43

*Key: *insignificance difference at p < 0.05.*
LOS: Lodoxamide 0.1% ophthalmic solution
CSO: Cromolyn sodium 4% ophthalmic solution

tein suggesting a relation between this mediator and VKC related corneal damage and that reduction of eosinophil activation may be an important objective in treatment of VKC.

Lodoxamide significantly decreases mean eosinophil catonic protein level.[7] Lodoxamide is a newly available mast cell stabilizer more active than disodium chromoglycate in inhibiting the passive cutaneous anaphylaxis and conjunctival allergic reaction in animal models.[8]

In another studies lodoxamide has been shown to be more effective than sodium chromoglycate in alleviating signs and symptoms of VKC.[9]

In another study it was shown that Lodoxamide is more effective at decreasing steroid use.[10]

In other long term study lodoxamide was shown to decrease corneal epitheliopathy.[11,12]

With present data lodoxamide was shown to reduce eosinophil activation and the release of toxin protein.[13]

Lodoxamide significantly reduced histamine release during early phase of the allergic reaction only but reduce signs and symptoms during both early phase reaction (EPR) and late phase reaction (LPR) of allergic reaction. Lodoxamide reduced all cell counts significantly and in particular, eosinophil count during late phase of allergic reaction.[14]

In another study where both drugs lodoxamide and sodium chromoglycate were compared in patients suffering from different types of allergic conjunctivitis predominantly type I hypersensitivity reactions such as vernal keratoconjunctivitis, giant papillary conjunctivitis or atopic conjunctivitis. Lodoxamide was found superior to 4% opticrome in treating vernal giant papillary and allergic conjunctivitis.[14,15]

In another study lodoxamide was found to be significantly superior to sodium chromoglycate in reducing painful phenomenon, foreign body sensation, discharge and photophobia. Lodoxamide was more effective in reducing redness, punctuate keratitis. Electron microscopy showed that patient on lodoxamide showed a considerable reduction on interstitial oedema.[13,14]

Table 8: *Signs of hyperemia at different follow ups*

Follow up Visits	No.of patients		Significance	
	0.1% (LOS) n = 25	4 % (CSO) n = 25	X^2 - value	p – value*
Baseline	18 (72%)	16 (64%)	0.37	0.54
1st visit (2 weeks)	16 (64%)	15 (60.0%)	0.09	0.77
2nd visit (4 weeks)	15 (60.0%)	14 (66.0%)	0.08	0.77
3rd visit (6 weeks)	12 (48.0%)	13 (52%)	0.08	0.78
4th visit (8 weeks)	9 (36%)	11 (44%)	0.33	0.56
5th visit (10 weeks)	8 (32%)	9 (36%)	0.09	0.77
6th visit (12 weeks)	6 (24%)	8 (32.0%)	0.29	0.59

*Key: *insignificance difference at p < 0.05.*
LOS: Lodoxamide 0.1% ophthalmic solution
CSO: Cromolyn sodium 4% ophthalmic solution

Table 9: *Signs of trantos dots at different follow ups*

Follow up Visits	No.of patients		Significance	
	0.1% (LOS) n = 25	4 % (CSO) n = 25	X^2 - value	p – value*
Baseline	14 (56%)	15 (60%)	0.08	0.77
1st visit (2 weeks)	12 (48%)	13 (52%)	0.08	0.77
2nd visit (4 weeks)	9 (36%)	11 (44%)	0.33	0.56
3rd visit (6 weeks)	8 (32%)	10 (40%)	0.35	0.57
4th visit (8 weeks)	7 (28%)	9 (36%)	0.37	0.54
5th visit (10 weeks)	6 (24%)	8 (32%)	0.40	0.53
6th visit (12 weeks)	5 (20%)	7 (28%)	0.44	0.51

*Key:*insignificance difference at p < 0.05.*
LOS: Lodoxamide 0.1% ophthalmic solution
CSO: Cromolyn sodium 4% ophthalmic solution

In another study it was shown that lodoxamide reduced papillae and follicles when used upto five months and was free of side effects.[15]

In our study lodoxamide was more effective than sodium chromoglycate in resolving threre of the key signs of VKC. Tranta's dots Gelantious infiltration of limbus, hyperemia. It was also found to be more effective than sodium chromoglycate in alleviating four of the primary symptoms of disease of itching, redness, foreign body sensation and discomfort.

Conclusion:

It can be concluded that vernal conjunctivitis is a disease of unknown etiology and is self limiting upto age of 18 years in majority of cases. No treatment is curative but we can make the patient symptom free as much as possible and can prevent its complications.

In my study both drugs i.e. sodium chromoglycate 4% and lodoxamide 0.1% are effective in long term management of vernal conjunctivitis especially in mild to moderate cases. But lodoxamide Tromethamine 0.1% is more effective than sodium cromoglycate in long term management. The patients should be requested to consult the qualified doctors for proper assessment of the disease and follow up.

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