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A Comparative Study of Efficacy and Safety of Topical Loteprednol Etabonate 0.5% and Cyclosporin A 0.05% for the Treatment of Vernal Keratoconjunctivitis

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a recurrent, bilateral, interstitial, allergic seasonal conjunctivitis. Topical steroids are one of the most effective drugs for management of signs and symptoms of VKC. Cysclosporin is a calcineurin inhibitor that abolishes T cell proliferation, decreasing histamine release from mast cells and basophils. This study was conceptualized to evaluate the safety and efficacy of loteprednol etabonate 0.5% and cyclosprin-A 0.05% to generate evidence for managing VKC more effectively.

Material and methods: This non blinded comparative study included 200 patients with mild to moderate VKC who were randomized to two groups A and B. Group A received topical loteprednol etabonate 0.5% four times a day and group B received topical cyclosporin-A 0.05% two times a day. Five symptoms and four signs were evaluated on day 0 and second, fourth and 12th week after starting treatment. Data was analyzed by using student t-test. p value <0.05 was considered significant.

Results: The mean age in this study was 11.18 ± 4.9 years with 75% males and 25% females. The mean grade scores were lower for loteprednol 0.5% group than cyclosporin-A 0.05% with regards to symptoms and blepharitis, conjunctival congestion, and papillae. In, punctate keratopathy group, mean grade scores were lower in cyclosporin-A 0.05% group. No significant adverse effects were noted with both the drugs over 12 weeks.

Conclusions: Both the drugs were equally safe but loteprednol etabonate 0.5% was more efficacious as well as cost effective than cyclosporin-A 0.05% in relieving symptoms and signs of vernal keratoconjunctivitis.

Key words: Vernal keratoconjunctivitis, Loteprednol Etabonate, Cyclosporin A

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a recurrent, bilateral, interstitial, allergic seasonal conjunctivitis occurring more commonly in young boys. The onset of VKC generally occurs before the age of 10 years. It lasts for about 2-10 years, and usually resolves during late puberty [1,2]. Males predominate in the younger age group, but male-female distribution is equal in older patients. The pathophysiology of VKC is derived from both type 1 and cell mediated hypersensitivity reactions [3] Allergen binds to IgE on conjunctival mast cells in a sensitized individual. This causes mast cell degranulation, which releases histamine, leukotrienes, prostaglandins, and cytokines. This mediates early phase of allergic reaction [4].

VKC presents with itching, redness, watering which is mediated by prostaglandins; photophobia; blurring of vision due to tear instability; thick and ropy mucoid discharge [5]. Conjunctival signs of VKC include papillae, more common on upper tarsal conjunctiva, which have characteristic cobblestone appearance; gelatinous limbal epithelial deposits and Horner trantas spots. Corneal signs include superficial punctuate keratitis, shield ulcer, pseudogernotoxon [6].

Vasoconstrictors, antihistaminics, mast cell stabilizers, non-steroidal anti-inflammatory drugs, mild steroids, cyclosporin-A and tacrolimus are effective in managing ocular allergic conjunctivitis [3]. Topical steroids are one of the most effective drugs for management of signs and symptoms of VKC. Due to intraocular pressure raising effect of steroids, modified steroids such as loteprednol etabonate has been developed, which have superior safety profile [7,8].

Although corticosteroids are most efficacious drugs, steroid resistant and steroid responder forms of VKC may necessitate an alternative therapy like immunomodulators. Cysclosporin is a calcineurin inhibitor that abolishes T cell proliferation via inhibition of CD4+ T cell receptor transduction and downregulation of interleukin-2 receptor expression, thereby decreasing histamine release from mast cells and basophils [9,10]

Since, patients with VKC experience significant morbidity, which affects the quality of life, this study was conceptualized to evaluate the safety and efficacy of loteprednol etabonate 0.5% and cyclosporin-A 0.05% in a effort to generate evidence for managing VKC more effectively.

MATERIALS AND METHODS

The present non blinded comparative study was conducted over a period of one year, in ophthalmology department of a tertiary care teaching hospital in North India after obtaining ethical clearance from Institutional Ethics Committee.

This study included 200 patients with mild to moderate VKC presenting to Ophthalmology out-patient clincs. Diagnosis of VKC was made on the basis of history and clinical signs and symptoms. Patients who fulfilled the following criteria were included in the study and a written informed consent was taken from all the study participants after explaining the purpose of study.

Inclusion criteria

Patients with newly diagnosed moderate to severe VKC

Patient of either gender in age group of 5-25 years.

Exclusion criteria

Patients with one-blind eye

Patients with best corrected visual acuity of 6/12 or worse in any of the eye without a justifying cause

Patient at any stage of other ocular inflammatory disease besides VKC

Patient receiving medication through topical ocular route which could have interfered in results.

Contact lens users.

Patients which known history of steroid induced glaucoma.

Pregnant and lactating females.

Patients were randomized to two groups A and B. Group A received topical loteprednol etabonate 0.5% four times a day and group B received topical cyclosporin-A 0.05% two times a day. A detailed ocular and systemic history were taken. Visual acuity was recorded with Snellen chart. Slit lamp examination was done for anterior segment and intraocular pressure was recorded with non-contact tonometer. Fundus examination was also done after pupillary dilatation.

Five symptoms (ocular itching, foreign body sensation, tearing, photophobia, discharge) and four signs (conjunctival congestion, papillae, punctuate keratitis and blepharitis) were evaluated on day 0 and second, fourth and 12th week after starting treatment.

Grading of signs and symptoms was done as depicted in Table 1.

Intra-ocular pressure (IOP) was measured at each visit for steroid responsiveness. In group B, blood was collected by ante-cubital venipuncture before and at 12 weeks after initiation of treatment. Complete blood count, blood urea nitrogen, creatinine, serum sodium, serum potassium, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase levels (SGPT) and serum bilirubin were done to monitor side effects (Table 2).

Statistical analysis

All the data was entered into Microsoft excel and analyzed and estimated with help of OpenEpi online software version 3.Mean grade scores(±SD) was estimated for each sign and symptom and statistical significance assessed with the help of student t-test. A p-value <0.05 was considered as statistically significant. All p values used were two tailed.

RESULTS

The mean age in this study was 11.18 ± 4.9 years with 75% males and 25% females Table 3.

The mean grade score for symptoms (ocular itching, foreign body sensation, tearing, photophobia, discharge) is shown in Table 4. The mean grade scores were lower for loteprednol etabonate 0.5% group than cyclosporin-A 0.05% with regards to itching, discharge, photophobia, watering, and foreign body sensation. No patient had discharge and photophobia at 12th week in the loteprednol etabonate 0.5% group. The mean grade score for signs is shown in Table 5. Like symptoms, mean grade scores were lower in the loteprednol etabonate 0.5% group with regards to conjunctival congestion and papillae. Whereas in the punctate keratopathy group, mean grade scores were lower in cyclosporin-A 0.05% group and in blepahritis group, mean scores were lower in cyclosporin-A group at second and fourth week. Blurring of vision and burning sensation was found to be statistically insignificant between two groups with p value of 0.34 and p value of 0.63, respectively. Increase in IOP with loteprednol was found to be significant ($p<0.01$) when eyes were compared individually. Since, steroid responsiveness is an individual entity an both eyes respond to it, analysis was therefore applied to the patient as a whole and this difference was found to be insignificant (p value 0.058). No significant alterations were noted in laboratory investigations.

Table 1: Grading of signs and symptoms of vernal keratoconjunctivitis.

Symptoms	**0**	**1**	**2**	**3**
Itching	Absent	Occasional desire to rub	Frequent need to rub or scratch	Constant need to rub
Tearing	Normal	Sensation of fullness of conjunctival sac without tears spilling over	Intermittent spilling of tears over the lid margin	Constant spilling of tears over lid margins
Foreign Body sensation	Absent	Mild	Moderate	Severe
Discharge	No abnormal discharge	Small amount of mucoid discharge noted in lower conjunctival sac	Moderate amount of mucoid discharge in lower eyelid or crusts on eyelashes on waking up	Matted eye lashes on waking up, requiring use of water-soaked cotton to remove it
Photophobia	Absent	Mild, causing squinting of eyes	Moderate requiring use of dark glasses	Severe, causing patient to stay indoors.
Signs	**0**	**1**	**2**	**3**
Bulbar conjunctival congestion	Absent	mild	Moderate	severe
Papillae	Absent	mild	Moderate, Hazy view of deep tarsal vessels	Severe, obscuring deep vessels
Punctate keratitis	Absent	One quadrant	Two quadrants	Three quadrants
Blepharitis	Absent	Mild with eyelid edema	Moderate with scales formation on eyelids	Severe with eyelid cracks and loss of eye lashes

Table 2: Side effect profile of both the drugs.

Side effects	**Group A**			**Group B**		
	No. of eyes	**n**	**Percentage**	**No.of eyes**	**n**	**Percentage**
Blurring of vision	4	2	4	2	1	2
Burning sensation	4	2	4	4	2	4
Increased IOP	8	4	8	0	0	0
Total	16	8	16	6	3	6

Table 3: Age and Gender distribution of patients.

Age (in years)	**Number of patients**	
	Males	**Females**
5-10	80 (40%)	22(11%)
11-15	44 (22%)	16(8%)
16-20	22 (11%)	6(3%)
21-25	4(2%)	6(3%)
Total	150(75%)	50(25%)

Table 4: Mean grade scores (± SD) for symptoms of Vernal keratoconjunctivitis.

Time	Mean grade (± SD)		p-value
	A	B	
	Itching		
0	1.85 ± 1.94	1.69 ± 1.85	
2nd week	0.48 ± 0.53	0.75 ± 0.66	0.003*
4th week	0.20 ± 0.40	0.47 ± 0.65	<0.001*
12th week	0.09 ± 0.31	0.16 ± 0.36	0.13
	Discharge		
0	0.61 ± 0.67	0.48 ± 0.53	
2nd week	0.26 ± 0.48	0.25 ± 0.47	0.83
4th week	0.16 ± 0.36	0.22 ± 0.50	0.001*
12th week	0	0.06 ± 0.31	<0.001*
	Photophobia		
0	0.58 ± 0.66	0.40 ± 0.56	
2nd week	0.10 ± 0.36	0.10 ± 0.30	0.07
4th week	0.04 ± 0.28	0.11 ± 0.37	0.005*
12th week	0	0.02 ± 0.19	<0.001*
	Watering		
0	1.37 ± 0.67	1.16 ± 0.75	
2nd week	0.39 ± 0.48	0.43 ± 0.60	0.02*
4th week	0.14 ± 0.34	0.33 ± 0.61	<0.001*
12th week	0.10 ± 0.30	0.10 ± 0..33	0.34
	Foreign body sensation		
0	0.65 ± 0.68	0.66 ± 0.68	
2nd week	0.27 ± 0.48	0.23 ± 0.46	0.67
4th week	0.10 ± 0.30	0.15 ± 0.38	0.019*
12th week	0.02 ± 0.14	0.04 ± 0.24	0.0001*
*= Significant			

Table 5: Mean grade scores (± SD) for signs of vernal keratoconjunctivitis.

Time	Mean Grade score (± SD)		
	A	B	
	Blepharitis		
0	0.21 ± 0.49	0.11 ± 0.37	
2nd week	0.08 ± 0.27	0.03 ± 0.22	0.04*
4th week	0.11 ± 0.37	0.05 ± 0.25	0.0001*
12th week	0	0.03 ± 0.22	<0.001*
	Conjunctival congestion		
0	1.80 ± 0.64	1.60 ± 0.60	
2nd week	0.61 ± 0.54	0.91 ± 0.67	0.03*
4th week	0.29 ± 0.60	0.72 ± 0.69	0.16
12th week	0.02 ± 0.14	0.30 ± 0.57	<0.001*
	Papillae		
0	1.44 ± 0.76	1.46 ± 0.71	
2nd week	1.18 ± 0.51	1.45 ± 0.71	0.001*
4th week	0.91 ± 0.44	1.37 ± 0.78	<0.001*
12th week	0.43 ± 0.49	0.97 ± 0.67	0.0007*
	Punctate keratopathy		
0	1.63 ± 1.00	1.33 ± 1.04	
2nd week	1.41 ± 0.87	1.11 ± 0.94	0.44
4th week	1.26 ± 0.86	0.81 ± 0.84	0.81
12th week	0.56 ± 0.85	0.12 ± 0.40	<0.001*
	*= Significant		

DISCUSSION

No literature could be found comparing the two drugs for treatment of VKC. The mean age in our study was 11.18 ± 4.9 years with 75% males and 25% females, which is consistent with study by Baiza-Duran LM et al., who reported mean age of 10.25±3.83 years with 64.3% males [11] and Keklikei U et al., who reported mean age of 9.8 years with 69.3% males [12].

In our study, itching started to improve within 2 weeks of initiation of treatment, with mean scores being lower and significant in loteprednol 0.5% group as compared to cyclosporin-A 0.05% group on second and fourth week after starting the treatment. Similar finding were noted by Dell SJ el at., who reported significantly reduced itching (p value <0.001) with loteprednol, when administered prophylactically over six weeks [13]. Shulman DG et al. reported that loteprednol etabonate 0.2% reduced itching better than placebo (p value <0.008).14 Baiza-Duran LM.et al, found significant improvement in itching with 0.05% and 0.1% cyclosporine eye drops over 60 days [11].

There was a statistically significant difference in improvement of discharge with treatment between two groups at fourth (p value =0.01) and 12th week (p value <0.001), with mean scores being lower in loteprednol etabonate group. Dell SJ et al. found improvement in discharge with loteprednol 0.5% over a period of six weeks [13]. Jameel A et al. found that discharge improved with 2% cyclosporin-A after six weeks of treatment.15 Similarly, Baiza-Duran LM et al. found significant improvement in discharge with 0.1% cyclosporin-A eye drops as early as 2 weeks after the treatment [11].

Photophobia improved with both treatment groups, with a statistically significant difference at fourth (p value =0.005) and 12th week (p value <0.001) after the treatment, with mean scores being lower in loteprednol etabonate 0.5% group. Shulman DG et al. reported that loteprednol 0.2% reduced photophobia better than placebo [14] and Jameel A et al. reported that 2% cyclosporin-A improved photophobia significantly (p value <0.02).15

Both drugs improved watering, with a statistically significant difference being noted at second week (p value = 0.02) and fourth week (p<0.001), mean score being lower in loteprednol etabonate 0.5% group. Similarly, Shulman DG et al. reported improvement in epiphora with loteprednol 0.5%14 and Jameel A et al. reported improvement in epiphora with 2% cyclosporin-A over six weeks [15].

Foreign body sensation improved with both treatment arms, with a statistically significant difference being noted at fourth week (p=0.019) and at 12th week (p<0.001) after the treatment, mean score being lower in loteprednol etabonate 0.5% group. Baiza-Duran LM et al. noted improvement in foreign body sensation as early as 2 weeks with 0.1% cyclosporin-A drops [11] and Dell SJ et al. noted improvement in foreign body sensation with loteprednol 0.5% [13].

With regards to signs, blepharits improved with both treatment arms, with mean scores being lower in cyclosporin-A 0.05% group at second week (p value=0.04), at fourth (p value =0.001) week and higher at 12th week (p value <0.001). Rhee SS et al noted improvement in blepharitis with loteprednol 0.5% [16] and Rubin M et al noted significant improvement in blepharitis with cyclosporin-A 0.05% after 12 weeks [17]. Conjunctival congestion improved with both treatment groups, mean score being lower in loteprednol 0.5% group and statistically significant difference was noted at second week (p value =0.03), at and at 12th week (p value <0.001). Dell SJ et al. noted significant improvement in conjunctival congestion with loteprednol etabonate over six weeks.13 Similarly, Oner V et al., reported that loteprednol significantly reduced hyperemia (p value <0.001) [18]. Baiza-Duran LM et al. noted significant improvement in conjunctival congestion with 0.1% and 0.05% cyclosporin-A [11]

Similarly, papillae improved with both treatment arms, with mean score being lower in loteprednol 0.5% group and a statistically significant difference was noted at second (p value =0.001), at fourth week (p<0.001) and at 12th week (p value =0.0007). Oner V et at. reported significant improvement of papillae with loteprednol (p value <0.001)[18] and Jameel A et al. reported improvement in papillae with 2% cyclosporin-A.15 Punctate keratopathy improved more significantly with cyclosporine-A 0.05% with a significant difference in mean scores at 12th week (p<0.001). Rhee SS et al.

noted an improvement in punctate keratopathy with 0.5% [16] and Jameel A et al. noted improvement in punctate keratopathy with 2% cyclosporine-A (p value <0.02) [15].

Regarding side effects, Ilyas H et al. noted no adverse effects like steroid induced rise in IOP or cataract formation with loteprednol 0.2%, when used for more than 12 months [19]. Jameel A et al. noted increase in neutrophils in differential leukocyte count, with total leukocyte count being within normal range with 2% cyclosporin-A. No significant difference was found with regards to IOP, renal function test and liver function tests [15].

CONCLUSION

Thus, we conclude that both the drugs were equally safe but loteprednol etabonate 0.5% was more efficacious as well as cost effective than cyclosporin-A 0.05% in relieving symptoms and signs of vernal keratoconjunctivitis.

LIMITATIONS

Patients with mild to moderate symptoms only were included in the study. Patients with severe disease were not included.

Longer follow-up (>12 weeks) is required to evaluate other side effects of both the drugs

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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