Original Article

Effectiveness of 0.05% Cyclosporine Versus Standard Treatment of Vernal Kerato-Conjunctivitis (VKC) in Young Patients

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ABSTRACT

Purpose: To compare the effectiveness of 0.05% cyclosporine eye drops versus standard treatment in patients of moderate to severe vernal kerato-conjunctivitis (VKC).

Study Design: Quasi experimental study.

Place and Duration of Study: Institute of Ophthalmology, Eye Unit-1, King Edward Medical University, Mayo Hospital, Lahore from June to December 2019.

Methods: This study includes 104 patients (age 5-16 years), with VKC. Patients were divided into two groups. Group A was given standard treatment for moderate to severe VKC, which included topical corticosteroids (FML 0.1% eye drops) QID, in addition to antihistamines and mast cell stabilizers (Olopat D 0.2% eye drops) QID and group B was given 0.05% Cyclosporine A(CyS-A) eye drops QID. The frequency of mild, moderate, and severe disease was determined for each group. Data was analyzed and independent sample t-test was applied. P value of < 0.05 was taken as significant.

Results: There were 60 males and 44 female patients. The mean age in Group A was 9.34 ± 2.09 years and in group B was 9.36 ± 2.71 years. There was significant difference in mean clinical symptoms and sign score between group A and group B (p <0.001) at 3 months, suggesting that topical 0.05% cyclosporine is more effective as compared to standard therapy in moderate to severe VKC.

Conclusion: 0.05% cyclosporine eye drops are effective in treating moderate to severe VKC in terms of reduction of clinical manifestations of disease.

Keywords: Vernal keratoconjunctivitis, cyclosporine eye drops, standard treatment, effective.

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INTRODUCTION

Vernal Kerato-conjunctivitis (VKC) is a common allergic disease of children and adolescents.[1] The disease aggravates in spring and summer season, which begins at the age of 04 years and declines in late teens in many patients.[2] VKC exacerbates in hot, dry, and dusty climates.[3] It is an allergic reaction where mediators are released from the mast cells and immunoglobulin (Ig) E-mediated release of histamine. In addition, there is also an inflammatory response with T-helper (Th) type 2 hypersensitivity reactions, eosinophilic infiltration and remodeling of extracellular matrix, which is a late-phase allergic response. Conjunctival eosinophils particularly express interleukin IL-3, IL-4, IL-5, IL-6 and granulocyte-

macrophage colony stimulating factor (GM-CSF).[4]The pathognomonic signs of VKC are Horner Trantas dots, cobblestone giant papillae at the upper tarsal lids, and shield ulcers[5]. VKC adversely affects the daily activities of the patients resulting from visual impairment.

VKC is more common in warm, dry regions. It has a prevalence of 15% worldwide, 3.2 per 10,000.[6] The epidemiology of VKC is poorly studied in many countries. It is an allergic conjunctivitis with activation of immune system. The treatment options available are topical antihistamines, mast cell stabilizers, corticosteroids. These options can be tailored to the individual's specific condition and needs.[7] Topical corticosteroids act as anti-inflammatory and inhibit the phagocytic responses in recurrent and severe VKC. However, with long-term use the risk of shield ulcers, cataract and glaucoma is increased.[7] Topical mast cell stabilizer, anti-histamines and non-steroidal anti-inflammatory agents are usually prescribed for the management of mild to moderate VKC. However, their effect decreases in severe form of VKC.[8,9]

Cyclosporine A (0.05-2%) and tacrolimus(0.1%) are topical immunomodulators, they are used in cases of severe, recurrent VKC when corticosteroids are ineffective and associated with undesirable side effects. The cyclosporine A reduces the inflammation by inhibiting the T-cell activation by limiting lymphocyte proliferation, it suppresses the cytokine production, and stabilizes the mast cells, reducing interleukin 1b production and fibroblast proliferation in the conjunctiva.[10,11] This study compares the response of topical 0.05% cyclosporine (CyS-A) eye drops in patients with moderate to severe VKC with conventional treatment.

METHODS

A Sample size of 104 patients was estimated by using 5% level of significance, 90% power of test with expected percentage of olopatadine as 47.7% and cyclosporine 28.13%. Both male and female of 5-15 years of age, diagnosed with VKC were included in the study. Patients with other ocular problems e.g., cataract or glaucoma and systemic disease were excluded from the study. After clinical assessment of the patient on the basis of signs and symptoms, VKC diagnosis was made based on grading as shown in Table–1.[12] The baseline signs and symptoms were documented for all patients. The treatment plan was thoroughly explained to the patients and their families, including counseling on drug administration, potential side effects, and the clinical benefits. Patients were then divided into two groups. Group A received the standard treatment for moderate to severe VKC, consisting of topical corticosteroids (FML 0.1% eye drops) four times daily, in combination with antihistamines and mast cell stabilizers (Olopat-D 0.2% eye drops) also four times daily. Group B was treated with 0.05% Cyclosporine A (CyS-A) eye drops, administered four times daily. Any serious side effects, such as a burning sensation in the eyes or abnormal liver and renal function tests, were assessed to determine whether to taper or continue the medication. The effectiveness of the treatment and relief of symptoms were evaluated at both 1-month and 3-month intervals. Data analysis was conducted using SPSS Version 26, with grading of signs and symptoms recorded. The frequency of mild, moderate, and severe cases was determined for each group. An independent samples t-test was applied, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

There were 60 male and 44 female patients in the study. The mean age in Group A was 9.34±2.09 years, and in Group B, it was 9.36±2.71 years. At the first visit (baseline), 20% of Group A had mild disease, 49% had moderate disease, and 45% had severe disease. In Group B, 47% had mild disease, 50% had moderate disease, and 52% had severe disease. By the second visit (1 month), in Group A, the distribution shifted to 38% with mild disease, 50% with moderate disease, and 19% with severe disease. In Group B, 52% had mild disease, 51% had moderate disease, and 2% had severe disease. By the third visit (3 months), Group A had 43% with mild, 29% with moderate, and 17% with severe disease. In contrast, Group B had 29% with mild, 2% with moderate, and 1% with severe disease.

Notably, the percentage of severe cases in Group A decreased from 45% at baseline to 19% at 1 month, with a slight further decrease to 17% at 3 months. In Group B, however, severe disease dropped from 52% at baseline to 2% at both 1 and 3 months, indicating a significant and sustained reduction in severity (Figure 1). The percentage of patients with moderate disease showed little change after 1 month in both groups

(50% in Group A and 51% in Group B). However, by 3 months, the rate of moderate disease was 29% in Group A and only 2% in Group B (Figure 1).

The significant difference in the mean clinical symptoms and clinical sign scores at 3 months between Group A and Group B ($p < 0.001$) suggests that topical 0.05% cyclosporine is more effective than standard therapy for moderate to severe VKC (Table-2).

Table 1: *Grading signs and symptoms of vernal keratoconjunctivitis.*[12]

Feature	Grade 0	Grade 1	Grade 2	Grade 3
Symptoms				
Itching	None	Occasional	Frequent	Constant
Watering	Normal	Wet eyes without tears on face	Intermittent tears on the face	Constant
Photophobia	None	Mild	Moderate	Severe
Discharge	None	Small	Moderate	Constant
Signs				
Conjunctival Hyperemia	None	Mild	Moderate	Severe
Tarsal Papillae	None	< 1mm	1-3 Mm	> 3 mm
Limbal Papillae	None	< 2 mm	2-4 mm	> 4 mm
Keratopathy	Normal cornea	Mild localized Punctate epithelial Keratitis	2 quadrants of epithelial keratitis	3 or more quadrants of epithelial keratitis or corneal ulcer
Corneal Neo-vascularization	None	< 1 mm	1-3 mm	> 4 mm

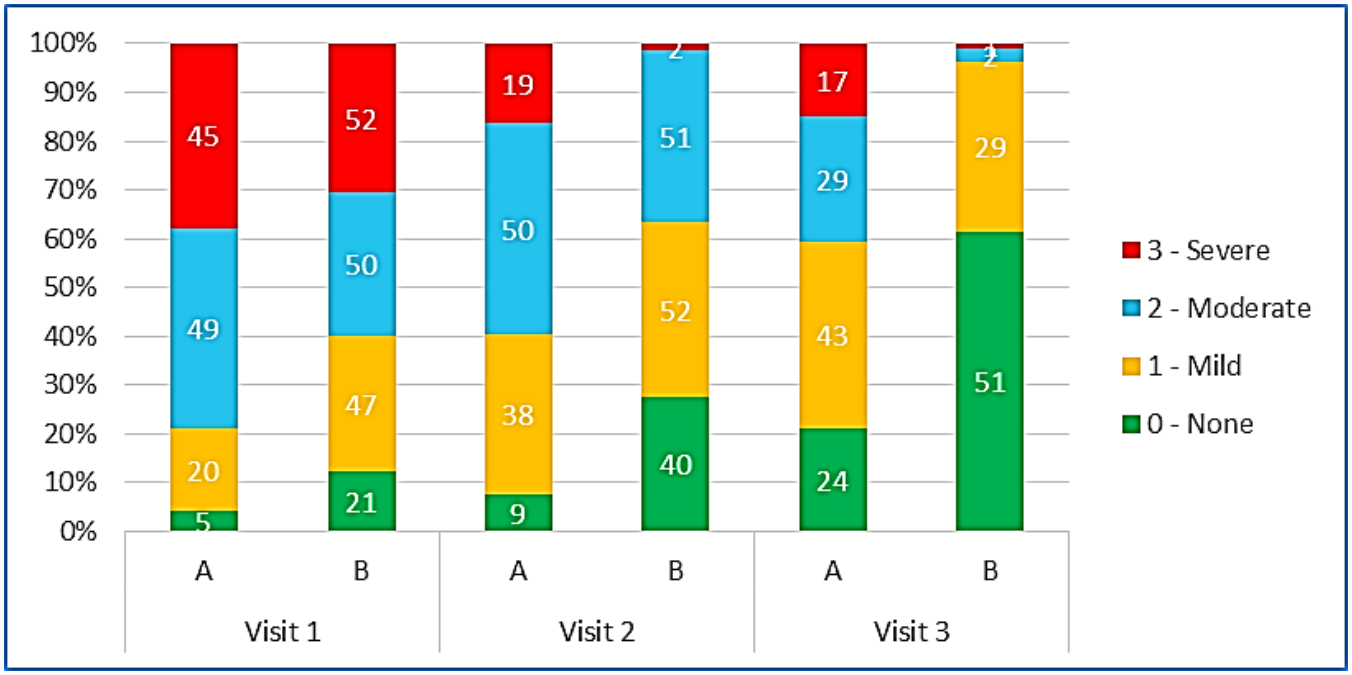

Figure 1: Comparison of clinical severity at Visits 1, 2 and 3 (Baseline, 1 month and 3 months).

Table 2: *Independent Sample t-test analysis at Visit 3 (3 months).*

Score	Group A		Group B		Sig.	
	Mean	SD	Mean	SD	t	p
Clinical Symptom	6.63	4.87	0.27	1.53	8.97	0.001*
Clinical Sign	5.63	3.34	0.86	1.41	9.45	0.001*

*p<0.001, highly significant

DISCUSSION

VKC is a chronic disease primarily affecting the children and teenagers. It has a seasonal pattern with worsening of symptoms in spring and summer season. Although the symptoms resolve spontaneously at the time of puberty, its management depends upon the individual patient characteristics and severity.

Cyclosporine A (CyS-A) is an immunosuppressive agent. It is an 11 amino acid polypeptide, which inhibits the calcineurin 2 and the transcription of nuclear factor of activated T-cells-dependent genes is blocked. Hence, T cell proliferation and activation of B-cell synthesis of IL-2, IL-4 and CD40 ligand is obstructed. CyS-A is also responsible for the inhibition of mast-cell degranulation and the transcription of IL-3, IL-5 and leukotriene. In 1980, it was prescribed for the prevention of corneal graft rejection.[13,14]

In 2005 Cyclosporin was approved by FDA for dry eye diseases. CyS-A has antiapoptic effect which has its fruitful role in ocular surface diseases such as VKC.[15]0.05% Cyclosporin has minimal access in plasma, aqueous humor and vitreous and the immunomodulating effect can be achieved by very low concentrations.[16]

In a study, 2% CyS-A was used in severe VKC, ocular clinical effects were improved in 14 days. However, few patients required a short course of topical steroids, it was found that 2% was safe and effective in refractory VKC.[3] In another study, 1.25% vs 1% CyS-A efficacy in VKC patient was studied.[17] Some patients had watering and ocular burning complaint with 1% CyS-A eye drops. It was concluded that 1% concentration may be minimally effective in severe VKC.

Baiza-Duran et al, reported that CyS-A 0.01% and 0.05% was safe in moderate to severe steroid dependent children with VKC. The symptomatology improved in both the groups after 60 days with no adverse effects.[18] This was attributed to low concentration of CyS-A, and increased bioavailability in the cornea. Ozcan et al, studied 10 pediatric patients with severe ocular allergic disorder not responding to topical steroids. On additional therapy with topical CyS-A in 0.05%, severe VKC patients showed improvement.[19] Westland et al, treated 8 children with shield ulcer with 0.05% cyclosporine eight times a day, there was complete reepithelization with healing of shield ulcer.[20] Cyclosporine acts on the corneal stroma, sub-basal nerves and epithelium to restore the corneal microstructure ($p < 0.001$).[21]

0.1% Tacrolimus (TCL) eye drops, are also being prescribed for severe VKC in Pediatric patients and the response comes within 4 weeks. Tacrolimus controls the ocular inflammation. These remedies are safe and well tolerated by most patients.[10]

Our study is comparable to the above studies as the results showed significant improvement in ocular symptom and clinical sign score among the patients, with CyS-A 0.05% when compared to standard treatment for moderate to severe VKC cases. There were no serious side effects with this lower strength of therapy.

The limitations of our study are lack of masking, environmental factors and systemic associations. Multi center studies with larger sample size and long-term follow-up will help to dig into the effective concentration of topical CyS-A needed to control the disease.

In addition, quality of life assessment should be an important part of patient follow-up at the first consultation and then at least annually. Questionaries' like QUICK, modified QUICK, and Juniper questionnaires, are available and some of them are also presented as digital applications for children.[22]

CONCLUSION

It is concluded that cyclosporine in comparison to standard treatment of VKC produces effective treatment outcomes in terms of reduction of clinical manifestations.0.05% cyclosporine A eye drops is a safe alternative in moderate to severe VKC, thereby reducing the risk of developing topical steroid induced glaucoma and cataract in patients receiving long term therapy for VKC.

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Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(18334/REG/KEMU/2020)**.

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