Original Article

Clinical Effectiveness and Local Side Effects of Topical 0.05% Cyclosporine in Treatment of Children with Severe Vernal Keratoconjunctivitis

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ABSTRACT

Purpose: To evaluate the therapeutic response of topical cyclosporine (CyS-A) in patients with vernal keratoconjunctivitis (VKC), resistant to topical mast cell stabilizer (MCS) and anti-histamine therapy.

Study Design: Quasi experimental study.

Place and Duration of Study: Qazi Hussain Ahmad Medical Complex, Nowshera, from April 2019 to August 2019.

Methods: Forty patients, 30 males and 10 females, less than 18 years of age and diagnosed with Vernal Keratoconjunctivitis were enrolled in the study. All participants were graded based upon severity of the disease at presentation with a score of 0 for normal, 1 for mild, 2 for moderate and 3 for severe, for both symptoms and signs. Each patient received topical CyS-A 0.05%in QID regimen in addition to lubricating tear substitute. Followup was done for 04 months.

Results: Clinical scoring was done at baseline and at the 1st, 2nd-and 4th month following therapy. After 4 months of topical application, not only the patients improved symptomatically but their clinical signs also improved, which achieved a level of statistical significance ($p < 0.05$). All participants completed the follow-up duration of therapy. Although Horner Tranta's dot showed improvement, but comparison of baseline with 1st month values were statistically non-significant ($p = 0.048$). However, during 2nd and 4th month, the improvement achieved statistical significance ($p = 0.013$ and $p = 0.006$ respectively). None of the participants reported any bothersome local side effect.

Conclusion: Topical cyclosporine 0.05% is effective in alleviating the symptoms and signs without any local side effects in resistant VKC.

Key Words: Vernal keratoconjunctivitis, Cyclosporine, Cobblestone Papillae.

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a serious allergic eye disorder, with aggravation during spring and summer seasons, affecting adolescent population in particular.[1] Vernal keratoconjunctivitis typically begins after 04 years of age and wanes in the late teens in majority of the patients.[2] The disease affects the daily activities of adolescents including schooling and socialization which make their parents worried. Clinically VKC manifests itself in the form of excessive light sensitivity, lacrimation, ocular irritation, secretion, cobble-stone papillae, vernal

keratopathy, horner Tranta's dots, bulbar conjunctiva hyperemia/congestion, limbus edema, shield corneal ulcers and pannus.[3] In addition to steroid induced raised intraocular pressure (IOP) and lens opacification, structural damages occur to the ocular surface permanently, such as conjunctival fibrosis, corneal structural instability and shield ulcer develops during the acute phase and may cause profound vision loss.[4] Histo-pathological specimens have shown the accumulation of Th-2 subset of T lymphocytes i.e. helper T-cells in tears and biopsy specimens from conjunctiva in VKC patients with abundance of activated mast cells and eosinophils identified in conjunctival scrapings.[5,6] Different types of interleukins particularly interleukine-5 and GMCS factors are expressed in conjunctival eosinophils.[7]

Steroids in the topical form is the most efficacious therapy for VKC, suppressing the inflammatory pathways and inhibiting the phagocytic responses.[8] Some serious adverse effects, including steroid induced increased IOP, lens opacification, corneal infections with opportunistic organisms and re-activation of herpetic eye diseases are the consequences of prolonged topical steroid therapy.[3]As a result of serious side effects, steroids are not indicated for long term in VKC. Topical MCS, topical anti-histamines and non-steroidal anti-inflammatory agents are other therapeutic options available in the management of mild to moderate VKC. However, these are less effective in severe form of the disease.[9-10]

CyS-A is an immunosuppressive agent that inhibits Th-4 lymphocyte multiplication and IL-2 formation. In addition, CyS-A blocks the release of histamine from mast cells and basophils.[11-13] However, CyS-A doesnot have adverse ophthalmic consequences like cataract or steroid induced glaucoma.[14]

Several studies have reported the usefulness of topical CyS-A therapy in VKC in various strengths.[15,16] In this study, we evaluated the effectiveness of topical CyS-A 0.05% (Ropsol, Atco Inc. Khi. Pak.) in pediatric age group with vernal keratoconjunctivitis who were resistant to topical MCS and anti-histamines.

METHODS

Forty patients with VKC were chosen, consecutively by non-probability sampling in a retrospective design by review of their medical records, they were subjected to topical cyclosporine 0.05% for at least 04 months. The study was conducted at an Eye Out patient department, Qazi Hussain Ahmad Medical Complex, Nowshera, from April 2019 to August 2019. Study was approved by the institutional ethical review board. We adhered to the tenets of declaration of Helsenki and guidelines of good clinical practice for the study. Participants with documented allergies to tacrolimus (TCL) or cyclosporine (CyS-A), ocular infections and diseases like glaucomatous eyes, intraocular inflammatory disorders, any keratitis, systemic inflammatory disorders other than atopic disorders, and age more than 18 years were screened out.

We enrolled 30 males and 10 females, with a mean age of 12.0 ± 3.5 years. All the participants were previously treated with either MCS or combination drugs (olopathidine) for at least 04 weeks prior to initiation of topical CyS-A therapy but the response was minimal. The parents/guardians and where necessary participants were informed about the possible side effects and an informed consent was obtained prior to the study.

Participants underwent thorough ocular assessment, including best-corrected visual acuity (Snellen chart) and slit lamp biomicroscopy. Subjective symptoms such as ocular irritation, foreign body sensations, light sensitivity and lacrimation were recorded. Patients were asked to grade their symptoms as follows; 0 = normal, 1 = mild, 2 = moderate and 3 = severe. Ocular signs were also graded as above. The objective signs were tarsal conjunctival congestion, upper tarsal conjunctival papillae, limbal hypertrophy, Horner Trantas dots and superficial punctate keratitis (Table 1a & 1b). Participants were started on topical CyS-A 0.05% (Ropsol, Atco Inc.Khi. Pak.) in a four times a day regimen along with ocular lubricants. Clinical scoring for the symptoms and signs were documented at baseline and at 1st, 2nd and 4th month after treatment.

Data analysis was performed using the SPSS 19.0. Continuous data variables were expressed as mean ± standard deviation (SD). Descriptive variables such as symptoms and signs of VKC were represented in percentages, 1-month, 2nd month and 4th month data values comparison was undertaken by using the Wilcoxon signed ranked analysis. $P < 0.05$ was taken as significant.

Table 1a: Score grading system for symptoms in Vernal Keratoconjunctivitis.

Symptoms	0 (Normal)	1 (Mild)	2 (Moderate)	3 (Severe)
Irritation	No	Occasional itching	Frequent itching	Constant itchy eyes
Foreign body sensation	No	Occasional	Frequent	Constant
Light sensitivity	Not at all	Slightly bothersome	Using tinted glasses for eyes comfort	Marked not relieved with sun glasses
Lacrimation	Normal	Fullness with no overflow on lid margins	Occasional over-flowing on the lid margins	Constant or frequent overflow of tears
Secretion	No secretions	Small amount in lower fornix	Present both in lower fornix and marginal tear strip, crusts on eye lashes upon awakening	Eyelids tightly matted together upon awakening, warm soaks necessary to clean eyelids during day.

Table 1b: Score grading system for signs in Vernal Keratoconjunctivitis.

Signs	0 (Normal)	1 (Mild)	2 (Moderate)	3 (Severe)
Tarsal conjunctival congestion	None	Several vessels dilated	Numerous vessels Dilated	Individual blood vessels indistinguishable
Upper tarsal conjunctival papillae	None	Diameter 0.1 – 0.2mm	Diameter 0.3 – 0.5mm	Diameter > 0.6 mm
Limbal hypertrophy	None	Less than half limbus involved	More than half of the limbus involved	Annular limbal involvement
Horner Trantas dots	None	1 – 3	4 – 7	> 8
Superficial punctate keratitis	None	Superficial punctuate keratitis	Desquamatory superficial punctuate keratitis	Shield ulcer or epithelial erosion

RESULTS

Clinical scoring for different ocular symptoms of 40 patients at baseline and at follow-up visits (1st, 2nd and 4th month) are depicted in Table 1a and b. All the participants completed the follow-up. Slight irritation on topical application was taken as insignificant. Clinical scoring for symptoms including ocular irritation, lacrimation, foreign body sensation, secretion and light sensitivity reduced significantly as compared to baseline at each follow-up visit during 04 months of CyS-A therapy ($p < 0.0001$, for each). Shown in Table 2.

Table 3 shows that ocular signs improved which achieved a level of statistical significance throughout the follow-up period of 4 months ($p < 0.05$). Although Horner Trantas dots showed improvement, but comparison of baseline with 1st month values were statistically non-significant ($p= 0.048$). However, during 2nd and 4th month, the improvement achieved statistical significance ($p = 0.013$ and $p = 0.006$ respectively).

Table 2: Score wise distribution of patients for clinical symptoms.

Symptoms	0 (N)	1 (N)	2 (N)	3 (N)	p- value
Irritation					
Baseline	-	-	10	30	Ref.
1st Month	-	14	26	-	0.0001%
2nd Month	08	26	O6	-	0.0001%
4th Month	24	12	04	-	0.0001%
Foreign body Sensation					
Baseline	-	05	15	20	Ref.
1st Month	06	14	20	-	0.0001%
2nd Month	10	26	04	-	0.0001%
4th Month	34	06	-	-	0.0001%
Light sensitivity					
Baseline	05	10	20	05	Ref.
1st Month	05	25	10	-	0.0001%
2nd Month	26	10	04	-	0.0001%
4th Month	34	06	-	-	0.0001%
Lacrimation					
Baseline	01	05	14	20	Ref.
1st Month	04	12	22	-	0.0001%
2nd Month	12	26	02	-	0.0001%
4th Month	28	10	02	-	0.0001%
Secretion					
Baseline	02	08	18	12	Ref.
1st Month	10	24	06	-	0.0001%
2nd Month	26	12	02	-	0.0001%
4th Month	34	06	-	-	0.0001%

Table 3: Score wise distribution of patients for clinical signs.

Ocular Signs	0 (N)	1 (N)	2 (N)	3 (N)	p- value
Tarsal Conjunctival Congestion					
Baseline	-	15	16	24	Ref.
1st Month	-	20	20	05	0.0001%
2nd Month	18	14	08	-	0.0001%
4th Month	26	-	-	-	0.0001%
Upper Tarsal Conjunctival Papillae					
Baseline	02	06	10	22	Ref.
1st Month	04	08	24	04	0.0001%
2nd Month	08	22	08	02	0.0001%
4th Month	20	18	02	-	0.0001%
Limbal Hypertrophy					
Baseline	-	02	16	22	Ref.
1st Month	-	10	26	04	0.0001%
2nd Month	08	20	10	02	0.0001%
4th Month	18	18	04	-	0.0001%
Horner Tranta's Dots					
Baseline	26	04	06	04	Ref.
1st Month	28	06	04	02	0.048%
2nd Month	30	08	02	-	0.013%
4th Month	34	06	-	-	0.006%
Superficial Punctate Keratitis					
Baseline	-	20	16	04	Ref.
1st Month	06	24	08	02	0.0001%
2nd Month	16	18	05	01	0.0001%
4th Month	26	12	02	-	0.0001%

DISCUSSION

Vernal keratoconjunctivitis (VKC) is a sight-threatening inflammatory disease of the conjunctiva and cornea. Although VKC is classified as an allergic

ocular disorder, the role of allergens as inducers is unclear. The pathophysiology of VKC involves IgE, cytokines, chemokines and inflammatory cells (T and B lymphocytes, mast cells, basophils, neutrophils, and eosinophils), with liberation of their granular factors, multiplication of fibrocytes and formation of excessive amount of collagen fibrils in the conjunctiva. Mild disease of VKC tends to remit with non-specific and supportive therapy. On the other hand, severe cases are usually more prolonged, with remissions and flare-ups over a long duration.

In patients with severe VKC, treatment with topical anti-histamines and MCS is usually insufficient. These patients need topical steroids therapy during flare ups of the disease. However, due to their adverse effects, topical steroids are not used for long duration, particularly in pediatric population. In this study, we used topical 0.05% CyS-A in 40 patients for up to 04 months. The patients improved both symptomatically and clinically. Numerous trials have reported that topical CyS-A 2% is effective in VKC, requiring less need for topical steroids.[15,16] Cyclosporine A (CyS-A) is an immune-modulatory agent that blocks the multiplication and stimulation of T-cells.

Ben Ezra et al treated 21 children with severe VKC resistant to steroids and 2% di-Sodium Cromoglycate with cyclosporine 2% eye drops in oil solution.[17] Symptoms such as redness, irritation, light sensitivity, watering, discomfort, mucinous secretions and difficulty in routine activities were documented. Eighty six percent of the participants improved symptomatically after 02 weeks of therapy. In addition to that, use of topical and systemic steroids was reduced significantly in majority of the patients.[17]

Studies have shown that CyS-A 2% in QID dose is effective in controlling VKC.[18] In a double-masked, randomized control trial, 2% CyS-A was topically applied to 24 patients with severe VKC and 5 to 15years of age.[18] Most of the effects of topical Cyclosporine 2% on ocular symptoms and signs were achieved after 14 days of therapy. A short course of topical steroids were needed in few patients while rest were stabilized with CyS-A 2%. It was deducted from the trial that CyS-A 2% strength was safe and efficacious in the management of refractory VKC.[18]

In another study, topical CyS-A1% strength was given to 195 children with resistant VKC for about 16 weeks.[19] Ocular symptoms and signs were graded on a 4-point scale at baseline, 2 weeks, 4 weeks and 16 weeks after treatment. The mean score for severity of symptoms and clinical signs reduced 02 weeks post treatment. Cyclosporine serum values were non-detectable at the end of treatment, they also did not observe any corneal endothelial cell loss with therapy.

Spadaveccia et al evaluated the effectiveness of 1.25% versus 1% CyS-Ain children with severe/ resistant form of VKC.[20] In each group, the mean score for ocular symptoms and clinical signs were significantly reduced on day 14 and then 16 weeks post-treatment. The investigators concluded that 1% concentration of CyS-A might be minimally effective strength for controlling the symptoms and clinical signs of severe form of VKC. The most likely local reaction with 2% CyS-A were redness and stingy ocular sensation after couple of minutes of topical application.[17,18] Despite the local stinging sensations after topical applications, most of the patients continued the treatment due to improvement in symptoms of VKC. Feeling of ocular burning and watering soon after the application of 1.25% CyS-A were also noted in some patients.[20,21]

Topical CyS-A has also proved to be effective in the treatment of corneal-shield ulcers in chronic resistant types of VKC.[21] Four patients with corneal-shield ulcers, who were non-responders to topical steroids, H1-blockers and MCS were treated with 0.05% – 2% strengths of topical CyS-A in QID doses. The concentration entration was titrated to the severity of clinical signs, beginning with 2% and finally at the end of the study it was concluded that the minimally effective concentration entration was 1%.

Ozcan et al[22] gave topical CyS-A in 0.05% concentration twice or 4 times daily in 10 patients of pediatric age group with severe ocular allergic disorder not responding to topical steroids. Six patients had vernal keratoconjunctivitis, while four patients had atopic keratoconjunctivitis. All the participants of the study were symptomatic at the time of recruitment despite being on topical steroids. The investigators observed that by adding topical CyS-A in 0.05% strength, a significant improvement was seen. In addition, the requirement for topical steroids were decreased or even stopped.[22]

Severe VKC effectively responds to topical CyS A and Tacrolimus (TCL), normally within 04 weeks post treatment. Long-term use of CyS- A and TCL in VKC is safe and tolerated by most of the patients without having any serious side effects.[23] Topical CyS-A, at either 1% or 2% concentration was safe and effective

for long-term therapy of VKC in 160 children. Ophthalmic assessment at regular intervals and systemic evaluation tests at certain intervals allowed investigators to rule out the possibility of local or systemic adverse effects over a time span of 7 years.[24] Similarly, in a case report, a 6 years old child with severe VKC was treated effectively with oral cyclosporine. It was impossible to control the patient's symptoms with topical steroids, CyS-A and MCS. The patient responded dramatically with oral cyclosporine therapy.[25]

In this study, we used topical CyS-Ain 0.05% strength in 40 children with resistant form of VKC for 04 months in QID regimen. The clinical signs and ocular symptoms responded effectively with CyS-A therapy, not a single patient in our study needed topical steroids for controlling the disease. Similarly, no patient in our study reported any serious side effects from topical application resulting in cessation of therapy. The reason could be due to lower strength of CyS-A i.e. 0.05% used in our study.

The limitations of our study are its retrospective design, lack of masking in the study, small sample size and relatively short follow-up period. Further double-blinded, randomized control clinical trials with larger sample size and long-term follow-up are needed to explore the efficacy of topical CyS-A and the minimal strength needed for controlling the disease.

CONCLUSION

It is concluded that topical CyS-Ain 0.05% concentration is safe and efficacious in the management of resistant VKC. Not only the patients improved symptomatically but also the clinical signs improved with therapy without having serious local adverse reactions. The topical therapy also reduces the need for topical steroids in controlling the disease hence, preventing the local adverse effects of steroids such as cataract and glaucoma. Further double-blinded, randomized control clinical trials are needed to unveil the mystery of topical CyS-A in VKC.

Ethical Approval

The study was approved by the Institutional review board/ Ethical review board (**0921/ R&D/ IERB/ NMC).**

Conflict of Interest

Authors declared no conflict of interest.

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Authors' Designation and Contribution

Adnan Ahmad; Assistant Professor: *Concepts, Design, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Mubashir Rehman; Associate Professor: *Concepts, Design, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Muhammad Farhan; Senior Registrar: *Concepts, Design, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Jawad Humayun; PG Trainee: *Literature search, Statistical analysis, Manuscript review.*