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STUDY OF EFFICACY AND SAFETY OF TOPICAL CYCLOSPORINE IN VERNAL KERATOCONJUNCTIVITIS

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ABSTRACT

The purpose of this study was to evaluate the efficacy and adverse effects of topical cyclosporine 0.05% in patients suffering from vernal keratoconjunctivitis(VKC). A total of 100 patients of VKC were treated with topical cyclosporine 0.05% eye drops. Symptoms and signs were observed while starting the treatment and at 4, 8 and 12 weeks of follow up. Scores for symptoms and signs and any ocular side effect were evaluated. There was significant reduction in symptom and sign scores of VKC with treatment by cyclosporine eye drop. No significant side effects were reported. Topical cyclosporine 0.05% is an effective and safe alternative treatment of VKC which helps to reduce the need for corticosteroids.

KEYWORDS : Vernal Keratoconjunctivitis, Cyclosporine, Corticosteroid

Vernal keratconjunctivitis (VKC) is an ocular disease predominantly observed in children and young adults, especially those living in dry and temperate areas(Avunduk et al.,2000). The disease is usually bilateral and more common in males5. Itching, burning, foreign body sensation, photophobia, lacrimation, hyperemia and mucoid discharge may occur in VKC. On examination conjunctival hyperemia can be observed on the bulbar and tarsal conjunctiva. Thick ropy, mucoid or frankly purulent discharge is present but no glued eyes which is a sign of bacterial conjunctivitis. In significant number of patients rhinitis, atopic conditions and asthma are associated problems which share the same allergic etiology. Usually clinical features of this disease may present throughout the year but severity is increased in spring and summer and it is considered as a type I hypersensitivity reaction. Cornea can be involved in VKC inflammation taking the form of a superficial punctate keratitis or epithelial macro erosion or ulcers. An oval- shaped epithelial defect known as shield ulcer may be present in upper half of visual axis in severeVKC. Decrease of vision or blindness may occur due to corneal ulcer and extensive corneal pannus of prolonged duration. Commonly, VKC can be divided into three distinct phenotypes, that is, tarsal, limbal and mixed VKC. Cobble stone appearance of tarsal VKC results from studded giant papilla formation and gelatinous infiltrations of inflammatory infiltrates around limbus-The Horner-Trantas dot in limbus VKC are present. Management of allergic conjunctivitis involves prevention and treatment with pharmaceautical agents.Prevention includes steps like avoiding the allergens, applying cold compresses,frequent washing hands and face,avoiding rubbing of eyes and reduce exposure to dust. Drugs used for treatment of allergic conjunctivitis depend on severity of disease. Different treatment option for VKC includes vasoconstrictors, antihistamines, mast cell stabilizers and corticosteroids (Hosclaw et al.,1996). Corticosteroids are most effective treatment which are used as topical, sub-tarsal and systemic route but corticosteroid also carries considerable risk of complications including cataract, glaucoma, corneal ulcer and dry eyes. The topical steroids are effective in management of acute flare-ups and hyper acute cases of ocular allergy as well as late response seen in chronic cases.In case of severe VKC for prolonged duration, corneal complication and corticosteroids side effect may lead to permanent impairment of vision. Cyclosporine is an immunosuppressive agent that specifically inhibits helper T-lymphocyte proliferation and production of interleukin(Bleik et al.,1991). Cyclosporine has direct inhibitory effects on eosinophil activation, release of granule proteins and cytokines. It also has direct and indirect inhibitory effects on mast cell activation, cytokine and mediator release, which are likely to be important in its role in the treatment of allergic inflammation(Hingorani et al., 1998) Topical cyclosporine has been proven to be effective in long term treatment of VKC,significantly improving signs and symptoms(BenEzra et al.,1986).The aim of present study was to evaluate the efficacy and

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adverse effects of topical cyclosporine 0.05% in patients of vernal kerato conjunctivitis.

MATERIALS AND METHODS

A total of 100 patients with vernal keratoconjunctivitis presenting in Regional Institute of Ophthalmology, PGIMS were included in the present study. All patients had active disease during their enrollment. Informed consent was obtained from the patients parents in case of minors. A detailed medical history was obtained and a complete ophthalmologic examination was performed. Visual acuity was noted in patients who did not have symptoms of photophobia, blepharospasm. Intraocular pressure was noted with applanation tonometry. Anterior segment was evaluated with slit-lamp examination and dilated fundus examination was performed. Symptoms and signs were noted before the start of treatment and at follow up of 4,8 and 12 weeks after starting of treatment. Symptom scores were assigned between 0-3 and were calculated by grading itching, discomfort, discharge, tearing and photophobia. Sign scores were calculated by grading conjunctival hyperemia, limbal papillae, tarsal papillae, keratopathy and corneal neovascularization. Size and extensiveness were considered when grading the tarsal conjunctival and limbal papillae. Corneal signs were scored according to the extensiveness of punctate epithelial keratitis and/or presence of ulceration. Corneal revascularization was graded according to corneal quadrants and by measuring the dimension from the limbus to the central cornea.(Table-1)

Topical cyclosporine 0.05% four times a day was added to each patient's treatment. Evaluation was done on above mentioned interval. All data was analyzed using SPSS software. P-value of <0.05 was considered statistically significant.

RESULTS

Among the 100 patients with VKC who were recruited for the study, 66 were male and 34 were female. The mean age of patients was 12.7+/- 3.7 (range 6-25) years. The severe VKC of bulbar, tarsal and mixed type was found in 30, 7 and 63 patients, respectively. (Table-2).

Before treatment the median values of the symptoms and sign scores were 11.0 (range 5.0-15.0) and 7.0 (range 2.0-14.0), respectively. These scores were reduced at week 4 of therapy (symptom score 3.0 and sign score 3.0) when compared with baseline scores, the reductions in the symptoms and sign scores at weeks 4, 8 and 12 of treatment were statistically significant ($p<0.05$).

DISCUSSION

In this study, efficacy of topical cyclosporine on those patients of vernal keratoconjunctivitis who were in active phase of disease was evaluated.In this study efficacy of topical Cyclosporine(0.05%) on clinical signs and symptoms of VKC was evaluated. Significant reductions in sign and symptoms scores were detected at week 4 of initiation of therapy. When compared to baseline scores, the reductions in the sign and symptoms scores were statistically significant. After 4 weeks further reductions in sign scores were noted as compared with symptoms scores.

Topical cyclosporine was well tolerated by all of our patients.

In this study statistically significant improvement was observed for symptoms(itching,photophobia,mucous discharge) and signs (conjunctival hyperemia,punctate keratitis) of VKC.There was also improvement for other symptoms(watering,foreign body sensation) and signs(limbaloedema,palpebral conjunctival papillae) of VKC.These results were compatible with the studies carried out by Gupta et al., 2001 and Sechhi et al., 1998. No significant side effects occurred, except for mild stinging and burning upon administration, which was also noted in studies carried out by Hingorani et al., 1998 and secchi et al.,1998. Cyclosporine was similarly effective in controlling acute allergy in a study done by Ozcan et al., 2007. However in study carried out by Bleik et al.,1991, no adverse effects and no detectable levels of cyclosporine were noted in the blood in the cyclosporine treated groups. Topical cyclosporine appears to carry none of the serious,sight threatening complications of topical steroids,such as glaucoma, cataract and exacerbation of corneal infection. Cyclosporine an immunosuppressive agent,most commonly inhibits T-lymphocytes proliferation

Table 1 : Grading of Symptoms and Signs of VKC Patients

Variable	Score			
	0	1	2	3
Symptoms				
Itching	None	Occasional	Frequent	constant
Discomfort	none	Mild	Moderate	severe
Tearing	normal	Wet eyes only	Intermittent tears on face	Constant tears on face
Discharge	none	Small amount	Moderate amount	Severe amount
Photophobia	none	Mild	Moderate	Severe
Signs				
Conjunctival hyperemia	none	Mild	Moderate	Severe
Tarsal papillae	none	<1 mm	1-3 mm	>3 mm
Limbal papillae	none	<90 or < 2 mm	90-180 or 2-4 mm	>180 or > 4 mm
Keratopathy	none	Localized punctate epithelial keratitis	Two quadrants of epithelial keratitis	Three or more quadrants of epithelial keratitis/ corneal ulcer
Corneal neovascularisation	none	<90 or <1 mm	90-180 or 1-3 mm	>180 or >4 mm

Table 2 : Symptom and Sign Scores of VKC Patients Before and After Tacrolimus Therapy

Variable	Median (Range)	25^{th} Percentile	75^{th} Percentile	P-value
Symptom Score				
Baseline	11.0(5.0-15.0)	9.0	13.0	
Week 4	3.0 (0.0- 13.0)	1.0	9.0	<0.001
Week 8	3.0 (0.0- 13.0)	1.0	9.0	<0.001
Week 12	3.0 (0.0- 13.0)	1.0	9.0	<0.001
Sign Score				
Baseline	7.0 (2.0- 14.0)	5.0	10.0	
Week 4	3.0 (0.0- 8.0)	2.0	5.0	<0.001
Week 8	2.5 (0.0-9.0)	1.2	5.0	<0.001
Week 12	2.0 (0.0-8.0)	1.0	5.0	<0.001

and production of interleukin-2. It therefore acts on T-cell-dependent inflammatory mechanisms. Cyclosporine also has direct inhibitory effects on eosinophil activation and release of granule proteins and cytokines and both direct and indirect inhibitory effects on mast cell activation, cytokine and mediator release, which are likely to be important to its role in the management of allergic inflammation. Patients with active VKC have a significant increase in the T-lymphocyte-dependent mast cells in the epithelial cells of conjunctival biopsy specimens. Cyclosporin likely modulates the local IgE production by the B cell via its effect on the T-helper cells and possibly by influencing the T-lymphocyte-dependent mast cells.Topical cyclosporine has been used to treat a number of anterior segment conditions including Sjogren's syndrome,ligneous conjunctivitis,ocular cicatricialpemphigoid,Mooren's ulcer

and autoimmune corneal melting.It also has been used in high risk penetrating keratoplasy to suppress local immunity and prevent rejection of corneal graft.Literature shows that topical cyclosporine is not going to be absorb into the systemic circulation in sufficient concentration to reach therapeutic or toxic dosages and therefore is not associated with any systematic side effects. Prolonged use of topical cyclosporine has been reported, and the only serious side effects reported are lid maceration and corneal epitheliopathy, both of which resolve on cessation of treatment and which do not necessarily preclude further use of cyclosporine.In few patients only mild stinging and burning sensation is evident as a side effect. Topical cyclosporine appears to carry none of the serious, sight threatening complications of topical steroids, such as glaucoma, cataract and exacerbation of corneal infection(Hoang-Xuan et al.,1997). Hence topical cyclosporine is a good alternate to steroids to treat VKC with minimal side effects.

CONCLUSION

The study suggests that topical cyclosporine (0.5%) is safe and effective in treatment of severe vernal keratoconjunctivitis. Most of its effects on signs and symptoms were achieved after 2 weeks of treatment. The only side effect was mild burning sensation and tearing soon after the instillation of the eye drops.

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