Effect of Topical Cyclosporine in grading of Vernal keratoconjunctivitis.

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Abstract:

Background & Objective: To evaluate efficacy of topical aqueous solution of 0.05% cyclosporine in first time diagnosed vernal keratoconjunctivitis (VKC) including palpebral, bulbar and mixed form. **Methods**: 25 patients of VKC received CsA 0.05% aqueous ophthalmic solution in a dosage of one drop every 12 hours in both eyes for 6 months. Follow up visits (day 1, 2 weeks, 1 month, 2 months, 3 months and 6 months). Five symptoms were evaluated and six clinical signs were charted. Total objective score of 13 or more over atleast 3 variables was included (CART – scoring system). **Results:** Comparison of 1st Day with 2 weeks score showed no significant effect in the score value ($t=0.90$, $df = 24$, $p<0.1$). 1st Day with 3rd month score showed maximum effect in the score value ($t = 35.76$, $df = 24$, $p<0.0001$). 3rd month with 6th month score showed sustained effect of cyclosporine showing no major change in the score line (t test, $t = 1.80$, $df = 24$, $p <0.05$). **Conclusion:** Topical application of a 0.05% CsA aqueous solution has been shown to be effective in the treatment of patients with VKC. CsA could be an important alternative to steroid treatment.

Keywords: Cyclosporine, Grading, Vernal Keratoconjunctivitis.

Introduction:

Vernal Keratoconjunctivitis (VKC) is one severe chronic form of seasonally exacerbated allergic conjunctivitis. It is more common in children and young adults having an atopic background.[1-3]

This ocular allergy is characterized by bilateral inflammation of the palpebral conjunctiva, itching, irritation and conjunctival congestion and chemosis among others signs and symptoms. Allergens in the air, especially plant pollen triggers the condition, leading to seasonal exacerbations during the spring and summer months.[4]

Topical steroids are the conventional treatment for practically all severe kind of allergic conjunctivitis.[1,5] Long term use of steroids has clinical limitations due to their side effects and may result in severe complications such as ocular hypertension, glaucoma, cataract and secondary infections.[6] There is a subset of VKC patients that become refractory to the corticosteroids treatment over time.[7] Consequently, the development of agents that could be used effective and chronically without serious adverse effects is very important, for the management of chronic ocular disorders such as VKC.[1] This is

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where immunomodulatory agents such as Cyclosporine A (CsA) may be important.

Cyclosporine selectively suppresses T lymphocyte function along with synthesis and production of Interleukin 2 which is an important cascade in VKC.[8] So cyclosporine is highly effective on a long run.

Materials and Methods:

This was a prospective clinical study of 25 patients (22 males, 3 females). Study conducted at Nagri eye hospital. Written informed consent was obtained from each volunteer's father, mother or guardian.

First time diagnosed VKC patients were considered with no past history of any antiallergic medication, similar complaint or systemic illness. VKC was diagnosed based on the presence of itching, mucus discharge, papillae on the superior tarsal conjunctiva and limbal hyperplasia. The eligibility approval for all the subjects was determined after concluding the clinical evaluation in the basal visit.

The patients received the CsA 0.05% aqueous ophthalmic solution in a dosage of one drop every 12 hours in both eyes (8:00 h and 20:00 h ±1 hour) during the 6 months of the study.

All patients were evaluated by the same investigator in the screening period, as well as in the subsequent programmed follow up visits (day 1, 2 weeks, 1 month, 2 months, 3 months and 6 months).

For the purpose of this study, five symptoms (ocular itching, discharge, photophobia, tearing, and discomfort) were evaluated and also six clinical signs (conjunctival hyperemia, Tarsal conjunctival papillary hypertrophy, punctuate keratitis, neovascularisation of cornea, cicatrizing conjunctivitis and blepharitis) were charted. Other variables (anterior segment condition, posterior segment condition) that are related to ocular health were also evaluated. The investigators used identical forms to evaluate and measure these variables.

To be included in the study, patients needed a total objective score (sum of scores of both the eyes) of 13 or more over atleast 3 variables, with a minimum score of 5 in one eye.

A complete washout period from any type of drug of atleast 10 days was established for all study participants.

All Eyes that received cyclosporine eye drops did not receive any other eye drops except 0.5% lubricating (Carboxy methyl cellulose) eye drops.

The basal examination (day 0 of the study) was carried out. In this visit, the parents were asked to sign the informed consent. Demographic information, clinical history and specific symptoms were obtained. A complete ophthalmic examination including visual acuity determination (Snellen chart), biomicroscopy, intraocular pressure (IOP) measurement (Goldmann aplanation tonometer) and funduscopy under pupillary dilation was conducted. Patients meeting eligibility criteria during the basal visit were included in the study.

Follow-up visits on day 1, 2 weeks, 1 month, 2 months, 3 months and 6 months.

Table 1 Grading of 5 symptoms of VKC[9]

Symptoms	0	1	2	3
Itching	No desire to rub or stretch the eye	Occasional desire to rub or stretch	Frequent need to rub or stretch	Constant need to rub or stretch
Tearing	Normal tear production	Positive sensation of fullness of conjunctival sac without tears spilling over the lid margin	Intermittent, infrequent spilling of tears	Constant spilling of tears
Discomfort (including burning, stinging and foreign body sensation)	Absent	Mild	Moderate	Severe
Discharge	No abnormal discharge	Small amount of mucoid discharge in lower cul-de-sac	Moderate amount of mucoid discharge, presence of crust upon awakening	Eyelids tightly matted upon awakening, warm soaks necessary to clean eyelids
Photophobia	No difficulty experienced	Mild difficulty with light causing squinting	Moderate difficulty, necessitating dark glasses	Extreme photophobia, cannot stand natural light even with dark glasses

On each follow-up visit, visual acuity, biomicroscopy, and IOP were obtained. Funduscopy under pupillary dilation was performed only on 3 months and 6 months with full compliance.

Inclusion criteria

- Patients with a clinical diagnosis of Vernal Keratoconjunctivitis
- Patients of either gender, 5 years or older.

Exclusion criteria

- Patients with one blind eye.
- Patients with visual acuity of 6/24 or worse.
- Patients who are in an active stage of any other ocular inflammatory disease besides of VKC.
- Patients receiving medication through topical ocular route of administration or any other that can in a very determinant way interfere in the results of the study.
- Patients with history of hypersensitivity
- Contact lenses users.
- Patients who cannot comply with the medical appointments or with all the protocol requirements.
- Patients who disagree to participate in this clinical trial.

Table 2 Grading of 6 signs of VKC[9]

Signs	0	1	2	3
Bulbar conjunctival hypermia	Absent	Mild	Moderate	Severe
Tarsal conjunctival hypertrophy	No evidence of papillary formation	Mild papillary hyperaemia	Moderate papillary hypertrophy with edema of palpebral conjunctiva and hazy view of deep tarsal vessels	Severe papillary hypertrophy obscuring deep tarsal vessels
Punctuate keratitis	No evidence of punctuate keratitis	1 quadrant of punctuate keratitis	2 quadrant of punctuate keratitis	3 or more quadrant of punctuate keratitis
Neovascularisation of cornea (new vessel formation crossing the limbus on to the clear cornea by ≥ 2mm)	No evidnce of new vessel formation	Presence of neovascularisation in quadrant of cornea	Presence of neovascularisation in 2 quadrants of cornea	Presence of neovascularisation in 3 or more quadrant of cornea
Cicatrizing conjunctivitis (superficial scarring)	No evidence of cicatrization	Presence of subepithelial fibrosis	Presence of fornix fore-shortening	Symblepharon formation
Blepharitis and meibomian gland dysfunction	No evidence of blepharitis	Presence of mild redenss and edema of eyelids	Moderate inflammation with hyperaemia, scales and meibomian gland dysfunction	Severe inflammation with cracks in eyelid skin, loss of lashes

Analysis:

Paired t-test was used to test the significance in the difference in the effect of 0.05% cyclosporine at different stages of treatment

Result:

In our study males (88%) are affected more than females (12%).

Comparison of 1st Day with 2nd week score showing no significant effect in the score value. We have used paired t test, t=0.90 at degree of freedom = 24 at p<0.1 Showing difference is not significant. [Image 1]

Image 1 Comparison of 1st Day and 2nd week with cyclosporine treatment

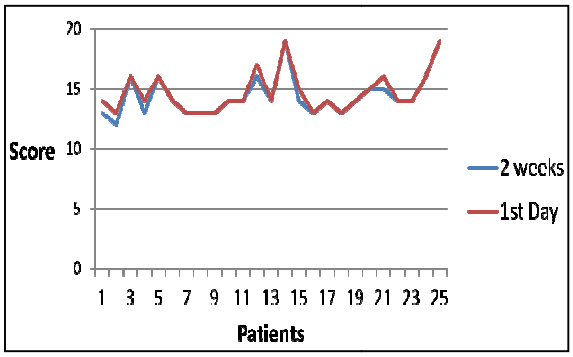
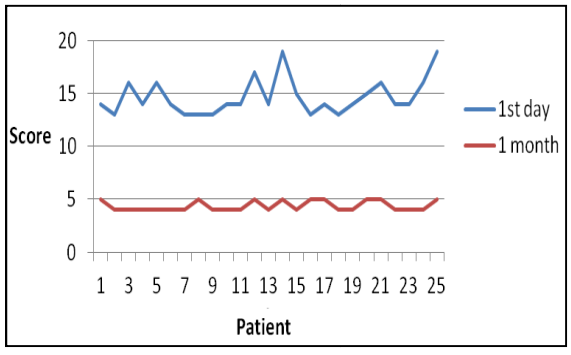


Image 2 Comparison of 1st Day and 1 month with cyclosporine treatment



Comparison of 1st Day with 1 month score showing significant effect in the score value. We have used paired t test, t = 32.25 at df = 24 at p<0.0001 showing difference is highly significant. [Image 2]

Comparison of 1st Day with 3rd month score showing maximum effect in the score value. We have used paired t test, t = 35.76, degree of freedom = 24, p<0.0001 showing difference is highly significant. [Image 3]

Comparison of 3rd month with 6th month score showing stabilized effect in the score value. We have used paired t test, t = 1.80, degree of freedom = 24, p <0.05 showing difference is not significant. [Image 4]

Image 3 Comparison of 1st day and 3rd month with Cyclosporine treatment

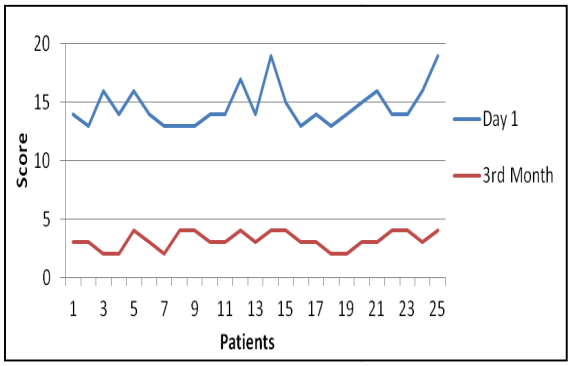


Image 4 Comparison of 3rd month and 6th month with cyclosporine treatment

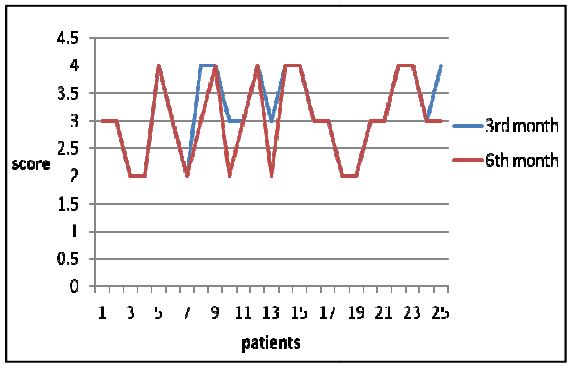


Image 5 Bulbar form of VKC (A) 1st day of treatment (B) After 6 months of treatment

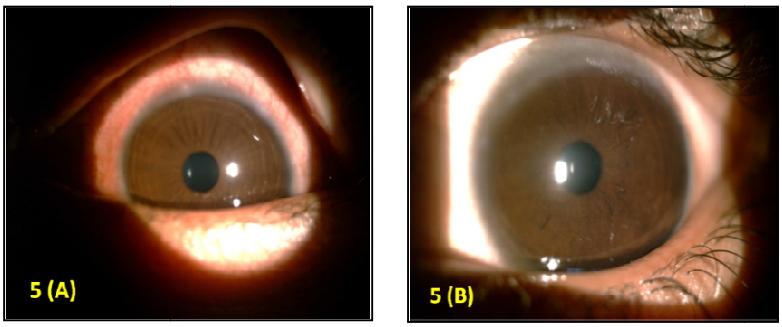
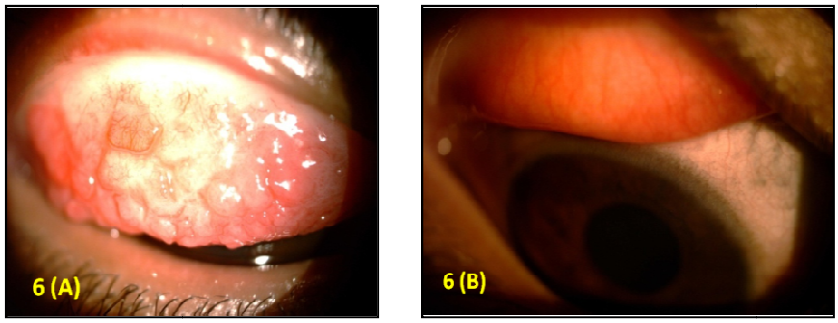


Image 6 Palpebral form of VKC (A) 1st day of treatment (B) After 6 months of treatment



Discussion:

The results of the present study confirm the beneficial effect of topical CsA 0.05% aqueous solution in improving the symptoms and clinical manifestations of moderate to severe allergic conjunctivitis type VKC.

On the basis of our results, comparison of 1st Day with 2 weeks score showed no significant effect in the score value (t=0.90, df = 24, p<0.1). Comparison of 1st Day with 1 month score showed significant effect in the score value (t = 32.25, df = 24, p<0.0001). Comparison of 1st Day with 3rd month score showed maximum effect in the score value (t = 35.76, df = 24, p<0.0001). Comparison of 3rd month with 6th month score showed sustain effect of cyclosporine showing no major change in the score line (t test, t = 1.80, df = 24, p < 0.05).

A prospective, observational, all-prescribed-patients study of cyclosporine 0.1% ophthalmic solution in the treatment of vernal keratoconjunctivitis was also done. Its aim was to evaluate the effectiveness and safety of topical cyclosporine 0.1%. All scores for symptoms and signs in patients with VKC significantly decreased throughout a 6-month follow-up.

A study which showed efficacy of topical cyclosporin A 0.05% in conjunctival impression cytology specimens and clinical findings of severe vernal keratoconjunctivitis in children[10] had 54 patients treated with topical cyclosporin A (CsA) 0.05% for 3 months. The mean scores for severity of signs and symptoms significantly decreased after 3 months compared with those at entry (P<0.001). The density of inflammatory cells in the conjunctival impression cytology specimens decreased significantly.

A study of topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis[11] included twenty patients with severe vernal keratoconjunctivitis. All were treated with topical 2% cyclosporine A eye drops. A statistically significant decrease was observed in both sign and symptom scores (p < 0.001)

It is important to emphasize that, in the present study; it was evident that statistical improvements were seen in the 0.05% treatment. It seems that the positive effect in VKC could be due to the suppression of T lymphocytes proliferation and also to the drug's effect on mast cells and eosinophils.[12]

Our results are consistent with the results that Ebihara found in VKC patients with a 0.1% CsA formulation with an aqueous vehicle.[13]

Significant therapeutic effect was achieved after 1 month followed by maximum effect which was seen at 3 months and was maintained till 6 months.

Conclusion:

Topical application of a 0.05% CsA aqueous solution has been shown to be effective in the treatment of patients with VKC. CsA could be an important alternative to steroid treatment. In our study, no significant therapeutic effect was noticed in the first 2 weeks post treatment. However, significant effect was seen after 1 month of treatment which was highly significant at the end of 3 months and maintained till 6 months.

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