Original Article

Role of Cyclosporine Eye Drops In Allergic Conjunctivitis

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Purpose: To evaluate the effects of topical 2% cyclosporin eye drops in patients with active vernal keratoconjunctivitis.

Material and Methods: Thirty seven patients with active vernal keratoconjunctivitis diagnosed at least one year before and treated with a variety of topical medications except cyclosporin were included in the study. All patients were treated with 2% cyclosporin eye drops four times daily in both eyes for 6 weeks. Symptoms (itching, watering, photophobia, mucous discharge and foreign body sensation) and signs (conjunctival hyperemia, trantas' dots, limbal oedema, epithelial punctate keratitis and palpebral conjunctival papillae) of vernal keratoconjunctivitis were recorded before treatment and at the end of treatment period.

Results: There was a statistically significant improvement in itching, photophobia, mucous discharge, conjunctival hyperemia, punctate keratitis and trantas' dots after 6 weeks treatment period. No significant adverse effect of treatment with topical cyclosporin was observed except for mild to moderate stinging and burning upon administration.

Conclusion: Topical cyclosporin is an effective and safe agent in the treatment of vernal keratoconjunctivitis.

Vernal keratoconjunctivitis (VKC) is an ocular allergic disease predominantly observed in children and young adults[1]. The disease is usually bilateral and is seen more commonly among males[2]. Patients with vernal keratoconjunctivitis may suffer from symptoms throughout the year, but the intensity of the disease may increase in spring and summer. The precise immunopathogenic mechanism

is unknown but it is thought to be more complex than a simple type I hypersensitivity reaction[3].

Therapy of vernal keratoconjunctivitis includes the use of topical vasoconstrictors, antihistamines, mast cell stabilizers and corticosteroids[4]. The most effective treatment for vernal keratoconjunctivitis is stopical and supratarsal injection of corticosteroids, but this treatment carries considerable risk of complications[5].

Although the disease is self limiting, signs and symptoms are often severe and difficult to control. Corneal complications in untreated cases and prolonged steroid treatment in treated cases may lead to permanent impairment of vision. Therefore the search for new, effective and safe treatments of this potentially blinding disease continues.

Cyclosporin is an immunosuppressive agent that specifically inhibits helper T-lymphocyte proliferation and production of interleukin-2[6]. It is therefore inhibitory to many T-cell-dependent inflammatory mechanisms. It 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[7].

To avoid the complications of current treatment of severe VKC (especially steroid), the efficacy of cyclosporin regarding the control of symptomatology of VKC was studied.

MATERIALS AND METHODS

The study was conducted at the Institute of Ophthalmology, Mayo Hospital Lahore from March to May 2002. A total of 37 patients were included in this Quasi experimental study.

Patients included in the study were known cases of active palpebral or limbal vernal keratoconjunctivitis diagnosed at least one year before and treated with a variety of topical medications, except cyclosporin with poor response.

Patients excluded from the study were patients with associated ocular or systemic disease, patients who had history of periocular injections of steroids within a period of six months, patients taking systemic corticosteroids, anti-inflammatory agents or antihistamines and patients with shield ulcer.

Patients with VKC were selected according to inclusion and exclusion criteria. VKC was defined as recurrent bilateral conjunctivitis with giant papillae in the upper palpebral conjunctiva or by gelatinous hypertrophy of the limbus, associated with typical vernal epithelial keratitis.

After taking informed consent patients were enrolled in the study. All patients were placed on a one week washout period. During that period patients were requested not to instill any eye drops in their eyes and parents were instructed to apply cold compresses whenever their children complained of symptoms related to the disease. After this washout period detailed ophthalmic and systemic history for associated disorders was recorded and a complete ophthalmological examination was performed. Specific evaluation of the following symptoms and signs was carried out. Symptoms include itching, watering, photophobia, mucous discharge and foreign body sensation. Signs include conjunctival hyperemia, punctate keratitis, trantas' dots, limbal oedema and palpebral conjunctival papillae. All patients were given 2% cyclosporin eye drops four times daily in both eyes. Symptoms and signs were recorded before treatment and after 1st, 3rd and 6th week of treatment.

Grading of Symptoms

Symptoms were graded as follows:

- 0= indicating no symptoms
- 1+= mild symptoms of discomfort which were just noticeable.
- 2 + = moderate discomfort noticed most of the day but did not interfere with daily routine activities.
- 3+ = severe symptoms interfering with daily routine activities.

Grading of Signs

Conjunctival hyperemia was graded as follows:

- 0= no evidence of bulbar hyperemia.
- 1+ = mild bulbar hyperemia.
- 2+ = moderate bulbar hyperemia.
- 3+ = severe bulbar hyperemia.

Palpebral conjunctival papillae were graded as follows:

- 0= no papillary hypertrophy of the palpebral conjunctiva.
- 1+ = mild papillary hypertrophy.
- 2+ = moderate papillary hypertrophy (hazy view of the deep tarsal vessels).
- 3+ = severe papillary hypertrophy (deep tarsal vessels not visible in more than 50% of the surface).

Punctate keratitis was graded as follows:

0= no evidence of punctate keratitis.
1+ = one quadrant of punctate keratitis.
2+ = two quadrants of punctate keratitis.
3+ = three or more quadrants of punctate keratitis.

Trantas'dots were graded as follows:

0 = no evidence of dots.
1 + = 1 to 2 dots.
2 + = 3 to 4 dots.
3 + = more than 4 dots.

Limbal oedema was graded as follows:

0 = no evidence of limbal oedema.
1 + = less than 90^o of limbal oedema.
2 + = less than 180^o of limbal oedema but more than 90^o.
3 + = more than 180^o of limbal oedema.

Blood was collected by antecubital venipuncture before and 6 weeks after the initiation of treatment. Complete blood count, blood urea nitrogen, creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) levels were determined to monitor the systemic side effects of cyclosporin.

Because 2% cyclosporin eye drops were not commercially available in the market they were prepared by us. These drops were prepared from the commercially available injection of cyclosporin (SANDIMMUN) 250 mg /5ml. Two millilitre solution (100mg) was withdrawn from this vial and diluted 5 times with 8 ml of Artificial tears (Tears Naturale II eye /drops) to get 2% cyclosporine eye drops.

Data was collected in terms of scores for different variables. Wilcoxon signed rank test (non-parametric test) was used for before and after treatment comparison.

RESULTS

There were 32 males and 5 females enrolled in the study. Patients had mean age of 9.8 years (ranged 5 to 18 years). Twenty four (64.9%) of 37 patients were 10 years of age or younger (Table 1)

Table 1: Distribution Age and Sex (n =37)

Age	05-10 Years	24 (64.9)
	11-15 Years	10 (27.0)
	16-18 Years	3 (8.1)
Sex	Male	32 (86.5)
	Female	5 (13.5)

In general, patients after using topical cyclosporin remained comfortable. No significant side effect occurred, except for mild to moderate stinging and burning upon administration. There was statistically significant improvement in itching, photophobia and mucous discharge. There was also improvement in watering and foreign body sensation, although not statistically significant. Thirty six (97.3%) patients had decrease in itching after treatment with topical cyclosporin ($p<0.01$). Tearing improved in 23(62.2%) patients after treatment with topical cyclosporin ($p>0.05$). Photophobia improved in 32(86.5%) patients ($p<0.02$), Mucous discharge improved in 33(89.2%) patients ($p<0.05$), Foreign body sensation improved in 30(81.1%) patients ($p>0.05$) (Table 2).

Conjunctival and Corneal signs:

There was a statistically significant improvement in the conjunctival and corneal signs after using topical cyclosporin. Bulbar conjunctival hyperemia improved in 36(97.3%) patients ($p<0.01$). Punctate keratitis improved in 34(91.9%) patients ($p<0.02$). Trantas' dots showed decrease in number in 31(83.8%) patients ($p<0.01$). Limbal oedema improved in 33(89.2%) patients ($p>0.05$). Palpebral conjunctival papillae showed improvement in 19(51.4%) patients ($p>0.05$) (Table 3).

The intraocular pressure was measured in patients who were co-operative, before, during and six weeks after treatment with topical cyclosporin. There was no significant change in the intraocular pressure after treatment.

Complete blood count showed normal white blood cells counts with differential count showing slight increase in the number of eosinophils. The number of eosinophils in patients of VKC entered in this study ranged between 3% and 13%. No significant difference was found after treatment with topical cyclosporin (Table 4).

Kidney and liver function tests showed no significant change before and after treatment.

DISCUSSION

Vernal Keratoconjunctivitis (VKC) is recurrent bilateral interstitial inflammation of the conjunctiva, afflicting children and young adults and usually of periodic seasonal incidence[5]. The immunopathogenic mechanism is complex and may be mediated by both IgE and IgG. A cell mediated immune process has also been postulated. Untreated corneal complications as well as prolonged treatment with steroids may lead to impairment of vision. Because the condition eventually resolves, usually after adolescence, the treatment should be conservative and aimed at preventing potential complications.

The management of VKC often is difficult and is determined by availability of medications, safety and cost effectiveness[8]. Milder cases can often be treated with tear substitutes, topical vasoconstrictors or topical antihistamines. More advanced cases may be treated with combinations of topical mast cell stabilizers and topical corticosteroids[4] but unsupervised treatment may lead to glaucoma and cataract. Therefore a drug which is effective in advanced cases of VKC with no or little side effects is highly desirable.

Our clinical trial demonstrated that topical cyclosporin was effective is controlling the symptoms and signs of patients with VKC. Statistically significant improvement was observed for symptoms (itching, photophobia, mucous discharge) and signs (conjunctival hyperemia, punctate keratitis, trantas' dots) of VKC. There was also improvement for other symptoms (watering, foreign body sensation) and signs (limbal oedema, palpebral conjunctival papillae) of VKC, although statistically not significant. These results are comparable with the studies carried out by

Table 2: Symptom (before and after) n=37

Symptom	0		1+		2+		3+	
	Before n (%)	After n (%)	Before n (%)	After n (%)	Before n (%)	After n (%)	Before n (%)	After n (%)
Itching		7 (18.9)	1 (27)	27 (73.0)	29 (78.4)	3 (8.2)	7 (18.9)	
Watering	1 (2.7)	9 (24.3)	17 (46)	22 (59.5)	15 (40.5)	6 (16.2)	4 (10.8)	
Photophobia	(%)	10 (27)	10 (27)	24 (64.9)	21 (65.8)	3 (8.1)	6 (16.2)	(%)
Mucous discharge	(%)	10 (27)	10 (27)	25 (67.6)	24 (64.9)	2 (5.4)	3 (8.1)	(%)
Foreign body	1.(2.7)	5 (13.5)	5 (13.5)	25 (67.6)	25 (67.6)	7 (18.9)	6 (16.2)	(%)

Table 3: Signs (before and after) n=37

Sings	0		1+		2+		3+	
	Before n (%)	After n (%)	Before n (%)	After n (%)	Before n (%)	After n (%)	Before n (%)	After n (%)
Conjunctival Hyperemia	(%)	10 (27.0)	2 (5.4)	24 (64.9)	31 (83.8)	3 (8.1)	4 (10.8)	(%)
Punctate Keratitis	(%)	24 (64.9)	19 (51.4)	11 (29.7)	15 (40.5)	2 (5.4)	3 (8.1)	(%)
Trantas' dots	3 (8.1)	18 (48.65)	9 (24.3)	18 (48.65)	23 (62.2)	1 (2.7)	2 (5.4)	(%)
Limbal oedema	1 (2.7)	15 (40.5)	12 (32.4)	20 (54.1)	21 (56.8)	2 (5.4)	3 (8.1)	(%)
Palpebral Conjunctival Papillae	6 (16.2)	20 (54.1)	23 (62.2)	13 (35.1)	5 (13.5)	3 (8.1)	3 (8.1)	1 (2.7)
Eosinophils in blood								

Table 4: Eosinophils in blood (Before and after) (n-37)

No of Eosinophils	No. of patients n (%)

3-5	9 (24.3)
6-10	22 (59.5)
11-13	6 (16.2)

Gupta et al[9] and secchi et al[10]. However in studies carried out by mendicute et al[11] and Bleik et al[6] there was statistically significant improvement in palpebral conjunctival papillae which is not observed in our study. Mendicute et al's study was carried out on only two patients, while in Bleik et al's study, the authors did not record the effect of topical cyclosporin on palpebral conjunctival papillae, but misinterpreted the result in abstract.

Topical cyclosporin was well tolerated by all of our patients. 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[7] and secchi et al[10]. However in study carried out by Bleik et al[6], no adverse effects and no detectable levels of cyclosporin were noted in the blood in the cyclosporin treated groups. Literature shows that topical cyclosporin is not going to be absorbed 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 2% cyclosporin 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 cyclosporin. Topical cyclosporin appears to carry none of the serious, sight threatening complications of topical steroids, such as glaucoma, cataract and exacerbation of corneal infection[12].

Cyclosporin an immunosuppressive agent, most commonly used in organ transplantation has a selective inhibitory effect on helper T-lymphocytes proliferation and production of interleukin-2. It is therefore inhibitory to many T-Cell- dependent inflammatory mechanisms. Cyclosporin 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 treatment of allergic inflammation[7].

Two types of mast cells have been recognized in humans based on neutral protease composition and T-lymphocyte dependency. The T-lymphocyte-dependent mast cells contain tryptase but not chymase whereas the T-lymphocyte independent mast cells contain both tryptase and chymase. Patients with active VKC have a significant increase in the T-lymphocyte-dependent mast cells in the epithelial cells of conjunctival biopsy specimens. The exact mechanism of action of cyclosporin on the mast cell is unknown but it may be postulated that cyclosporin modulates the local IgE production by the B cell via its effects on the T-helper cells and possibly by influencing the T-lymphocyte-dependent mast cells[6].

Topical cyclosporin has been used to treat a number of anterior segment conditions including Sjogren's syndrome, ligneous conjunctivitis, ocular cicatricial pemphigoid, Mooren's ulcer and autoimmune corneal melting. It also has been used in high risk penetrating keratoplasty and is also under trial for the treatment of steroid dependent atopic keratoconjunctivitis[7].

Cyclosporin 0.05% is now available commercially (Restasis, Allergan, USA) in some countries and has been reported to be effective for allergic conjunctivitis[13]. We would suggest that topical cyclosporin 2% is also safe and effective therapy in patients with VKC who are resistant to conventional treatment or when there is danger of developing complications with conventional treatment. Further studies are needed to compare the difference in results and complications of the two concentrations.

CONCLUSION

Topical cyclosporin is effective in controlling the symptoms and signs of patients with vernal kerato-conjunctivitis who are refractory to conventional treatment and can be used safely without any significant side effect.

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