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Research Article

Efficacy of Topical Cyclosporine in the Treatment of Atopic and Vernal Keratoconjunctivitis

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Abstract

Background: Atopic and vernal keratoconjunctivitis can be treated with a variety of medications, including topical antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. But none proven to be effective and safe for long term use.

Methods: An intervention study was conducted on 70 atopic and 70 vernal keratoconjunctivitis patients in NIO&H Dhaka during the period of August 2010 to January 2011. All the subjects received topical cyclosporine 0.05%. 20 patients were lost to follow up and remaining 120 patients' (60 patients were atopic and 60 patients were vernal keratoconjunctivitis) data was analyzed.

Result: Mean age of the vernal and atopic keratoconjunctivitis mean age were 7.32 ± 3.52 (SD) and 32.07 ± 9.80 respectively. In both the group male were more than female (VKC male vs female 73.3% vs 23.7%, AKC 53.3% vs 46.7%). At the baseline, 100% of the vernal and atopic keratoconjunctivitis patients had itching, discharge, redness and irritation. Photophobia was more in vernal keratoconjunctivitis 40% than atopic keratoconjunctivitis 6.7% ($p < 0.001$). Allergy was more common in atopic keratoconjunctivitis (93.3%) than vernal keratoconjunctivitis (46.7%) ($p < 0.001$). Co-existence of asthma was equal in atopic and veneral keratoconjunctivitis 40%), but eczema was more in atopic keratoconjunctivitis patients 93.3% than veneral atopic keratoconjunctivitis patients 18.3% ($p < 0.001$).

After 15 days of treatment, lacrimation status improved in 93.3% of atopic and 60% of veneral keratoconjunctivitis patients. There was no significant improvement of other symptoms after 15 days and 1 month. After completion of 3 months treatment 93.3% patients improved in case of atopic keratoconjunctivitis and 91% in vernal keratoconjunctivitis.

Conclusion: In our study topical cyclosporine 0.05% was found effective in both atopic and vernal keratoconjunctivitis.

Keywords: *Cyclosporine; Atopic; Vernal; Keratoconjunctivitis*

Introduction

Atopic and vernal keratoconjunctivitis are chronic forms of allergic eye disease. Atopic keratoconjunctivitis (AKC) can cause chronic conjunctival scarring associated with a high rate of visual impairment and management is often difficult. Its corneal complications are neovascularization, sub epithelial haze, pannus and pseudopterygium formation seen in 60% to 70% of patients, leading to blindness [1,2] and approximately 30% of patients require corneal transplantation [3]. Vernal keratoconjunctivitis (VKC) is also a chronic, poten-

tially severe bilateral allergic inflammation of the superior and limbal palpebral conjunctiva that affects children mainly in temperate areas, with exacerbations in spring and summer and has a high rate of corneal complications [4]. Furthermore, there are iatrogenic risks of cataracts or glaucoma due to long use of steroids [5]. VKC generally subsides within or after puberty, but AKC is seen in an adult life. The estimates of VKC prevalence in Western Europe ranged from 1.16 to 10.55 per 10,000 inhabitants. The prevalence of VKC with corneal complications ranged from 0.30 to 2.26 per 10,000 inhabitants [6]. AKC occurs in 25% to 40% of patients with atopic dermatitis [7]. In Bangladesh about 10 - 15 percent of population suffer from chronic allergic eye diseases [8,9]. A number of medicine have been used for the treatment of AKC and VKC. Most important of these are H_1 topical antihistamine eye drops, mast cell stabilizers, topical corticosteroids, topical NSAIDs and artificial tears. In 1995, Hingorani and Lightman stated that mast-cell stabilizers (cromolyn sodium 2% or 4%, lodoxamide tromethamine 0.1%,nedocromil sodium 2%) can be applied topically and may be suitable for severe forms of allergic conjunctivitis but it do not cure the disease. Discontinuation of this drug results in recurrence. Moreover, these drugs are unable to treat the aggressive behaviour of AKC and VKC [10].

Topical corticosteroids are very effective in treating AKC and VKC. They are able to treat the inflammatory nature of these two diseases very successfully with minimum recurrence. Currently they are the main drugs for treating these two diseases in our country. But unfortunately, prolonged use of these drugs is associated with very grave vision threatening complications. In 1963 Valerio showed that use of topical corticosteroid four times a day for one year can result in posterior subcapsular cataract [12]. In 1971 Kolker showed that topical use of corticosteroids (dexamethasone 1%) four times a day for six weeks result in rise of IOP above 31 mm of Hg in 5% people and 20 to 31 mm of Hg in 33% of people [13]. Topical NSAID eye drops were thought as an alternative to steroid but in 2007, Swamy showed that topical NSAIDs did not reduce the allergic signs of conjunctival chemosis, conjunctival mucus, eyelid swelling and corneal disturbance. Topical NSAIDs had a significantly higher rate of burning or stinging sensation on application [14]. In view of the complications of the above used drugs used for treating AKC and VKC, the investigators have always searched for a safe alternative drug. Cyclosporine A (CsA) is a neutral, hydrophobic, cyclic undecapeptide metabolite of the fungus *Tolypocladium inflatum*. It is most frequently used in solid organ transplantation. Cyclosporin A produces calcium-dependent, specific, reversible inhibition of interleukin -2 transcription [15,16]. This reduces the production of a range of cytokines which inhibit is the activation and maturation of various cell types involved in atopy. CsA has selective action on T helper lymphocytes and weak myelotoxicity. These are the key advantages of this drug in the treatment of AKC and VKC patients. The topical application of CsA was first used to inhibit corneal allograft reaction in the early 1980s [17-19]. Later on the drug was found useful in patients with various inflammatory ocular surface disorders [19-25]. Recent studies showed that patients treated with topical CsA improved the signs and symptoms of AKC and VKC. CsA oil in water emulsion formulation significantly improved the ocular signs and symptoms of chronic allergic eye diseases and was found to be well tolerated.

In our country AKC and VKC patients have been treating with topical corticosteroids, mast cell stabilizer, anti-histamine and NSAID eye drops with poor success rate. So far, there is no study on topical trail of CsA (0.05%) on AKC and VKC. So the present study has been designed to see the effect of topical CsA (0.05%) on AKC and VKC.

Materials and Methods

It is an intervention study, carried out from August 2010 to January 2011 to explore efficacy of topical Cyclosporine 0.05% among diagnosed patients of vernal and atopic keratoconjunctivitis. Atopic and vernal keratoconjunctivitis patient who were attended in outdoor and indoor of National Institute of Ophthalmology, Dhaka were included in our study. Purposive sampling technique was used to collect the sample. Total 140 patients was included 70 Atopic keratoconjunctivitis and 70 vernal keratoconjunctivitis patients. Patient with contact lens, affected by other ocular disease like bacterial conjunctivitis, viral conjunctivitis, with active corneal ulcer, patient subjected to ocular surgery in the preceding 6 months, patients under eye drop or systemic treatment for other disease and patients enrolled in experimental trials in the preceding 6 months were excluded from our study.

Intervention technique

70 patients of AKC and 70 patients of VKC was separated and marked full history of the patients was taken including family and personal history of allergic disease, drug history. The patients stopped all medications for at 1 week as a wash out period before eye examination for evaluation and grading of symptoms and signs of allergic conjunctivitis as in table 1 modified from Bonini's report [13]. Classification into mild, moderate and severe cases was performed according to this criterion. Patients with moderate to severe grading were selected for this study. Informed consent was obtained from the parents or the patient if aged over 18 years.

Symptoms and signs	1=mild	2=moderate	3=severe
Itching	Occasionally	Frequently, tolerable rub eye	Rubs all day long
Foreign body sensation	Occasionally	Frequently	All day
Tearing	Occasionally	Frequently	All day
Photophobia	Occasionally	Eye(s) sometimes Closed	Eye(s) frequently closed
Discharge	Occasionally	Frequently	All day
Burning	Occasionally	Frequently	All day
Swollen lid	Feels full in morning	All day	Interpalpebral fissure decreased
Chemosis	Conjunctiva separated from sclera	Raised conjunctiva	Ballooning of conjunctiva
Conjunctival Injection (red eye)	Minimal	Obvious	Diffuse redness
Papillae size	< 0.2 mm	0.2 - 0.9 mm	≥ 1 mm
Giant papillae Size, area	1 - 1.9 mm, < 25%	2 - 5 mm, 25 - 50%	> 5 mm, > 50%
Punctate epitheliopathy	< 1/2 cornea	> 1/2 cornea	Confluent with mucous plaque and ulcer
Sheild ulcer	Transparent base	White deposits	Elevated plaque
Horner Trantus Dot	1 quadrant	2 quadrants	≥ 3 quadrants

Table 1: *Grading of severity of symptoms and signs of allergic keratoconjunctivitis used in this study modified from Bonini's report [26].*

0.05% topical cyclosporine was instilled on both eyes of the AKC and VKC patients 6 times a day for first 15 days than 4 times a day for next 2 and 1/2 months. They were asked to wear sunglasses and avoid eye rubbing. They were also asked to close eyes for three minutes after application of drugs for better contact of drug with eyes and reduce systemic absorption. They were asked to visit at 2 weeks, 1 month and 3 months after starting treatment. Outcome of the drug was evaluated by the presence of symptom and sign of the study patient.

Data collection technique

The data was collected in a pre-formed standard printed data collection form after taking written informed consent of the patient. The procedure and purpose of study was explained to the patient. A detailed history was taken from the patient by interview. Every patient was examined thoroughly.

Data analysis

After collection all the data were checked, cleaned and edited. Then data were entered into computer with the help of software SPSS for windows programmed version 13.5. After frequency run, data were cleaned and frequencies were checked. An analysis plan was developed keeping in view with the objectives of the study. Cross tabulation was prepared and a comparison had been made.

Ethical consideration

After getting the approval of the research proposal from the honorable faculty members, ethical permission was taken from Ethical Review Committee for data collection. Consent was received from each individual prior to inclusion. They were informed of their right to withdraw from the study at any stage. Assurance had been given that the data would be collected anonymously and the confidentiality concerning their information would be maintained strictly. The research was conducted in full accord with ethical principles.

Results

In this study our sample size was 140, but 120 was analyzed, because 20 patients drop out from follow up. There were 60 patients with acute vernal conjunctivitis, mean age was 7.32 ± 3.52 (SD), maximum 45% were 6 to 10 years age group, more than two-thirds of the vernal conjunctivitis patients were male (73.3%) and the rests were female (23.7%). Among the acute atopic keratoconjunctivitis patients (n = 60), mean age was 32.07 ± 9.80 years, 40% were 38 to 46 years age group, male (53.3%) were more than female (46.7%) (Table 2).

Acute vernal conjunctivitis (n = 60)		**Acute atopic keratoconjunctivitis (n = 60)**	
Mean age	7.32 ± 3.52 years	Mean age	32.07 ± 9.80 years
Age range	2-15 years	Mean age	18-46 years
Age group 0 to 5 years	36.7% (22)	Age range 18 to 27 years	40% (24)
Age group 6 to 10 years	45% (27)	Age group 28 to 37 years	20% (12)
Age group 11 to 15 years	18.3% (11)	Age group 38 to 46 years	40% (24)

Table 2: *Showing age group of the acute vernal conjunctivitis and acute atopic keratoconjunctivitis patients.*

At the baseline, 100% of the vernal and atopic keratoconjunctivitis patients had itching, discharge, redness and irritation. Photophobia was more in vernal keratoconjunctivitis 40% than atopic keratoconjunctivitis 6.7% ($p < 0.001$). Allergy was more common in atopic keratoconjunctivitis (93.3%) than vernal keratoconjunctivitis (46.7%) ($p < 0.001$) (Table 3).

Symptoms	**Vernal Keratoconjunctivitis (n = 60)**		**Atopic Keratoconjunctivitis (n = 60)**	
	Frequency	**Percentage (%)**	**Frequency**	**Percentage (%)**
Itching	60	100	60	100
Discharge	60	100	56	93.3
Redness	60	100	60	100
Irritation	60	100	60	100
Pain	52	86.7	56	93.3
Photophobia	24	40	4	6.7

Table 3: *Showing symptoms of the acute vernal conjunctivitis and acute atopic keratoconjunctivitis patients at baseline.*

Co-existence of asthma was equal in atopic and veneral keratoconjunctivitis 40%), but eczema was more in atopic keratoconjunctivitis patients 93.3% than veneral atopic keratoconjunctivitis patients 18.3% ($p < 0.001$).

After 15 days of treatment, lacrimation status improved in 93.3% of atopic and 60% of veneral keratoconjunctivitis patients. Lacrimation status of 100% atopic and 93.3% of the veneral keratoconjunctivitis patient improved after 3 months. There was no significant improvement of other symptoms after 15 days and 1 month. After 1 month of treatment less than two thirds (62.5%) of the atopic keratoconjunctivitis patient's condition improved and more than two thirds (79%) of the patients of vernal keratoconjunctivitis improved. After completion of 3 months treatment 93.3% patients improved in case of atopic keratoconjunctivitis and 91% in vernal keratoconjunctivitis (Table 4).

Symptoms	After 15 days		1 month later		3 months later	
	Atopic keratoconjunctivitis	Veneral keratoconjunctivitis	Atopic keratoconjunctivitis	Veneral keratoconjunctivitis	Atopic keratoconjunctivitis	Veneral keratoconjunctivitis
Discharge	13.3%	8.3%	97.4%	80%	100%	93%
Swollen lid	6.7%	20%	93.3%	95%	100%	100%
Chemosis	20%	33%	90.0%	93.0%	97%	100%
Conjunctival injection	6.7%	8.3%	86.7%	70%	93%	90%
Changes of papillae size	12.3%	3%	63.7%	63%	100%	89%
Improvement of Superficial pannus	6.7%	2%	62.5%	75%	93%	91%

Table 4: *Showing improvement of symptoms of atopic keratoconjunctivitis patients after treatment.*

Adverse events were minimum, 2% patients developed lid swelling, redness increased in 2% and prolonged stinging were found in 5%.

Discussion

Males are more commonly affected than females in VKC. In one series, the male-to-female ratio was 3.2:1 in patients < 20 years of age but was nearly equal in older patients. Our study also found similar result; more than two-thirds of the VKC patients were male. In VKC the most common concomitant atopic diseases are asthma and allergic rhinitis. Aeroallergen sensitization, by skin prick testing or allergen-specific immunoassay, was reported in over 50 percent of patients in one study [26]. Atopic keratoconjunctivitis not only occurs in 20 - 40% of individuals with atopic dermatitis, it is associated with a 95% prevalence of concomitant eczema and an 87% prevalence of asthma. This condition is more prevalent in men than in women, and the peak age of incidence is in persons aged 30 - 50 years (range, late teens to 50y) [27]. But in our study we have found 40% of the AKC patient had asthma and eczema was in 93.3%. Presence of eczema can be differentiating point between atopic and vernal keratoconjunctivitis. Eczema was significantly more common in patient with atopic keratoconjunctivitis than vernal keratoconjunctivitis ($p < 0.001$).

Distinguishing between vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) can be challenging. Historically, AKC is rarely recognized as a diagnostic entity before puberty and is thought to occur predominantly in adults. If a young patient were to present with AKC-like symptoms and atopic dermatitis, they might be diagnosed with VKC [28]. Our study found similar result. Mean age of the

VKC patients of our study were 7.32 ± 3.52 years and the patients of AKC were postpubertal, mean age was 32.07 ± 9.80 years. Children with VKC may present with atopic dermatitis; however, it is not a prerequisite for diagnosis. In contrast, evidence of atopic dermatitis must be present for a diagnosis of AKC to be made [29].

AKC-related clinical features and the absence of VKC-related clinical features, in combination with a history of eczema and conjunctivitis/keratitis, may promote accurate diagnosis of AKC in children [30]. In our study itching, discharge, redness and irritation was present in all the patients of AKC and VKC. Photophobia, allergy and presence of eczema may be the differentiating features between AKC and VKC. Photophobia was significantly more in vernal keratoconjunctivitis than atopic keratoconjunctivitis ($p < 0.001$). On the other hand allergy and eczema were more common in atopic keratoconjunctivitis than vernal keratoconjunctivitis ($p < 0.001$). S Taltlipinar and EK Akpek [31] observed the effect of topical cyclosporine in the treatment of ocular surface disorder. Topical cyclosporine was proved to be successful in both vernal and atopic keratoconjunctivitis and seemed to be safe and had some effect in alleviating signs [25,30,32-34] and symptoms of severe AKC refractory to topical steroid treatment [36]. The improvement produced by topical cyclosporine A in VKC usually took an average of 2 weeks using 1% or 2% CsA in oil solvents, four times daily [25,30,32-34]. The duration of treatment depended on the activity of the inflammation. In our study after 2 weeks lacrimation status was improved in both AKC and VKC. There was no significant improvement of other symptoms after 15 days and 1 month. After 3 months of treatment almost all the symptoms resolved in both the group of patients. No major adverse effect was reported with cyclosporin, except for mild burning and stinging. A rebound phenomenon occurred soon after discontinuation of the treatment, indicating the need for a slow taper [35]. We have found minimum adverse effects in our study e.g. 2% patients developed lid swelling, redness increased in 2% and prolonged stinging were found in 5%.

Conclusion

In our study topical cyclosporine 0.05% was found effective in both atopic and vernal keratoconjunctivitis.

Limitation of the Study

Sample size was small, long term follow up to see any recurrence of symptoms was not evaluated.

Future Direction

Further study with large sample size, with long term follow up will be needed to determine the efficacy of cyclosporin in AKC and VKC.

Conflict of Interest

There was no conflict of interest.

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