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Effect of Topical Cyclosporine A (0.05%) in Treatment of Corneal Subepithelial Infiltrates after Adenoviral Keratoconjunctivitis

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Abstract

A retrospective study was done in Bangladesh Naval Ship Patenga Hospital at Chattogram, Bangladesh, from July 2021 to December 2022, to evaluate the clinical benefit and effectiveness of 0.05% cyclosporine A (CsA) eye drop in the treatment of symptomatic corneal sub-epithelial infiltrates (SEIs) related with adenoviral keratoconjunctivitis that are resistant to tapering of corticosteroid eye drops. We reviewed 15 patients (20 eyes) who had symptomatic corneal SEIs after adenoviral keratoconjunctivitis that were resistant to tapering of corticosteroids eye drops and later, who were subsequently treated with cyclosporine A (0.05%) eye drops. Data was collected and recorded including best corrected visual acuity (BCVA), intra ocular pressure (IOP), evaluation of severity of corneal SEIs, i.e., corneal subepithelial infiltrate scoring (CSIS) prior to beginning of treatment and at the last follow-up visit. Ten males (66.6%) and Five females (33.3%), mean age of 34.2±15.4 years were included in this study. The patients average topical CsA 0.05% use duration was 4.5 months (3-6 months). The mean BCVA (logarithm of minimum angle of resolution) before and after the treatment were 0.17±0.16 and 0.06±0.06 respectively, CSIS 1.072±0.69 and 0.33±0.23 respectively, IOP 20.06±2.82 and 14.73±2.60 mm of Hg respectively. There were statistically significant improvements in BCVA (P=0.003), reduction of CSIS (p=0.002) and reduction of IOP (p=0.001) at the last follow-up visit. 17 eyes (85%) showed clinical improvement and 3 eyes (15%) showed decreased SEI which did not fully disappear within 3-6 months. The no of eyes which had clinical improvement with CSIS score 0 were decided to discontinue of CsA treatment in the last follow-up visit. Patients reported a reduction in the severity of symptoms after the treatment. The patients reported foreign body sensation, glare or other side effects with topical CsA treatment, but overall patients noted improvement of vision and satisfaction with topical CsA treatment. Topical CsA (0.05%) is a safe and effective corticosteroid sparing alternative drug for the treatment of corneal SEIs after adenoviral keratoconjunctivitis, especially in patients who did not respond to other treatment modalities and have undesired side effects from using long term topical steroid.

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Introduction

Epidemic keratoconjunctivitis (EKC) is an ocular infection most commonly caused by Adenovirus serotypes 8,9,37,53 and 54.[1] In some cases, EKC may be characterized by a mild and self-limiting course. Disease presents itself after an incubation period which usually takes 2 to 14 days. However, if the virus replicates in the corneal epithelium, which is manifested as punctate keratitis, this leads to the gradual development of subepithelial infiltrates (SEIs) located in the anterior part of the corneal stroma. Clinically observed corneal opacities can become chronic or recurrent, significantly worsening visual acuity for months or even years.[2]

Mixed papillary and follicular response of the conjunctiva, eye pain, burning eyes, itching of eyes, diffuse hyperemia, chemosis, serous discharge and ipsilateral preauricular lymphadenopathy can be observed during the course of the disease. In approximately 80% of the cases, keratitis in the form of diffuse

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superficial punctuate keratitis, focal epithelial punctate keratitis and subepithelial infiltrates (SEIs) follow the conjunctivitis. Subepithelial infiltrates are small, round, and grayish lesions. Studies suggest that SEIs are composed of lymphocytes, histiocytes and fibroblasts and are thought to occur as a result of delayed immune response to viral antigens in the corneal stroma. The lesions disappear without causing scarring and neovascularization. They may stay dormant in the cornea for months or even years or they may cause acute symptoms such as decreased visual acuity, halo, glare and photophobia.[3]

Topical corticosteroids may suppress the symptoms and findings of EKC, however due to extended use of these agents, problems such as cataract, glaucoma and tendency of superinfections may occur.[4] Despite highly infectious community epidemics which causes significant patient discomfort and sometimes permanent visual compromise and persisting symptoms, there is no specific antiviral therapy approved by the Food and Drug Administration of the United States. As a result, there is presently no approved drug that shortens the course of the infection, improves the distressful clinical symptoms, avoids the development of corneal opacities, and stops viral replication.

There are reports that show the efficacy of topical cyclosporine A (CsA) 0.05% in the acute phase of adenoviral infections and in decreasing the incidence of early local symptoms and in decreasing the incidence of corneal opacities and in the therapy of active subepithelial infiltrates during the chronic phase.[3-6] However, there is no local study performed with topical cyclosporine A (CsA) in the therapy of corneal subepithelial infiltrates in Bangladeshi people. Therefore, this study aims to assess the efficacy of topical CsA (0.05%) in treating the corneal subepithelial infiltrates that have persisted more than 3.5 months in patients with adenoviral epidemic keratoconjunctivitis.

Methods

This retrospective study was done in Bangladesh Naval Ship Patenga Hospital at Chattogram, Bangladesh, from July 2021 to December 2022.

The study included 20 eyes of 15 patients, who were referred to our hospital and who had symptomatic corneal SEIs occurring after adenoviral keratoconjunctivitis that were resistant to tapering of corticosteroid eye drops or were discontinued due to their side effects and who were subsequently treated with CsA (0.05%) eye drops. Informed written consent forms from all the participants were obtained. Age, gender, affected eyes, best corrected visual acuity (BCVA), intra ocular pressure (IOP) (as measured by the with non-contact tonometer) were recorded and detailed anterior segment biomicroscopic examinations were performed to evaluate the severity of corneal SEIs, i.e., corneal subepithelial infiltrate scoring (CSIS). Corneal subepithelial infiltrates scoring (CSIS) varied between 0 and 4 were constituted according to the number of SEIs seen in biomicroscopic examination (0: no infiltrate, 1: 1-5, 2: 6-10, 3: 11-15, 4: more than 16 infiltrates).[7]

All patients were treated with topical 0.05% CsA as follows : 4 times for 2 months, then 2 times for another 2 months, then once in a day or once in every alternate day according to the symptoms intensity after topical corticosteroids were discontinued. At the end of the second month, treatment was discontinued in those patients with

a CSIS of 0 and monitorization of these patients began. In the patients with CSIS more than 0 were continued on topical 0.05% CsA therapy.

All the analysis was carried out by SPSS (Statistical Package for Social Sciences) version 17.0. Statistical values of $p<0.05$ were considered to be significant. The study was approved by the Ethical Review Committee of the Bangladesh Naval Ship Patenga Hospital, Chattogram, Bangladesh.

Results

Twenty eyes of fifteen patients were included in this study, of these 10 males (66.6%) and 5 females (33.3%). The mean age of the patients was 34.2±15.4 years (15-60 years). Subepithelial infiltrates were in the right eye in 13 patients and in the left eye in 7 patients. Before initiating the treatment, BCVA was 0.00 LogMAR in 7 eyes and there were varying degrees of visual loss in 13 eyes with values of 0.40-0.10 LogMAR. Prior to initiation of therapy, the mean CSIS score was 1.07±0.69 and mean intra ocular pressure was 20.06±2.82 mmHg (14-25 mmHg) (Table-I).

The average duration of corticosteroid use of the patients was 5 months (3-6 months). Before receiving topical CsA 0.05% therapy, 7 eyes were on anti-glaucomatous medication. After the second month of treatment with CsA, CSIS scale was found to be 0 in 15 eyes. In these patients, the treatment was discontinued and follow up of the patients was done at a regular interval. There was no recurrence during the further follow-up visit in improved eyes. In 5 eyes, topical 0.05% CsA treatment was continued 2 times for another 2 months then once in a day or once in every other day according to the symptom's intensity and their examination findings (BCVA, CSIS). In one eye with a CSIS scale of 3 and in two eyes with a CSIS scale of 2 at the beginning of treatment, scale did not revert to 0 despite the treatment. The average topical CsA use duration of the patients was 4.46 months (3-6 months) (Table- I). On the last follow-up visit, the mean BCVA after the treatment was 0.06±0.06, while CSIS was 0.33±0.23 and mean IOP was 14.73±2.60 mmHg respectively. There were statistically significant improvements in BCVA ($p=0.003$), reduction of CSIS ($p=0.002$) and

Table-I: Clinical course of patients treated with topical cyclosporin A (0.05%)

Serial number of the patient	Age/ Sex	Affected Eye	Initial BCVA	Initial CSIS	Duration of follow up with steroid (month)	Duration of follow up with 0.05% CsA (month)	CSIS at last follow-up visit	BCVA at last follow-up visit	Initial IOP (mm of Hg)	IOP at last follow-up visit
1	36/M	RE	0.00	0.5	3.5	2	0	0	15	12
2	15/M	LE	0.00	1	4	2	0	0.1	18	15
3	45/M	BE	0.00	1	3.5	2	0	0	19	14
4	28/F	RE	0.10	0.25	4	2	0	0	25	17
5	35/F	BE	0.40	1	4	2	0	0	21	14
6	35/M	RE	0.20	1	3	2	0	0.2	25	17
7	48/M	BE	0.40	0.5	3	2	0	0	24	14
8	20/M	LE	0.00	3	5	6	2	0.15	24	16
9	43/M	BE	0.20	1	9	2	0	0.1	18	13
10	24/M	RE	0.30	1	8	2	0	0	14	13
11	30/M	RE	0.00	2	7	5	1	0.1	20	16
12	18/F	RE	0.20	2	6	6	1	0.15	19	15
13	54/M	BE	0.40	0.5	5	3	0	0	23	16
14	60/F	RE	0.30	0.5	4	2	0	0	16	15
15	30/F	RE	0.00	1	6	2	0	0	20	14

reduction of IOP (p=0.001) respectively at the last follow-up visit (Table-II). 17 eyes (85%) showed clinical improvement and 3 eyes (15%) showed decreased SEI which did not fully disappear within 3-6 months. In the last follow up visit, patients' symptoms such as photophobia, glare and discomfort in the eye that were present were completely resolved except in 3 eyes. In 3 eyes, which had sub-epithelial infiltrates, photophobia and glare were still present. After the treatment in the last follow-up visit there were no eyes on anti-glaucomatous therapy.

Table-II: Patient data before and after treatment with cyclosporin A (0.05%)

Variables	Before treatment	After treatment	p-value
BCVA	0.17±0.16	0.06±0.06	0.003
CSIS	1.072±0.69	0.33±0.23	0.002
IOP (mm Hg)	20.06±2.82	14.73±2.60	0.001

Discussion

Coneal subepithelial infiltrates are mainly composed of lymphocytes and fibroblasts and they develop as a result of immune response to viral antigens.[8] They may cause visual disturbances such as reduced visual acuity, photophobia and halo effect and lead to the development of irregular astigmatism. Therefore, starting an effective treatment is so important. Steroids eye drops with long term therapy, there is a risk of developing glaucoma or cataract.[9] In some patients, subepithelial infiltrates do not respond to steroid treatment or they experience a recurrence of opacities after the eye drops discontinuation. In such cases cyclosporine A (0.05%) eye drops may be used. In ocular adenovirus infections, anti-viral agents such as trifluridine, vidarabine and ganciclovir were tried but none were found to be effective in treatment.[10] It is reported that long term steroid use in adenovirus infections are effective but can cause cataracts, glaucoma and super infections.

Cyclosporine A is an 11-amino acid cyclic peptide. The substance exhibits immunomodulatory effects by reversibly inhibiting the activation and proliferation of T cells and reducing the secretion of proinflammatory cytokines. Applied topically, it decreases inflammation on the ocular surface.[11] It is reported that topical CsA 0.05% is effective in various concentrations in ocular inflammation cases.[5,6] In our study, there were improvements in the signs and symptoms caused by SEIs, that developed after EKC infections, by using topical 0.05% CsA and no ocular or systemic side effects was observed.

About using topical CsA 0.05% in the treatment of acute and chronic adenovirus infections, it was reported that CsA 0.05% was effective in concentrations of 1% and 2% and that the SEIs were completely obliterated, or majority reduced after a 3 to 4 week therapy.[12] In the present study, the average topical 0.05% CsA use of the patients was 4.46 months (3-6 months). The increase in best corrected visual acuity (p=0.003), decrease in CSIS score (p=0.002) and the reduction of intraocular pressure (p=0.001) as observed in the last follow up visit – all were statistically significant. No patient was on antiglaucomatous therapy. In the last follow-up visit, 17 eyes (85%) out of 20 had a CSIS of 0 and 3 eyes (15%) had a decrease in SEIs numbers. Our results are comparable to findings of the study done by Okumus *et al.*[13]

Romanowski and colleagues reported that in their trials 0.5% and 2% topical CsA treatments were effective in decreasing the no of SEI formations, however it was claimed that this agent could facilitate the risk of endemics by increasing viral replication.[7]

In this study, we had no recurrent cases who were treated with CsA 0.05% for 3 to 6 months which is comparable to study done by Okumus *et al.*[13] As our experience, treatment of subepithelial infiltrates by using topical CsA 0.05% should be continued until the CSIS is seen 0. However, whether SEI will recur after treatment or when it will recur cannot be foreseen. Therefore, follow up visit duration should be as long as possible. Therefore, further studies regarding the ideal follow up visit duration after treatment with CsA are warranted.

However, there were some limitations of our study. The evidence of efficacy of topical 0.05% CsA was not based on controlled trial and the number of patients sample was small. Prospective, double-masked, placebo controlled further studies are needed to show the efficacy of topical CsA in different concentrations. For this type of study clinician must choose and apply the most reliable treatment strategy which resolves patient complaints and improves clinical findings for SEIs. Since our data were acquired without a control group, we cannot resolve the possibility of spontaneous remission of SEIs as the natural history of the disease in this study. Also we could not clearly state that the initial improvements in symptoms was only due to topical 0.05% CsA treatment, it could be due to either topical steroid or topical 0.05% CsA. However, the anti-inflammatory effect of topical 0.05% CsA might reduce the need for topical steroids and made contributions to the symptomatic relief of patients during the follow-up without having the risk of steroid induced side effects. A masked controlled study of topical 0.05% CsA in human subjects with larger patient populations could better define the natural history and effect of treatment of such type of disorder.

Conclusion

In view of its good safety profile, it can be concluded that topical cyclosporine A (0.05%) is a safe and effective option in the treatment of symptomatic corneal opacities in patients predispose to an increase in the intraocular pressure following corticosteroid eye therapy. Besides, cyclosporine A (0.05%) has beneficial therapeutic effects in the treatment of sub epithelial infiltrates resistant to topical steroids.

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