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Combined Topical Corticosteroid and Topical Cyclosporine-A 0.05% for Management of COVID-19 Keratoconjunctivitis: A pilot study.

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ABSTRACT

Purpose: To evaluate the effectiveness and safety of combined use of topical corticosteroids and topical Cyclosporine-A 0.05% in the treatment of COVID-19 acute Keratoconjunctivitis.

Study design: A pilot study.

Methods: Twelve patients (13 eyes) with COVID-19 acute Keratoconjunctivitis received topical 1% prednisolone acetate 4 times daily, 0.05% cyclosporine-A 4 times daily together with non-preserved artificial tears. Symptoms and signs were recorded before and after treatment.

Results: Seven females and 5 males with a mean age of 42.5 ± 10.89 years (range 23-61 years) were included. Baseline examination of all patients revealed variable degrees of eyelid swelling, conjunctival hyperemia and follicular conjunctivitis. Keratitis had a characteristic pattern of small (<1mm), gray-white marginal subepithelial infiltrates raising the overlying epithelium without associated epithelial defect. They were separated from the limbus by about 1 mm of clear space and in some cases; they extended for 12 o'clock hours circumlimbal. With treatment, patients reported rapid improvement of symptoms with a mean duration of 3.25 ± 1.6 days (range 1-6 days). At the 7th day of treatment, all signs disappeared in all patients, except for patient number 5, who had persistent mild conjunctival hyperemia and SEI which resolved completely by the 10th day of treatment. No recurrence of SEI was noted after 3 weeks. No ocular side effects of prednisolone acetate or cyclosporine-A were noted in any patient.

Conclusion: Combined topical 1% prednisolone acetate and 0.05% cyclosporine-A appears to be effective, and safe in the treatment of COVID-19 Keratoconjunctivitis.

Keyword: Covid-19; keratoconjunctivitis; restasis

INTRODUCTION:

The novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) first emerged in Wuhan City, China in December 2019, causing the coronavirus disease 2019 (COVID-19) outbreak[1], which was confirmed by the World Health Organization (WHO) as an international public health emergency on January 30, 2020[2] and declared a pandemic on the 11th of March 2020[3]. The disease presents with fever, myalgia, and cough, and may progress to severe acute respiratory syndrome. However, most cases only present mild, even no symptoms[4].

Ocular manifestations were reported in about one third of COVID-19 cases including chemosis, epiphora, and conjunctival hyperemia[5]. Conjunctivitis and keratoconjunctivitis have been reported as a presenting symptom of COVID-19 disease before the characteristic respiratory symptoms are evident[6-11]. To the best of our knowledge, there is no FDA approval for any medications for COVID-19 keratoconjunctivitis. The use of corticosteroids and immunosuppressive agents show promise for treatment of viral keratoconjunctivitis especially corneal sequelae[12,13]. Hence, we performed this pilot study to explore the effectiveness and safety of combined topical corticosteroid and topical cyclosporine-A 0.05% in COVID-19 patients with keratoconjunctivitis.

Patients and Methods

This was a pilot study conducted at ophthalmology department of Farawanyia Hospital, Kuwait, which is a large COVID-19 referral center in Kuwait, from July through August 2020. This study was approved by Ethics Committee for Medical Research of Ministry of Health, Kuwait and was registered and publicly available at clinicaltrials.gov (NCT04451239). The study strictly followed the tenets of the Declaration of Helsinki. Before enrollment, each participant signed an informed written consent after assuring confidentiality. Patients were included in the study if they were diagnosed with COVID-19 and keratoconjunctivitis. Diagnosis of COVID-19 was based on positive naso-pharyngeal swab using real-time reverse transcription polymerase chain reaction (RT-PCR) with or without typical COVID-19 manifestations. Conjunctival swab was not performed as positive conjunctival swab for COVID-19 has been reported only in about 5% of the patients[5].

History taking involved recent travelling abroad, contact with COVID-19 confirmed cases, the presenting COVID_19 manifestations and the time point at which eye symptoms developed in the course of COVID-19 disease. All patients had baseline examination at first presentation then on the 3rd, 5th and 7th days of treatment or until complete recovery. Patients with associated ocular pathology or disease, other causes of keratoconjunctivitis -for example allergic or herpetic- were excluded from the study. Patients with history of contact lens use were also excluded.

On each visit, all patients answered a questionnaire inquiring about five symptoms: eye redness, eye itching, foreign body sensation, tearing, and eyelid swelling using a 4-point scale (0= none, 1= mild, 2= moderate, 3= severe).

Baseline and follow-up examinations involved measurement of best corrected visual acuity (BCVA), assessment of lid swelling, conjunctival injection, discharge or tarsal conjunctival pseudo-membranes, corneal superficial punctate keratitis (SPK) and corneal subepithelial infiltrates (SEI). To judge the severity of the disease and the improvement on follow-up, a three-point (0–2) clinical scale was used to grade all signs, where 0 means no; 1 means mild and 2 means severe[13] and for SEI we indicated the extent by the number of clock hours of the cornea involved.

All patients received topical 1% prednisolone acetate (Pred Forte; Allergan USA, Inc., Madison, NJ) 4 times daily, 0.05% cyclosporine-A (Restasis 0.05%; Allergan, Irvine, Calif., USA) 4 times daily together with non-preserved artificial tears. We noted the time needed until subjective improvement of symptoms and the regression of signs at each follow-up. Prednisolone acetate was stopped after disappearance of signs,

maximum after 10 days, while we continued to use cyclosporine-A and tear substitute for a maximum of 3 weeks to avoid recurrence of SEIs, however, the frequency was reduced to twice daily after the 10th day.

RESULTS

Twelve patients (13 eyes) were included in the study, 7 females and 5 males. Mean age of the patients was 42.5 ± 10.89 (range 23-61) years. Nine patients were in-patients in COVID-19 wards of Farawanyia hospital, who developed eye symptoms after admission. Demographic and baseline clinical data of these patients are listed in table (1).

Table (1): demographic and pretreatment clinical data of in-patients:

	Patient ID								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age (years)	52	43	61	29	38	47	38	23	54
Gender	M	M	F	F	M	F	M	M	M
Presenting COVID-19 symptoms									
• Fever, malaise	+	+	+	+	+	+	+	+	+
• Sore throat	+	+	-	+	-	-	+	-	+
• Respiratory symptoms	+	+	+	+	+	+	+	-	+
• GIT symptoms	-	-	+	-	-	+	-	-	-
RT-PCR CT value*	30	24	21	26	13	17	21	29	22
Travel History	+	-	+	-	-	+	+	-	-
Contact with COVID patient	-	+	-	+	+	+	-	+	-
Day of onset of eye symptoms	13th	9th	8th	10th	5th	7th	12th	9th	6th
Eye affected	OD	OS	OS	OS	OS	OD	OD	OD	OS
Presenting eye symptoms**									
• Itching	0	1	0	0	1	0	0	0	1
• Foreign body sensation	0	1	1	1	1	1	1	0	0
• Tearing	1	2	2	1	2	1	1	1	2
• Redness	2	3	3	2	3	3	3	2	2

*Real Time Reverse Transcription PCR cycle threshold value [5]:

Cts <29 are strong positive reactions indicative of abundant target nucleic acid in the sample.

Cts of 30–37 are positive reactions indicative of moderate amounts of target nucleic acid.

Cts of 38–40 are weak reactions indicative of minimal amounts of target nucleic acid, which could represent an infection state or environmental contamination.

**Eye symptoms questionnaire score: 0=absent, 1=mild, 2=moderate and 3=severe

The other three patients were referred by their general practitioner to our ophthalmology outpatient clinic for eye symptoms. Of those, one female (patient 10) had been diagnosed as COVID-19 positive by nasopharyngeal swab two weeks earlier following recent travel abroad and was home isolated and treated for mild symptoms (fever, malaise and cough). However, her general condition improved, and her last nasopharyngeal swab turned negative 2 days before presentation to our clinic. The other two patients (patients 11 and 12) had no history of COVID-19 symptoms or previous testing; however, they gave history of contact with COVID-19 patients. Given the current COVID-19 pandemic situation and

that keratoconjunctivitis has been described as an early and sometimes the sole presentation of SARS- Co V-2 infection [8-10], these 2 patients were referred for nasopharyngeal swab which turned up to be positive for COVID-19.

However, we already started treatment for them even before the results of nasopharyngeal swabs were available. The three outpatients were sent home and asked to quarantine themselves and were followed up for symptoms by phone. None of the three patients developed COVID-19 manifestations and they reported improvement of eye symptoms by the end of one week, so they were asked to come at the day 7 of presentation for clinical examination and they were examined in a special examination room for suspected COVID-19 patients. Demographic and baseline clinical data of the three outpatients are listed in table (2).

Table (2): demographic and pretreatment clinical data of outpatients

	Patient ID		
	10	**11**	**12**
Age (years)	47	45	33
Gender	F	F	M
RT-PCR CT value*	40[#]	14	18
Travel History	-	-	-
Contact with COVID-19 patient	-	-	+
Eye affected	OS	OS	OU
Presenting eye symptoms**			
• Itching	0	1	0
• Foreign body sensation	1	2	1
• Tearing	1	2	1
• Redness	2	3	3

*Real Time Reverse Transcription PCR cycle threshold value [5]:

Cts <29 are strong positive reactions indicative of abundant target nucleic acid in the sample.

Cts of 30–37 are positive reactions indicative of moderate amounts of target nucleic acid.

Cts of 38–40 are weak reactions indicative of minimal amounts of target nucleic acid, which could represent an infection state or environmental contamination.

**Eye symptoms questionnaire score: 0=absent, 1=mild, 2=moderate and 3=severe

[#]One week before presentation to our clinic

Baseline examination of all patients revealed variable degrees of eyelid swelling, conjunctival hyperemia and follicular conjunctivitis. Keratitis had a characteristic pattern of small (<1mm), gray-white marginal subepithelial infiltrates raising the overlying epithelium without associated epithelial defect. They were separated from the limbus by about 1 mm of clear space and in some cases; they extended for 12 o'clock hours circumlimbal. None of the cases had associated anterior chamber cells or flare. Fundus examination was unremarkable for all cases. Eight patients had palpable ipsilateral pre-auricular lymph nodes, while 2 patients had tender swelling of ipsilateral submandibular lymph nodes. Table (3) demonstrates clinical signs of all patients at baseline examination.

Table (3): clinical signs of all study patients at baseline examination

signs	Patient ID												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 OD**	**12 OS**
Lid oedema	1	1	1	2	1	0	1	0	0	1	2	1	1
Conjunctival hyperemia	2	1	1	2	2	2	2	1	1	1	2	0	1
Discharge	2	1	2	2	2	1	2	1	0	1	1	0	1
Pseudo membrane	0	0	0	0	0	0	0	0	0	0	0	0	0
SPK	0	0	1	2	0	0	1	1	0	0	1	1	0
SEI Severity	2	1	2	2	2	1	2	1	1	1	2	2	1
SEI Extent (O'clock hours)	4	2	2	5	12	2	6	4	3	2	12	8	3
BCVA (Log MAR)	0.00	0.2	0.00	0.2	0.3	0.2	0.1	0.2	0.1	0.00	0.3	0.3	0.2

With treatment, patients reported rapid improvement of symptoms. The mean duration for subjective symptom improvement was 3.25 ± 1.6 days (range 1-6 days). Figure (1) shows clinical progress of inpatients (patients 1-9) at each follow-up. At the 7th day of treatment, all signs disappeared in all patients, except for patient number 5, who had persistent mild conjunctival hyperemia and SEI which resolved completely by the 10th day of treatment. Outpatients were only examined at the 7th day and resolution of all clinical signs was observed at this time. Six (60%) out of 10 eyes with impaired vision before treatment reached BCVA of 0.00 LogMAR at the 7th day after treatment, 3 eyes (30%) reached BCVA of 0.1 LogMAR and only one eye (10%) reached 0.2 LogMAR. No increase of intraocular pressure was noted in any of the patients with use of prednisolone acetate. None of the patients experienced glare, foreign body sensation, or other side effects of topical Cyclosporine-A treatment, which was continued for a total of 3 weeks despite resolution of signs for fear of recurrence of SEI. All patients were examined, and absence of recurrence was noted before stoppage of Cyclosporine-A.

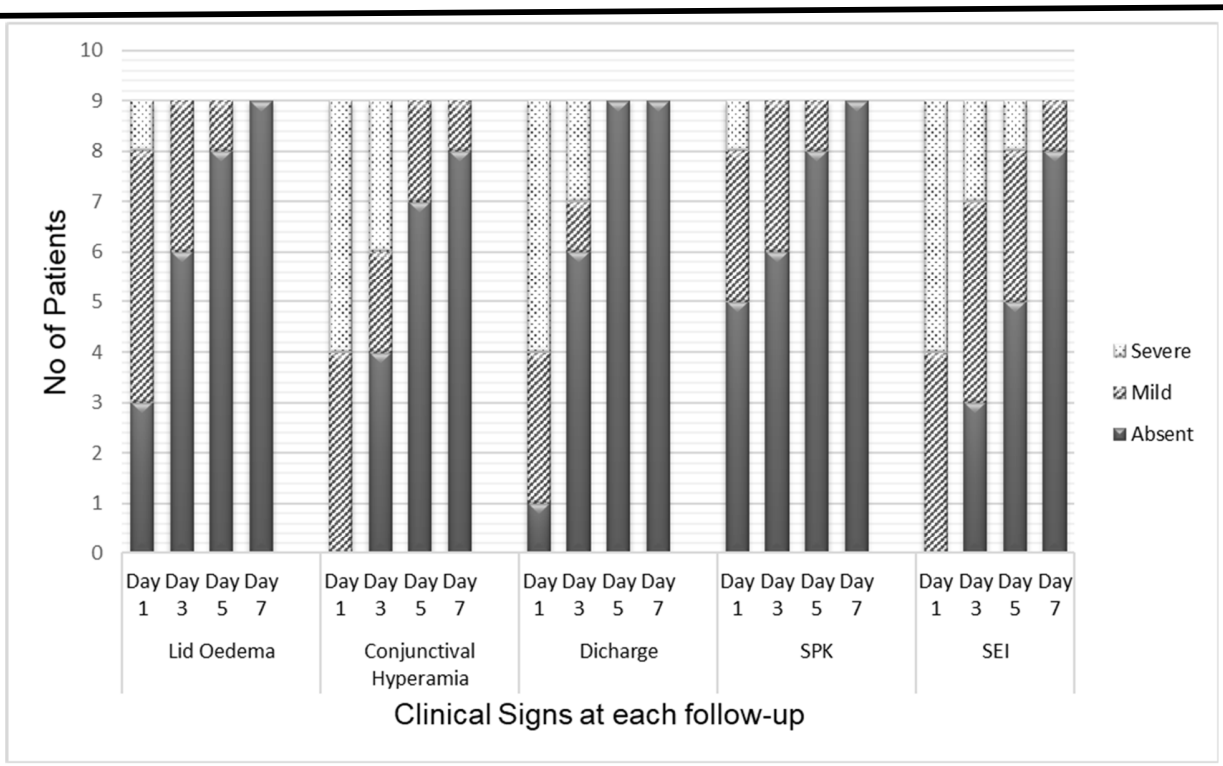

Figure (1): clinical progress of inpatients (patients 1-9) at each follow-up.

DISCUSSION:

Since the first appearance of COVID-19 in China in December 2019, conjunctival transmission of the virus, viral shedding in tears of patients and ophthalmic manifestations have been questioned by many ophthalmologists around the world[14]. Despite those ocular affections were most commonly reported in patients having severe systemic disease[5], in the middle phase of the disease[7], conjunctivitis has been observed as the first presentation[8]. Moreover, keratoconjunctivitis has been reported as an initial presentation of COVID-19 in a young Canadian patient with only mild respiratory symptoms[10]. Thus, it has been settled that SARS-CoV-2 should be considered in patients presenting with viral conjunctivitis or keratoconjunctivitis, especially with a travelling history or history of contact with known COVID-19 patients[10].

Conjunctivitis due to Covid-19 have been treated by antiviral eye drops,[7,10] together with antibiotic eye drops and lubricants[8,15]. Khan and Mack suggested mild steroids for persistent symptoms[16]. However, due to the characteristic subepithelial infiltrates in all cases in this study, we tended to believe that SARS-CoV-2 keratoconjunctivitis involves an abnormal autoimmune response. This could be supported by failure of previous studies to prove local invasion and replication of SARS-CoV-2 on the ocular surface[17].

In addition, Guo et al.,[18] reported recurrence of keratoconjunctivitis in 53 years old COVID-19 patient 5 days after satisfactory relieve of symptoms and suggested that the disease is caused by a "topical cytokine surge", rather than direct invasion and destruction by SARS-Co V-2. Consequently, we designed our treatment regimen using combined Topical Corticosteroid and Topical Cyclosporine-A. Topical steroid eye drops have been proved effective for viral keratoconjunctivitis in the short term, but their stoppage is often followed by recurrence of SEI[19]. Cyclosporine-A is an immunosuppressant used successfully for the prophylaxis against transplant rejection[20].

Topical cyclosporine-A has been proven effective for treatment of various immune-mediated ocular surface disease[21-

[26]. It has also been used for corneal subepithelial infiltrates (SEIs) due to adenoviral keratoconjunctivitis especially if resistant to or recurrent following tapering or discontinuation of steroid eye drops[27]. Moreover, early use of topical cyclosporine-A, in acute adenoviral keratoconjunctivitis, in varying concentrations between 0.5 and 2% have been shown effective in ameliorating the distressing symptoms, minimizing the recurrences of corneal subepithelial infiltrates and preventing the late development of corneal opacities[28-32].

To the best of our knowledge, this is the first study describing treatment of COVID-19 keratoconjunctivitis using combined Topical Corticosteroid and Topical Cyclosporine-A. We used topical Cyclosporine-A in a low concentration (0.05%) which is commercially available as nanoemulsion formulation eye drops. The efficacy of this low concentration of cyclosporine-A has been reported by some authors[29,33].

In the study by Okumus et al.,[29] patients were treated with topical 0.05% Cyclosporine-A (Restasis®) for a month as follows: 4 times a day of topical 0.05% CsA (Restasis®), in addition to the topical corticosteroids they were using for the first 15 days, and then 2 times a day of topical 0.05% CsA (Restasis®) after topical corticosteroids were discontinued. Complete resolution of SEIs was obtained after one month in 8 (36.3%) eyes, at the last follow up visit in 10 eyes (45.45%), while only decrease in number was obtained in 4 eyes (18.2%). They discontinued the treatment in the eyes that had complete resolution of SEI, while continued it once daily or once every other day for eyes with residual SEIs.

In our study, rapid reduction in the severity of symptoms was reported by all patients, by the end of the first week and regression of all clinical signs was obtained at the seventh day in all patients except one patient, who had complete resolution at the tenth day after the treatment. We continued the use of topical cyclosporine for 3 weeks to avoid recurrence of SEI described in cases of epidemic keratoconjunctivitis. No recurrences were observed till the third week. However, for accurate evaluation of this entity, a further long-term study would be recommended. In our study, no irritating side effects noted, either from topical steroids or cyclosporine-A.

CONCLUSION:

Combined use of topical 1% prednisolone acetate and 0.05% cyclosporine-A might be effective and well-tolerated therapy for COVID-19 acute keratoconjunctivitis. However, the natural history and recurrence of subepithelial infiltrate after stoppage of this combined treatment would necessitate further long-term. Limitations of the study includes the limited numbers of participants, the relatively short follow-up period and lack of control group.

Also, the sole effect of each drug alone needs further evaluation

DATA AVAILABILITY

All data are included in this article.

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None

Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Mona A. Nassief1, Omar K. Alduwailah2, Sherein M. Hagras3, Ameera G. Abdelhameed all authors have no conflicts of interest that are directly relevant to the content of this review.

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