E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2023; 5(2): 18-23
Received: 13-12-2022
Accepted: 19-01-2023

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Topical cyclosporine: A versus prednisolone in the treatment of herpetic stromal keratitis

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DOI: https://doi.org/10.22271/27069567.2023.v5.i2a.473

Abstract
Background: Herpetic stromal keratitis (HSK) is an immune-mediated disease due to primary infection with herpes simplex virus (HSV). It is now known about Cyclosporine A (CSA) that it selectively inhibits T-helper cell production of growth factors essential for B cell and cytotoxic T-cell differentiation and proliferation, so that the immune response which is considered the main cause of stromal lesion and opacity will be formed masking the transparent cornea affecting vision of the patients. The aim of our study was to compare between topical CSA ED versus Prednisolone ED in the treatment of HSK.
Methods: The study is prospective, randomized, non-invasive and comparative on 30 eyes with HSK. Participants were divided randomly in numeric manner into 2 groups, each group included 15 eyes: Group (A): treated by topical CSA ED 0.4% and Group (B): treated by topical prednisolone acetate 1%. Comparison between both groups regarding effect on visual acuity, stromal haze, corneal edema, duration of healing, complications, HSV recurrence, vascularization and opacity was done.
Results: There was no statistically significant difference between both groups in VA before treatment however, it was statistically significant lower in group B after treatment. There was no statistically significant difference between both groups in grade of stromal infiltration before treatment but there was a statistically significant difference after treatment. Duration of healing was statistically significant lower in group B compared to group A
Conclusions: According to our study, CSA ED (0.4%) is effective and comparable to corticosteroid in management of HSK. It may be less tolerable and take longer duration of action but it is superior to steroids as regard the effect on corneal opacity. It has the advantage to decrease corneal vascularization as well. Using corticosteroids is associated with complications especially in more complicated cases like thin cornea and epithelial defects. It causes disease recurrence and IOP elevation so CSA ED is recommended to be used in these cases.

Keywords: Cyclosporine, prednisolone, herpetic stromal keratitis

Introduction
Herpetic stromal keratitis (HSK) is an immune-related illness that is thought to be a significant cause of infectious blindness owing to corneal scarring caused by HSK rather than the original infection with herpes simplex virus (HSV) [1]. HSV can affect any and all layers of the cornea but recurrent attacks affect more stromal and epithelial layer causing deterioration of vision through corneal scarring and neovascularization [2].
HSK is primarily diagnosed clinically, with the aid of a history of repeated herpetic ocular illness and a slit lamp examination of the eye that reveals classic herpetic lesions. PCR analysis, enzyme-linked tests, and viral culture of the tear film may also show HSV-1 DNA, protein, or live virus. But when there isn't an active corneal ulcer, such as in non-necrotizing HSK, the sensitivity of these investigations is drastically diminished [3].
HSK is often treated with a mix of antiviral drugs and local immunosuppressive therapy, with the objective of minimizing local symptoms, inflammation, and scar formation. Among the current local therapy options, local steroid eye drops are known to decrease neutrophil chemotaxis and thereby diminish the collagenase and cytokine load, which leads to ulceration and eventually scarring development. Side effects of topical corticosteroids include the probable return of herpetic illness, increased intraocular pressure (IOP), the development of glaucoma, and cataract formation. Furthermore, despite the use of topical corticosteroids, some individuals experience prolonged inflammation. If the effectiveness of

an alternative immunosuppressant drug targeting T-cells is demonstrated, it might be used instead of corticosteroids [4, 5].

Knowing that the pathogenic cause of HSK is not the actual viral infection, but rather viral antigens starting T-lymphocytic stromal destruction helps predict the potential success of cyclosporin A (CSA) for the noninfectious immunologic HSK [6]. CSA is an immunomodulatory drug that inhibits cytotoxic T –lymphocytes activity, interferes with the induction of cytokines, inhibits macrophage function by inhibiting antigen presentation, inhibits both B-lymphocytes proliferation, its production of T-helper dependent antibody, permits T-suppressor lymphocytes activation and amplification and promotes its action, permits the clonal expansion of activated T-cells, binds with a cytoplasmic receptor inhibiting the influx of ca++, suppresses corneal neovascularization induced by IL-2, decrease leukocytes access to the corneal stroma, and has direct inhibitory impact on eosinophils, mast cells activation and mediators release, so that it can be used in treatment of all allergic inflammation and atopy with dramatic clinical improvement [7-9].

For HSK, topical corticosteroids can be used in the absence of epithelial disease. They are accessible in a variety of forms, but the preferable agents were the preserved dexamethasone 0.1% ophthalmic suspension, preserved prednisolone acetate 1%, and unpreserved dexamethasone sodium phosphate 0.1% ophthalmic solution. They are recommended at various intervals, such as once, twice, three times, four times a day, once at night, or every 1 or 2 hours. Corticosteroids influence ocular inflammation by limiting local antibody-forming B lymphocytes, blocking corneal collagen, and decreasing PMN cell infiltration [7].

The aim of our study was to compare between topical CSA ED versus Prednisolone ED in the treatment of HSK.

Patients and Methods

The study is prospective, randomized, noninvasive and comparative carried out in the cornea unit of the Tanta University Ophthalmology Hospital, which is a tertiary referral center, after receiving authorization from the Institutional Review Board (IRB) and Human Research Ethics Committee at Tanta University, Faculty of Medicine, and adhering to the principles that are outlined in the Declaration of Helsinki. The duration of the study was 6 months, starting from October 2020 to March 2021.

This study involved 30 eyes with HSK. HSK was diagnosed clinically by history of recurrence, clinical examination using slit-lamp, decreased corneal sensation, double stain test lab. We excluded other forms of herpetic keratitis, cases with epithelial defects, corneal thinning, scarring and corneal degeneration or dystrophy.

All participants of HSK were distributed into 2 group randomly in numeric manner. Group A was treated mainly by CSA 0.4% ED (4times/day) and Group B was treated mainly by prednisolone acetate 1% ED (5times/day). All patients received systemic antiviral drugs in the form of oral acyclovir (400mg 1-2 tab/day), in addition vitamin c, lubricant, IOP lowering ED, cycloplegic agent, moxifloxacin 0.5% ED (5 times/day) and topical vitamin A: (4times/ day) if indicated.

All patients in this study were subjected to: full history taking, VA assessment as uncorrected distance visual acuity (UCDVA) and BDVA were measured using Landolt`s chart and expressed by log MAR notation, comprehensive ocular examination: using Slit-lamp examination, intra ocular pressure measurement, post segment examination, complications: (if present) as anterior uveitis, vascularized corneal opacities, glaucoma or recurrence of HSV infection, cornea, corneal examination using a tip of cotton, endothelial involvement if present and presence of corneal vascularization. Double stain test and microbiological investigations to exclude mixed infections were done.

Characteristics of the lesion

Size (using slit lamp beam): by the mean of vertical and horizontal meridian (add vertical to horizontal meridian then divide by two). Shape: round (disciform) or irregular post dendritic haze. Site: peripheral or central. Presence of corneal edema: all patients by had corneal stromal edema at baseline examination, some of them had also epithelial edema. Stromal infiltration (haze): presented in all patients with variable depth and density as follows:

Depth of lesion was examined by using oblique /retro illumination of slit lamp microscopy scaled from 1 to 3 as [10]:

Scale 1: If the lesion was <20% of stromal thickness.
Scale 2: If the lesion was 20-50%of stromal thickness.
Scale 3: If the lesion was >50% of stromal thickness.

Grading of stromal infiltration density: seen by retro and oblique illumination. The infiltration was graded as follows [10]: Grade 0 had a cornea that was entirely clear. With careful oblique illumination and slit-lamp bio-microscopy, grade 0.5 had a trace haze visible. Grade 1 had a haze that was more noticeable but did not obscure the visibility of minute iris details. Mild iris detail obscuration received a grade 2. Iris and lens obscuration received a grade 3.

Diagnosis of herpes simplex cases

Slit-lamp examination is the primary method for diagnosing HSK due to the disease's clinical physical appearance.

Treatment protocol

All participants of HSK were distributed into 2 group randomly in numeric manner. Group A was treated mainly by CSA 0.4% ED (4times/day) and Group B was treated mainly by prednisolone acetate 1% ED (5times/day). Both groups were treated under cover of systemic antiviral drugs in the form of oral acyclovir (400mg 1-2tab/day) as a prophylaxis, in addition to supportive drugs when needed.

CSA ED was prepared by sterile container in Laboratory Theater as follows: (0.8 mg CSA in 0.5 ml artificial tears adding 0.5 ml paraffin oil base) forming emulsion form of CSA (0.4 mg /ml). CSA ED was prescribed 4 times daily for (8-16) weeks according to the severity of the disease then was tapered as all immunosuppressant agent for one week reducing one time every 2 days. Adding the oily base was to reduce or even prevent the undesired effect of the drug (irritation, itching and discomfort).

Prednisolone ED

Prednisolone was taken in Group B in one form 5 times/day with close follow up for IOP and other complications. It was tapered for about one week at the end of treatment.

Follow up: At first every three days then every week for the first month. Additional follow-up visits every month for 3

months up to 6 months. If a noticeable response was not obtained after 3months, we considered the case resistant to treatment. Routine ophthalmic examination was done with special attention to the signs of corneal healing decreased surrounding edema, stromal infiltration, density of ciliary injection, difference IOP pressure and presence of corneal vascularization.

Statistical analysis

The mean, standard deviation, Chi-square, and linear correlation coefficient were used in the statistical presentation and analysis of the current research using SPSS V20.

Results

There was no statistically significant difference between both groups regarding age, gender and ocular history but there was a statistically significant difference regarding medical history. (table.1)

Table 1: Demographic characteristics, medical and ocular history of study patients

		Group A	Group B	t. test	p. value
Age	Range	23.00–67.00	22.00–75.00	0.669	0.509
	Mean ± S.D	43.20±13.545	46.867±16.340		
Sex			Group A	Group B	Total
Male		N	8	9	17
		%	53.3%	60.0%	56.7%
Female		N	7	6	13
		%	46.7%	40.0%	43.3%
Total		N	15	15	30
		%	100.0%	100.0%	100.0%
Chi-square	X^2	0.136			
	P-value	0.713			
Medical History					
No		N	6	9	15
		%	40.0%	60.0%	50.0%
DM		N	7	1	8
		%	46.7%	6.7%	26.7%
HTN		N	0	4	4
		%	.0%	26.7%	13.3%
Rheumatoid		N	2	1	3
		%	13.3%	6.7%	10.0%
Total		N	15	15	30
		%	100.0%	100.0%	100.0%
Chi-square	X^2	9.433			
	P-value	0.024*			
Ocular history			Group A	Group B	Total
No		N	11	10	21
		%	73.3%	66.7%	70.0%
Cataract		N	3	5	8
		%	20.0%	33.3%	26.7%
Glaucoma		N	1	0	1
		%	6.7%	0%	3.3%
Total		N	15	15	30
		%	100.0%	100.0%	100.0%
Chi-square	X^2	1.548			
	P-value	0.461			

There was no statistically significant difference between both groups regarding site, shape and size of lesion. (Table.2)

Table 2: Site, shape and size of lesion

Site of lesion			Group A	Group B	Total
Central		N	13	12	25
		%	86.7%	80.0%	83.3%
Peripheral		N	2	3	5
		%	13.3%	20.0%	16.7%
Total		N	15	15	30
		%	100.0%	100.0%	100.0%
Chi-square	X^2 0.241				
	P-value 0.624				
Shape			Group A	Group B	**Total**
Disciform		N	9	6	15
		%	60.0%	40.0%	50.0%
Multiple		N	4	5	9
		%	26.7%	33.3%	30.0%

Irregular		N	2			4			6	
		%	13.3%			26.7%			20.0%	
Total		N	15			15			30	
		%	100.0%			100.0%			100.0%	
Chi-square	$X^2$1.382									
	P-value0.502									
		Group A				Group B			t. test	p. value
Size	Range	2	–	5		3	–	6	1.140	0.264
	Mean ± S.D	3.50	±	0.85		3.87	±	0.92		

There was no statistically significant difference between both groups in UDVA before treatment however, it improved in group A after treatment and it was statistically significant lower in group B after treatment. (Table.3)

Table 3: Visual acuity before and after treatment

VA before treatment	Group A	Group B	t. test	p. value
Range	0.10 - 0.500	0.10 – 0.500	0.489	0.629
Mean ± S.D	0.238 ± 0.117	0.217 ± 0.120		
VA after treatment				
Range	0.2 – 0.801	0.1 – 0.6	3.930	0.001*
Mean ± S.D	0.506 ± 0.197	0.242 ± 0.171		

Duration of healing was statistically significant lower in group B compared to group A. This shows that corticosteroids (group B) have short duration of action and produces more rapid effects. (table.4)

Table 4: Duration of healing in both groups.

		Group A			Group B			t. test	p. value
Healing	Range	7.00	–	16.00	4.00	–	7.00	7.933	0.001*
	Mean ± S.D	11.133	±	3.044	4.733	±	0.704		

Short period of follow up was applied in this study however group B (two cases) was reported to have more recurrence than group A (one case). (Table 5)

Table 5: Recurrence of HSV after treatment and

Recurrence of HSV after treatment		Group A	Group B	Total
No	N	14	13	27
	%	93.3%	86.7%	90.0%
Yes	N	1	2	3
	%	6.7%	13.3%	10.0%
Total	N	15	15	30
	%	100.0%	100.0%	100.0%
Chi-square	X^2	0.370		
	P-value	0.543		

In group A, 12 of 15 HSK patients (86.3%) responded to topical CSA A 0.4% four times daily after 4 months of treatment, only one case underwent recurrent episode of HSK two months away of the last free follow up due to systemic immunosuppressant disease and Two cases developed progression of corneal vascularization after treatment of stromal keratitis. In group B, 9 of 15 HSK patients (60.7%) responded to topical prednisolone acetate 1% four times daily in almost 2 months of treatment. Two cases underwent recurrent episode of HSK after different intervals. One case ended with neurotrophic ulcer and three cases with persistent corneal vascularization after treatment
There was no statistically significant difference between both groups regarding complications. (Table 6).

Table 6: Complications of HSV after treatment

Complications		Group A	Group B	Total
No	N	12	9	21
	%	80.0%	60.0%	70.0%
Recurrence	N	1	2	3
	%	6.7%	26.7%	10.0%
Neurotrophic ulcer	N	0	1	1
	%	.0%	6.7%	3.3%
Corneal vascularization	N	2	3	5
	%	13.3%	20.0%	16.7%
Total	N	15	15	30
	%	100.0%	100.0%	100.0%
Chi-square	X^2	1.962		
	P-value	0.580		

Case 1

A 52-year-old male presented with drop of vision, redness and lacrimation in his left eye for one month. Visual acuity was 6/60 (0.1). Ocular examination showed disciform legion measured 3 x 4 mm with stromal edema, infiltration and massive KPs under it (Fig 1- A). Cornea showed small peripheral vascularization nearby the lesion. Diminished Corneal sensation, intact epithelium and normal IOP were presented. The patient was diagnosed clinically as Disciform Herpetic Stromal Keratitis and he was treated by Prepared Ophthalmic Suspension of Cyclosporine-A 0.4% eye drops with prophylactic systemic antiviral and other supportive treatment. After 3 weeks of treatment the lesion started to improve. Complete healing was within 14 weeks with faint opacity almost seen and obvious regression of corneal vascularization. Final visual acuity was 6/18 (0.4). (Fig 1-B).

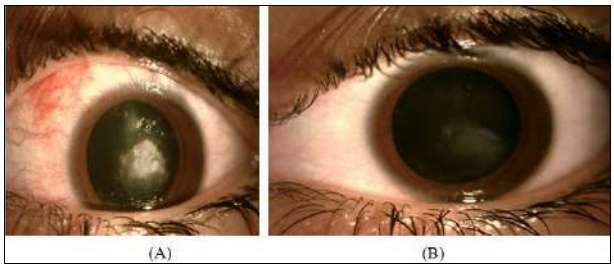

Fig 1: case 1

Case 2

A 58-year-old female presented with drop of vision, burning sensation, lacrimation and redness in her left eye for10 days. The patient has history of recurrent viral keratitis, the last episode was 6 months ago. Visual acuity was 6/24 (0.3). Ocular examination showed irregular opacity measured around 4:5 mm with massive stromal edema and dense infiltration. Also Post Herpetic Sub Epithelial Haze was presented. (Fig 2- A). Corneal sensation was diminished, normal epithelium and clear AC without inflammation. Also IOP was within normal range. The patient was diagnosed

clinically as Herpetic Stromal Keratitis and she was treated by Prednisolone acetate 1% eye drops with prophylactic systemic antiviral and other supportive treatment. After 2 weeks of treatment the lesion showed improvement as edema subsided. Complete healing was within 4 weeks with very faint foot print opacity. Visual acuity was 6/12 (0.5). One month later with follow up, the patient had recurrent Herpetic Epithelial legion dendritic form. And was treated by topical antiviral therapy and other supportive treatment. Final visual acuity was the same. (Fig 2- B).

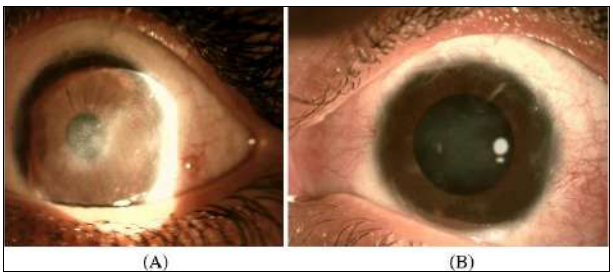

Fig 2: Case 2.

Discussion

In group A, 12 of 15 HSK patients (86.3%) responded to topical CSA 0.4% four times daily after 4 months of treatment, only one case underwent recurrent episode of HSK and two cases developed progression of corneal vascularization. In group B, 9 of 15 HSK patients (60.7%) responded to topical prednisolone acetate 1% four times daily in almost 2 months of treatment. Two cases underwent recurrent episode of HSK after different intervals. One case ended with neurotrophic ulcer and three cases with persistent corneal vascularization after treatment.

Comparable to our trial was one conducted by Gunduz *et al.* [11] in which 10 patients were given a combination of acyclovir 3% ointment and topical Cs-A 2% on a four-times-daily basis. After a period of two months, all of the patients were free of stromal infiltration. Also in Heiligenhaus *et al.* [12], keratitis cleared up in 12 out of 18 patients after treatment with topical Cs-A 2% three times daily in conjunction with topical acyclovir 3%.

In addition, in the research conducted by Rao [8], patients who had been treated with local prednisolone acetate 1% for at least four weeks were analysed. The findings of this series show that HSK may be adequately treated with topical 0.05% CSA.

Similarly, the research by Knickelbein *et al.* [13] was a combination of the studies by Gunduz *et al.* [11], Rao [8], and Heiligenhaus *et al.* [12], and it found that these three studies demonstrated remission of stromal inflammation in 83% of individuals suffering from non-necrotizing HSK who were treated with CSA. The findings of these other investigations are similar to those of our own.

In comparison with our study, Peyman *et al.* [14] study revealed that CSA has same effect of prednisolone acetate 1% but can be used more in cases that have contraindication for using steroid therapy. This is different than our study as CSA Group has better clearance of stromal haze but in longer duration but Group B has shorter duration of healing but with more complications especially recurrence of the disease.

However, it is not entirely obvious whether or if the therapeutic benefit of Cs-A in HSK is related to a decrease in IL-2 production [8]. In Hernandez *et al.* [15], CSA reduces T cell function, interferes with the generation of cytokines and other inducible genes essential for immune response, and reduces angiogenesis, limiting T cell access to the corneal stroma.

Opposing the corticosteroid therapy effect on angiogenesis CSA inhibits selectively Vascular Endothelial Growth Factor–mediated Angiogenesis as in Hernandez *et al.* [15]. This is similar to our study as CSA has better effect on corneal vascularization.

In terms of the adverse events that are associated with Cs-A, the side effects that were seen in our research were temporary and not very severe. On the other hand, toxic epitheliopathy from topical Cs-A 2% was only recorded in 6 out of 18 patients in one trial that was carried out by Heiligenhaus *et al.* [12]. We employed a CsA oil-based solution at a concentration of 0.4% without seeing any significant detrimental effects on the cornea epithelium.

Obviously, there was a difference in group A treated with CSA 0.4% ophthalmic suspension ED and group B treated with Prednisolone 1% ED as CSA effect in Group A had taken longer duration of action, also CSA needed mostly one month to show minute improvement but CSA was better in reducing corneal stromal haze, with a dramatical effect on corneal vascularization by reducing severity and density also CSA improved patients symptoms of dry eye diseases. On the other hand, prednisolone was faster in duration, effect on corneal edema but 2 of 15 patients had recurrent attack of herpetic activation.

In addition, there was a problem with the sample size, which was quite low, and there was no polymerase chain reaction (PCR) available for molecular validation. It was not feasible to boost the statistical power of the research by expanding the sample size since there were only a restricted number of instances that were eligible for the analysis.

All these studies agree with our results for using CSA in treatment of HSK but needed to be completed with more studies with different concentration and more reliable data about CSA effect in HSK.

We recommend other future studies including comparative studies between different concentration of CSA and also between CSA and other forms of steroid therapy with a large sample size and searching on more cases with randomization and longer period of follow up

Also, we recommend dual therapy Protocol in treatment of HSK by application of CSA therapy in loading dose together with steroid therapy at first then tapering of steroid agents and completing treatment by CSA till reaching pleasant healing of stroma. Dual Therapy is waiting to be discussed in further studies.

Conclusions

According to our study, CSA ED (0.4%) is effective and comparable to corticosteroid in management of HSK. It may be less tolerable and take longer duration of action but it is superior to steroids as regard the effect on corneal opacity. It has the advantage to decrease corneal vascularization as well. Using corticosteroids is associated with complications especially in more complicated cases like thin cornea and epithelial defects. It causes disease recurrence and IOP elevation so CSA ED is recommended to be used in treatment of HSK.

Financial support and sponsorship
Nil

Conflict of Interest: Nil

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How to Cite This Article
Abd El-Rahman MZ, Nasef MH, Sabry MM, Shaheen MAE Topical cyclosporine: A versus prednisolone in the treatment of herpetic stromal keratitis. International Journal of Advanced Research in Medicine. 2023;5(2):18-23.