IJAM

INTERNATIONAL JOURNAL OF ADVANCED MEDICINE

RESEARCH PAPER

STUDY OF CORNEAL ENDOTHELIUM CHANGES FOLLOWING TOPICAL CYCLOSPORINE 0.1% EYE DROPS

Mallikarjun M.H [MBBS, DO, DNB (Ophthalmology), Cornea & Refractive surgery consultant] Sankara Eye Hospital, Shivamogga, Karnataka

Shrikant R. Sonawani (MBBS, DO) Sankara Eye Hospital, Shivamogga, Karnataka

ABSTRACT

AIM: To study the changes of corneal endothelium, central corneal thickness and intraocular pressure following topical cyclosporine 0.1% eye drops.

METHOD: A single group observational pre-post clinical study. 60 eyes of 30 patients (20 males and 10 females; mean age: 12.2 ± 3.52 years, interquartile range: 6 - 20 years) fulfilling inclusion and exclusion criteria were evaluated. All patients were treated with only topical Cyclosporine 0.1% eye drops, twice a day for six months. Before treatment and at 15 days, one month, three months, six months post treatment, detailed ophthalmological examination; IOP and specular microscopy were done for all patients. The endothelial cell density (ECD), coefficient of variation (CoV), percentage of hexagonal cells (Hex%), central corneal thickness (CCT) and intraocular pressure (IOP) were analyzed.

RESULT: The ECD, CoV, Hex%, CCT and IOP were not significantly different at baseline and follow up visits ($p>0.05$). No serious side effects were seen at follow up visits.

CONCLUSION: Topical Cyclosporine 0.1% eye drops does not cause significant changes in corneal endothelium in terms of ECD, CoV, Hex% after using for a period of six months, and also it does not cause significant changes in CCT and IOP.

KEY WORDS : Corneal endothelium, topical 0.1% cyclosporine, specular microscopy

Background:

The corneal endothelium is important for the maintenance of corneal transparency. Topical Cyclosporine is used for various ocular conditions like dry eye, vernal keratoconjunctivitis, allergic conjunctivitis for long term. [1-7]

We found only two studies, namely Perez-Rico C et al [8] and Kara N et al [9], reported that no corneal endothelial changes following topical Cyclosporine 0.05% eye drop. But we did not find any study related to corneal endothelial changes following topical cyclosporine of higher concentration more than 0.05% like 0.1%. So this might be the first study of corneal endothelial changes following topical Cyclosporine 0.1% eye drops.

Method:

The study was started after getting clearance from the ethical committee institutional review board, Sankara Eye Hospital, Shivamogga, Karnataka, India. A written informed consent was taken from the patients who fulfilled the inclusion criteria. In case of children, a written informed consent was taken from his/her parents.

A single group observational pre-post clinical study was conducted at Sankara Eye Hospital, Shivamogga, Karnataka from July 2017 to April 2018.The sample size of this study was 30 patients (60 eyes) (confidence level of 95% and confidence interval of 18) and patients were recruited by convenient sampling technique.

Inclusion criteria:

Patients of any age group of either sex, patients with dry eye, vernal keratoconjunctivitis, seasonal allergic conjunctivitis, atopic keratoconjunctivitis, superior limbic keratoconjunctivitis, meibomitis, ocular rosacea, and patients willing to get involved in the study and for follow up.

Exclusion criteria:

Patients who have undergone previous intraocular surgery, patients who have undergone previous ocular trauma, patients with corneal endothelial dystrophies, diabetes mellitus, any other corneal disease affecting endothelial cell function, glaucoma, patients having known sensitivity to Cyclosporine, patients wearing contact lenses, pregnancy and lactation.

Examination procedure:

Patients fulfilling above inclusion and exclusion criteria were included in this study for following ophthalmological examination:

A detailed history regarding any pre-existing ocular inflammations and all the aforesaid ocular and systemic conditions in the inclusion and exclusion criteria was taken.

Measurement of uncorrected visual acuity (UCVA), visual acuity with the pinhole (PHVA), best corrected visual acuity (BCVA) at distance using Snellen's chart were noted.

A detailed ophthalmological examination was done using slit lamp biomicroscope.

Dilated fundus examination using slit lamp biomicroscopy with +90D and indirect ophthalmoscopy with +20D was done.

Corneal endothelial cell study was done using the Specular microscope
(Topcon SP 3000) including:

endothelial cell density (ECD)
a coefficient of variation of cell size (CoV)
percentage of hexagonal cells (%Hex)
central corneal thickness (CCT)

Intraocular pressure was recorded using non-contact tonometer (TOPCON CT80) / Goldmann's applanation tonometer (OPTILASA,S.L. SPAIN) whichever was applicable.

Patients were treated with only topical Cyclosporine 0.1% eye drops, twice a day for six months.

Article History	Received	Accepted	Published
	10/02/2017	14/04/2017	20/05/2017

***Corresponding Author** Shrikant R. Sonawani

(MBBS, DO) Sankara Eye Hospital, Shivamogga, Karnataka, shrikant.sonawani@gmail.com

Patients were explained about the need for strict and regular follow up.

Each patient was called for follow-up after 15 days, one month, three months, and six months (considering all follow up in patients who needed frequent follow up).

During each follow-up visit, detailed ophthalmological examination, IOP and specular microscopy were done.

Any complications were noted and treated appropriately.

Statistical analysis:

Quantitative data was presented with the help of Mean and Standard deviation (SD). Comparison among the study group was done with the help of unpaired t-test as per results of normality test. Qualitative data was presented with the help of frequency and percentage table. Association among the study group was assessed with the help of Fisher test, student's t-test, and Chi-Square test. 'p' value less than 0.05 was taken as significant. Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 was used for statistical analysis.

Result:

In our study, majority of the studied 30 patients, 11(36.7%) were in the age group of 12-14 years followed by 7(23.3%) in the age group of 15-17years, 6(20%) in the age group of 6-8 years, 5(16.7%) in the age group of 9-11 years and 1(3.3%) in the age group of 18-20 years. The mean age of the studied 30 patients was 12.2 ± 3.52 years ranging from 6 to 20 years. This study included 20(66.7%) male and 10(33.3%) female patients.

There was no significant difference in baseline parameters of the right and left eye values as per Student t-test (p>0.05) (Table 1)

There were no significant changes in Endothelial Cell Density (ECD) values, Coefficient of Variation in the Cell Area (CoV) values, and Percentage of Hexagonal Cell (Hex %) values in the follow-up period (p>0.05) as shown in Table 2, Table 3,and Table 4 respectively.

Similarly, there were no significant changes in Central Corneal Thickness (CCT) values and intraocular pressure (IOP) values in the follow-up period (p>0.05) as shown in Table 5 and Table 6 respectively.

In our study, no serious side effects were seen at follow up visits.

Table 1: Baseline Parameters of patients

Baseline Parameters	Right Eye		Left Eye		p Value
	Mean	SD	Mean	SD	
CCT (mm)	0.51	0.02	0.52	0.03	0.134
IOP (mmHg)	13.87	2.11	14.37	2.46	0.402
ECD (cells/mm2)	3177.38	290.52	3195.90	279.75	0.802
CoV	28.35	4.87	27.91	4.25	0.711
Hex (%)	64.27	9.39	66.00	7.77	0.440

CCT - Central Corneal Thickness; IOP – Intraocular Pressure; ECD - Endothelial Cell Density; CoV - Coefficient of Variation in the Cell Area; Hex % - Percentage of Hexagonal Cells

Table 2: Comparison of ECD values in follow up of patients

ECD (cells/mm2)	Baseline		15 Days		1 month		3 months		6 months		p Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Right Eye	3177.38	290.52	3179.98	290.52	3183.71	290.51	3186.28	290.49	3187.99	290.49	0.972
Left Eye	3195.90	279.75	3198.50	279.75	3202.17	279.75	3204.78	279.76	3206.34	279.76	0.971

ECD- Endothelial Cell Density

Table 3: Comparison of CoV values in follow up of patients

CoV	Baseline		15 Days		1 month		3 months		6 months		p Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Right Eye	28.35	4.87	28.94	4.88	29.19	4.89	28.53	4.89	29.75	4.71	0.641
Left Eye	27.91	4.25	28.47	4.25	28.69	4.25	28.07	4.24	29.17	4.25	0.612

CoV- Coefficient of Variation in the cell area

Table 4: Comparison of Hex % values in follow up of patients

Hex %	Baseline		15 Days		1 month		3 months		6 months		p Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Right Eye	64.27	9.39	64.89	9.36	65.93	9.35	66.16	9.32	66.26	9.32	0.798
Left Eye	66.00	7.77	66.52	7.74	67.40	7.71	67.60	7.70	67.70	7.70	0.796

Hex % - Percentage of Hexagonal Cells

Table 5: Comparison of CCT values in follow up of patients

CCT (mm)	Baseline		15 Days		1 month		3 months		6 months		p Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Right Eye	0.51	0.02	0.54	0.03	0.55	0.03	0.50	0.04	0.54	0.04	0.202
Left Eye	0.52	0.03	0.53	0.03	0.55	0.03	0.52	0.02	0.56	0.03	0.124

CCT - Central Corneal Thickness

Table 6: Comparison of IOP values in follow up of patients

IOP (mmHg)	Baseline		15 Days		1 month		3 months		6 months		p Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Right Eye	13.87	2.11	13.56	2.08	13.14	2.07	13.40	2.08	13.27	2.07	0.569
Left Eye	14.37	2.46	14.09	2.44	13.78	2.43	14.10	2.45	13.94	2.48	0.659

IOP – Intraocular Pressure

Discussion:

In day to day practice, various topical ocular medications are used for ocular diseases. These topical ocular medications penetrate through the cornea and may cause various effects on different layers of the cornea. In all the layers of the cornea, corneal endothelium is one of the important layer for transparency of the cornea. But once it is destroyed, it does not regenerate.

In many ophthalmological surgeries and procedures, corneal parameters are important. Such as, ECD is important while planning cataract surgery or refractive lens surgery, CCT is important for assessment of intraocular pressure measurement and preoperative LASIK (Laser in situ keratomileusis) examinations. Also corneal evaluation is helpful for differentiation of healthy corneas from abnormal corneas and preoperative screening for refractive surgery. [10-12]

Topical CsA has been reported to be effective for a number of ocular surface diseases. It has been approved for treatment of moderate to severe dry eye disease by the United States Food and Drug Administration. The CsA likely passes into the cornea through the tear film and limbus. After administration of topical CsA, CsA accumulates at the ocular surface and cornea, and very little drug penetrates to intraocular tissues. Among the three corneal tissues, epithelium has the highest CsA concentration, followed by endothelium and stroma. It has been also reported that the

Cyclosporine has poor penetration into the anterior chamber. [13] In our study, there was no significant difference in Mean±SD of baseline parameters of the right and left eye values as per Student t-test (p>0.05).

Our study reported that there were no significant changes in ECD following topical Cyclosporine 0.1% eye drops after 15 days, one month, three months and six months (P>0.05). This result is comparable with the similar study done by Perez-Rico C et al [8] and Kara N et al. [9]

In our study, we also found that there were no significant changes in CoV and Hex% following topical Cyclosporine 0.1% eye drops after 15 days, one month, three months and six months (P>0.05). This result is similar to the study done by Perez-Rico C et al. [8]

Our study reported that there were no significant changes in CCT and IOP following topical Cyclosporine 0.1% eye drops after 15 days, one month, three months and six months (P>0.05). This result is comparable with the study done by Kara N et al. [9]

Intense stinging, blurred vision, allergic reaction to oil solvent or CsA itself, tearing, and toxic keratitis are reported side effects of different concentration of topical CsA. [14-20] Kachi S et al [21] has reported a case of patient who developed bilateral corneal opacities five days after beginning topical 2% cyclosporine. But in our study, there was no such side effect of topical Cyclosporine 0.1% eye drops using for period of six months which is comparable to Kara N et al [9] study.

This study had one limitation. The corneal endothelial changes following topical Cyclosporine 0.1% eye drops were studied for six months, a short period. Long-term follow up is needed.

Conclusion:

Topical Cyclosporine 0.1% eye drops does not cause significant changes in corneal endothelium in terms of endothelial cell density (ECD), Coefficient of variation (CoV), the percentage of hexagonal cell (Hex%) after using for a period of six months, and also it does not cause significant changes in central corneal thickness (CCT) and intraocular pressure (IOP).

Financial support and sponsorship:

Nil.

Conflicts of interest:

There are no conflicts of interest.

References:

1. Jeng BH and Holsclaw DS. Cyclosporine A 1% eye drops for the treatment of subepithelial ınfiltrates after adenoviral keratoconjunctivitis. Cornea 2011 Sept 1; 30:958–961, 2011.
2. BenEzra D, Pe'er J, Brodsky M et al. Cyclosporine eye drops for the treatment of severe vernal keratoconjunctivitis. Am. J. Ophthalmol. 1986 Mar1; 101:278–282.
3. Cosar CB, Laibson PR, Cohen EJet al. Topical cyclosporine in pediatric keratoplasty. Eye Contact Lens 2003 Apr; 29:103–107.
4. Gordon YJ and Mokete M. Penetrating keratoplasty in children. J. Pediatr. Ophthalmol. Strabismus 1979 Sep; 16:297–300.
5. Perry HD, Doshi-Carnevale S, Donnenfeld EDet al. Topical cyclosporine A 0.5% as a possible new treatment for superior limbic keratoconjunctivitis. Ophthalmology 2003 Aug 1; 110:1578–1581.
6. Hingorani M, Calder VL, Buckley RJet al. The immunomodulatory effect of topical cyclosporin A in atopic keratoconjunctivitis. Invest. Ophthalmol. Vis. Sci. 1999 Feb1; 40:392–399.
7. Kiang E, TesavibulN, Yee Ret al. The use of topical cyclosporin A in ocular graftversus- host-disease. Bone Marrow Transplant. 1998 July; 22:147–151.
8. Perez-Rico C, Germain F, Castro-Rebollo Met al. Effect of topical 0.05% cyclosporine A on corneal endothelium in patients with dry eye disease..Int J Opthalmol 2013; 6(4):471-474.
9. Kara N, Altinkaynak H, Goker Y, Yuksel K, Yildirim Y. Evaluation of corneal morphologic and functional parameters after use of topical cyclosporine-a 0.05% in dry eye. Journal of Ocular Pharmacology and Therapeutics. 2012 Dec 1; 28(6):593-7.
10. Fontes BM, Ambrosio R Jr, Jardim D et al. Corneal biomechanical metrics and anterior segment parameters in mild keratoconus. Ophthalmology 2010 Apr 1; 117:673–679.
11. Prata TS, Sousa AK, Garcia Filho CA et al. Assessment of corneal biomechanical properties and intraocular pressure in patients with rheumatoid arthritis. Can. J. Ophthalmol. 2009 Oct 1; 44:602.
12. Goldich Y, Barkana Y, Gerber Y et al. Effect of diabetes mellitus on biomechanical parameters of the cornea. J. Cataract Refract. Surg. 2009 Apr 1; 35:715–719.
13. Theng J, Zhou L, Tan D et al. Distribution of Cyclosporin A in the Cornea After Topical or Oral Administration. J. Ocul. Pharmacol. Ther. 2002 Feb 1; 18:83–88.
14. Sahin A, Bozkurt B, Irkec M. Topical cyclosporine a in the treatment of superior limbic keratoconjunctivitis: a long-term follow-up. Cornea 2008 Feb 1; 27:193–195.
15. Bleik, JH, Tabbara KF. Topical cyclosporine in vernal keratoconjunctivitis. Ophthalmology 1991 Nov 1; 98:1679–1684.
16. Mendicute J, Aranzasti C, Eder F et al. Topical cyclosporine A 2% in the treatment of vernal keratoconjunctivitis. Eye 1997 Jan; 11:75–78.
17. Secchi AG, Tognon MS, Leonardi A. Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. Am. J. Ophthalmol.1990 Dec 1; 110:641–645.
18. Hingorani M, Moodaley L, Calder VL et al. A randomized, placebo-controlled trial of topical cyclosporine A in steroid-dependent atopic keratoconjunctivitis. Ophthalmology 1998 Sep 1; 105:1715–1720.
19. Theng JT, Ti SE, Zhou L et al. Pharmacokinetic and toxicity study of an intraocular cyclosporine DDS in the anterior segment of rabbit eyes. Invest. Ophthalmol. Vis. Sci. 2003 Nov 1; 44:4895–4899.
20. Kachi S, Hirano K, Takesue Y et al. Unusual corneal deposit after the topical use of cyclosporine as eyedrops. Am. J. Ophthalmol. 2000 Nov 1; 130:667–669.