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## OPHTHALMOLOGY | RESEARCH ARTICLE

# Efficacy of topical carboxymethyl cellulose 0.5% and cyclosporine A 0.05% in dry eye syndrome

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**Abstract:** *Context:* Dry eyes has been associated with inflammation and apoptosis of the ocular surface which is responsible for conjunctival goblet cell loss in long term. *Aim:* To study the efficacy of carboxymethylcellulose and topical cyclosporine A 0.05% in the treatment of dry eyes and their effect on the density of conjunctival goblet cells (GCD). *Settings and design:* Hospital based, Randomized clinical trial. *Methods and material:* A total of 90 patients of dry eyes were enrolled and were randomly divided into two groups of 45 each. Group A was treated with topical cyclosporine A 0.05% twice daily and group B with preservative free carboxymethyl cellulose 0.5% (CMC) four times daily for 6 weeks. Different parameters like dry eye symptoms through visual analogue score (VAS), tear break up time (TBUT), Schirmer's tests (SCH), fluorescein stain (FLU) and goblet cell density (GCD) were obtained prior to treatment and compared with the results after 6 weeks of treatment. *Statistical analysis used:* SPSS software, version 12.0. *Results:* After 6 weeks of treatment both the groups showed significant improvement from baseline values of all the parameters ( $p < 0.001$ ). Comparison between these two groups after treatment showed that all the parameters except FLU score ( $p < 0.001$ ) were statistically not significant. *Conclusions:* Both the topical CMC 0.5% and cyclosporine A 0.05% showed improvement of ocular surface at 6 weeks interval. However, there was no significant difference between the outcome of two groups.

**Subjects:** Ophthalmology; Primary Health Care & Family Practice; Pharmaceutical Medicine

**Keywords:** cyclosporine A; conjunctival impression cytology; goblet cells

### ABOUT THE AUTHOR

Dr Sangeeta Shah is an assistant professor of Ophthalmology at B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal. She has been working in this field for about 8 years. Along with her colleagues, she has conducted research on various aspects of eye-related diseases including on dry eyes among normal population, among diabetics and in post ocular surgeries. Her research papers (published/unpublished) are mostly related with dry eyes, orbital cellulitis and pregnancy related ocular changes. She believes that for a developing countries like Nepal, the best treatment is the one which cures fast with minimum cost. At present, she lives at BPKIHS with her husband and a son.

### PUBLIC INTEREST STATEMENT

Millions of people around the world suffer from dry eyes and many of them remain undiagnosed. Increase in the severity of the disease leads to deterioration in quality of life. This can be prevented if treated early with artificial tears. To decrease the inflammatory portion of the disease, steroids are also used. Topical steroids can lead to formation of cataract and glaucoma if used for a long duration. To avoid this, newer anti-inflammatory agents such as "cyclosporine A" are being used with a promising result. Though our study did not find any significant difference between the use of an artificial tear and topical cyclosporine A in the treatment of dry eyes, it does strengthen the fact that the topical cyclosporine is safe to use. In future, it might be used as a standard treatment not only in dry eyes but also in different ocular surface diseases.

## 1. Introduction

Dry eyes is a common entity encountered by millions of people around the world. There are varieties of causes leading to dry eye syndrome: evaporative factors and aqueous deficient. Initially the patients will present with vague ocular complaints like burning sensation, headache, watering, foreign body sensation etc. but at a long run, it affects the quality of life of the patient be it psychologically or financially. Therefore, early diagnosis and treatment is recommended.

The patients of dry eyes are usually managed with artificial tears of high, medium and low viscosity according to the severity of the disease. In last few years, emphasis has been given to the inflammatory process as the underlying cause of dry eyes and this changed the conventional treatment protocol. Nowadays, the patients are managed with topical anti-inflammatory such as steroids and cyclosporine A (CsA) with adjunct to artificial tears. Cyclosporine A is a fungal derived peptide that acts as a partial immunomodulator by preventing activation and nuclear translocation of cytoplasmic transcription factors required for T-cell activation and inflammatory cytokine production (Agrawal, Sangwan, & Fernandez, 2006).

Topical cyclosporine has been reported to have an anti-inflammatory and apoptosis—suppressing effects which improve aqueous tear production, increase conjunctival goblet cell density and has a therapeutic effect on various ocular disorders (Gilbard, 2000).

The tear substitutes can induce treatment-specific modifications of the conjunctival epithelium with particular regard to goblet cell structure and ultra structure (Albietz, Lenton, McLennan, & Earl, 2002). But topical CsA may have a better effect on enhancing tear film stability and goblet cell density and thus a better symptomatic relief than ocular surface lubricants (Pflugfelder, De Paiva, Villarreal, & Stern, 2008).

There are limited comparative studies between these two drugs. So the purpose of this study was to evaluate the efficacy of ocular lubricants and topical CsA 0.05% in treatment of dry eye syndrome and to compare their effects on the density of conjunctival goblet cell density so that the better drug could be used in our standard treatment protocol.

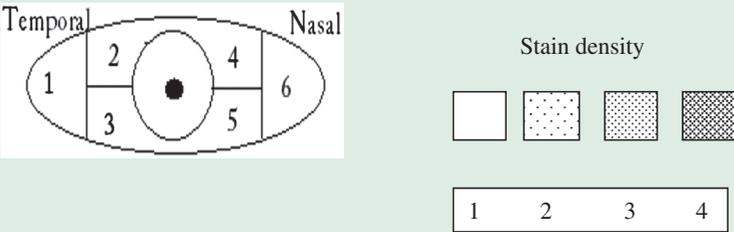
## 2. Materials and methods

In this study, a randomized clinical trial was conducted to compare the efficacy of carboxymethyl cellulose (CMC) 0.5% and CsA 0.05% in dry eye syndrome. All the patients with dry eye syndrome presenting in the out-patient department of our institute in the year May 2011–May 2012 were included in the study. Those with inflammatory, neoplastic or other associated ocular pathology affecting the ocular surface, any systemic illness leading to dry eyes like rosacea, seborrheic dermatitis or arthritis and children were excluded from the study. Total of 90 patients of dry eye syndrome were eligible for this study and were enrolled. The tear break-up time (TBUT) of 10 s or less, Schirmer's I (SCH I) score of 10 mm or less wetting over 5 min and fluorescein stain (FLU) score (Table 1) more than 3 out of 18 were considered to establish the diagnosis of dry eye syndrome.

Informed consent was obtained from all the subjects and the study was approved by our Institutional Research Committee. These 90 patients were randomly divided into two groups (group A and B) with 45 patients in each by envelope technique. The female to male ratio was 49:51. Age distribution was in the range of 21–52 years.

The baseline variables of both groups were recorded. The patients were asked about the most common symptom they suffered with and it was recorded in the proforma. The severity of the effect of these symptoms (foreign body sensation, gritty sensation, redness, pain, burning sensation and stickiness of lids) were recorded by using visual analogue scale (VAS) which reflected the composite score. The score ranged from 0 to 10 where 0 denoted maximum symptoms and 10 if asymptomatic. The VAS from 0 to 8 was taken as symptomatic while value of >8 was taken as normal. TBUT was measured after staining the ocular surface with an impregnated 2% fluorescein strip and was graded as: mild—6 to 8 s, moderate—3 to 5 s, severe— 0 to 2 s (Shah et al., 2008). SCH I was done without anaesthesia and was graded after 5 min as: mild—11 to 14 mm, moderate—10 to 6 mm, severe—5 to 1 mm (Shah et al., 2008). FLU scoring of the cornea and conjunctival epithelium was done. For this, the ocular surface was divided into 7 zones including the cornea (Agrawal et al., 2006). The stain density was then graded as shown in Table 1. Conjunctival impression cytology (CIC) was obtained using Millipore cellulose acetate paper strips (3 × 10 mm with a diagonal edge). The specimens were fixed on albumin glass slides and stained with periodic acid Schiff (PAS) and hemotoxylin stain. The goblet cells were then graded according to modified (Saini, Rajwanshi, & Dhar, 1990) (Table 2).

**Table 1. Grading of fluorescein staining (Agrawal et al., 2006)**



Grading of stain density	Score for total area
Absent	0-3
Mild	4-7
Moderate	8-12
Severe	13-18

Note: Total score of more than 3 of 18 was considered abnormal.

**Table 2. Cytological grading carried out according to criteria laid down by modified Saini et al. (1990)**

Grade	Goblet cells/2 HPF	Goblet cell shape
1	15	Small round epithelium with nucleocytoplasmic ratio of 1:2
2	7-14	Larger polygonal epithelial cells and nucleocytoplasmic ratio of 1:3
3	2-6	Decreased nucleocytoplasmic ratio
4	<2	Large epithelial cells with pyknotic nuclei visible

Group A was treated with topical CsA 0.05% twice daily while group B was treated with CMC 0.5% four times daily. The idea of prescribing CsA four times daily was discussed in order to avoid bias but it was turned down after considering the side effects of the drug in case of poor compliance and potential failure of the patients to follow up. The patients had to buy the drugs themselves. CMC costs about US \$ 2.5 while CsA costs approximately US \$ 5. At the end of the month, both party had to spend almost the same amount for drugs because of frequency difference between them.

All the patients were asked to follow up at 6 weeks after initiation of treatment and again the parameters were re-evaluated and recorded.

### 3. Statistical analysis

The collected data was entered into computer through Microsoft Excel program and analysis was done by using SPSS software, version 12.0.

Paired *t*-test, independent sample test and Chi Square test were used to test the significance difference between the variables.  $p < 0.05$  was considered significant in all the statistical testing.

### 4. Results

There were no difference among the dry eye patients in both the groups with regard to age and gender and other parameters as showed in Table 3.

The most common symptoms in both the groups were feeling of dryness (26%), ocular discomfort (20%), gritty sensation (18%) and burning sensation of eyes (15%). The other symptoms (rest 21%) present were redness of eyes, stickiness of eye lids, headache and itching.

The symptoms were measured with the use of visual analogue score (VAS). The majority of the dry eye patients had score range of 4–7 (48.8%). The VAS between group A and B was not statistically significant ( $p = 0.575$ ).

The baseline parameter values and the post-treatment values of the dry eyes patients treated with CMC 0.5% in 6 weeks duration showed significant changes (Table 4). The parameter showing maximum improvement was SCH I score followed by VAS. There was only slight improvement with the density of goblet cells in CIC.

The baseline values and the post treatment values of the dry eyes patients treated with CsA 0.05% in 6 weeks duration showed that there were significant changes in the two readings (Table 5). The most improved parameter was SCH I score followed by VAS. There was also improvement in the density of goblet cells in CIC.

**Table 3. Initial characteristics of each group with dry eye syndrome before ocular lubricants and topical cyclosporine A 0.05% were administered**

Parameters	Group A (CMC 0.5%)	Group B (CsA 0.05%)
Total subjects (eyes)	45	45
Age (years)	35.87 ± 7.95	37.51 ± 6.78
Gender (M:F)	22:23	23:22
VAS	4.96 ± 2.50	3.96 ± 2.65
SCH (mm)	6.29 ± 3.07	5.49 ± 2.80
TUBT (s)	3.53 ± 2.01	3.11 ± 1.88
FLU	8.60 ± 3.94	12.87 ± 4.29
GCD (cell/100 epithelial cells)	3.20 ± 2.78	3.16 ± 2.61

**Table 4. Comparison of different parameters in group A before and after 6 weeks of treatment with carboxymethylcellulose 0.5%**

Parameters	Baseline (mean ± SD)	Follow up (mean ± SD)	p-values
VAS	4.96 ± 2.50	7.27 ± 2.22	<0.001
SCH	6.29 ± 3.07	10.11 ± 5.24	<0.001
TUBT	3.53 ± 2.08	4.24 ± 2.08	<0.001
FLU	8.60 ± 3.94	6.93 ± 4.79	<0.011
GCD	3.20 ± 2.78	3.73 ± 2.98	<0.004

Notes: Significant improvement was seen in the baseline parameters after 6 weeks of treatment. VAS—visual analogue scale, SCH—Schirmer’s test, TBUT—tear breakup time, FLU—fluorescein stain, GCD—goblet cell density.

**Table 5. Comparison of different parameters in group B before and after 6 weeks of treatment with cyclosporine A 0.05%**

Characteristics	Baseline	Follow up	p-values
VAS	3.96 ± 2.65	7.78 ± 1.66	<0.001
SCH	5.49 ± 2.80	11.80 ± 5.67	<0.001
TUBT	3.11 ± 1.88	5.22 ± 2.38	<0.001
FLU	12.00 ± 4.29	6.16 ± 2.54	<0.001
GCD	3.16 ± 2.61	4.91 ± 3.26	<0.001

Notes: This table shows significant improvement with the use of cyclosporine A 0.05% after 6 weeks of treatment. VAS—visual analogue scale, SCH—Schirmer’s test, TBUT—tear breakup time, FLU—fluorescein stain, GCD—goblet cell density.

**Table 6. Comparison of different parameters in group A and group B after 6 weeks of treatment**

Parameters	Group A (mean value ± SD)	Group B (mean value ± SD)	p-value	Remarks
VAS	7.27 ± 2.22	7.78 ± 1.66	=0.053	Not significant
SCH	10.11 ± 5.24	11.80 ± 5.67	=0.445	Not significant
TUBT	4.24 ± 2.08	5.22 ± 2.38	=0.267	Not significant
FLU	6.93 ± 4.79	6.16 ± 2.54	<0.001	Significant
GCD	3.73 ± 2.98	4.91 ± 3.26	=0.642	Not significant

Notes: This table shows significant difference of FLU between the two groups after 6 weeks of treatment. VAS—visual analogue scale, SCH—Schirmer’s test, TBUT—tear breakup time, FLU—fluorescein stain, GCD—goblet cell density.

Comparison of different parameters after six weeks of treatment between group A and B showed that the parameters (VAS, SCH, TBUT, GCD) were not significant statistically except FLU which was significant ( $p < 0.001$ ) (Table 6). However, the absolute mean values of FLU were 6.93 vs. 6.16, the clinical significance of which may be small.

Both the ocular lubricants and topical cyclosporine 0.05% showed increase in the number of goblet cells in CIC after 6 weeks of treatment and was statistically significant ( $p < 0.001$ ). Comparing the increase in goblet cells of both group A and B, it was seen that the number of cells increased more in group B ( $3.73 \pm 2.98$  vs.  $4.91 \pm 3.26$ ) but statistically it was not significant ( $p = 0.642$ ).

## 5. Discussion

Ocular surface diseases include a large group of disorders of varied aetiology, symptoms and signs which damage and produce inflammation of the ocular surface and dry eye is the most frequent entity encountered by an ophthalmologist (Morales-Fernández, Pérez-Álvarez, García-Catalán, Benítez-del-Castillo, & García-Sánchez, 2010).

Various studies have shown that the maximum age distribution for dry eyes were in adult group and in ours the mean age was seen to be  $36.69 \pm 7.39$  which is similar to a study conducted by Kim, Choi, and Joo (2009). Literatures have shown that male:female for this disorder is 1:3 unlike ours which was 1:1 and the reason maybe that male patients visit the hospital more frequently as compared to the female counterparts which happens in most of the developing countries maybe due to male dominated society and female dependency on males for travelling, finance etc.

A study done by Schein et al. showed a lack of correlation between symptoms, tear deficiency (Schirmer's test) and ocular surface damage (Rose Bengal stain) perhaps indicating that these parameters do not reflex all those event that contribute to symptoms (Kim et al., 2009).

According to a study done by Lee, Ahn, Kim, and Kim (2011) ocular lubricants showed significant improvements in ocular surface stain score, TBUT and VAS after 4 and 8 weeks post-treatment. Our study showed that there was significant difference of GCD after 6 weeks of treatment with the use of artificial tear (CMC) whereas other studies have shown no significant difference in GCD with the use of same (Gilbard, 2000; Moon et al., 2007).

Use of topical cyclosporine in group B showed significant improvement in the all the parameters specially TBUT similar to other studies done (Byun et al., 2009; Sahli, Hoşal, Zilelioğlu, Gülbahçe, & Üstün, 2010; Sall, Cohen, & Christensen, 2006). This is explained by the fact that the ocular surface, lacrimal glands and the neuronal feedback loop that make up a single functional unit for the maintenance of ocular surface homeostasis leading to improvement of the ocular surface (Sall, Stevenson, Mundorf, Reis & The CsA Phase 3 Study Group, 2000).

Our study showed that the change in GCD in group B regarding GCD was not significant unlike the studies done by Kunert, Tisdale, and Gipson (2002) and Strong, Farley, Stern, and Pflugfelder (2005) where there was significant changes in GCD after treatment because of the anti-inflammatory nature of topical cyclosporine A. The most probable explanation for this dissimilarity is short post-treatment follow up (6 weeks). As per other studies, it takes about 3–6 months for significant increase in GCD with the use of cyclosporine A 0.05% (Gilbard, 2000; Lemp, 1995; Moon et al., 2007). As per our knowledge (source: PubMed), there are no other studies done to detect the changes in GCD at six weeks with the use of topical CsA.

In our study, none of the patients showed any drug related adverse effects which was consistent with previous extensive preclinical and clinical safety studies of topical cyclosporine A (Kinoshita, Kiorpes, Friend, & Thoft, 1983; Small et al., 2002; Stevenson, Tauber, & Reis, 2000).

## 6. Conclusion

This study demonstrates similar improvement in signs and symptoms of dry eye disease with the use of both topical cyclosporine A 0.05% and ocular surface lubricants after 6 weeks of treatment. However, there is no significant change in the outcome between the two groups. It also strengthens the fact that topical cyclosporine A 0.05% has no adverse effect when used twice daily.

## 7. Limitations

The limitations of this study are:

Short follow up time (6 weeks) which may be the reason for statistically insignificance between the two groups.

The study was not conducted according to the severity of the dry eye which might have interfered with the final outcome in either group.  
Small sample size—45 subjects in each group.

#### Competing Interests

The authors declare no competing interest.

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