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RESEARCH ARTICLE

Comparative evaluation of efficacy and safety of cyclosporine 0.1% add-on therapy with artificial tears (carboxymethylcellulose 0.5%) with artificial tears alone in post cataract surgery patients

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ABSTRACT

Background: Cataract is the most common cause of preventable blindness and to surgically remove the affected lens and replace it with an artificial lens is the only effective treatment**.** Most patients post cataract surgery, complain of dry eye. Artificial tears are commonly used symptomatic treatment in dry eye. Since there is an underlying inflammatory cause; therefore, recently topical immunomodulator therapy is gaining acceptance. **Aims and Objective:** The present prospective, randomized, open-label, the study was undertaken to evaluate the efficacy of cyclosporine 0.1% as add-on therapy with artificial tears (carboxymethylcellulose 0.5%) in post cataract surgery patients suffering from moderate-to-severe dry eye symptoms. **Materials and Methods:** A total of 69 patients were selected after application of inclusion and exclusion criteria with 37 patients in artificial tears 0.5% group and 32 patients in cyclosporine 0.1% + artificial tears 0.5% group, respectively. Patients were followed up to 8 weeks. Grading of the severity of dry eye was done on the basis of ocular surface disease index scale (OSDI), and patients with >23 score were selected for the study. Safety and tolerability were based on adverse events reported by the participants. **Results:** Treatment in both the group's cyclosporine 0.1% + artificial tears 0.5% and artificial tears 0.5% leads to a significant improvement in the OSDI score in the patients at 4 weeks and 8 weeks interval ($P < 0.0001$). On intergroup comparison, the effect on OSDI score was more favorably affected by combination therapy than artificial tears alone. Both treatments were well tolerated, itching/burning and redness were common adverse drug events, all the events reported were mild in nature and did not warrant any cessation of therapy or change of therapy. **Conclusion:** Cyclosporine 0.1% + artificial tears 0.5% and artificial tears 0.5% topical therapy caused improvement in moderate-to-severe dry eye condition. However, combination treatment was more effective than artificial tears alone, therefore, suggesting its clinical superiority in the improvement of overall symptoms of dry eye in the patients after cataract surgery.

KEY WORDS: Post Cataract Surgery Dry Eye; Artificial Tears; Cyclosporine Drops; Ocular Surface Disease Index Scale

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INTRODUCTION

Cataract is the clouding of the lens leading to a decrease in the vision affecting one or both the eyes commonly due to aging. It can also be congenital, traumatic, due to radiation exposure, post-eye surgery, and chronic use of drugs such as steroids and prolonged intake of tobacco and alcohol. It is one

of the leading causes of preventable blindness worldwide. About 20 million people suffer from age-related cataract globally accounting for 51% of blindness. Blindness due to cataract occurs in 10–40/100,000 children in the developing world and about 1–4 of 100,000 children in the developed world.[1] To surgically remove the affected lens and replace, it with an artificial lens is the only effective treatment.[2]

Most patients, who have undergone cataract surgery, complain of dry eye and symptoms of irritation postoperatively. Dry eye leads to eye discomfort and inflammation of the ocular surface and accounts for 18–45% of the patient visits to the ophthalmology clinics making it one of the most common ocular conditions in India.[3] The post-operative dry eye can be due to tear film instability, exposure of eyes to the light of operating microscope, nerve cell injury during surgery, or ocular epithelial injury.[4] Tear hyperosmolarity and ocular surface inflammation are important factors involved in dry eye pathogenesis**.**

Dry eye syndrome treatment includes artificial tears, corticosteroids, autologous serum, sodium hyaluronate, and immune modulators. Mild dry eye primarily needs lifestyle changes and use of artificial tears while the moderate-to-severe disease may require anti-inflammatory medications or surgery.[5]

Artificial tears (ocular lubricants) typically include one or more water-soluble polymers (carmellose, polyvinyl alcohol, polyethylene glycol, or carboxymethylcellulose) to improve retention, increase the duration of action, lubrication, and hydration of the ocular surface. Although artificial tears are a mainstay treatment for the mild dry eye, it provides only symptomatic relief in moderate-to-severe cases without affecting inflammatory pathology. Thus, there is a need for better drugs and treatments in this direction.

Topical corticosteroids target the inflammatory pathways in ocular inflammation and improve symptoms in of dry eye, but their use is limited due to long-term side effects.

Eye drops made by separating the liquid and cellular components of the patient's blood, known as autologous serum eye drops, have been shown to possess many of the same biological nutrients found in natural tears. Due to their cost and limited availability, the use of autologous serum eye drops is not popular or widespread.

Cyclosporine, an immune modulatory drug is of proven use in diseases with underlying inflammation, such as psoriasis, rheumatoid arthritis, ulcerative colitis, as well as ocular inflammation. It is beneficial in the moderate-to-severe dry eye[6] and is shown to decrease in the levels of inflammatory markers in the conjunctival epithelium with a dramatic increase in the number of goblet cells.

Approved by the FDA for treatment of dry eye disease in the year 2003[7] the topical cyclosporine does not inhibit wound healing nor produce any detrimental changes in the lens and also lack systemic adverse effects. Moreover, the topical formulation of the drug and has no detectable serum levels according to most trials, hence, having a wider safety profile.

Although some of the studies have evaluated the role of cyclosporine (0.1%) in the treatment of dry eye,[8] there is a paucity of research examining the efficacy of cyclosporine as an add-on therapy with artificial tears in the moderate-to-severe dry eye after cataract surgery. Moreover, we have not come across any such study done in Indian set up, and no earlier work in the said subject has been done in our institute.

Therefore, the current prospective, randomized, open-label, add-on, the study was done with the aim of evaluating the efficacy and tolerability of cyclosporine (0.1%) in the dry eye following cataract surgery over a period of 1 year. It was done so that the outcome would be of help to clinicians for better treatment modalities in moderate-to-severe dry eye cases.

MATERIALS AND METHODS

A prospective, randomized, open-label study to evaluate the efficacy of cyclosporine 0.1% as add-on therapy with artificial tears (carboxymethylcellulose 0.5%) in post cataract surgery patients, was conducted in the Department of Pharmacology in Collaboration with the Department of Ophthalmology, Government Medical College, Jammu, over 1 year. The study protocol was approved by the Institutional Ethics Committee (IEC) vide No. IEC/Pharma/Thesis/Research/T_{12}B/2016/294 dated October 07, 2016.

The study participants included the patients who have undergone cataract surgery in the past 1 week or more attending ophthalmology outpatient department (OPD), above 45 years of age, suffering from moderate-to-severe dry eye, of either gender. While patients with mild dry eye; history of dry eye before the surgery; pterygium; previous refractive surgery; ocular allergies or any active ocular disease; connective-tissue disorders such as rheumatoid arthritis, Sjogren's disease, scleroderma, diabetes mellitus, thyroid diseases, Vitamin A deficiency, any uncontrolled systemic disease; and pregnant or lactating females were excluded.

A written informed consent was obtained from the patients fulfilling inclusion, exclusion. Clinical evaluation with complete medical history, with baseline investigations, was done. Grading of the severity of dry eye was done on the basis of ocular surface disease index scale (OSDI).

Study Design

Selected patients were randomized (by block permutation method) in the ratio of 1:1 into two groups to receive either the artificial tears or cyclosporine as add-on the

drug with the artificial tear. Duration of the study was 8 weeks. The total study period was 1 year. Artificial tears (carboxymethylcellulose 0.5%) were the baseline treatment in both the groups. Cyclosporine (0.1%) was used as an add-on therapy to look for its efficacy in comparison to the artificial tear alone [Figure 1].

Group 1 patients received artificial tears (carboxymethylcellulose 0.5%) alone instilled three times daily, while Group 2: Received Artificial tears (carboxymethylcellulose 0.5%) instilled 3 times daily and cyclosporine (0.1%) instilled 2 times daily. The doses selected were most common clinically used dose and based on the previous study.[9] Both the treatment arms were also allowed to continue the prescribed post-operative medications. In case of need, autologous serum eye drops were kept as rescue therapy. Pre-drug evaluation was done at 0 day. Post drug evaluation was done at 4 and 8 weeks.

The assessment was carried out by the OSDI score. It was a 12 items scale that grades the severity of dry eye on the basis of visual symptoms, functional limitations, and environmental factors related to dry eye.

Monitoring of any local or systemic adverse drug events (ADEs) and safety assessment of vital signs such as blood pressure, pulse, heart rate, and respiratory rate was done.

OSDI Scale

It is a subjective scale that consists of 12 items divided to three subscales to assess the visual symptoms (5 questions), functional limitations (4 questions), and environmental factors (3 questions) related to dry eye, respectively. Each item has the same five-category Likert-type response option ("none of the time" (score = 0) "some of the time" (score = 1), "half of the time" (score = 2), "most of the time" (score = 3), and "all the time" (score = 4). OSDI score is calculated as the sum of scores for all the questions/number of questions answered X 25. The scale is from 0 to 100 with higher values showing greater disability. Subscale scores are computed similarly with only the questions from each subscale used to generate its own score.[10]

Scoring criteria indicate 0–12: Normal, 13–22: Mild dry eye, 23–32: Moderate dry eye, and >32: Severe dry eye. It is a valid and reliable scale that grading the dry eye symptoms.

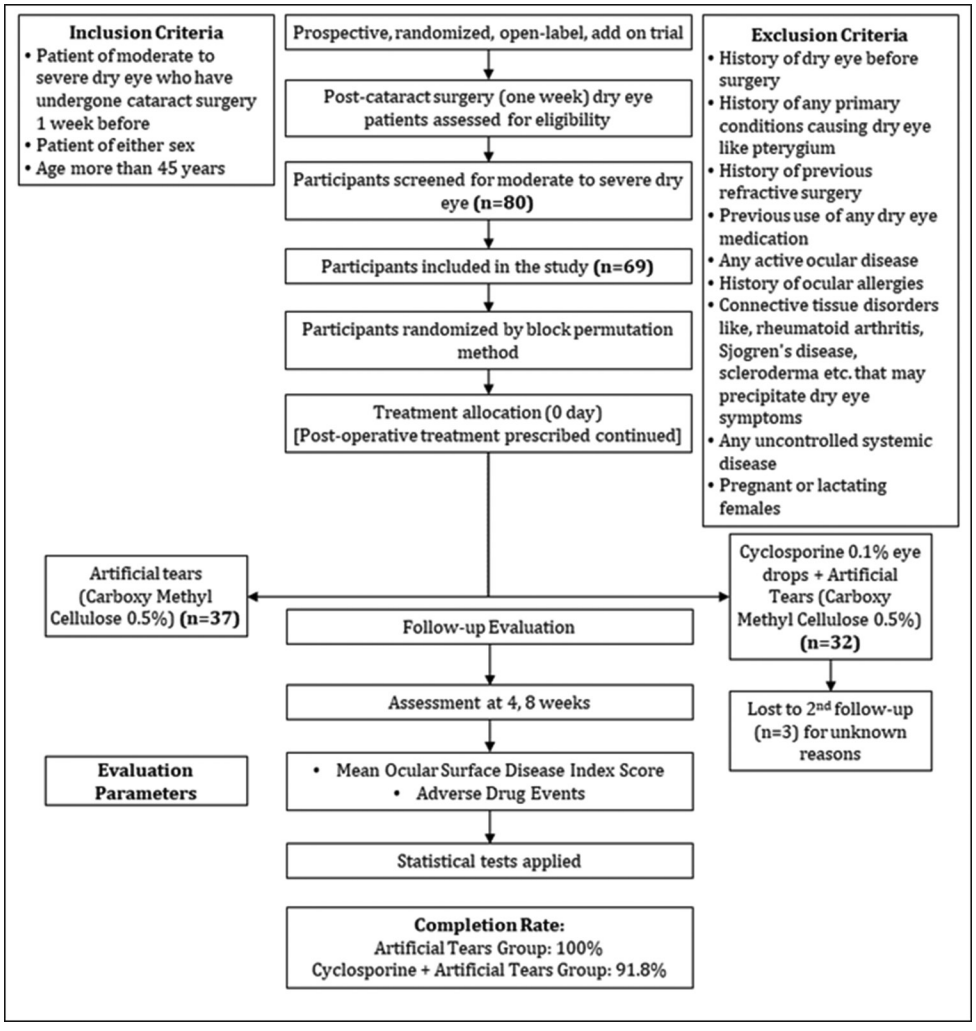

Figure 1: Study design

Safety Assessment

ADEs recorded in the study were based on spontaneous reporting, as reported by the patients, a casual relationship was assessed, and severity and seriousness of the reactions were recorded as per the standard operating procedure of Pharmacovigilance Programme of India. The drug tolerability and completion rate were also recorded and compared between the two treatment arms.

Statistical Analysis

The evaluation of patients in both the groups was done by the OSDI scores and reported as the mean ± standard deviation values. The change in the scores from baseline was noted and assessed by the use of paired *t*-test, while intergroup comparison between two groups was done by unpaired *t*-test. $P < 0.05$ was considered statistically significant. The evaluation was done on an intention to treat basis.

RESULTS

A total of 69 patients comprised 37 patients in Group A (artificial tears 0.5%) and 32 in Group B (artificial tears 0.5% and cyclosporine 0.1%) were evaluated. All the patients completed their follow-up in the Group A, while in Group B three patients were lost during follow-up due to unrelated reasons. Demographic and baseline values in both groups were comparable and are shown in Table 1. Hypertension and diabetes were most common comorbidities in both groups [Table 2].

Effect on OSDI

Mean OSDI score in both groups showed a significant reduction in comparison to baseline at 4 and 8 weeks ($P < 0.0001$). Difference between the mean values of the two groups was statistically significant both at 4 weeks ($P < 0.0001$) and 8 weeks ($P < 0.0001$) [Table 3].

In both groups, the biochemical profile in patients remained unaltered as hemoglobin, blood sugar, renal function test, and liver function test did not show any significant change from baseline values.

ADEs

In the artificial tears group, the most common adverse event was itching/burning in the eye (50%) followed by redness

Table 1: Demographic profile of patients in artificial tears 0.5% and artificial tears 0.5%+cyclosporine 0.1% group

Parameter	Artificial tears 0.5% (*n*=37)	Artificial tears 0.5%+cyclosporine 0.1% (*n*=32)
Mean age (mean±SD)	60.29±10.10 years	63.18±11.25 years
Male: Female	1:1.05	1.13:1
Rural: Urban	1.64:1	1:1.9
Literate: Illiterate	1:1.84	1.46:1
Meantime interval between date of surgery and date of examination (mean±SD)	14.4±6.33 days	15.4±7.03 days
Occupation (%)		
Farmer (%)	10 (27.04)	8 (25)
Housewife (%)	13 (35.13)	10 (31.2)
Government sector (%)	4 (10.8)	6 (18.7)
Business (%)	1 (2.7)	2 (6.25)
Other (%)	9 (24.3)	6 (18.7)
Eye involved (%)		
Left (%)	16 (43.24)	17 (53.12)
Right (%)	16 (43.24)	8 (25)
Both (%)	5 (13.51)	7 (21.8)

SD: Standard deviation

Table 2: Comorbidities associated with artificial tears 0.5% and artificial tears 0.5%+cyclosporine 0.1% group

Condition	Artificial tears 0.5% (*n*=25)	Artificial tears 0.5%+cyclosporine 0.1% (*n*=22)
Hypertension	11 (44)	9 (39.13)
Diabetes	8 (32)	7 (30.4)
Hypothyroidism	3 (12)	3 (13.04)
Tuberculosis	2 (8)	2 (8.6)
Others	1 (4)	2 (8.6)

(33.3%) and discharge from the eye (16.6%). Similarly, in the cyclosporine + artificial tears group, itching/burning (38.4%) was the most common adverse event followed by redness (30.7%) and discharge (15.3%). One patient in this group presented with pain in the eye and blurring of vision (7.6%). All the adverse events were mild in nature with the established causal relationship as assessed by the WHO UMC scale as probable. None of the reactions were severe/serious [Table 4].

All the ADEs recorded were mild in nature with the established causal relationship as assessed by the WHO UMC scale as probable. None of the events was severe or serious; thereby, it did not warrant any cessation of therapy or change of therapy.

DISCUSSION

The cornea is innervated by long ciliary nerves of the ophthalmic branch of the trigeminal (fifth) nerve. In the normal conditions, these nerves send afferent stimuli to the brain stem and parasympathetic and sympathetic signals stimulate the lacrimal gland for tear production and secretion.[11] For normal blinking and tear reflexes, intact corneal innervations is necessary, and damage to this circuit leads to dry eye. Ocular surgical procedures may cause denervation of the cornea resulting in decreased blinking, reduction in tear production, increased epithelial permeability, and impaired epithelial wound healing.[12] Cataract surgery is the most successful procedure for restoring visual acuity in the patients of cataract, and current study was done to contribute toward the better treatment protocol in these post-operative patients of moderate-to-severe dry eye.

A total of 69 patients were selected after application of inclusion and exclusion criteria with 37 patients in artificial tears 0.5% group and 32 patients in cyclosporine 0.1% + artificial tears 0.5% group, respectively. However, three patients were lost at second follow-up in cyclosporine group due to unaccounted reasons and intention to treat analysis was done. A total number of 81 eyes were involved in the study. Most of the basic demographic profile (mean age, sex, occupation, mean time interval between surgery and examination, and eye involvement) in both the groups was statistically comparable. Most common comorbidity was hypertension followed by diabetes and hypothyroidism in both the groups.

Treatment in both the groups cyclosporine 0.1% + artificial tears 0.5% and artificial tears 0.5% leads to a significant improvement in the OSDI score in the patients at 4 weeks ($P < 0.0001$) and at 8 weeks interval ($P < 0.0001$), respectively. On intergroup comparison, the effect on OSDI score was statistically significant in favor of Cyclosporine group with respect to those being given only artificial tears at both 4 weeks ($P < 0.0001$) and 8 weeks ($P < 0.0001$). Therefore, suggesting its clinical superiority in the improvement of overall symptoms of dry eye in the patients after cataract surgery.

Both the groups, recorded mild ADEs with the established causal relationship as assessed by the WHO UMC scale as probable. Almost all the events were mild in nature, and none of the reaction was severe/serious. Thereby, it did not warrant any cessation of therapy/change of therapy. Therefore, both the groups were relatively safe and free from serious adverse events signifying that overall, both the treatments were well tolerated.

Aging is an established risk factor for dry eye as androgen deficiency associated with aging has been reported to be a

Table 3: Comparative effect of artificial tears 0.5% versus artificial tears 0.5%+cyclosporine 0.1% on mean OSDI score

Duration	Artificial tears 0.5% (*n*=37)	Artificial tears 0.5%+cyclosporine 0.1% (*n*=32)	*t* value	*P* value	Statistical significance
Baseline	29.16±3.09	29.96±3.80	0.964	0.338	NS
4 weeks	23.45±2.7$^{\#\#\#\#}$	20.6±3.03$^{\#\#\#\#}$	4.1316	<0.0001***	HS
8 weeks	18.40±2.7$^{\#\#\#\#}$	11.8±1.53$^{\#\#\#\#}$	12.121	<0.0001***	HS

The data are shown as mean±SD showing paired *t*-test in comparison to respective baselines $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$, $^{\#\#\#\#}P<0.0001$. Comparison between the groups at baseline, 4 weeks and 8 weeks using student unpaired *t*-test *$P<0.05$, **$P<0.01$, ***$P<0.001$ ocular surface disease index, SD: Standard deviation

Table 4: ADEs in artificial tears 0.5% versus artificial tears 0.5%+cyclosporine 0.1% group

ADE	Artificial tears 0.5% *n*=6 (%)	Artificial tears 0.5%+cyclosporine 0.1% *n*=13 (4%)
Itching/burning	3 (50)	5 (38.4)
Redness	2 (33.3)	4 (30.7)
Discharge	1 (16.6)	2 (15.3)
Pain in the eye	Nil	1 (7.6)
Blurring of vision	Nil	1 (7.6)

ADE: Adverse drug event

contributing factor to dry eye,[13] and in the current study also the patient population was also more than 45 years. All patients reporting to OPD with dry eye had a history of cataract surgery of more than 2 weeks and this is in concurrence with Li *et al*., 2007; Kasetsuwan *et al*., 2013 demonstrated that dry eye appeared mostly 1 week after cataract surgery.[14,15]

The present study clearly demonstrates that cyclosporine 0.1% in combination with 0.5 icial % artificial tears is more efficacious than artificial tears alone in the treatment of dry eye patients as suggested by both subjective parameters of OSDI.

There is a number of studies that have shown a beneficial effect of cyclosporine in dry eye.[16] Hardten *et al*., 2007, similar to our study used cyclosporine 0.05% in conjunction with carboxymethylcellulose and showed better improvement in subjective symptoms of ocular surface disease (OSDI scores) compared to artificial tears alone.[17]

Kang and Kim, and Hamada *et al*., 2016, have shown a significant change in tear film parameters with cyclosporine 0.05% compared to carboxymethylcellulose eye drops in dry eye patients following cataract surgery.[18,19]

The results of the current study, however, are contrary to results of Altiparmak *et al.,* 2012, as their study suggested that cyclosporine 0.05% with artificial tears drops is not more advantageous than artificial tears alone for the dry eye patients of thyroid orbitopathy. The possible reason for these variations might be a different design, duration of the study and dose of cyclosporine and different the disease entity.[20]

Topical cyclosporine A is a well-known immunomodulatory agent used in dry eye syndrome.[21] It causes inhibition of cytokine production by the activated T lymphocytes, which are a feature of keratoconjunctivitis sicca.[22] The cell-mediated anti-inflammatory responses are modulated through downregulation of interleukin-2 receptor expression and gene transcription. Cataract surgery induces an inflammatory condition, possibly mediated by activation of T lymphocytes on the ocular surface and cyclosporine with its immunomodulatory function, T cell inactivation and increase in reflex tear production improved various parameters of dry eye.[23]

In the present study, it was observed that both the treatment regimes were well tolerated. No significant change was seen in the biochemical parameters in both groups. This is supported by the number of authors.[9,16,18,23] A total of six adverse events occurred in the artificial tears, and 13 adverse events occurred in the artificial tears 0.05% + cyclosporine 0.1% group. In both groups, itching/burning and redness in the eye were the most common adverse events, similarly, Laibovitz *et al*., 1993; Barber *et al*., 2005; Byun *et al*., 2011; Wan *et al*., 2015; and Leonardi *et al*., 2016, have shown that burning, redness, and pain are the most common side effect with the use of topical cyclosporine.[6,9,24-26]

Although our study clearly demonstrates the superior efficacy of cyclosporine and artificial tears combination treatment as compared to artificial tears with good tolerability, this being a short duration study, the results may vary in larger general population because of relatively small number of patients. Furthermore, small number of parameters was studied which is insufficient to establish the long-term efficacy of cyclosporine as an add-on drug in dry eye patients.

CONCLUSION

Cyclosporine 0.1% + artificial tears 0.5% and artificial tears 0.5% topical therapy caused improvement in moderate-to-severe dry eye condition. However, combination treatment was more effective than artificial tears alone, therefore, suggesting its clinical superiority in the improvement of overall symptoms of dry eye in the patients after cataract surgery.

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