

Original Article

Comparison of efficacy of treatment with cyclosporine 0.1% add on therapy with artificial tears (carboxy methyl cellulose 0.5%) & artificial tears alone on dry eye parameters in post cataract surgery patients

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ABSTRACT

Introduction -Cataract is the leading cause of preventable blindness and the only effective treatment is to surgically remove the affected lens and replace it with an artificial lens. Most patients complain of dry eye after cataract surgery. Artificial tears are commonly used symptomatic treatment in cases of dry eye. Recently topical immunomodulator therapy is gaining acceptance in lieu of the underlying inflammatory cause. **Aim** The present prospective, randomized, open label, 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 dry eye symptoms. **Material and methods** A total of 58 patients were selected after application of inclusion and exclusion criteria with 31 patients in Artificial tears 0.5% group and 27 patients in Cyclosporine 0.1% + Artificial tears 0.5% group respectively. Patients were followed up to 8 weeks. Dry eye was diagnosed on the basis of Tear Film Break Up Time(TBUT) and Schirmer's Test was used to measure the production of tear. **Results**-Treatment in both the groups Cyclosporine 0.1% + Artificial tears 0.5% and Artificial tears 0.5% lead to a significant improvement in the Schirmer's test and TBUT score in the patients at 4 weeks and 8 weeks interval (p<0.0001). On intergroup comparison, the effect on Schirmer's test and TBUT score were more favourably affected by combination therapy than artificial tears alone. **Conclusion**- Cyclosporine 0.1% + Artificial tears 0.5% and Artificial tears 0.5% topical therapy caused improvement in 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, Tear Film Break Up Time(TBUT), Schirmer's Test.

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INTRODUCTION

Cataract is defined as the clouding of the lens leading to a decrease in the vision affecting one or both the eyes most commonly caused due to aging. It can also be due to other causes such as congenital, traumatic, exposure, post eye surgery, chronic use of drugs like steroids, prolonged intake of tobacco and alcohol. It is one of the major cause of preventable blindness worldwide. The only effective treatment is to surgically remove the affected lens and replace it with an artificial lens.

Most patients who have undergone cataract surgery, complain of dry eye and symptoms of irritation in the eye

postoperatively.^[1] Post-operative dry eye can be caused due to tear film instability, exposure of eyes to the light of operating microscope, nerve cell injury that occurs during surgery or ocular epithelial injury. Ocular surface inflammation is one of the most important factor involved in dry eye pathogenesis.

Dry eye syndrome treatment includes modalities such as artificial tears, corticosteroids, autologous serum, sodium hyaluronate and immunomodulators. Mild cases primarily need lifestyle changes & use of artificial tears^[2] while

severe cases may require anti inflammatory medications or surgery.

Artificial tears are water soluble polymers (carmellose, polyvinyl alcohol, polyethylene glycol or carboxy methyl cellulose) to improve retention, lubrication, and hydration of the ocular surface. Though, artificial tears is a mainstay treatment for mild dry eye but it provides only symptomatic relief in severe cases without affecting inflammatory pathology.

Topical corticosteroids that 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.

Cyclosporine, an immunomodulatory drug is of proven use in diseases with underlying inflammation, like psoriasis, rheumatoid arthritis, ulcerative colitis, as well as in ocular inflammation. It is shown to decrease in the levels of inflammatory markers in the conjunctival epithelium with a dramatic increase in the number of goblet cells.^[3]

Approved by the FDA for treatment of dry eye disease in the year 2003^[4] the topical cyclosporine do not inhibit wound healing nor produce any detrimental changes in lens and also lack systemic adverse effects.^[5]

Though, some of studies have evaluated the role of cyclosporine (0.1%) in the treatment of dry eye but there is 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.

Therefore the aim of the current study was to evaluate the efficacy of cyclosporine 0.1% as add on therapy with artificial tears in post cataract surgery patients.

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 Department of Pharmacology in collaboration with Department of Ophthalmology, Government Medical College, Jammu over one year. The study protocol was approved by Institutional Ethics Committee (IEC) .

The study participants included the patients who have under gone cataract surgery past one week or more attending ophthalmology OPD, above 45 years of age ,suffering from dry eye , of either gender. While patients with history of dry eye before the surgery, pterygium ,previous refractive surgery, ocular allergies or any active ocular disease, connective tissue disorders like rheumatoid arthritis, sjogren's disease, scleroderma, diabetes mellitus, thyroid diseases, vitamin A deficiency, any uncontrolled systemic disease and pregnant or lactating females were excluded from the study.

A written informed consent was obtained from the patients fulfilling inclusion, exclusion. Clinical evaluation with

complete medical history, with baseline investigations was done.

Dry eye was diagnosed on the basis of Tear Film Break Up Time (TBUT) in which fluorescein dye was instilled into tear film and patient was asked not to blink while the tear film was observed under illumination. TBUT was recorded as the number of seconds that elapsed between the last blink & appearance of first dry spot in the tear film. A TBUT less than 10 seconds was taken as diagnostic of dry eye.^[6]

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 drug with the artificial tear. Duration of the study was 8 weeks. Total study period was one year. Artificial tears (carboxy methyl cellulose 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.

Group 1 patients received Artificial tears (carboxy methyl cellulose 0.5%) alone instilled three times daily , while

Group 2: received Artificial tears (carboxy methyl cellulose 0.5%) instilled three times daily and Cyclosporine (0.1%) instilled two times daily. The doses selected were most common clinically used dose and based on previous study.^[7] Both the treatment arms were also allowed to continue the prescribed postoperative 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.

Schirmer's test was done to grade the dry eye symptoms using the amount of wetness of filter paper.

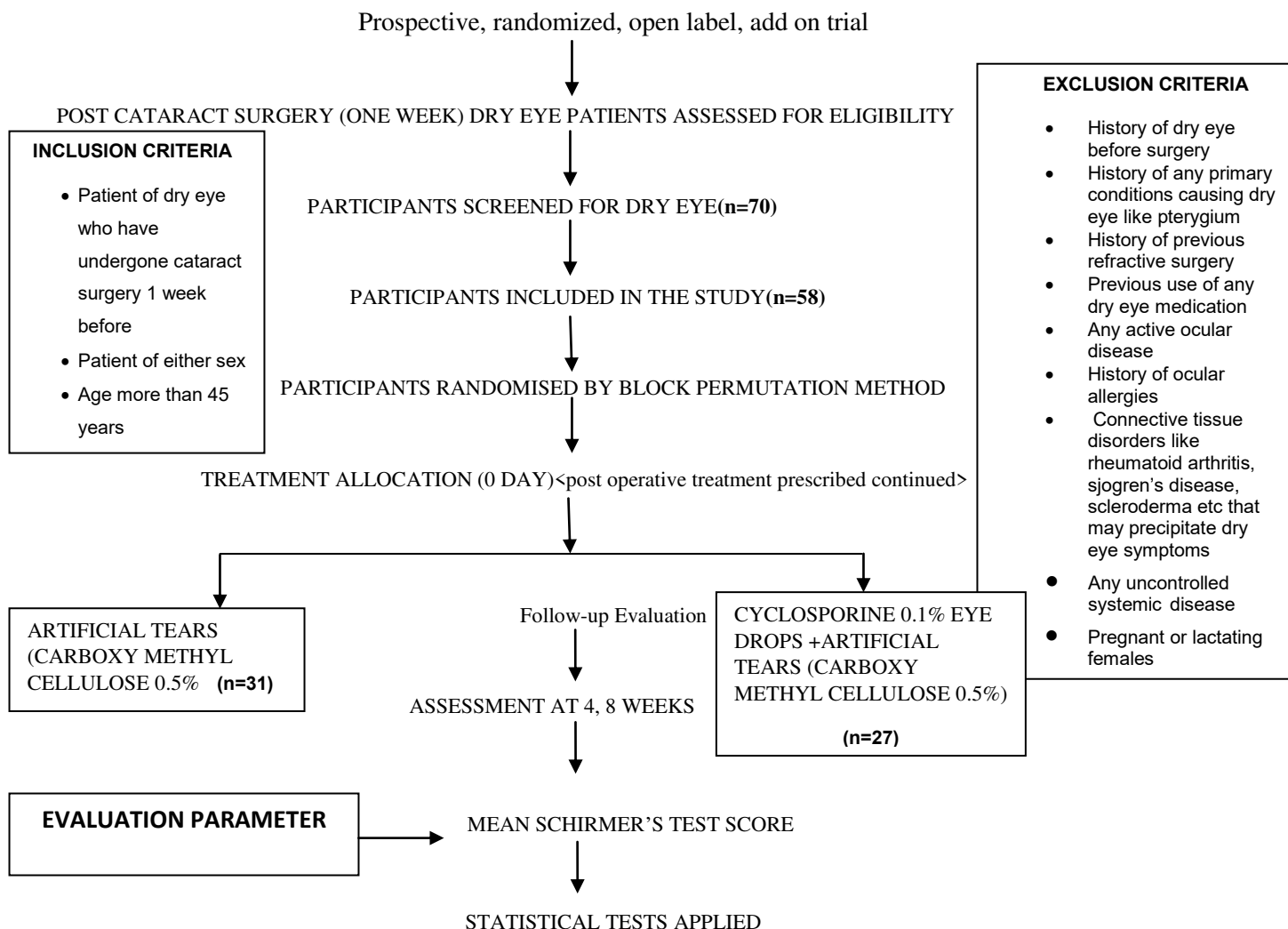
Schirmer's Test:

It uses paper strips inserted into the eye to measure the production of tears. Both eyes are tested at the same time. The eyes are closed for 5 minutes. The paper is then removed and the amount of moisture is measured. The use of the topical anesthetic ensures that only basal tear secretion is being measured. Interpretation indicate Normal (≥ 15 mm), Mildly dry (14-9 mm), Moderately dry(8-4 mm)and Severely dry eye(< 4 mm) wetting of the paper after 5 minutes.

Statistical analysis

The evaluation of patients in both the groups was done by the Schirmer's test & TBUT values and reported as the mean \pm S.D values. The change in the parameters from baseline was noted and assessed by the use of paired t test , while inter group comparison between two group was done by unpaired t-test. A p-value of < 0.05 was considered statistically significant. The evaluation was done on intention to treat basis.

RESULTS:



A total of 58 patients comprised of 31 patients in group A (Artificial tears 0.5%) and 27 in group B (Artificial tears 0.5% and Cyclosporine 0.1%) were evaluated. All the patients completed their follow up both in group A & group B. Demographic and baseline values in both groups were comparable and are shown in **table 1**.

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=31)	Artificial Tears 0.5% + Cyclosporine 0.1% (n=27)
Mean Age (mean ± S.D)	58.39 ± 11.18 years	61.19 ± 10.52 years
Male: Female	1.16:1	1.28:1
Rural: Urban	1.86:1	1.19:1
Literate: Illiterate	1:1.92	1.84:1
Mean Time Interval Between Date of Surgery & Date of Examination (mean ± S.D)	15.8 ± 6.23 days	15.9 ± 6.03 days
<u>Eye Involved (%)</u>		
Left (%)	14 (45.16)	13 (48.14)
Right (%)	14 (45.16)	6 (22.2)
Both (%)	3 (9.6)	8 (29.6)

EFFECT ON SCHIRMER’S TEST SCORE

Mean Schirmer’s test score in both groups showed increase from base line 4 and 8 weeks (p < 0.0001). Intergroup comparison revealed similar effect except at 8 weeks where group B had more improvement (p<0.0001). (Table 2)

Table 2: Comparative Effect of Artificial tears 0.5% Vs Artificial tears 0.5% + Cyclosporine 0.1% on Mean Schirmer’s Test Score

Duration	Artificial Tears 0.5% (mean ± S.D) n=31	Artificial Tears 0.5% + Cyclosporine 0.1% (mean ± S.D) n=27	t value	p value	Statistical Significance
Baseline	7.32 ± 1.15	7.31 ± 0.78	0.0416	0.967	NS
4 Weeks	10.64 ± 1.67####	11.31 ± 1.59####	1.6991	0.093	NS
8 Weeks	14.05 ± 2.09####	16.37 ± 1.80####	4.9603	<0.0001***	SS

The data is shown as Mean ± S.D showing Paired t test in comparison to respective baselines #p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001, NS not significant .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, NS not significant

EFFECT ON TBUT

Mean Tear film breakup time test (TBUT) score in both treatment groups increased significantly in comparison to baseline at 4 and 8 weeks (p < 0.0001). Difference between the mean values of the two groups was statistically significant at 4 wks (p<0.05) and at 8 weeks (p<0.0001). (Table 3)

Table 3: Comparative Effect of Artificial tears 0.5% Vs Artificial tears 0.5% + Cyclosporine 0.1% on Mean Tear Film Breakup Time Test Score

DURATION	Artificial Tears 0.5% (mean ± S.D) n=31	Artificial Tears 0.5% + Cyclosporine 0.1% (mean ± S.D) n=27	t value	p value	Statistical Significance
Baseline	7.4 ± 1.28	7.37 ± 0.83	0.1135	0.91	NS
4 Weeks	10.16 ± 1.40####	10.84 ± 0.95####	2.3227	0.023*	S
8 Weeks	13.10 ± 1.80####	14.31 ± 1.28####	3.1497	0.002**	SS

The data is shown as Mean ± S.D showing Paired t test in comparison to respective baselines #p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001, NS not significant .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, NS not significant

In both groups the biochemical profile in patients remained unaltered as Hemoglobin, blood sugar ,RFT, LFT did not show any significant change from baseline values

DISCUSSION

Cornea is innervated by the 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. 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.^[8] Corneal incisions release inflammatory mediators that may change the actions of corneal nerves, resulting in reduced corneal sensitivity and tear film instability. Cataract surgery is the most successful procedure for restoring visual acuity in the patients of cataract and current study was done to contribute towards the better treatment

protocol in these post-operative patients of moderate to severe dry eye. Aging is an established risk factor for dry eye as androgen deficiency associated with aging has been reported to be a contributing factor to dry eye^[9] and in the current study also the patient population taken was more than forty five years . All patients reporting to OPD with dry eye had history of cataract surgery of more than 2 weeks and this is in concurrence with Li XM et al, 2007; Kasetuwan M et al, 2013 demonstrated that dry eye appeared mostly one week after cataract surgery.^[1,10] The present study clearly demonstrates that Cyclosporine 0.1% in combination with 0.5 % artificial tears is more efficacious than artificial tears alone in the treatment of dry eye patients as suggested by both the objective parameters Schirmer’s test and Tearfilm Breakup Time (TBUT) scores respectively. There are number of studies that have shown beneficial effect of cyclosporine in dry eye.^[11,12] In current study

similar results were obtained on TBUT in cyclosporine with artificial tear treated group .

Hardten DR et al, 2007 similar to our study used cyclosporine 0.05% in conjunction with Carboxymethyl Cellulose and showed significant increase in Tear film Breakup time compared to artificial tears alone.^[13]

In agreement to our results, Demiryay E et al, 2011 demonstrated that the treatment of Cyclosporine 0.05% as an add-on with Artificial tears was superior to those being given only Artificial tears in increasing the TBUT & Schirmer's test values in dry eye patients.^[14]

Kang WK et al, 2014, Hamada S et al, 2016 have shown significant change in tearfilm parameters and Schirmer's test with Cyclosporine 0.05% compared to Carboxymethyl cellulose eye drops in dry eye patients following cataract surgery.^[15,16]

The results of the current study however, are contrary to results of Altiparmak UE 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.^[17]

Topical Cyclosporine A, is a well known immunomodulatory agent used in dry eye syndrome. It cause inhibition of cytokine production by the activated T lymphocytes, which are a feature of keratoconjunctivitis sicca.^[18] The cell mediated anti inflammatory responses are modulated through down regulation of IL-2 receptor expression & 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.

In the present study, no significant change was seen in the biochemical parameters in both groups. This is supported by the number of authors.^[3,7,12,15,19,20]

CONCLUSION-

Cyclosporine 0.1% + Artificial tears 0.5% and Artificial tears 0.5% topical therapy caused improvement in 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. Being a relatively short duration study with less number of parameters being studied, the results may vary in a larger population, which will be necessary in establishing the long term efficacy of Cyclosporine as an add on in dry eye patients.

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