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Comparison of topical cyclosporine alone and topical loteprednol with cyclosporine in moderate dry eye in Indian population: A prospective study

Shaveta Singla, Lopamudra Sarkar, Mukesh Joshi

Abstract:

PURPOSE: The purpose of this study is to compare the efficacy of topical cyclosporine (Cs) 0.05% alone and topical Cs 0.05% with loteprednol 0.5% in patients with moderate dry eye.

STUDY DESIGN: This was a comparative, prospective, interventional study.

PATIENTS AND METHODS: A total of 140 patients diagnosed with moderate dry eyes were randomly divided into two groups. Group A patients received treatment with topical loteprednol 0.5% started as QID dosage for 2 weeks and tapered to BID dosage over the next 6 weeks, topical Cs 0.05% BID and artificial tears. Group B patients received treatment with topical Cs 0.05% BID and artificial tears. All patients were followed over a period of 6 months with ocular surface disease index (OSDI) questionnaire, tear film break up time (TBUT), corneal fluorescein, and lissamine green staining scores.

RESULTS: There was a significant difference in the symptoms and signs of dry eye in the group receiving combination of loteprednol 0.5% and Cs 0.05% as compared to the group receiving Cs alone evident by greater reduction in OSDI score, corneal staining, and improvement in TBUT and Schirmer's test values over a follow-up of 6 months.

CONCLUSION: Combination therapy with topical loteprednol and Cs is significantly better than topical Cs alone on alleviating symptoms and signs in moderate dry eye patients.

Keywords:

Cyclosporine, loteprednol, moderate dry eye, ocular surface disease index score

Introduction

Dry eye is a multifactorial disease of the tear film and ocular surface that results in symptoms of discomfort, visual disturbance, tear film instability with potential damage to the ocular surface. It is associated with increased osmolarity of the tear film and ocular surface inflammation.[1] Hospital-based studies in population from Northern and Eastern India showed that the prevalence of dry eye varies between 18.4% and 40.8%.[2-5] Tear hyperosmolarity and tear film instability are central in the pathogenesis of dry eye.[6] Tear hyperosmolarity leads to increased inflammation and damage to the ocular surface.

Mild dry eye cases can be managed by tear supplementation, but artificial tears alone are not effective for moderate and severe dry eye cases as the basic pathology is not targeted.[7] Anti-inflammatory agents should be the first-line agent for dry eye as ocular surface inflammation is central to the pathogenesis of dry eye. A positive response with topical steroids in moderate and severe dry eye has been repeatedly shown by various studies. Topical steroids use leads to

Department of Ophthalmology, Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

Address for correspondence:
Dr. Mukesh Joshi, Room No 430, Eye Opd, 4th Floor, New Opd Building, Safdarjung Hospital, New Delhi - 110 029, India.
E-mail: drmukeshjoshi5@gmail.com

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subjective improvement as well as reduction in corneal fluorescein staining and expression of inflammatory markers.[8-12] Prolonged use of topical steroids, however, is limited by adverse effects such as cataract formation and raised intraocular pressure (IOP).

Topical cyclosporine (Cs) 0.05% is another anti-inflammatory agent that reduces ocular surface inflammation and improves tear film dynamics.[13,14] Cs is a calcineurin inhibitor that reduces inflammation by specifically inhibiting T-cell activity, a mechanism very different from steroids. Systemic side effects after topical administration are minimal due to lack of absorption into systemic circulation.[15] Treatment with Cs, however, takes a longer time for symptoms to resolve, leading to reduced compliance. Topical steroids can be used during this lag time to ensure compliance.[14] Topical Cs has been repeatedly studied as a treatment modality for dry eye. Currently, topical Cs is available in 0.05%–2% concentration. In these concentrations, the local and systemic side effects are minimal as compared to steroids.[16] Previous studies on Cs have shown beneficial effect in dry eye due to contact lens wear, after refractive surgery, and after cataract surgery.[17-19]

Role of topical steroids in dry eye has also been extensively studied from time to time. Low potency steroids such as loteprednol reduce ocular surface inflammation and improve symptoms of the moderate-to-severe dry eye without causing significant IOP elevation as compared to high potency steroids such as prednisolone or dexamethasone.[20,21] Tear film osmolarity and levels of inflammatory cytokines are seen to reduce after initiating treatment with topical loteprednol.[22] However, the long-term use of loteprednol is limited by side effects like raised IOP and cataract formation although not so much as potent corticosteroids.

Topical steroids treatment in dry eye secondary to Sjogren's syndrome or hematopoietic stem cell transplantation shows faster symptomatic improvement and may be as effective as Cs.[23,24] Adverse effects of steroids particularly after prolonged treatment and with potent agents such as prednisolone have always been a concern. Short-term use of methylprednisolone in combination with Cs is documented to show better improvement in symptoms in a small study group.[25] The current study was undertaken to evaluate whether combination therapy of loteprednol in tapering dosage and Cs is better in alleviating signs and symptoms of moderate dry eye when compared to Cs monotherapy. Since both drugs have a different mechanism of action, the combination could be more effective than monotherapy by either.

Patients and Methods

This was a comparative, prospective, interventional study that was conducted over a period of 18 months (IRB No. IEC/VMMC/SJH/Thesis/October-2014/396). One-hundred-and-forty patients with moderate dry eye disease satisfying the study criteria were randomly divided into two groups of 70 each. Both the groups had comparable baseline parameters, and there was no statistically significant difference between the two groups in terms of ocular surface disease index questionnaire (OSDI) scores, tear film break up time (TBUT) values, Schirmer's test values, corneal fluorescein staining scores, and lissamine green conjunctival staining scores [Tables 1-3]. Randomization was done by using table of random numbers. Group A patients received treatment with topical loteprednol 0.5%, topical Cs 0.05%, and artificial tears. Group B patients received treatment with topical Cs 0.05% and artificial tears. Topical loteprednol 0.5% was given for 8 weeks, started as QID for the first 2 weeks and tapered to BID dosage for 3rd to 8th week, and topical Cs 0.05% was given in BID dosage for 3 months in both

Table 1: Baseline characteristics of the study groups

Variable	Eye	Group A	Group B	*P*
OSDI	Right eye	22.85±3.73	22.76±3.57	0.774
	Left eye	23.03±3.44	22.55±3.68	0.383
TBUT	Right eye	6.26±1.06	6.34±1.11	0.754
	Left eye	6.16±1.07	6.35±1.14	0.425
Schirmer's test	Left eye	6.48±1.5	6.59±1.38	0.593
	Right eye	6.49±1.47	6.42±1.29	0.960
Corneal fluorescein staining	Left eye	5.98±1.72	5.66±1.73	0.248
	Right eye	6.03±1.78	5.83±1.49	0.352
Lissamine green staining	Left eye	2.34±1.8	2.51±1.71	0.478
	Right eye	2.39±1.73	2.46±1.8	0.934

OSDI=Ocular surface disease index, TBUT=Tear film break up time

Table 2: Age distribution of study subjects

Age (years)	Group A (%)	Group B (%)	Total (%)
≤30	6 (8.57)	8 (11.43)	14 (10.00)
31-40	23 (32.86)	19 (27.14)	42 (30.00)
41-50	19 (27.14)	20 (28.57)	39 (27.86)
51-60	18 (25.71)	17 (24.29)	35 (25.00)
≥60	4 (5.71)	6 (8.57)	10 (7.14)
Total	70 (100.00)	70 (100.00)	140 (100.00)

Both the groups were compared according to age distribution and as *P*>0.05 (*P*=0.891, using Chi-square test), the difference in age distribution was not statistically significant

Table 3: Sex distribution of study subjects

Sex	Group A (%)	Group B (%)	Total (%)
Female	45 (64.29)	45 (64.29)	90 (64.29)
Male	25 (35.71)	25 (35.71)	50 (35.71)
Total	70 (100.00)	70 (100.00)	140 (100.00)

Both the groups were compared according to sex distribution, and as *P*>0.05 (*P*=1, using Chi-square test), the difference in sex distribution was not statistically significant

the groups. All patients were provided with a patient information sheet and written informed consents were taken before commencing the study. Approval of the Institute's Ethics Committee was obtained before starting the study. Patients diagnosed as cases of moderate dry eye disease (according to Dry Eye Workshop, 2007 classification) were enrolled for the study [Table 4].

Patients above 18 year of age diagnosed with moderate dry eye and who were not wearing contact lenses for at least 1 month before the study and agree not to wear the same during the study period were included in the study. Patients with a history of Steven–Johnson syndrome or ocular pemphigoid, those having punctual plugs or cautery or any intraocular surgery in the past 3 months, pregnant or lactating women or those on oral contraceptive pills, patients on anti-glaucoma medications, those with unstable diabetes mellitus and patients allergic to study medications were excluded from the study. Patients having a history of topical steroid or Cs within 1 month were also excluded from the study. Patients who could not complete 6 months of follow-up were also excluded from the study.

Ophthalmological evaluation

Pretreatment assessment

Meticulous history was taken and patients were evaluated for symptoms such as foreign body sensation, grittiness, irritation, burning sensation, itching, redness, photophobia, blurred vision, discomfort, and fatigue. OSDI questionnaire was used for grading the severity of dry eye. This questionnaire consists of 12 questions and is graded on a scale from 0 to 100. OSDI score of 16–30 was included for the diagnosis of moderate dry eye disease. A thorough examination of the anterior and posterior segment was done. Tear film was examined for evaluation of meniscus height or presence of any tear film debris.

Investigations – included as follows:

1. TBUT test: 1 mg fluorescein strip was moistened and placed in the lateral one-third of the lower lid in anaesthetized eye and patient was asked to blink only once or twice to avoid pooling of fluorescein, following which the strip was removed. Using the cobalt blue light of the slit lamp, the time lapse between the last blink and the appearance of the first randomly distributed dark spot in the fluorescein-stained tear film was the tear break up time. A value of 5–10 s was included in our study
2. Schirmer's test: Schirmer's test was done in both eyes simultaneously with the help of Whatman no. 41 paper strip (5 by 35 mm) without anesthesia, with strip kept at junction of medial two-third and lateral one-third of lower lid for 5 min. A value of 5–10 mm was included in our study
3. Corneal fluorescein staining inspection, National Eye Institute (NEI) scale: Corneal fluorescein stain grading is based on a scale of 0–3 (0 = normal, 1 = mild, 2 = moderate, and 3 = severe staining) in five areas of cornea: central, superior, inferior, nasal, and temporal quadrant. The maximum possible score is 15. Score of 1–8 was used for the diagnosis of moderate dry eye disease
4. Lissamine green staining inspection, NEI scale: Conjunctival staining was recorded for three areas each of temporal and nasal conjunctiva of each eye and graded 0–3 as above for each zone with a maximum score of 18. Score 1–7 was included in our study.

Table 4: Grading of the severity of dry eye disease

	Mild	Moderate	Severe	Very severe
OSDI score (0-100)	12-15	16-30	31-45	>45
Corneal fluorescein staining score (NEI Scale) (0-15)	0-3	4-8	9-14	14-15
Conjunctival staining score (NEI Scale)	0-3	1-7	8-14	15-18
Schirmer's test (mm/5 min)	<10-15	<10	<5	<2
Tear film break up time (s)	8-15	<10	<5	Immediate

OSDI=Ocular surface disease index, NEI=National Eye Institute

Posttreatment assessment

All patients were followed at 2 weeks, 6 weeks, 3 and 6 months. Compliance to treatment regimen was ensured at each follow-up visit by history taking and by looking at number of vials of medicine consumed.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± standard deviation and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, non parametric test was used. Quantitative variables were compared using Unpaired *t*-test/Mann–Whitney test (when the data sets were not normally distributed) between the two groups and Wilcoxon ranked sum test (as the data was nonparametric) between pre and post. Qualitative variables were correlated using Chi-square test/Fisher's exact test. $P < 0.05$ was considered statistically significant. The data were entered into Microsoft Excel (Microsoft Corp., Seattle, WA, USA) spreadsheet, and analysis was done using Statistical Package for Social Sciences version 21.0 Inc., Chicago, IL, USA.

Results

This was a comparative, interventional study to compare the effect of topical Cs 0.05% alone versus

topical loteprednol 0.5% and topical Cs 0.05% in the treatment of moderate dry eye disease. This study was conducted over a period of 18 months. A total of 140 patients diagnosed as cases of moderate dry eye disease (according to Dry Eye Workshop, 2007 classification) were enrolled for the study. They were randomly divided into two groups of 70 each. Group A patients received treatment with topical loteprednol 0.5%, topical Cs 0.05% and artificial tears. Group B patients received treatment with topical Cs 0.05% and artificial tears. Mean age in group A was 44.4 years, with age ranging from 25 to 68 years. Mean age in Group B was 44.64 years, with age ranging from 23 to 69 years.

OSDI score reduced in both the groups; however, there was no significant difference in the OSDI score between two groups at 6 weeks. There was, however, a significant difference in the OSDI score at the end of 3 and 6 months with group A showing better resolution of symptoms $P = 0.002$ and $P < 0.0001$ at 3 months and 6 months, respectively [Table 5]. TBUT improvement was seen in both groups at 2 weeks and onwards. Improvement in TBUT values was more in Group A but was statistically significant only after 3 months [Table 6]. Fluorescein and lissamine staining of the ocular surface reduced significantly in both groups, and the reduction was more in Group A , which was statistically significant at 3 and 6 months of follow-up [Tables 7 and 8]. Shirmer's test values were significantly better in the Group A starting from 6 weeks of follow-up and persisting till 6 months [Table 9].

There was no significant rise of intraocular pressure in any of the patients receiving topical loteprednol over observation of 6 months.

Discussion

Our study results showed that combination therapy with topical loteprednol and topical Cs drops had a better outcome than topical Cs drops alone in patients with moderate dry eye disease. OSDI score, corneal staining score with fluorescein, and conjunctival staining score with lissamine green all showed a significantly greater reduction in the group receiving both topical Cs and topical loteprednol than those receiving topical Cs alone at 3 and 6 months of follow-up. Schirmer's test values were significantly better in Group A at 6 weeks, 3 and 6 months. TBUT score was significantly better in group A at 3 and 6 months. Most common side effect reported by the study subjects was a stinging sensation in eye and hyperemia. These side effects were less in the group receiving combined treatment as compared to those receiving Cs alone resulting in a better adherence to treatment. Although loteprednol drops were tapered and stopped at 8 weeks, improvement in OSDI score, Schirmer's, TBUT, and staining scores continued in the combined treatment group. This could be due to lesser side effects experienced by these patients and therefore better compliance to treatment. Sheppard *et al*. reported the similar results with the use of loteprednol drops before use of topical Cs in the treatment of chronic dry eye.[26] Our study further confirms the results of the previous study.

Table 5: Ocular surface disease index score changes over a period of 6 months

OSDI score at visit	Group A	Group B	*P*
0	22.91±3.52	22.69±3.59	0.574
1 (2 weeks)	20.16±4.16	21.2±3.53	0.170
2 (6 weeks)	17.95±3.07	18.46±3.67	0.370
3 (3 months)	13.56±3.47	15.44±3.57	0.002
4 (6 months)	8.91±3.27	11.8±3.3	<0.0001

OSDI=Ocular surface disease index

Table 6: Tear film break up time score changes over the period of 6 months

TBUT score/visit	Group A	Group B	*P*
0	6.23±1.01	6.34±1.09	0.653
1 (2 weeks)	6.71±1.02	6.68±1.05	0.781
2 (6 weeks)	7.69±1.01	7.45±1.11	0.171
3 (3 months)	8.86±1.01	8.31±1.03	0.001
4 (6 months)	10.55±1.14	9.54±1.21	<0.0001

TBUT=Tear film break up time

Table 7: Corneal fluorescein staining scores changes over the period of 6 months

Fluorescein staining score/visit	Group A	Group B	*P*
0	6±1.7	5.76±1.58	0.355
1 (2 weeks)	5.23±1.52	5.06±1.57	0.439
2 (6 weeks)	3.99±1.3	4.14±1.52	0.663
3 (3 months)	2.56±1.29	3.21±1.44	0.010
4 (6 months)	1.31±1.03	2.34±1.18	<0.0001

Table 8: Lissamine green staining scores change over the period of 6 months

Lissamine green staining score/visit	Group A	Group B	*P*
0	2.37±1.72	2.49±1.7	0.833
1 (2 weeks)	2.12±1.51	2.41±1.62	0.307
2 (6 weeks)	1.48±1.19	1.88±1.33	0.083
3 (3 months)	0.96±0.98	1.41±1.18	0.028
4 (6 months)	0.54±0.7	1.04±0.95	0.001

Table 9: Schirmer's value changes over the period of 6 months

Schirmer's/visits	Group A	Group B	*P*
0	6.48±1.45	6.5±1.29	0.739
1 (2 weeks)	7.51±1.58	6.76±1.36	0.008
2 (6 weeks)	8.86±1.65	7.42±1.32	<0.0001
3 (3 months)	10.64±1.81	8.09±1.32	<0.0001
4 (6 months)	12.91±1.82	8.99±1.46	<0.0001

Inflammation plays a key role in the pathophysiology of dry eye apart from tear film hyperosmolarity. Increased cytokine production, activation of T-cells, and matrix metalloproteinase lead to apoptosis of cells on the ocular surface. Cs is an immunosuppressive drug that inhibits T cell activation by inhibiting calcineurin thereby decreasing inflammation. Efficacy and safety of topical Cs in moderate-to-severe dry eye disease has been demonstrated by multiple studies.[16] Steroids reduce inflammation by reducing the production of arachidonic acid derivatives, prostaglandins, and leukotrienes. Since the anti-inflammatory mechanisms of Cs and steroids are different, their combination can be better than either of them. Addition of a mild steroid, like loteprednol, can suppress inflammation as well as reduce the side effects of Cs drops such as stinging and ocular redness.

Our study recommends to start treatment with a combination of low-dose topical steroid such as loteprednol and topical Cs along with topical tear substitutes in patients with moderate dry eye and taper the steroid over a period of 6–8 weeks while continuing topical Cs. This treatment regimen results in better resolution of symptoms of dry eye and minimal side effects of Cs thus ensuring better compliance. Further studies need to be done with a longer follow-up period as the follow-up period in our study was limited to 6 months.

Conclusion

Combination therapy with topical loteprednol and cyclosporine is significantly better than cyclosporine alone in alleviating signs and symptoms of moderate dry eye.

Clearance for commencing the study was taken from the Ethical Committee of Vardhaman Mahavir Medical College and Safdarjung hospital. All patients provided written informed consent before enrolling in the study and were provided with a patient information sheet.

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Nil.

Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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