

ORIGINAL ARTICLE**To compare the effectiveness of carboxymethyl cellulose 0.5% eye drops alone with the combination of 0.5% carboxymethylcellulose eye drops with 0.1% tacrolimus ointment, used twice daily, for the treatment of severe dry eyes**¹Gaurav Bahuguna, ²Amrita Chauhan¹Assistant Professor, Department of Pharmacology, Major S D Singh Medical College & Hospital, Farrukhabad, Uttar Pradesh, India;²Assistant Professor, Department of Ophthalmology, Major S D Singh Medical College & Hospital, Farrukhabad, Uttar Pradesh, India**ABSTRACT:****Aim:** To compare the effectiveness of carboxymethyl cellulose 0.5% eye drops alone with the combination of 0.5% carboxymethylcellulose eye drops with 0.1% tacrolimus ointment, used twice daily, for the treatment of severe dry eyes.**Material and Methods:** In this study, 30 patients i.e 60 eyes were included in each group presenting with severe dry eye in eye OPD. Group 1 where patients used carboxy methyl cellulose 0.5% eye drops four times a day for treatment of severe dry eye. Group 2 in which patients used 0.5% carboxy methyl cellulose eye drops four times daily along with 0.1% tacrolimus ophthalmic ointment twice daily in treatment of severe dry eyes. All patients were evaluated on day 0, 2 weeks, 1 month, 3 month and 6 months for relief in ocular symptoms and diagnostic dry eye test were done. **Results:** The mean age in group I was 41.36 ± 7.58 years and in group II was 39.2 ± 5.28 years. Mean net score in group 1=14.58 Mean net score in group 2=17.62. Net score in group 2 is more than group 1. The difference in net score of 60 eyes from each group was found to be statistically significant $p < 0.05$. **Conclusion:** The present study demonstrates a statistically significant disparity in the response of patients treated with a combination of tacrolimus 0.1% ointment and CMC 0.5% drops, compared to those treated with 0.5% CMC eye drops alone, in terms of improvement in tear film profile tests and ocular symptoms.**Keywords:** Carboxymethyl cellulose, Tacrolimus ointment, Dry eyes**Corresponding author:** Amrita Chauhan, Assistant Professor, Department of Ophthalmology, Major S D Singh Medical College & Hospital, Farrukhabad, Uttar Pradesh, India**This article may be cited as:** Bahuguna G, Chauhan A. To compare the effectiveness of carboxymethyl cellulose 0.5% eye drops alone with the combination of 0.5% carboxymethylcellulose eye drops with 0.1% tacrolimus ointment, used twice daily, for the treatment of severe dry eyes. J Adv Med Dent Scie Res 2016;4(6):493-496.**INTRODUCTION**

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface[1]. Dry eye is one of the most common causes of ocular morbidity in patients presenting to an ophthalmology outpatient department. Approximately one out of seven individuals aged 65–84 years report symptoms of dry eye often or all of the time[2]. Management of dry eye depends on the cause and severity of the condition. Various strategies have been described for medical management of dry eye; these include, the topical use of lubricants (artificial tear substitutes), topical corticosteroids and anti-inflammatory therapies, cyclosporine ophthalmic emulsion, tacrolimus ointment and the systemic use of antioxidants (e.g., omega-3 fatty acids)[1,2]. Artificial tears are aqueous solutions containing polymers that determine their viscosity, retention time, and adhesion to the ocular surface. Various polymers currently in use include cellulose derivatives (e.g., hydroxypropyl methylcellulose [HPMC], “carboxymethylcellulose

[CMC]), polyvinyl derivatives (e.g., polyvinyl alcohol), chondroitin sulfate, and sodium hyaluronate. In mild-to-moderate cases, they are the mainstay of treatment. Artificial tears act by replenishing the deficient aqueous layer of the tear film and diluting the inflammatory cytokines[2,3]. A novel treatment therapy for severe dry eye cases with potent anti-inflammatory effects as well as sufficient safety is needed. Tacrolimus(FK 506) is a macrolactam derivative with immuno modulatory and anti-inflammatory activity[4]. Produced by the fungus *Streptomyces tsukubaensis*, it suppresses T cell activation and IL-2 production by binding to an immunophilin and inhibiting the enzymatic activity of calcineurin[4,5]. Extensive testing has shown systemic absorption of tacrolimus to be below quantifiable levels with no evidence of cancer risk or significant local side effects and only occasional reports of transient burning or pruritus at the application site[6]. Topical tacrolimus ointment is commercially available in two strengths 0.03% and 0.1%[7]. Topical tacrolimus 0.03% skin ointment has been used effectively for inflammatory conditions of the anterior segment[8-11]. The good safety profile of 0.1% tacrolimus ophthalmic suspension based on the

low blood concentration of tacrolimus, coupled with demonstrated better efficacy, make it an important tool for treating severe dry eye cases. Therefore we chose 0.1% tacrolimus ointment in this study. Side effects noted in use of tacrolimus ointment are burning sensation, activation of herpes simplex dendritic keratitis and development of molluscum contagiosum [12,13]. These are lack of studies regarding this topic in this area so we did this study to see efficacy of 0.1% tacrolimus ointment in treatment of severe dry eye cases.

MATERIAL AND METHODS

In this study, 30 patients i.e 60 eyes were included in each group presenting with severe dry eye in eye OPD. Patients were randomly divided in two groups. Patients with severe dry eye willing to participate in the study and follow up were included in the study. Patients with trachoma, Patients with infectious diseases of eye, Patients with hypersensitivity to tacrolimus, Patients who had less than 6 months follow up, Systemic administration of immunosuppressants within 2 weeks prior to study, pregnant or lactating females and patients with any cardiac, renal or hepatic disease or diabetes were excluded from the study.

METHODOLOGY

Study was approved by ethical committee of the institute. A valid written consent was taken from

patients after explaining study to them. Detailed history was taken. Appropriate laboratory work up was done. Group 1 where patients used carboxy methyl cellulose 0.5% eye drops four times a day for treatment of severe dry eye. Group 2 in which patients used 0.5% carboxy methyl cellulose eye drops four times daily along with .1% tacrolimus ophthalmic ointment twice daily in treatment of severe dry eyes. All patients were evaluated on day 0, 2 weeks, 1 month, 3 month and 6 months for relief in ocular symptoms and diagnostic dry eye test were done. Diagnostic dry eye test included SCH—Schirmer's test, TBUT—tear breakup time, FLU—fluorescein stain, Rose Bengal staining and marginal tear strip test. Each ocular symptom (ocular discomfort, foreign body sensation, itching, dryness, photophobia, lacrimation) and dry eye test were scored from 0 to 3 depending on severity and combined score of all symptoms and test was calculated on each follow up visit for each eye individually of each patient in both groups. Net score was calculated as difference between total score (of all symptoms and test) on day 0 and total score at 6 month follow up. Net score actually gives improvement score after use of drug for 6 months in both groups. Net score is then compared in both groups to find the comparative efficacy of drugs in both groups. Net score in both groups was compared using unpaired t test.

RESULTS

Table 1: Distribution of cases as per age and sex

Parameters	Group I	Group II
Total cases	30	30
Age (Mean±SD)	41.36 ± 7.58	39.2 ± 5.28
Gender (M:F)	17:13	15:15

The mean age in group I was 41.36 ± 7.58 years and in group II was 39.2 ± 5.28 years. Two groups were comparable with regards to age and sex in distribution of patients.

Table 2- Distribution as per symptoms

Symptoms	Total number
Ocular discomfort	58
Dryness Tearing	59
FB sensation	60
Itching Photophobia	47
Ocular discomfort	49
Dryness Tearing	51

Table 3: Parameters in both the groups on day 0

Parameters	Group I Mean score	Group II Mean score
Marginal tear strip test	1.69	1.49
SCH	1.70	2.12
TUBT	1.62	1.68
FLU	1.72	1.58
Rose Bengal staining	1.81	1.89
Ocular discomfort	2.14	2.13
Foreign body sensation	2.15	1.74
dryness	2.36	2.13

Itching	1.58	1.74
Photophobia	1.43	1.58
Tearing	1.92	1.61

SCH—Schirmer's test, TBUT—tear breakup time, FLU—fluorescein stain

Table 4: Different parameters in group I and group II after 6months

Parameters	Group I Mean score	Group II Mean score
Marginal tear strip test	0.68	0.11
SCH	0.49	0.28
TUBT	0.13	0.25
FLU	0.38	0.08
Rose Bengal staining	0.39	0.30
Ocular discomfort	0.91	0.28
Foreign body sensation	0.68	0.32
dryness	0.69	0.39
Itching	0.17	0.10
Photophobia	0.24	0.11
Tearing	0.78	0.41

Table 5: Comparison of score parameters between group 1 and group 2 of each ocular symptom and dry eye test between day 0 and 6 month

Parameters	Group 1 (Mean Change Score)	Group 2(Mean Change Score)
Marginal tear strip test	1.01	1.38
Schirmer test	1.21	2.4
TBUT	1.49	1.43
FLU	1.34	1.5
Rose Bengal staining	1.42	1.59
Ocular discomfort	1.23	1.85
Foreign body sensation	1.47	1.42
Dryness	1.67	1.74
Itching	1.41	1.64
Photophobia	1.19	1.47
Tearing	1.14	1.2

Net score-difference between total score of each ocular symptom and dry eye test between day zero and 6 month. Mean net score in group 1=14.58 Mean net score in group 2=17.62

Net score in group 2 is more than group 1. The difference in net score of 60 eyes from each group was found to be statistically significant $p < 0.05$ (unpaired t-test)

DISCUSSION

Dry eye is a common complaint among middle-aged and older adults and its prevalence increases progressively with age [14-16]. Studies from India reported that the prevalence varies between 18.4% and 63% [17-19]. This was a comparative study conducted on 60 severe dry eye cases presenting to eye OPD. The mean age in group I was 41.36 ± 7.58 years and in group II was 39.2 ± 5.28 years respectively. Similar study was concluded by Brjesky VV et al [20] In the present study the male to female ratio was 1.14:1 with 32 males and 28 females. Majority of patients reported dramatic symptomatic relief during treatment period. Patients showed improvement in terms of decrease in score values at different follow ups. All patients had relief in foreign body sensation, discomfort, tearing, photophobia, dryness and itching. At the end of study i.e. at 6 months, eyes having score 03 for different symptoms were 0 in both groups, those with moderate score 02 for different

symptoms were more in group 1 as compared to group 2 and greater percentage of eyes from group 2 had score 0 for different ocular symptoms. In the present study ocular discomfort, dryness, tearing was seen in almost all cases. While in a study by Liu XM et al [21] most frequent ocular surface symptom in confirmed cases of dry eye was itching. In another study by Lee AJ et al conducted in Indonesia burning sensation was the most common symptom [14]. In this study use of topical tacrolimus 0.1% ointment and CMC 0.5% in group II showed significant improvement in all the parameters specially TBUT and SCH which was in accordance to other studies like Brjesky VV et al [20] and Moscovici BK et al [22] and Aoki S et al [23]. 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. Moscovici et al [22] showed significant decrease in sandy or gritty feeling, dryness, itching and blurred vision in patients treated with

tacrolimus.03%.A study by Marco E S et al[23]showed improvement in signs and symptoms of dry eye diseases in patients treated with tacrolimus.03%.In our study results show better relief in all ocular symptoms in group 2.Therefore our study is in accordance with study of Moscoviki et al[22] and Marco E S et al[23].

Tacrolimus has immunomodulatory role so it effectively improves tear secretion in immune origin dry eye patients.Mean net score in group 2 was more than group 1 indicating more improvement in group 2.Difference in net score in both groups was found to be statistically significant. A recent publication by Steven P et al[25] also mentions the immunomodulatory role of 0.3% tacrolimus in treatment severe dry eye cases.In our study, only two patients from group 2 showed burning sensation after use of tacrolimus ointment but burning sensation subsided gradually and no patient discontinued the drug use which was consistent with study by Rustin et al[6]

CONCLUSION

The present study demonstrates a statistically significant disparity in the response of patients treated with a combination of tacrolimus 0.1% ointment and CMC 0.5% drops, compared to those treated with 0.5% CMC eye drops alone, in terms of improvement in tear film profile tests and ocular symptoms. Furthermore, it reinforces the evidence that the combination of topical tacrolimus 0.1% used twice daily together with CMC 0.5% does not cause any negative side effects.

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