Original Research Article

To Compare efficacy of carboxymethyl cellulose .5% eye drops versus use of 0.5% carboxymethylcellulose eye drop with combination of 0.1% tacrolimus ointment twice daily for treatment of severe dry eyes

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Abstract

Background: Dry eye disease is a common disorder provoking changes in tear film and ocular surface. Untreated dry eye could cause ocular infections, corneal ulcer and blindness. Only a few drugs are authorized so far for the treatment of severe dry eye disease and the possibilities of evolution in this sector are immense.**Objectives:** Compare efficacy of carboxy methyl cellulose .5% eye drops versus use of 0.5% carboxy methylcellulose eye drop with combination of 0.1% tacrolimus ointment twice daily for treatment of severe dry eyes.**Material and Methods:** 40 patient presenting with severe dry eye were selected randomly. They were divided into 2 groups. Group I received CMC.5% eye drops four times a day and group II received of 0.1%tacrolimus ointment two times daily and .5% CMC eye drops 4times a day. All patients were evaluated on day 0, 2 weeks, 1 month, 3 month and 6 month for relief in ocular symptoms and diagnostic dry eye tests.**Results:**The mean age in group I was 40.72 ± 6.85 years and in group II was 39.2 ± 5.28 years. Ocular discomfort, dryness and tearing were seen in all the cases. Comparison of different parameters after six months of treatment between group I and II showed that the comparision of net score in two groups is statistically significant($p < 0.05$). **Conclusion**: There was statistically significant difference between the outcome of two groups.Group 2 patients who used combination of of 0.1%tacrolimus ointment two times daily along with CMC 0.5% eye drops 4 times a day were better relieved as compared to patients in group 1 who used 0.5% CMC eye drops four times daily for treatment of severe dry eyes

Keywords: Carboxymethylcellulose, Tacrolimus, Dry eye

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 strenghts 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 is 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.

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Material and Methods

A comparative prospective study was carried out at Saraswathi Institute Of Medical Sciences Anwarpur(Hapur).Patients were enrolled from February 2019 to September 2019. 20 patients i.e 40 eyes were included in each group presenting with severe dry eye in eye OPD.Patients were randomly divided in two groups Inclusion criteria: 1. Patients with severe dry eye willing to participate in the study and followup

Exclusion criteria

Patients with trachoma 2.Patients with infectious diseases of eye 3.Patients with hypersensitivity to tacrolimus 4. Patients who had less than 6 months follow up 5.Systemic administration of immuno supressants within 2 weeks prior to study.6.pregnant or lactating females7.patients with any cardiac,renal or hepatic disease or diabetes.This study was conducted in compliance with the Declaration of Helsinki.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 .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 month 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 compaired using unpaired t test .

Results

Table 1: Distribution of cases as per age and sex

Parameters	Group I	Group II
Total cases	20	20
Age (Mean±SD)	40.72 ± 6.85	39.2 ± 5.28
Gender (M:F)	11:9	10:10

The mean age in group I was 40.72 ± 6.85 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

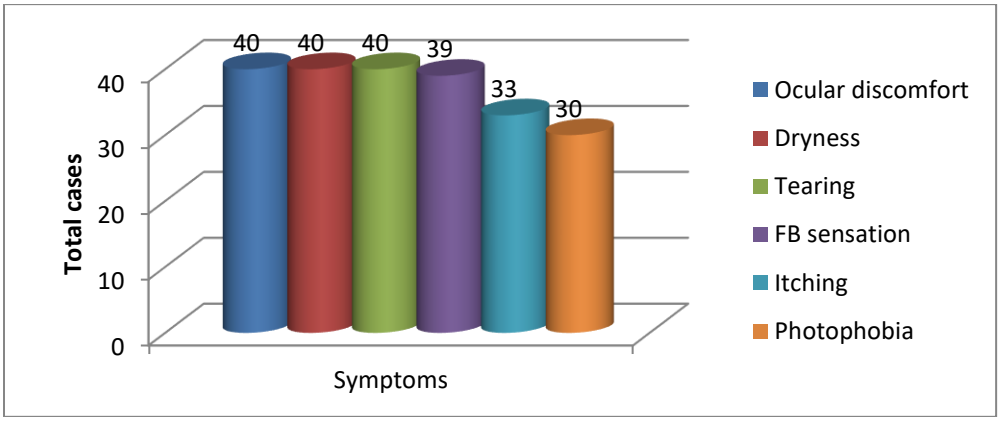

Fig 1: Distribution as per symptoms;Ocular discomfort, dryness and tearing was seen in all the cases.

Table 2: Parameters in both the groups on day 0

Parameters	Group I Mean score	Group II Mean score
Marginal tear strip test	1.75	1.55
SCH	1.72	2.0
TUBT	1.67	1.7
FLU	1.67	1.65
Rose Bengal staining	1.72	1.92
Ocular discomfort	2.20	2.02
Foreign body sensation	2.0	1.87
dryness	2.25	2.02
Itching	1.40	1.80
Photophobia	1.35	1.62
Tearing	1.87	1.65

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

Table 3: Different parameters in group I and group II after 6months

Parameters	Group I Mean score	Group II Mean score
Marginal tear strip test	0.72	0.15
SCH	0.55	0.30
TUBT	0.25	0.27
FLU	0.40	0.05
Rose Bengal staining	0.42	0.25
Ocular discomfort	0.65	0.32
Foreign body sensation	0.65	0.37
dryness	0.72	0.42
Itching	0.20	0.07
Photophobia	0.35	0.15
Tearing	0.85	0.40

Table 4: Comparision 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	1.03	1.40
Schirmer test	1.17	1.70
TBUT	1.42	1.43
FLU	1.27	1.60
Rose Bengal staining	1.30	1.67
Ocular discmfort	1.55	1.70
Foreign body sensation	1.35	1.50
Dryness	1.53	1.60
Itching	1.20	1.10
Photophobia	1.00	1.45
Tearing	1.02	1.25

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=13.75
Mean net score in group 2=16.45
Net score in group 2 is more than group 1
The difference in net score of 40 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 40 severe dry eye cases presenting to eye OPD. The mean age in group I was 40.72 ± 6.85years and group II was 39 ± 5.28 years respectively. Similar study was concluded by Moawad P et al[20] In the present study the male to female ratio was 1:1 with 21 (52.5%) males and 19 (47.5%) 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 group2 had score 0 for different ocular symptoms ·In the present study ocular discomfort, dryness, tearing was seen in all cases. While in a study by Kamalakshy J 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 tacrolimus0.1% 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 Moawad P et al[20] and MoscoviciBK 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.Moscoviki 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 Ashena Z 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

Present study concludes that there is statistically significant difference in response(in terms of improvement in tear film profile tests and ocular symptoms) in patients treated with combination of tacrolimus 0.1% ointment and CMC 0.5% drops as compared to patients treated with .5% CMC eye drops only.. It also strengthens the fact that topical tacrolimus0.1% twice daily plus CMC 0.5% has no adverse effect .

References

1. The Epidemiology of dry eye disease:Report of the Epidemiology Subcommittee of the International Dry Eye WorkShop.Ocul Surf. 2007; 5:93-107.
2. Schein OD, Muñoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. Am J Ophthalmol. 1997;124:723–8.

3. Moshirfar M, Pierson K, Hanamaikai K, Santiago-Caban L, Muthappan V, Passi SF et al. Artificial tears potpourri: A literature review. ClinOphthalmol. 2014;8:1419–33.
4. Rallis E, Korfitis C, Gregoriou S, Rigopoulos D. Assigning new roles to topical tacrolimus. Expert Opinion on Investigational Drugs. 2007; 16:1267-76.
5. Hessen M, Akpek EK.Dry Eye: an Inflammatory Ocular Disease, J Ophthalmic Vis Res. 2014; 9(2):240-250.
6. Rustin MH. The safety of tacrolimus ointment for the treatment of atopic dermatitis:a review. British Journal of Dermatology. 2007; 157:861-73.
7. Ngan.Tacrolimus.http://dermnetnz.org/treatments/ tacrolimus.html. Created 2004.
8. Attas-Fox L, Barkana Y, Iskhakov V et al. Topical tacrolimus 0.03% ointment for intractable allergic conjunctivitis: an open-label pilot study. Current Eye Research. 2008; 33:545-9.
9. Dhaliwal JS, Mason BF, Kaufman SC, Dhaliwal JS, Mason BF, Kaufman SC. Long-term use of topical tacrolimus (FK 506) in high-risk penetrating keratoplasty. Cornea. 2008; 27:488-93.
10. Joseph MA, Kaufman HE, Insler M, Joseph MA, Kaufman HE, Insler M. Topical tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. Cornea. 2005;24:417–20.
11. Kymionis GD, Goldman D, Ide T et al. Tacrolimus ointment 0.03% in the eye for treatment of giant papillary conjunctivitis. Cornea. 2008;27:228–9.
12. ZribiH, Descamps V, Hoang-Xuan T, Crickx B, Doan S. Dramatic improvement of atopic keratoconjunctivitis after topical treatment with tacrolimus ointment restricted to the eyelids. J EurAcad DermatolVenereol. 2009; 23(4):489–490.
13. Joseph MA, Kaufman HE, Insler M. Topical tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. Cornea. 2005; 24(4):417–4
14. Sahai A, Malik P. Dry Eye: Prevalence and attributable risk factors in a hospitalbased population. Ind J Ophthalmol. 2005; 53: 87-91.
15. Shah S, Badhu BP, Lavaju P, Chaudhary S, Sinha AK. Efficacy of topical carboxymethyl cellulose 0.5% and cyclosporine A 0.05% in dry eye syndrome.Cogent Medicine.2017; 4:1321869.
16. Behera S, Sahoo S, Hota G et al. Clinical profile of dry eye disease at a tertiary care centre in western Odisha. J. Evid. Based Med. Healthc. 2017; 4(72):4274-4277.
17. Lee AJ, Lee J, Saw SM et al. Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. The British Journal of Ophthalmology. 2002;86(12): 1347-1351.
18. Lee JH, Ahn HS, Kim EK, Kim T. Efficacy of sodium hyaluronate and carboxymethylcellulose in treating mild to moderate dry eye disease. Cornea. 2011;30(2):175-9
19. Solomon,Dursum D,Liu Z,Xie Y,Macri A, Pflugfelder SC. Pro and anti inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry eye disease.Invest Ophthalmol Vis Sci. 2001;42:2283-92
20. Moawad P,Shamma R,Hassanein D,Ragab G.Evaluation of the effect of topical tacrolimus 0.03% versus cyclosporine 0.05% in the treatment of dry eye secondary to Sjogren syndromeEur J Ophthalmol. 2021;1120672121992680.
21. Kamalakshy J, Nandini K, Vijayamma N, Rajesh PS. Proportion of dry eye disease and its clinical profile in patients presenting with ocular surface symptoms to the ophthalmology OPD of a tertiary care centre in South India over a period of one year.Indian Journal of Clinical and Experimental Ophthalmology. 2016;2(4):345-349.
22. Moscovici BK, Holzchuh R, Chiacchio BB, Santo RM, Shimazaki J, Hida RY. Clinical treatment of dry eye using 0.03% tacrolimus eye drops. Cornea. 2012; 31:945-949
23. Aoki S,Mizote H,Suzuki M,Mishima HK.Systemic FK506 improved tear secretion in dry eye associated with chronic graft versus host disease Br J Ophthalmol. 2005;89(2):243-4.
24. Marco ES,Udaondo P,Delpech SG. Treatment of refractory dry eye associated with graft versus host disease with 0.03% tacrolimus eyedropsJOculPharmacolTher. 2013;29(8):776-83.
25. Ashena Z,Dashputra R,Nanavaty M.Autoimmune Dry Eye without Significant Ocular Surface Co-Morbidities and Mental Health.Vision (Basel). 2020; 4(4):43

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