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Original Research Article

Single Blind, Prospective, Comparative Assessment of the Efficacy of Chloroquine Phosphate 0.03% and Sodium Carboxymethyl Cellulose 1% in Dry Eye

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Abstract

Aim: To compare the efficacy of chloroquine phosphate 0.03% (CQP) eye drops with sodium carboxymethyl cellulose 1% (CMC) eye drops in the management of DED.

Material & Method: A single blind, prospective, comparative study was done in Department of Ophthalmology, Patna Medical College & Hospital, Patna, Bihar, India for the duration of 1 year. 100 patients of either gender, between the age of 30 to 70 years diagnosed with DED were included.

Results: In all follow-up visits, the mean TBUT recorded in group 1 was better than that recorded in group 2 (p0.001). Group 1 demonstrated statistically significant improvement in the quality of the Marginal Tear Strip (MTS), indicating a delayed initiation of CMC action. In group 2 , the FS improved significantly from pre-treatment value to 4 weeks and from 8 weeks to 12 weeks ($p=0.003$, $p<0.001$) indicating an early and sustained improvement in FS in group 2.

Conclusion: On ocular surface staining tests and Schirmer's test, both CQP and CMC were found to be similarly effective in treating DED. However, CQP had a faster onset of action.

Keywords: sodium carboxymethyl cellulose, chloroquine phosphate, dry eye

Introduction

Dry eye syndrome (DES) is “a disorder of the tear film attributable to tear deficiency or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort." [1] Recent studies have revealed that inflammatory component as the main causative factor of the disorder. Cytokine and receptor mediated inflammatory cascade disintegrates the tear film layer by affecting the lacrimal gland acini and ducts and [2] disturbs ocular surface homeostasis. Apoptosis has also [3] been implicated in the pathogenesis of dry eyes.

Symptoms of dry eye vary among patients, and most commonly they include itching, grittiness, burning, sensitivity to bright light, foreign-body sensation, irritation, pain, blurred vision, and contact lens intolerance. In severe cases, dry eye disease can also lead to permanent visual

impairment. Clinical signs of dry eye also vary among patients depending on the specific cause of the disease and include decreased tear film stability as measured by tear break-up time (TBUT). Patients with severe DES may lose the ability to tear in response to neural stimulation, and are prone to sight-threatening corneal infection and ulceration.[4]

Patients usually present to the ophthalmologist with complaints of foreign body sensation, ocular dryness, ocular grittiness, hyperemia, ocular irritation, burning, itching, photophobia and fluctuation or blurring of vision associated with redness of eyelids and conjunctiva. Ocular examination may reveal stringy mucus and particulate matter in the tear film. Ocular surface becomes lusterless. There is conjunctival xerosis or Bitot's spots in the conjunctiva and filamentary keratitis may be present.[5]

Current therapies for the management of dry eye include drugs for tear supplementation, retention, and stimulation;[6] anti- inflammatory agents; and environmental strategies. Palliative therapies like tear substitutes are currently the most common choice of treatment but have failed to yield high success rates because they give only symptomatic improvement but do not treat underlying cause of disease. The major anti-inflammatory agents currently in use include topical corticosteroids and immunomodulatory agents.[7,8]

Carboxy Methyl Cellulose (CMC) ocular drops are one of the widely used Artificial Tears for DES. It is an ocular lubricant, contributing to an alleviation of subjected symptoms seen in mild to moderate DES. The properties of CMC include viscoelasticity which contributes to lubrication of eye surface and decrease the evaporation of tear film. It may also increase humectation of corneal surface. This increases the stability of tear film which, in turn, protects the eye surface against environmental aggressions (exposure to wind, dust, sun etc.)[9]

Chloroquine is a well-known anti-inflammatory drug used in the treatment of rheumatoid arthritis,[10-12] discoid lupus erythematosus,[13] and amoebic hepatitis, [14] Yavuz et al. conducted a study to evaluate effects of systemic hydroxychloroquine on dry eye disease associated with primary Sjogren syndrome and concluded that there is a significant relief on symptoms of DED.[15]

Thus, this study aims to compare the efficacy of chloroquine phosphate 0.03% (CQP) eye drops with sodium carboxymethyl cellulose 1% (CMC) eye drops in the management of DED.

Material & Method:

A single blind, prospective, comparative study was done in Department of Ophthalmology, Patna Medical College & Hospital, Patna, Bihar, India for the duration of 1 year. 100 patients diagnosed with DED, ranging in age from 30 to 70 years. The Declaration of Helsinki's tenets were followed.

Inclusion and exclusion criteria

Patients diagnosed with DED, ranging in age from 30 to 70 years were included. Patients with systemic or local ocular disorders known to produce dry eyes or ocular surface abnormalities, as well as those who had already undergone ocular procedures, were excluded. Patients with dry eyes or ocular surface problems who were taking local or systemic drugs were also excluded from the research.

Grouping

Participants were placed into two groups of 70 patients each at random. Patients in Group 1 received CMC 1 percent 4 times a day for 12 weeks, while patients in Group 2 received CQP 0.03 percent 2 times a day for 12 weeks.

Methodology

After informed and written consent, a detailed history of ocular complaints was taken as per the questionnaire in Table 1. [16]

Table 1: Depicting a questionnaire on DED

Sr. No.	A questionnaire of ocular symptoms pertaining to dry eye:
1	Do your eyes ever feel dry?
2	Do you ever feel a gritty or sandy sensation in your eyes?
3	Do your eyes ever have a burning sensation?
4	Do your eyes ever feel sticky?
5	Do your eyes ever feel watery?
6	Are your eyes ever red?
7	Do you notice crust or discharge on your lashes?
8	Do you find it difficult to open your eyes in the morning?

Answers to these questions were recorded as rarely (at least once in 3–4 months), sometimes (once in 2–4 weeks), often (at least once a week) or all the time. Presence of one or more symptoms often or all the time were taken as positive.

After a brief general and systemic examination, a detailed ocular examination was performed, which included recording visual acuity with Snellen's chart, evaluating the condition of the lids, Meibomian glands, conjunctival surface, and corneal surface, and evaluating the condition of the lids, Meibomian glands, conjunctival surface, and corneal surface. A thorough examination of the anterior and posterior segments was carried out. The DED profile includes TBUT, marginal tear strip evaluation, Schirmer's 1 test, and fluorescein, Rose Bengal, and Lissamine green staining of ocular surfaces. The cornea and conjunctiva stains were graded using the Van Bijsterveld grading system. Patients with no symptoms but positive clinical evidence or tests were also diagnosed with dry eye.

Follow up was done after every 4 weeks for 12 weeks by evaluating symptoms, signs, testing and scoring in both the groups. Grading was assessed by Khurana's grading system

(Tables 2 and 3).

Table 2: Showing scoring system for Khurana's grading system for dry eye

Tear function test	Score0	Score1	Score 2	Score 3
TBUT (in sec)	>10	6.1-10	3.1-6	0-3
Marginal tear strip	Intact	Scanty	Markedly diminished or discontinuous	Absent
Fluorescein staining	No staining	Fine punctate	Coarse punctate	Diffuse
Schirmer's 1 test (in mm /5min)	>10	5-10	3-4	0-2
Rose Bengal staining score	0-3	4-5	6-7	8-9
Lissamine green staining score	0-3	4-5	6-7	8-9

Table 3: Showing grading of dry eye as per Khurana's grading system of DED

Total score	Severity of dry eye
0-1	No Dry eye
2	Dry eye suspect
3-8	Mild dry eye
9-13	Moderate dry eye
14-18	Severe dry eye

Statistical analysis

The results were entered into Microsoft Excel sheet and then in SPSS software for statistical analysis. Qualitative data were analysed using Chi square test and quantitative data with student t test. Degree of improvement of parameters on subsequent follow up visits was assessed using repeated ANOVA. Degree of improvement between the two groups was compared using Two Way ANOVA test. Marginal Homogeneity test was used to measure change in severity of parameters.

Results:

In terms of age and gender distribution, the two groups were comparable. The majority of patients were between the ages of 61 and 70, demonstrating that DED is an old age condition.

Figure 1 & 2: In all follow-up visits, the mean TBUT recorded in group 1 was better than that recorded in group 2 (p0.001). The difference in TBUT values between the two groups after 12 weeks of treatment from pre-treatment levels was statistically significant (p0.001), indicating that both medications have a significant effect on TBUT. The rate of improvement was likewise similar in the two groups (p=0.209), meaning that the time taken by both medicines to restore the TBUT to normal levels is about identical.

Figures 3 & 4: Between 8 and 12 weeks (p0.001), Group 1 demonstrated statistically significant improvement in the quality of the Marginal Tear Strip (MTS), indicating a delayed initiation of CMC action. Group 2 on the other hand, demonstrated a significant improvement in MTS quality for the first 8 weeks before plateauing, indicating early commencement of action and rapid attainment of maximum respite with CQP (p=0.015 at the first visit, p=0.040at the second visit, and p=0.887 at the third visit). The maximum improvement with CMC was higher than with CQP (p=0.001 at 12 weeks).

Figure 5 & 6: The severity of fluorescein staining (FS) of ocular surface did not change significantly from pre-treatment levels to 8 weeks (p=0.118, p=0.637) in group 1, whereas it improved significantly from 8 weeks to 12 weeks with p = 0.006; thus, suggesting delayed improvement in group 1. In group 2 , the FS improved significantly from pretreatment value to 4 weeks and from 8 weeks to 12 weeks (p=0.003, p<0.001) indicating an early and sustained improvement in FS in group 2.

On rose bengal staining (RBS) score, there was no statistically significant difference between the two groups (p=0.443, p=0.792 at 4 and 8 weeks, and p=0.581 at 12 weeks). As a result, it can be stated that the degree of improvement in this DED parameter is comparable for both medicines. As a result, the medications had the same efficacy in improving RBS score.

In both groups, the difference in Schirmer's test values from pre-treatment levels to those attained after 12 weeks of treatment was statistically significant (p0.001). When the rates of improvement of the mean Schirmer's test value in both groups were compared, however, a statistically significant difference was found. (p=0.119). As a result, although both medications are equally beneficial in

terms of the Schirmer's score at the end of the trial (p=0.228 at 12 weeks), it can be reasonably inferred that the rate of improvement of this DED parameter is greater in group 2 patients treated with CQP.

The severity of DED was graded into mild, moderate and severe according to the Khurana's grading system and was compared at each follow up. In both the groups, the improvement in severity of DED was significant from pre-treatment to 12 weeks post treatment (p<0.001). The observed p value at 4 weeks was 0.058 indicating no significant difference between the two groups whereas a significant difference was observed at 8 weeks and 12 weeks (p=0.005, p=0.007). Therefore, both the drugs reduce severity of the disease with CQP having faster onset of action.

Figure 1: Linear trend of improvement of all parameters in group 1

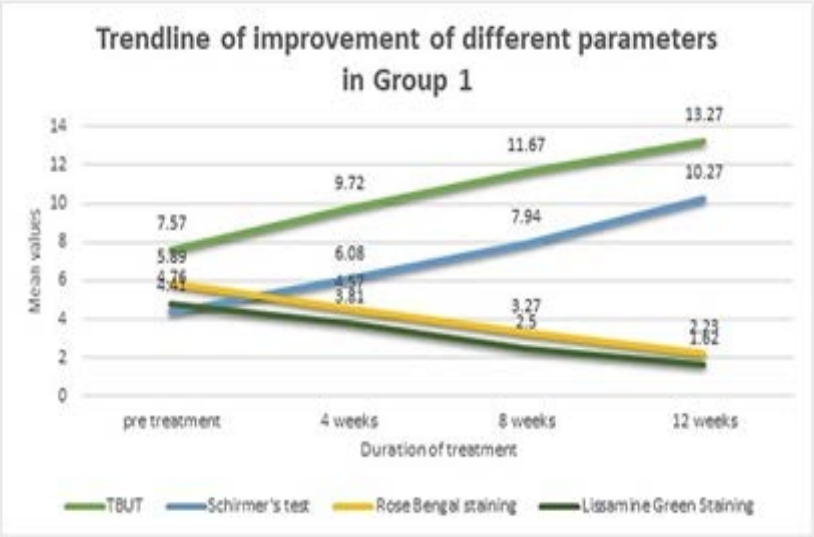


Figure 2: Trend lines of improvement of different parameters in group 2

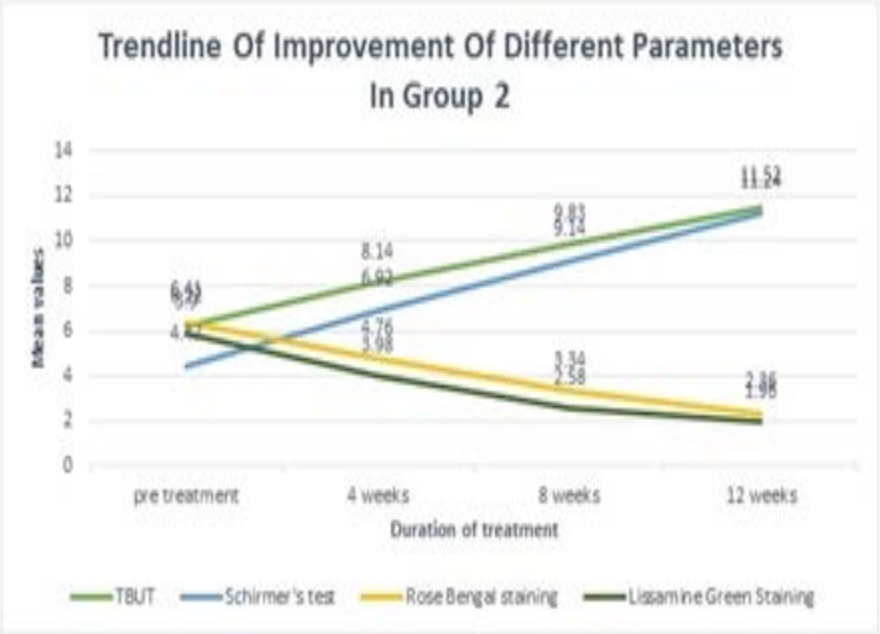


Figure 3: Distribution of marginal tear strip in group1

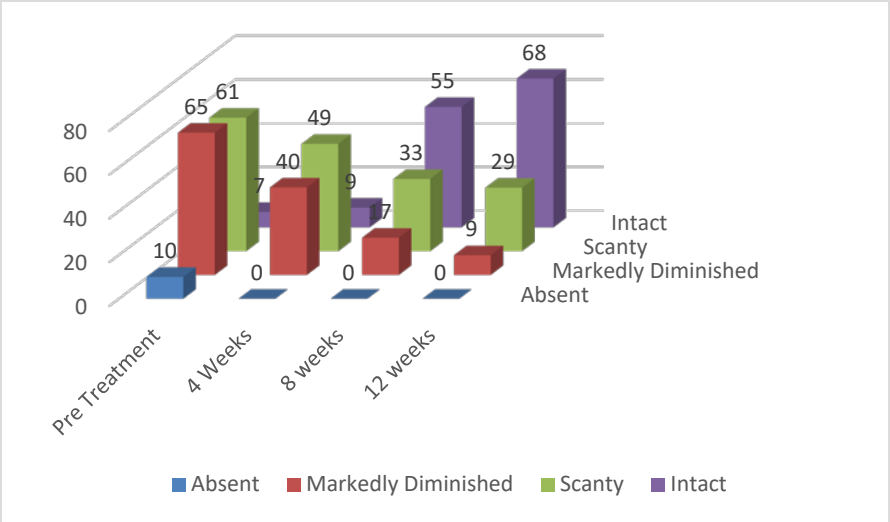


Figure 4: Marginal tear strip in group 2

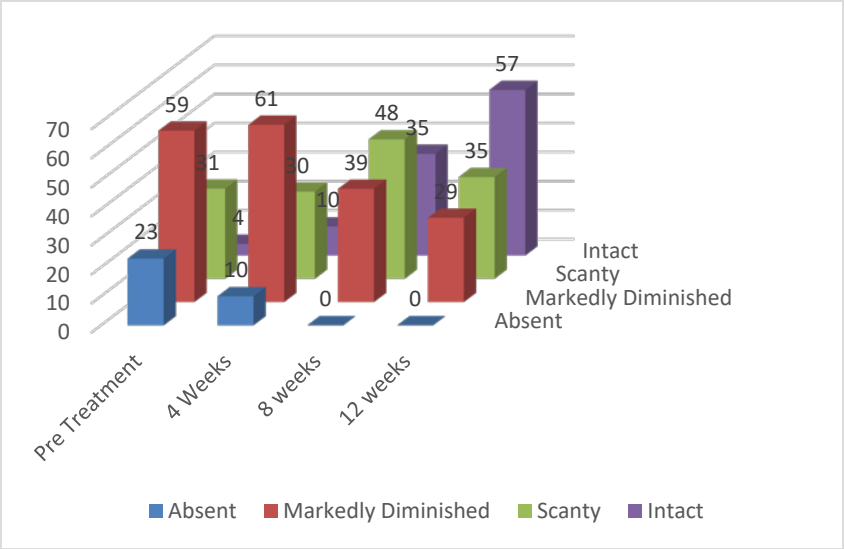


Figure 5: Fluoroscein staining patterns in DED in group 1

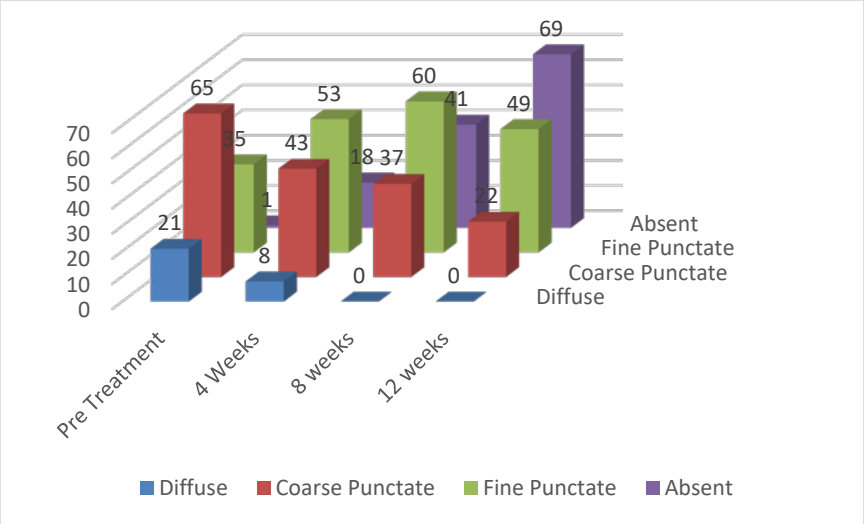
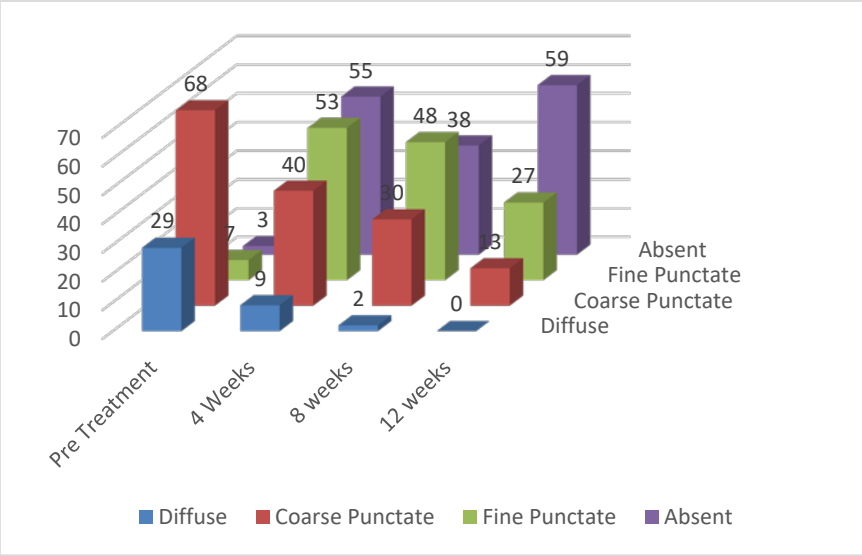


Figure 6: Showing fluoroscein staining pattern in group 2



Discussion:

Ageing and post menopause known to be associated with DED. In a study conducted by Kinoshita et al., on a total of 308 patients with dry eye, the mean age was 55.2 years.[17, 18]

Many of the clinical trials have already proved the superiority of CMC over Sodium hyaluronate.[19] When a viscous, anionic charged Carboxy Methyl Cellulose (CMC, 100,000 mw) solution was compared with a neutral Hydroxyl Methyl Cellulose (HPMC) solution, CMC was shown to have a significantly slower rate of clearance from the eye.[20]

Chloroquine Phosphate group showed early improvement than CMC group. However, overall improvement in tear film at the end of 12 weeks was similar in both groups. In a similar study conducted by Bhavsar et al.,[17] significant changes in Schirmer's test value were reported and it was concluded that both drugs are efficacious but CQP is more efficacious than CMC. These findings are not consistent with our study.[21]

Kaercher et al. conducted a multicenter, non interventional, observational, open-label study. The purpose was to evaluate the efficacy and tolerability of a dry eye product containing Sodium CMC (0.5%) and glycerol (pure glycerin) (0.9%), in patients with KCS. Disease severity, tear break-up time (TBUT), tolerability, and change in clinical symptoms were recorded at baseline and at final visit (2 to 4 weeks after first treatment) on 5277 patients. 85.4% of the total patients reported improvement in local comfort where as 75.1% of patients felt an improvement in symptoms after changing their treatment. The study concluded the eye drops with Sodium CMC 0.5% with Glycerol 0.9 % was well tolerated and improved DES. [22]

A statistically significant reduction in Lissamine green staining score as early as 4 weeks in both the groups was seen which was continuous over the period of 12 weeks as compared to their pretreatment levels. Statistically significant better response was seen in group-2 (CQP) as compared to group-1 (CMC).

Conclusion:

On ocular surface staining tests and Schirmer's test, both CQP and CMC were found to be similarly effective in treating DED. However, CQP had a faster onset of action. Differences in findings can be attributed to different mechanisms of action of CMC and CQP. CMC acts as an

eye lubricant with little effect on pathophysiology of DED. CQP is postulated to act as an anti-inflammatory and also has an anti-apoptotic effect on ocular surface epithelial cells. This might be the reason behind early improvement in ocular surface staining scores in the CQP group.

References:

1. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J 1995;21:221–32.
2. Narayana S, Miller WL, Mc Dermott AM. Conjunctival cytokine expression in symptomatic moderate dry eye subjects. Invest Ophthlmol Vis Sci 2006;47:2445-50.
3. Gao J, Schwalb TA, Addeo JV, et al. The role of apoptosis in the pathogenesis of canine keratoconjunctivitissicca: the effect of topical cyclosporine A therapy. Cornea 1998;17:654–63.
4. Nichols KK. Et al., Patient-reported symptoms in dry eye disease. Ocular Surface. 2006; 4:137–145.
5. Mishra B. Prevalence of Dry Eye and Its Association with Various Risk Factors in Rural Setup of Western Uttar Pradesh in a Tertiary Care Hospital. Open J Prev Med. 2016;6(10):4236.
6. Pflugfelder SC. Antiinflammatory therapy for dry eye. Am J Ophthalmol 2004;137:337-42.
7. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 2006;25:900-7.
8. Pflugfelder SC. Antiinflammatory therapy for dry eye. Am J Ophthalmol 2004;137:337-42.
9. AQUASURGETM Eye Drops, Full prescribing information, BAUSCH+ LOMB.
10. Titus EO. Recent developments in the understanding of the pharmacokinetics and mechanism of action of chloroquine. Ther Drug Monit. 1989;11(4):369–79.
11. Augustijns P, Geusens P, Verbeke N. Chloroquine levels in blood during chronic treatment of patients with rheumatoid arthritis. Eur J ClinPharmacol. 1992;42(4):429–33.
12. Augustijns P, Verbeke N. Stereoselective Pharmacokinetic Properties of Chloroquine and De-Ethyl-Chloroquine in Humans. Clin Pharmacokinetics. 1993;24(3):259–69.
13. Meinão IM, Sato E, Andrade L, Ferraz MB, Atra E. Controlled trial with chloroquinediphosphate in systemic lupus erythematosus. Lupus. 1996;5(3):237–41.
14. Abdi AY, Gustafsson LL, Ericsson O, Hellgren U. Drug recommendations. In: Abdi AY, Gustafsson LL, Ericsson O, Hellgren U, editors. Handbook of drugs for tropical parasitic infections. London: Taylor & Francis Ltd; 1995. p. 5 – 6.
15. Yavuz S, Asfuroglu˘ E, Bicakcigil M, Toker E. Hydroxychloroquine improves dry eye symptoms of patients with primary Sjogren's syndrome. Rheumatol Int. 2011;31(8):1045–9.
16. Parag Tyagi1, Vandana Sharma 1,*, J P Chugh1, R S Chauhan1, Ashok Rathi. A comparative study of efficacy of chloroquine phosphate 0.03% and sodium carboxymethylcellulose 1% in dry eye. Indian Journal of Clinical and Experimental Ophthalmology 2021;7(2):302–307
17. Dorennavar L, Maurya RP, Singh VP, Singh MK, Sharma K, Sharma R. The role of Rebamipide ophthalmic suspension in management of dry eye disease. Indian J ClinExpOphthalmol. 2015;1(4):191–6. doi:10.5958/2395-1451.2015.00025.6.
18. Kinoshita S, Awamura S, Oshiden K, Nakamichi N, Suzuki H,

Yokoi N, et al. Rebamipide (OPC-12759) in the Treatment of Dry Eye: A Randomized, Double-Masked, Multicenter, PlaceboControlled Phase II Study. Ophthalmology. 2012;119(12):2471–8.

19. Baudouin et al., Randomized, phase III study comparing osmoprotectiveCarboxymethyl cellulose with sodium hyaluronate in dry eye disease. Eur J Ophthalmol. 2012; 22(5):751-61
20. Management and Therapy of Dry Eye Disease: Report of the Management and Therapy Subcommittee of the International Dry Eye Work Shop (2007)
21. Hernández, P. C., Pinedo, C. M., Rodríguez, R. P., Higuera, E. J., Peláez, D. S., Camuñas, Ángel F., & Fernández, J. M. (2021). Coloduodenal fistula in right colorectal cancer: Case report and review of the literature. Journal of Medical Research and Health Sciences, 4(1), 1135–1138. https://doi.org/10.15520/jmrhs.v4i1.303
22. Bhavsar AS, Bhavsar SG, Jain SM. Evaluation of the effects of chloroquine phosphate eye drops in patients with dry eye syndrome. Int J Biomed Adv Res. 2011;2(6):198–214. doi:10.7439/ijbar.v2i6.34.