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A Single Blinded, Prospective Trial to Compare the Efficacy of Rebamipide 2% And Sodium Carboxymethyl Cellulose 1% in Patients of Dry Eye Disease

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Abstract		Original Research Article

Dry eye is a multifactorial disease of the tears, due to tear deficiency or excessive evaporation. Recently, Rebamipide has been introduced in the market for the treatment of dry eye disease. It is an amino acid derivative of 2- (1H) - quinolone. Only a few studies are available pertaining to its efficacy on dry eye disease. The study was conducted to compare the efficacy of Rebamipide 2% and sodium carboxymethyl cellulose 1% in patients with dry eye disease. It was a single blinded, prospective, comparative study of 100 patients randomly divided into two groups of 50 patients each. Group-1 was given sodium carboxymethyl cellulose 1% and Group-2 was given rebamipide 2% as the treatment modality of choice, 4 times a day for 12 weeks. The efficacy and side effects of both the drugs were evaluated and compared in both the groups individually. Tests like Schirmer's test, tear film break up time (TBUT) and tear film staining were employed to compare the efficacy of these drugs between the groups. There was a significant improvement in mean Schirmer's test (p<0.001) and mean tear film break up time (TBUT) (p=0.008) and a significant reduction in staining scores in REB group as compared to CMC group. The REB group gave better results at the end of 12 weeks in improvement of multiple evaluating criteria as compared to CMC group i.e.1.82± 2.21 vs. 1.10 ± 1.92 respectively and the difference was statistically significant (p=0.015). It was concluded that treatment with rebamipide and carboxymethyl cellulose lead to a generalized improvement in all the objective signs for assessment of dry eye disease. Both the drugs decreased the severity of dry eye disease. Also, the efficacy of rebamipide has been found to be better than carboxymethyl cellulose.
Keywords: Dry eye disease, Carboxymethylcellulose, Rebamipide.

INTRODUCTION

Dry eye is a multi-factorial 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. It occurs either due to tear deficiency or excessive evaporation which causes damage to the inter-palpebral ocular surface. Ocular surface comprises the entire epithelial surface of the cornea, limbus and conjunctiva [1].

The symptoms of dry eye are foreign body sensation, ocular dryness, ocular grittiness, hyperemia, ocular irritation, burning, itching, photophobia, fluctuating or blurring of vision associated with redness of eyelids and conjunctiva. Signs include stringy mucus, particulate matter in the tear film, lusterless ocular surface, conjunctival xerosis, Bitot's spots and filamentary keratitis [2].

The diagnosis of dry eye disease (DED) is made by combining information obtained from the proper clinical history, physical examination and performing diagnostic tests. In addition to the clinical history, use of a validated symptom questionnaire is helpful. A number of questionnaires are available for evaluation of various aspects of DED symptomatology, including severity, effect on daily activities, and quality of life. Physical examination includes visual acuity measurement, external examination, and slit-lamp biomicroscopy. Poor correlation between clinical signs and patient`s symptoms would require the use of multiple tests. Various tests for diagnosing dry eye, as per DEWS II report, are Tear film break up time (TBUT), Rose Bengal staining, Schirmer's Test, lissamine green staining, Tear pH, Marginal Tear Strip

Test, tear film osmolarity, tear lactoferrin, Tear lysozyme, ocular ferning and conjunctival impression cytology [3-9].

Though dry eyes cannot be cured, there are a number of steps that can be taken to treat dry eyes which may include artificial tear drops and ointments, temporary punctal occlusion, non-dissolving punctual plugs and punctal occlusion by cautery, lipiflow and other medications and nutrition. Many drugs have been used for the treatment of dry eye disease, but artificial tears like sodium carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose and sodium hyaluronate are the most common ones. Recently, rebamipide 2% eye drops (REB), an amino acid derivative of 2- (1H)-quinolone, have been introduced in the market for the treatment of dry eye disease [10-13].

As prevalence of dry eye disease is increasing progressively worldwide, this study has been conducted in our institute to compare the efficacy of rebamipide 2% and sodium carboxymethyl Cellulose 1% in Patients with dry eye disease.

MATERIALS AND METHODS
The present study was conducted in Regional Institute of Ophthalmology, Pt. B.D. Sharma PGIMS, Rohtak, India. It was a single blinded, prospective, comparative study including 100 patients of dry eyes diagnosed by questionnaire and ocular examination (Precorneal tear film, TBUT, Marginal tear strip test, Schirmer's test, Rose Bengal staining and Lissamine green stain). These 100 patients were randomly divided into two groups using computer generated randomization table, each consisting of 50 patients. Group-1 was given Sodium carboxymethyl cellulose 1% and Group-2 was given Rebamipide 2% as the treatment modality 4 times a day for 12 weeks. The efficacy and side effects of both the drugs were evaluated and compared in both the groups individually. Hundred consecutive individuals of either gender, between the ages of 30 to 70 years, diagnosed to have dry eyes were included.

We have studied both the right and left eyes in all the patients. As the severity of dry eye was similar in both right and left eyes, therefore right eye observations were taken into consideration for the statistical analysis in our study. Ethical clearance was taken from institutional ethical committee.

Exclusion criteria
Patients with systemic or local ocular diseases known to cause dry eyes or ocular surface abnormalities, patients with history of chronic contact lens wear and history of ocular surgeries in the past were excluded. Also patients on local or systemic medications known to cause dry eyes or ocular surface disorders were excluded from the study. After taking written informed consent, detailed history including

patient's particulars, nature of presenting complaints and associated conditions were recorded.

Questionnaire
A questionnaire of ocular symptoms pertaining to dry eye was used. It included the following questions [14,15].
- Do your eyes ever feel dry?
- Do you ever feel a gritty or sandy sensation in your eyes?
- Do your eyes ever have a burning sensation?
- Do your eyes ever feel sticky?
- Do your eyes ever feel watery?
- Are your eyes ever red?
- Do you notice crust or discharge on your lashes?
- 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. Presences of one or more symptoms often or all the time were taken as positive.

Examination
A brief general and systemic examination was carried out. Ocular examination included recording visual acuity with Snellen's chart. Condition of lids, meibomian glands, conjunctival surface and corneal surface were noted. Detailed anterior segment examination was done under slit lamp. Detailed Posterior segment evaluation was done using direct and indirect ophthalmoscopic examination. For comparison purpose right eye of both the groups was taken for analysis.

Tear film evaluation was done in the following order
Pre-corneal tear film
It was observed for presence of debris (mucous/oil droplets/debris).

Tear film break up time (TBUT)[3]
No anesthesia was used. A dry fluorescein strip touched to the inferior fornix with the patient looking up. The cornea was scanned on slit lamp under low magnification using cobalt blue filter light. The patient was instructed to blink once or twice and then stare straight ahead without blinking. The time period for appearance of the first dry spot (small black spots within the blue-green field) since the last blink will be calculated as TBUT. Values <10 seconds was taken as abnormal (Photograph 1).

Marginal Tear Strip Test [4]
Patient was allowed normal blinking and after 2-3 minutes, marginal tear strip, stainedwith fluorescein was observed under diffuse cobalt blue light of slit lamp and was graded asintact, scanty, markedly diminished or absent. Fluorescein staining of the cornea was noted for patterns such as fine punctate, coarse punctate or

diffuses. (Photograph 2). Fluorescein staining was also done to grade the severity of dry eye [16].

Rose Bengal Stain and Lissamine Green Stain [5, 6, 17]

A moistened strip of Rose Bengal dye, without anesthesia was applied in the inferior cul-de-sac. Van Bijsterveld scoring system was used to grade the staining of cornea and conjunctiva on a scale of 0-3 in 3 areas: nasal conjunctiva, temporal conjunctiva, and cornea. Score of 0 was for absent staining, 1 for just present, 2 for moderate and 3 for gross staining [18]. With this system, the maximum possible score was 9 and a score of more than 3 was considered positive for keratoconjunctivitis sicca. Lissamine Green staining was performed in a similar manner 30 minutes after Rose Bengal staining. (Photograph 3 & 4)

Schirmer's-1 test [12, 20]

It was performed by placing a pre-cut strip of filter paper (Wattman41), of size 35X5mm, at the junction of medial 2/3 and lateral 1/3 of the inferior cul-de-sac. Patient was instructed to blink normally and the amount of wetting of the paper strip after 5 minutes was measured. Wetting of ≤10 mm was taken as abnormal. (Photograph 5)

Diagnosis of Dry Eye Disease

Dry eye was defined as having one or more symptoms of dry eyes like ocular irritation, burning, itching, foreign body sensation, photophobia, blurring of vision associated with redness of eyelids and conjunctiva present often or all the time along with one or more positive clinical findings based on slit lamp examination and one or more positive clinical tests (tear film break up time of ≤10 seconds, Schirmer's test score ≤ 10mm, Rose Bengal stain score of >3). Asymptomatic patients with positive clinical signs or tests were also being considered to have dry eye.

In this study, follow up was done after every 4 weeks for 12 weeks by evaluating symptoms, signs, testing and scoring in both the groups. A simple and effective objective criterion of confirming and grading dry eye based upon points scoring system derived from the results of various tear film tests was suggested by khurana *et al*. So grading was assessed by Khurana's grading system [16].

Table-1: The severity of the dry eye was graded as per Khurana's scoring system [16]

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

Table-2: Khurana's scoring system for severity of dry eye

	Total score	Severity of dry eye
Grading criteria	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 was done through randomized controlled study. In case of qualitative measures Chi square test was applied and in case of quantitative measures t test was applied at the end of the study.

RESULTS

In group-1 there were 70% males and 30% females and in group-2 there were 78% males and 22% females.

The table 3 describes the total score and statistical significance amongst Group 1 and Group 2. The results have been depicted across time period of 12 weeks at an interval of 4 weeks. Mean total score showed a significant improvement from their respective pretreatment levels to follow up after 4, 8 and 12 weeks in both the groups (Table 3).

Table-3: Change in mean total score of various clinical findings (Tear film BUT (in sec), Marginal tear strip, Schirmer's 1 test etc. from pre-treatment values to follow up in Group 1 and 2

Characteristic	Total Scores of various clinical findings		
	After 4 week	After 8 weeks	After 12 weeks
Group 1 (n=50)			
Change from baseline	-2.94 ± 1.44	-6.04 ± 1.98	-7.56 ± 2.84
Significance	p<0.001	p<0.001	p<0.001
Group 2 (n=50)			
Change from baseline	-4.51 ± 2.04	-7.48 ± 3.03	-8.90 ± 3.68
Significance	p<0.001	p<0.001	p<0.001

On comparing the mean total score of various clinical findings across time period of 12 weeks at an interval of 4 weeks, it was observed that a significant improvement occurred in both the groups. After 12 weeks the change in score was statistically significant in group 2 (Table 4).

Table-4: Mean total score of various clinical findings during pre-treatment and on follow up in Group-1 & Group-2

Characteristic	Total score		
	Group 1 (n=50)	Group 2 (n=50)	Significance (Group 1 vs Group 2)
	Mean ± S.D.	Mean ± S.D.	
Pre-treatment	9.38± 3.86	10.00 ± 4.20	p=0.278
After 4 weeks	6.44± 3.54	5.49 ± 3.13	p=0.046
After 8 weeks	3.34± 2.84	2.52 ± 2.42	p=0.029
After 12 weeks	1.92± 2.21	1.00 ± 0.92	P<0.001
Significance	p<0.001	p<0.001	-

Table-5: Comparison of tear function test in group 1 and group 2

Test	Group I (CMC)			Group II (PPM)			Comparison
	Pre-treatment	Post treatment after 12 weeks	Significance (p-value)	Pre-treatment	Post treatment after 12 weeks	Significance (p-value)	Group 1 versus Group 2
Tear film Break Up Time (sec)	7.77±1.74	13.66±1.66	P<0.001	7.52±1.74	14.29±1.68	P<0.001	P =0.008
Mean Marginal Tear Strip score	1.60±0.75	2.72±0.45	P<0.001	1.46±0.67	2.62±0.57	P<0.001	P=0.280
Mean Fluorescein Staining score	2.08±0.66	1.34±1.47	P<0.001	1.86±0.75	0.58±1.17	P<0.001	P<0.001
Mean Schirmer's test value (mm)	4.42±2.47	10.52±3.03	P<0.001	4.64±2.59	13.08±3.94	P<0.001	P<0.001
Mean Rose Bengal staining score	5.84±1.76	2.06±1.69	P<0.001	6.07±2.09	0.86±1.50	P<0.001	P<0.001
Mean Lissamine Green staining	4.73±1.94	1.42±1.41	P<0.001	5.32±2.34	0.5±1.26	P<0.001	P<0.001
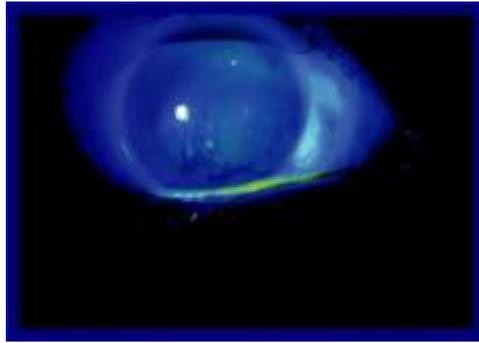
Photograph-1: Tear film break-up time

Photograph-2: Marginal Tear Strip Staining
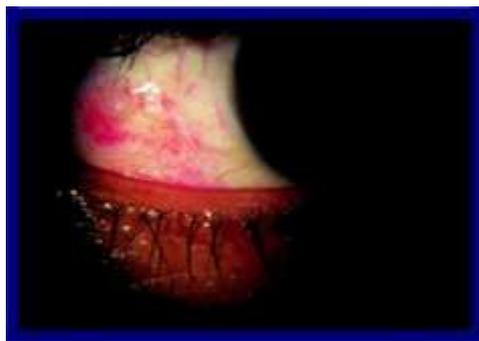
Photograph-3: Rose Bengal Staining

Photograph-4: Lissamine Green Staining

Photograph-5: Schirmer's Test

Intra-group and inter-group comparison of tear function test was done in two groups (Table 5). Statistical comparison of both the groups was found to be significant from their pre-treatment scores to follow up after 12 weeks (p<0.001) in all tear function tests.

When the results were compared between the group-1 and group-2, it was observed that the patients in group-2 showed statistically significant more improvement than in group-1 (p<0.001) in all tear function test except TBUT and Mean marginal tear strip score.

In the CMC group out of the 50 patients treated for 12 weeks, 27 patients had improved to having no dry eye, 10 patients had become dry eye suspect, 10 patients still had mild dry eye and 3 patients had moderate dry eye.

Similarly in the REB group 34 patients had improved to having No dry eye, 10 patients had become Dry eye suspect, 4 patients still had mild dry eye and 2 patients had moderate dry eye. No group had severe dry eye at the end of 12 week treatment period.

Both the drugs i.e. Sodiumcarboxymethylcellulose 1% (CMC) and Rebamipide 2% (REB) were found to be safe and efficacious in patients suffering from dry eye disease (led to improvement in tear film stability, reduction in severity of disease).On comparing the response to the two drugs, Rebamipide 2% was found to be more efficacious than Sodiumcarboxymethylcellulose 1%.

DISCUSSION
The burden of DED will continue to increase, due to increased life expectancy, as well as projected population growth among the elderly.

In our study the mean age of population was 50.31 years (±11.24). In another study also DED was found to be a common disorder of eyes affecting a significant percentage of the population, especially those older than 50 years of age i.e. in the range of 5% to 30% [21]. However, Shah *et al*. have reported a younger age of onset.In a randomized clinical trial study conducted on 90 patients of dry eye syndrome the mean age reported by Shah *et al*. was 35.87 years (±7.95) in group-1 and 37.51years (±6.78).in group-2 [22]. Middle-aged and older adults are the most commonly affected groups because of the high prevalence of contact lens usage, systemic drug effects, autoimmune diseases and refractive surgeries [23].

In our study the REB group gave better results at the end of 12 weeks in improvement of Schirmer`s score as compared to CMC group i.e 13.08±3.94 vs 10.52±3.03 respectively and the difference was statistically significant (p<0.001). When Kinoshita *et al*. compared Rebamipide and Sodium hyaluronate in 188 eyes they did not find any significant change in Schirmer's scores after four weeks of treatment or LOCF [5]. In a study done by Sindhu *et al*. sixty patients were divided in two equal groups. Patients were stabilized initially for the period of 2 weeks with topical carboxymethyl cellulose (artificial tears) and then were divided in two groups. In first group, Loteprednol 0.5% was given along with artificial tears while in other group Artificial tears were given alone. On comparing these groups, statistically significant better response was observed with loteprednol along with artificial tears as compared to artificial tears alone in Schirmer's scores [24].

In study conducted by Dipak B. Patel *et al*. was found that 2% Rebamipide ophthalmic solution was more efficient in improving both the subjective symptoms and objective signs of dry eye in comparison to the CMC group in this 8 week study. These findings showed that 2% Rebamipide is the more effective drug for dry eye. These results also correspond to our study [25].

In a multicenter, open-label, single-arm study, a total of 154 patients received 2% rebamipide four times per day for 52 weeks [26]. Lissamine green conjunctival staining, corneal fluorescein staining, TBUT and subjective symptoms improved significantly at week 2 compared with baseline, and further improvements were observed at every visit up to week

52. Topical rebamipide is also potentially effective in treating other ocular surface disorders such as short TBUT dry eye [27], lid wiper epitheliopathy [28], and alkali ocular damage [29,30]. Rebamipide has also proven to be effective at improving the ocular surface appearance and optical quality in patients with dry eye undergoing refractive surgery [31].

In our study we found that treatment with CMC and REB showed statistically significant reduction in Lissamine staining score as early as 4 weeks in both the groups which was continuous over a period of 12 weeks. Statistically significant better response was seen in group-2 as compared to group-1 over a period of 12 weeks i.e. $p<0.001$. According to both studies done by Kinoshita et al, it was found that there was statistically significant difference between Lissamine green staining scores after 4 weeks of treatment with REB over Sodium hyaluronate and placebo [5, 12].

We observed in our study that both the groups were comparable regarding the baseline fluorescein staining scores. In REB group there occurred more improvement as compared to CMC in converting maximum number of eyes with fluorescein staining to absent staining by 12 weeks which was statistically significant ($p<0.001$). The two studies conducted by Kinoshita *et al.* observed that there was statistically significant difference between fluorescein staining scores after treatment with REB over placebo and Sodium hyaluronate for four weeks or last observation carried forward (LOCF) [5,12].

CONCLUSION

Treatment with Rebamipide and CMC leads to a generalized improvement in all the objective signs for assessment of DED, namely, TBUT, Schirmer's test score, Fluorescein staining score, Rose Bengal staining score, Lissamine green staining score and Marginal tear strip score. Thus, study indicates that both drugs used as part of the study were safe and effective but Rebapimide was more efficacious than CMC.

Abbreviations-: REB – Rebamipide, CMC - Carboxymethyl Cellulose, TBUT– Tear Film Breakup Time, DED – Dry Eye Disease

REFERENCES

1. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop (2007). Ocul Surf. 2007; 5:75-92. http://www.tearfilm.org/dewsreport/. Published April 2007. Accessed February. 13, 2008.
2. American Academy of Ophthalmology Basic and Clinical Science Course Subcommittee. Basic and Clinical Science Course. External Disease and Cornea: Section 8, 2008-2009. San Francisco, CA: American Academy of Ophthalmology. 2008: 71-2.
3. Pflugfelder SC, Tseng SC, Sanabria O, Kell H, Garcia CG, Felix C, Feuer W, Reis BL. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea. 1998 Jan;17(1):38-56.
4. Feenstra RP, Tseng SC. Comparison of fluorescein and rose bengal staining. Ophthalmology. 1992 Apr 1;99(4):605-17.
5. Norn MS. Lissamine green: Vital staining of cornea and conjunctiva. Acta ophthalmologica. 1973 Aug;51(4):483-91.
6. Manning FJ, Wehrly SR, Foulks GN. Patient tolerance and ocular surface staining characteristics of lissamine green versus rose bengal. Ophthalmology. 1995; 102: 1953-7.
7. Farris RL, Gilbard JP, Stuchell RN, Mandel ID. Diagnostic tests in keratoconjunctivitis sicca. Eye & Contact Lens. 1983 Jan 1;9(1):23-8.
8. Clinch TE, Benedetto DA, Felberg NT, Laibson PR. Schirmer's test. A closer look. Arch Ophthalmol.1983; 101: 1383-6.
9. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tsubota K, Stapleton F. TFOS DEWS II definition and classification report. The ocular surface. 2017 Jul 1;15(3):276-83.
10. Moshirfar M, Pierson K, Hanamaikai K, Santiago-Caban L, Muthappan V, Passi SF. Artificial tears potpourri: a literature review. Clinical ophthalmology (Auckland, NZ). 2014;8:1419.
11. Ohba E, Dogru M, Hosaka E, Yamazaki A, Asaga R, Tatematsu Y, Ogawa Y, Tsubota K, Goto E. Surgical punctal occlusion with a high heat-energy releasing cautery device for severe dry eye with recurrent punctal plug extrusion. American journal of ophthalmology. 2011 Mar 1;151(3):483-7.
12. Greiner JV. A single Lipiflow Thermal Pulsation System treatment improves meibomian gland function and reduces dry eye symptoms for 9 months. Curr Eye Res. 2012; 37(4): 272-8.
13. Bhargava R, Kumar P, Kumar M, Mehra N, Miashra A. Trial of omega-3 fatty acids in dry eye syndrome, Int J Ophthalmol. 2013; 6(6): 811–6.
14. Kinoshita S, Awamura S, Nakamichi N, Suzuki H, Oshiden K, Yokoi N, Rebamipide Ophthalmic Suspension Long-term Study Group. A multicenter, open-label, 52-week study of 2% rebamipide (OPC-12759) ophthalmic suspension in patients with dry eye. American journal of ophthalmology. 2014 Mar 1;157(3):576-83.
15. Anjum S. Evaluation of dry eye status in diabetes mellitus and correlation with diabetic retinopathy.http://14.139.159.4:8080/jspui/bitstream/123456789/1198/1/ CDMOPTH00005.pdf
16. Khurana AK, Chaudhary R, Ahluwalia BK, Gupta S. Tear film profile in dry eye. Acta Ophthalmol. 1991; 69: 79- 86.

17. Pflugfelder SC, Tseng SC, Yoshino K. Correlation of goblet cell density and mucosal epithelial membrane mucin expression with rose Bengal staining in patients with ocular irritation. Ophthalmology. 1997; 104: 223-35.
18. Bruix A, Adán A, Casaroli-Marano RP. Efficacy of sodium carboxymethylcellulose in the treatment of dry eye syndrome. Arch Soc Esp Oftalmol. 2006; 81(2): 85-92.
19. Goren MB, Goren SB. Diagnostic tests in patients with symptoms of keratoconjunctivitis sicca. American journal of ophthalmology. 1988 Nov 1;106(5):570-4.
20. Paulsen AJ, Cruickshanks KJ, Fischer ME, Huang GH, Klein BE, Klein R, Dalton DS. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. American journal of ophthalmology. 2014 Apr 1; 157(4):799-806.
21. 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 Jan 1;4(1):1321869.
22. Moss SE, Klein R, Klein BEK. Prevalance of and risk factors for dry eye syndrome. Arch of Ophthalmol. 2000; 118(9):1264–8.
23. Lemp MA, Baudouin C, Baum J, Dogru M, Foulks GN, Kinoshita S. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye Work-Shop. Ocular Surface. 2007;5(2):75-92
24. Patel DB, Menon P, Rathod A, Vyas A, Rana P. A comparative study of rebamipide 2% and carboxy methylcellulose (CMC) 0.5% eye drop in patients with dry eyes: A randomized, hospital-based study. Indian Journal of Clinical and Experimental Ophthalmology. 2018;4(4):526-9.
25. Kinoshita S, Awamura S, Nakamichi N, Suzuki H, Oshiden K, Yokoi N, Rebamipide Ophthalmic Suspension Long-term Study Group. A multicenter, open-label, 52-week study of 2% rebamipide (OPC-12759) ophthalmic suspension in patients with dry eye. American journal of ophthalmology. 2014 Mar 1;157(3):576-83.
26. Koh S, Inoue Y, Sugmimoto T, Maeda N, Nishida K. Effect of rebamipide ophthalmic suspension on optical quality in the short break-up time type of dry eye. Cornea. 2013;32(9):1219–1223.
27. Itakura H, Kashima T, Itakura M, Akiyama H, Kishi S. Topical rebamipide improves lid wiper epitheliopathy. Clinical ophthalmology (Auckland, NZ). 2013;7:2137.
28. Sasaki H, Kokubun T. Alkali burn treated with 2% rebamipide ophthalmic suspension: a case report. Case reports in ophthalmology. 2014;5(3):380-5.
29. Kashima T, Itakura H, Akiyama H, Kishi S. Rebamipide ophthalmic suspension for the treatment of dry eye syndrome: a critical appraisal. Clinical ophthalmology (Auckland, NZ). 2014; 8:1003.
30. Igarashi A, Kamiya K, Kobashi H, Shimizu K. Effect of Rebamipide Ophthalmic Suspension on Intraocular Light Scattering for Dry Eye After Corneal Refractive Surgery. Cornea 2015; 34(8):895–900.