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A Comparative Study to Evaluate the Efficacy of Carboxy Methyl Cellulose with Glycerin and Balanced Electrolytes as excipients vs Plain Carboxy Methyl Cellulose, for keeping the eye moist

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ABSTRACT

Introduction and Background – *Dry Eye is a multifactorial disease of the tear film and the ocular surface which may be due to reduced tear production or excessive tear evaporation resulting in discomfort, visual disturbance, and tear film instability with a potential damage to the ocular surface. Advantages of certain Excipients in an eye drop formulations of artificial tears are sometimes not fully appreciated. Glycerin is an excellent humectant and hygroscopic agent. It helps in maintaining moisture for a long time. Glycerin also acts as a lubricant because of its viscous nature. Glycerin at the concentration less than 1 % is devoid of its irritant potential. Balanced Electrolytes makes the solution isotonic and stable.*

Objective – *The purpose of this study was to compare the Efficacy of ophthalmic solution containing Sodium CMC 0.5% with Glycerin 0.9% and Balanced Electrolytes as excipient vs Plain Sodium CMC 0.5%.*

Methodology – *This was a two-arm, open label, parallel design study conducted in 52 subjects with the symptoms of dry eyes (irritation, light sensitivity, pain or blurred vision). Schirmer's test was conducted on the subjects giving informed consent. This gives the baseline value of moisture in both the eyes of the volunteer. One drop of the artificial tears containing Carboxy Methyl Cellulose (CMC) 0.5% eye drop with Glycerin 0.9% and Balanced Electrolytes as excipients was instilled in the right eye and one drop of the artificial tears containing plain CMC eye was instilled into the left eye. Schirmer's test was repeated on these subjects at 1 hour and 3 hour after instillation of the drops in each eye.*

Results – *The baseline Schirmer's test reading in both the eyes was similar. On repeating the Schirmer's test after instilling the artificial tear eye drops in both the eyes, mean reading was 19.42 mm in the right eye and 15.76 mm in the left eye, at the end of one hour. The mean Schirmer's test reading was 19.38 mm in the right eye and 15.34 mm in the left eye, at the end of three hours. At one and three hours, the difference was statistically significant ($p<0.05$) in both the eyes with the difference of 3.65mm i.e. 23 % and 4.03 i.e. 26 % respectively. Thus the eye which received Sodium CMC 0.5% with Glycerin 0.9% and Balanced Electrolytes was better lubricated than the eye which received Plain CMC.*

Conclusion – *In the present study, better and prolonged efficacy of Carboxy Methyl Cellulose with Glycerin and Balanced Electrolytes as excipients is demonstrated as compared to Plain Carboxy Methyl Cellulose in keeping the ocular surface moist.*

Introduction, Background and Objective

Dry Eye Syndrome (DES) is caused by a chronic lack of sufficient lubrication and moisture on the surface of the eye. It is also called as Kerato-conjunctivitis Sicca (KCS) or Keratitis Sicca. DES is a multifactorial disease of the tear film and the ocular surface which may be due to reduced tear production or excessive tear evaporation.[1] Abnormality of any one of the three layers of tear film produces an unstable tear film, resulting in discomfort of DES.[2]

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.[3]

DES is a common ocular condition which significantly reduces quality of life, and affects 6–34% of the global adult population.[2] Women Health Study reported prevalence of 7.8% after screening 36995 subjects above 49 years, by interview.[4] The prevalence reported by Blue Mountain Study[5] was 15.3%. The Beaver Dam Study[6] and Shiphai Eye studies[7] are other studies reporting prevalence of 14.5% and 33.7% respectively.

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.)[8]

Glycerin is one of the Excipients used in some ophthalmic solutions for the management of DES. It acts as a lubricant because of its viscous nature. Glycerin at the concentration less than 1 % is devoid of its irritant potential. Glycerin in ophthalmic solution also clears corneal haze by attracting water through semi permeable corneal epithelium.[9]Balanced electrolytes makes the solution isotonic and stable. Even the normal physiological tear film includes a few electrolytes like sodium, bicarbonate, calcium, magnesium, and bicarbonate. There are studies which mention that balanced electrolytes are essential in artificial tears for survival of the goblet cells in conjunctiva.[10] Currently there is a dearth of clinical data establishing the active role of Glycerin and Balanced Electrolytes as Excipients in CMC based artificial tears.

The purpose of this study was to compare the Efficacy of ophthalmic solution containing Sodium CMC 0.5% with Glycerin 0.9% and Balanced Electrolytes as excipient vs PlainSodium CMC 0.5%.

Methodology

Study Population

A study was conducted in fifty four adults of either sex with the symptoms of dry eyes (irritation, light sensitivity, pain or blurred vision). This was validated using a questionnaire for dry eye syndrome. Other Inclusion criteria were that a volunteer should be over 18 years of age, have ability to comply with the protocol, should have willingness to give written informed consent, should not have used any brand of artificial eye drops upto 1 day prior to the Trial. Subjects were excluded if they were unwilling to give written Informed Consent, if the Subjects are unlikely to comply with the protocol or if they have any evidence of Psychological disorder. The enrolled Subjects was explained the conduct of the study and the protocol. Upon satisfaction the volunteer signed the Informed Consent Form.

Study Design

An open label, parallel design study was conducted at a single centre in fifty-four Subjects who satisfied the above inclusion and exclusion criteria.

Schirmer's test was conducted on each eye of these Subjects. The bottom eyelid was pulled out and a special strip of paper was gently placed underneath the lid. Both the eyes were tested at the same time. The eyes were gently closed and were kept shut for about five minutes with the paper strip in place. After five-minutes, the paper strips were carefully pulled out from the bottom eyelid. The amount of moisture on each paper strip was measured which gave the initial baseline value of tear production in both the eyes. The Subjects who suffered from irritation or discom-fort during the study were discontinued from the trial.

One drop of artificial eye drop containing 0.5% of CMC with of Glycerin 0.9% and Balanced Electrolytes as the excipients was instilled in the Right Eye and 1 drop of artificial eye drop containing only 0.5% of CMC (plain CMC) was instilled into the Left Eye of the same volunteer. Thus two different brands of artificial tears were used in both the eyes of the same volunteer.

The Volunteer were then asked to close the eye for one minute. After one minute, Subjects were allowed to do their routine work.

Clinical Assessment

Schirmer's test was repeated on these Subjects at 1 hour and 3 hours after instillation of the artificial eye drops in each eye. The amount of moisture on each paper strip was measured at one hour and three hours respectively which gave the values of tear production in both the eyes.

The primary outcome of the trial was the comparison of all the three readings, that is, the initial baseline value, the value after one hour from instillation of eye drop and value after three hours from instillation of eye drops, from the Right eye (0.5% of CMC, 0.9% of Glycerin and electrolytes as the excipients) to those with the Left eye (0.5% of CMC eye drop from a leading competitor brand). The comparison was made vertically and horizontally.

Statistical Analysis

The data generated through this trial was subjected to Statistical Analysis. Statistical analysis was done by unpaired 't' test.

Data Entry and Data Analysis

The entries were recorded in the case record form. The accuracy of all data on the CRF was attested by the signature of the principal investigator.

Results

Out of fifty-four, the study was concluded in fifty-two subjects with dry eye symptoms. Two subjects discontinued the study due to irritation in their eye during the trial. Both the Subjects had similar irritation in both the eyes.

At Baseline, no statistical differences were observed in both the eyes. The mean moisture measure by Schirmer's test was 14.06 mm in the right eye and 14.56 mm in the left eye. (Table 1)

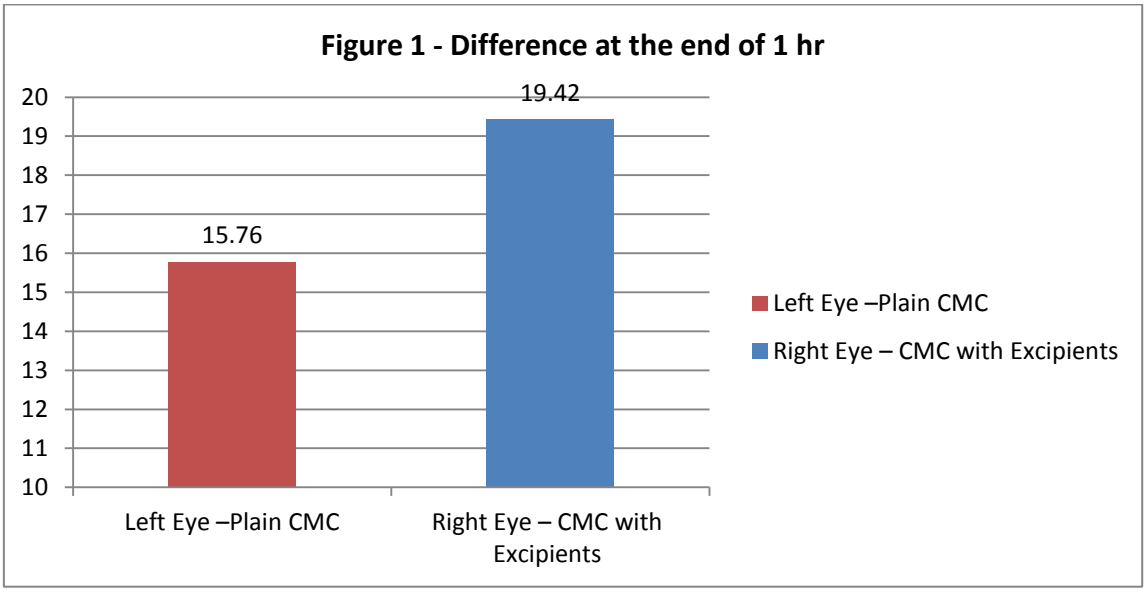
Table 1 – Baseline values before Instilling artificial tear eye drops

Baseline value on Schirmer's test in Left Eye	Baseline value on Schirmer's test in Right Eye
14.06	14.56

Twenty out of the fifty-two were having Schirmer's test reading < 15 mm i.e. 38% of the total study population had dry eyes.

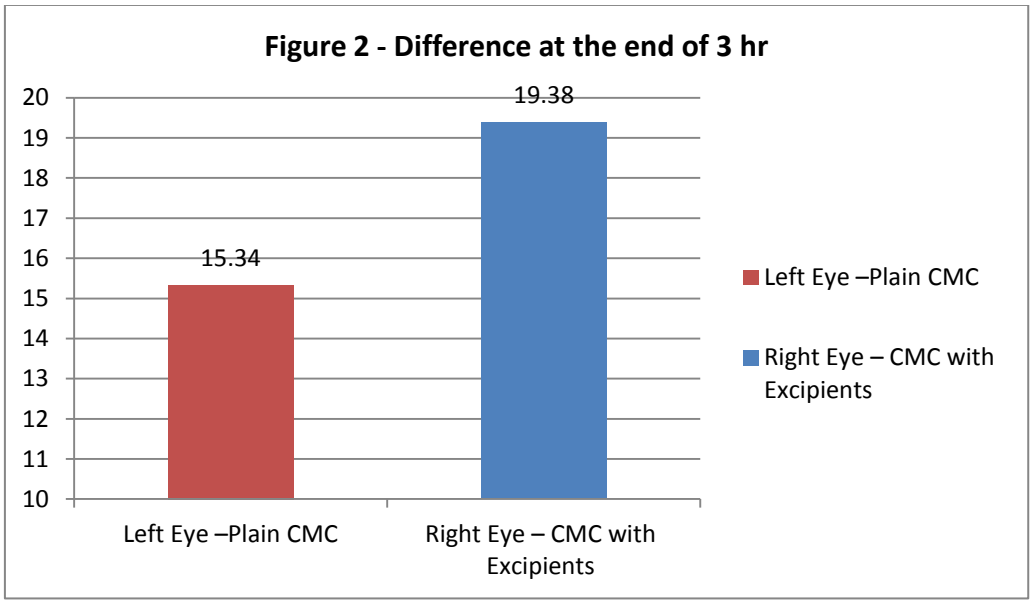
One hour after instilling the artificial tear eye drops in both the eyes, Schirmer's test was repeated. The mean moisture measure was 19.42 mm in the right eye and 15.76 mm in the left eye. The difference was statistically significant ($p<0.05$) in both the eyes with the difference of 3.65mm i.e. 23 % more in the eye which had received Sodium CMC 0.5% with Glycerin 0.9% and Balanced Electrolytes as opposed to Plain CMC. (Table 2 & Figure 1)

Table 2 – Difference in the readings of Schirmer's test between both the eyes at the end of 1 hr					
	Left Eye –Plain CMC	Right Eye – CMC with Excipients	Difference in favorof Excipients	% Difference in favor of Excipients	p value
1 hr	15.76	19.42	3.65mm	23%	0.0029 (<0.005)



Three hour after instilling the artificial tear eye drops in both the eyes, Schirmer's test was repeated. The mean moisture measure was 19.38 mm in the right eye and 15.34 mm in the left eye. The difference was statistically significant ($p<0.05$) in both the eyes with the difference of 4.03 mm mm i.e. 26 % more in the eye which had received Sodium CMC 0.5% with Glycerin 0.9% and Balanced Electrolytes as opposed to Plain CMC. (Table 3 & Figure 2).

Table 3 – Difference in the readings of Schirmer's test between both the eyes at the end of 3 hrs					
	Left Eye –Plain CMC	Right Eye – CMC with Excipients	Difference in favorof Excipients	% Difference in favor of Excipients	p value
3 hr	15.34	19.38	4.03 mm	26%	0.0034 (<0.005)



Though safety was not evaluated in this clinical study, provision for discontinuing the volunteer on account of irritation was explained to the volunteer during the signing of informed consent form. Two Subjects were discontinued from the study due to irritation with Schirmer's Strip. No drug related adverse event occurred during the study.

Discussion

The results of this study demonstrated that both Carboxy Methyl Cellulose with Glycerin and Balanced Electrolytes as excipients as compared to Plain Carboxy Methyl Cellulose increased the moisture levels of the tear film as demonstrated by Schirmer's test. But inhead-to-head analysis, a statistical difference of clinical efficacy was found in between the two formulations of CMC. This difference was consistent at 1 hr and 3 hr after instilling the artificial tears in both the eyes.

The mean moisture measure on Schirmer's test was 19.42 mm in the right eye and 15.76 mm in the left eye at the end of 1 hr. The difference was statistically significant ($p<0.05$) with the difference of 3.65 mm i.e. 23 % more for the eye which received Carboxy Methyl Cellulose with Glycerin and Balanced Electrolytes as excipientsas compared to the eye which received Plain CMC. Similarly, the mean moisture measure on Schirmer's test was 19.38 mm in the right eye and 15.34 mm in the left eye at the end of 3 hr. The difference was statistically significant ($p<0.05$) with the difference of 4.03 mm mm i.e. 26 % more for the eye which received Carboxy Methyl Cellulose with Glycerin and Balanced Electrolytes as excipientsas compared to the eye which received Plain CMC.

No drug related adverse event was occurred during the study. No serious adverse event occurred during the study period.

Pharmaceutics play an important role in the drug delivery and the dosage form. Many excipients are thought to play an active role in drug bioavailability and its efficacy. This has been proved with extensive data for the enteral and parenteral routes. It is very rarely studied for the topical routes, especially in the eye. Currently there is no study which substantiates the role of excipients like Glycerin and Balanced Electrolyte in CMC Artificial Eye Drops. This was the first study of its kind to validate the role of excipients in the eye drop preparation.

Many of the clinical trials have already proved the superiority of CMC over Sodium hyaluronate.[11] 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.[12]

As presently CMC Artificial Tears are extensively and most popular therapy used in ophthalmological clinical practice, the safety is also well established. Hence the safety was not studied in this present clinical study.

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.[13]

Hans-Walter Roth et al., conducted a multicenter, investigator-masked, randomized, parallel-group, active-controlled, clinical study enrolled patients with mild to moderate dry eye symptoms with CMC 0.5% and Glycerin 0.9% vs Sodium Hyaluronate 0.18%. At day 7 and 14 Both CMC/glycerin and sodium hyaluronate effectively relieved dry eye symptoms. Scores were

consistently similar across all measures, and both artificial tears were highly acceptable to patients.[14] Limitations of this present study are that it was conducted in fifty-two Subjects and the study duration was one day for 3 hours. Additional long-term studies are necessary to fully compare the long-term efficacy with TBUT, Corneal and Conjunctival Staining along with Schirmer's test as well as safety of these two formulations. In addition, this study was primarily designed to evaluate Subjects with dry eye symptoms and further comparisons are warranted to compare these formulations in patients with moderate to severe dry eye disease/syndrome. Our study hopes to provide a base for conducting such larger studies.

Although artificial tears have been shown to provide relief from many signs and symptoms of dry eye disease, they do not treat inflammation or increase the volume of natural tears. Thus they are physiological in nature, not pharmacological.[15,16]

Conclusion

In the present study, better and prolonged efficacy of Carboxy Methyl Cellulose with Glycerin and Balanced Electrolytes as excipients is demonstrated as compared to Plain Carboxy Methyl Cellulose in keeping the ocular surface moist.

Conflict of Interest and Declaration by the Authors

We declare that there is no conflict of interest of any of the authors with regards to the present clinical study. We have not received any grants or financial aid for conducting this study.

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