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Comparative efficacy of cyclosporine 0.1%, rebamipide 2%, and carboxymethylcellulose-cyclosporine 0.05% combination eye drops in the management of dry eye disease among the Indian population

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ABSTRACT

Purpose: This comparative research study aims to evaluate and compare the results of three different eye drop formulations of Cyclosporine 0.1%, Rebamipide 2%, and a combination of Carboxymethylcellulose & Cyclosporine 0.05%, in treating dry eye cases among the Indian population.

Materials and Methods: This investigation employed a randomized controlled trial design to assess the efficacy of three distinct eye drop formulations. A total of 120 patients diagnosed with dry eye disease participated in this study. Participants were assigned to one of three treatment groups: Group C (cyclosporine 0.1%), Group R (rebamipide 2%), or Group CC (combination of carboxymethylcellulose and cyclosporine 0.05%). Patients take prescribed medication for six weeks. Patients were evaluated at baseline for tear production time (TFBUT) at two weeks, four weeks, and six weeks, tear production score using the Schirmer test, and dry eye symptoms were assessed with the Ocular Surface Disease Index (OSDI). The collected data were analyzed using appropriate tests to compare the effectiveness of three eye drop formulations in treating dry eye in the Indian population.

Results: Disease improvement compared to baseline was seen in all groups based on scoring of Schirmer's score, OSDI score, and TBUT.

Conclusion: All three treatment groups demonstrated improvements in tear film stability, tear production, and a reduction in dry eye symptoms over the six-week treatment period. However, further research with larger sample sizes and longer treatment durations is needed to establish the long-term efficacy and compare the effectiveness of these treatments.

1. Introduction

Dry eye disease (DED), alternatively referred to as keratoconjunctivitis sicca, constitutes a form of ocular ailment. Eye disease affects most of the world's population. Eye discomfort is characterized by many symptoms, including burning, foreign objects, blurred vision, and tear film instability.[1] These symptoms significantly impact patients' quality of life and lead to reduced efficiency in work and learning.[2,3] DED occurs when the tear film that normally lubricates and nourishes the ocular surface breaks down, causing inflammation and damage to ocular tissue.[1] The cause of DED depends on multiple factors, in which ocular, anatomical and systemic factors play crucial roles.[4]

In recent years, many treatments have been developed to relieve symptoms and enhance the overall well-being. of dry eye patients. One way is to use eye ointments/drops containing drug like cyclosporine. It a calcineurin inhibitor, It has been extensively employed as an immunomodulatory

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agent in managing dry eye.[5] It helps to suppress ocular surface inflammation and promote tear production.[6,7]

Rebamipide, an innovative ophthalmic suspension, was initially developed for the treatment of gastric ulcers. It serves as an amino acid analog of 2 (1H)-quinolinone.[8] Rebamipide shown promising results in addressing dry eye concerns. It exerts its effects by increasing mucin secretion and stabilizing the tear film, thereby improving the ocular surface condition.[9,10]

Another approach involves the use of a combination of carboxymethylcellulose (CMC) and cyclosporine, which aims to provide both lubrication and anti-inflammatory effects. CMC displays favorable bioadhesive properties, and its anionic characteristics could be advantageous in extending the duration of tear retention.[11] CMC acts as a lubricant to reduce dry eye symptoms, while cyclosporine targets the underlying process.[12]

Although the effectiveness of these treatments has been investigated in different cultures, comparative studies are needed, especially in the Indian population. Geographic and genetic factors, as well as lifestyle and environmental influences, affect the prevalence and dryness of dry eye in many people. Therefore, it is important to assess the effectiveness of these treatments in the Indian population.

The objective of this research is to assess and compare the efficacy of cyclosporine 0.1%, rebamipide 2%, and a combination of carboxymethyl cellulose and cyclosporine 0.05% eye drops in managing dry eye among the Indian population. Through the analysis of treatment outcomes, our aim is to offer valuable insights into optimal dry eye therapies for individuals in India.

The results of this study added to the current knowledge on dry eye treatment and may guide doctors in choosing the most appropriate treatment for Indian patients. Additionally, these results may contribute in the development of new treatment strategies for dry eye in other populations with similar geographic and genetic characteristics.

2. Materials and Methods

This was a multidisciplinary study conducted at ESIC medical college & Hamdard Institute of medical sciences and Research. It is a prospective, randomized, interventional longitudinal observational study. According to the inclusion and exclusion criteria, 120 patients ranging in aged between 18 and 60 years of any gender were encompassed in this study. The study duration was within the specified research period of 1 year (May 1, 2022 - April 30, 2023), and the sample size (40 patients in each group, 120 patients in total) was determined based on disease evaluation using computer software (nMaster2.0).

2.1. Criteria for inclusion

1. Individuals aged 18-60, regardless of gender.
2. Dry eye signs and symptoms such as itching, redness, mucus, blurred vision in the eyes for at least 2 months
3. Conditions that meet the McMonnie Questionnaire and Dry Eye Rating Scheme
4. Participants who provided explicit written consent after being thoroughly informed about the study objectives and procedures were included in the research.

2.2. Criteria for exclusion

1. Pregnant women
2. Breastfeeding women
3. Having an eye infection.
4. Allergic to any of the study drugs.
5. Currently using contact lenses or any other eye medication.

2.3. Methodology

Patients attending OPD, Department of Ophthalmology, ESIC Medical College and Hospital were evaluated for manifestations and indications of dry eye as per the McMonnie Questionnaire were assessed during the individual's initial appointment. After assessment Patients were categorized based on the grading system established by the DEGS. A total of 120 dry eye disease (DED) patients, 40 in each group, were included in the study by counting and exclusion method after discussion and were allowed to write with signs on the patient's language. The patient's details are entered on the data sheet. When patients come to the OPD, they are randomized into three groups using a computer-based randomization method. Group C was administered 0.1% cyclosporine eye drops, group R was administered 2% rebamipide eye drops, and group CC was administered a combination of carboxymethylcellulose and 0.05% cyclosporine eye drops. To evaluate treatment outcomes, patients were evaluated at baseline, two weeks, four weeks, and six weeks. At the end of the 6th week, DEGS classification was made and patients who benefited from the medication and those who avoided the medication were treated according to the standard of care. During each appointment, patients underwent assessments utilizing the following tests:

1. TBUT (film degradation time): less than 10 seconds is questionable.
2. Schirmer Test – one and two: There is motivation to repeat the test.
3. Diseases of the Ocular surface index.
4. Individua/Participant's symptom score. (Mc Monnie's score)

A comparative analysis was conducted among all three patient groups by using these scores, and statistical analysis of this comparison was made. Sociodemographic features

and Adversarial outcomes were also investigated for each drug study.

2.4. Statistical assessment

The data underwent analysis through the SPSS version 26. The results are presented in words and numbers. Age, gender and scores were compared for all three groups. The mean score was compared with the unmatched T. P value ≤ 0.05 was considered significant.

3. Results

Table 1 indicates that there were 40 participants in each study groupi.e. cyclosporine, Rebamipide, and a combination of Carboxymethylcellulose & Cyclosporine 0.05% group respectively. Out of the total of 40 study subjects 57.5%, 65% & 55% were males in respective groups. The mean ages across all three groups did not exhibit a significant dissemblance (p>0.05).

In the follow-up period after the initiation of treatment at 2 weeks, 4 weeks & 6 weeks, there was no significant dissemblance in mean Schirmer test score between C, R, and CC groups at baseline and 2 weeks. At 4 weeks there was a significant dissemblance between group C and R and between group C and CC. At 6 weeks there was a significant dissemblance between group C and R. In all three groups, Schirmer's score was found to increase gradually from baseline to 6 weeks. At 2 weeks there was a significant dissemblance from baseline in the CC group. At 4 weeks the dissemblance from baseline is significant in group c and cc but a highly significant dissemblance was seen in group R. At 6 weeks Schirmer test score was highly significantly different from baseline reading.

In the follow-up period after initiation of treatment with drugs at 2 weeks, 4 weeks & 6 weeks, there was no significant dissemblance in mean TBUT score between C, R, and CC groups at baseline and 2 weeks. At 4 weeks there was a significant dissemblance between group C and R. At 6 weeks there was a significant dissemblance between group C and R.

In all the three groups, the TBUT score was found to increase gradually from baseline to 6 weeks. At 2 weeks there was a significant dissemblance from baseline in the R group. At 4 weeks the dissemblance from baseline is significant in group C and CC but a highly significant dissemblance was seen in group R. At 6 weeks TBUT score was highly significantly different from the baseline reading.

In the follow-up period after intiation of treatment with drugs at 2 weeks, 4 weeks & 6 weeks, there was no significant dissemblance in mean OSDI score between C, R, and CC groups at baseline and 2 weeks. At 4 weeks there was a highly significant dissemblance between group C and R and a significant dissemblance between group C and CC. At 6 weeks there was a significant dissemblance between groups.

In all the three groups, the OSDI score was found to Decrease gradually from baseline to 6 weeks. At 2 weeks there was a significant dissemblance from baseline in all the three groups. At 4 and 6 weeks the dissemblance from baseline is highly significant in all the three groups.

4. Discussion

In this study, we compared the effectiveness and safety of cyclosporine 1%, rebamipide 2% and the combination of carboxymethyl cellulose and cyclosporine 0.05% in the treatment of dry eye. According to our literature review, there is no study comparing these drugs. Therefore, we discuss the studies on each drug and compare these studies with our research.

Sahil E (2010) found in his study that the average Schirmer test scores were 3.00 and 4.00 months before and 6 months after topical cyclosporin A. The median TBUT score at baseline was observed 4.00 seconds and the mean post-treatment score was observed 5.00 seconds. At 6 months after treatment, the dissemblance between pre-treatment and post-treatment mean Schirmer and TBUT values was significant (P<0.05).[13]

Ji Hwan Lee (2011) conducted a randomized controlled trial to compare the effectiveness and safety of sodium hyaluronate (SH) and carboxymethylcellulose (CMC) in managing mild to moderate dry eye were assessed. The results indicated that both the SH and CMC cohorts demonstrated statistically significant enhancements in corneal and conjunctival staining sum scores, tear film breakup time, and dry eye symptom score four and eight weeks post-treatment initiation. Nonetheless, no statistically significant differences were observed in any of the indices between the two treatment groups.[14]

Pinnita Prabhasawat (2013) conducted a study evaluating the effectiveness of 0.05% cyclosporine eye drops in patients with Stevens-Johnson syndrome with dry eye. In their study, they found that everyone who completed the study showed a significant improvement (P<0.05) in symptoms of dry eye, conjunctival hyperemia, corneal staining, Schirmer I test, and FCT, and concluded that cyclosporine 0.05% eye drops would be beneficial. be effective. In the management of dry eye associated with SJS.[15]

In a study on rebamipide treatment, Shizuka Koh (2013) found an increase in tear film compared to baseline, but a significant change in Schirmer test score at two and four weeks after the start of treatment (P<0.001 for both). comparisons) at four weeks after treatment (P=0.033), but there was no significant dissemblance between Piam at week two.[16]

Yeon Woong Chung (2013) found in his study that after 0.05% cyclosporine treatment, tear breakup time started in the 1st month and increased in the 2nd and 3rd months (p =

Table 1: Categorization of study subjects based on drug type and population characteristics

Sociodemographic characteristics	Drug Type		
	Cyclosporine 0.1% (n=40)	Rebamipide 2% (n=40)	Combination of Carboxymethylcellulose & Cyclosporine 0.05%) (n=40)
Male	23	26	22
Female	17	14	18
Mean age (In Years)	43.25 ± 8.65	45.76 ± 9.35	44.89 ± 7.92

Table 2: Comparison of mean Schirmer score among the three groups over 6 weeks of follow-up

Time	Type of drug used		
	Cyclosporine (n=40)	Rebamipide (n=40)	Carboxymethylcellulose & Cyclosporine 0.05% eye drops
	Mean ± SD	Mean ± SD	Mean ± SD
Baseline,	5.74 ± 2.75	5.68 ± 3.32	5.96±2.64
2 weeks,	7.28 ± 5.16	7.37 ± 4.48	7.56±3.12#
4 weeks,	7.68 ± 2.67#	9.26 ± 2.22##*	9.14±3.17#@
6 weeks,	8.54 ± 2.18##	10.52 ± 2.44##*	10.11 ± 5.24##

- Significant dissemblance as compared to the baseline value ($p \leq 0.05$)
- Highly significant dissemblance as compared to the baseline value ($p \leq 0.001$)
* - Significant dissemblance between the group C and R ($p \leq 0.05$)
@ - Significant dissemblance between the group C and CC ($p \leq 0.05$)

Table 3: Comparison of mean TBUT score between the groups over 6 weeks of follow-up

Time	Type of drug used		
	Cyclosporine (n=40)	Rebamipide (n=40)	Carboxymethylcellulose & Cyclosporine 0.05% eye drops
	Mean ± SD	Mean ± SD	Mean ± SD
Baseline,	4.77 ± 3.86	4.55 ± 3.42	4.64±2.26
2 weeks,	5.87 ± 2.32	6.41 ± 2.44#	5.79±4.13
4 weeks,	6.77 ± 2.16#	8.35 ± 2.78*##	7.19±5.34#
6 weeks,	8.11 ± 2.88##	10.23 ± 3.14*##	9.24 ± 2.08##

- Significant dissemblance as compared to the baseline value ($p \leq 0.05$)
- Highly significant dissemblance as compared to the baseline value ($p \leq 0.001$)
* - Significant dissemblance between the group C and R ($p \leq 0.05$)

Table 4: Comparison of mean OSDI score between the groups over 6 weeks of follow-up

Period of follow up	Type of drug used		
	Cyclosporine (n=40)	Rebamipide (n=40)	Carboxymethylcellulose & Cyclosporine 0.05% eye drops
	Mean ± SD	Mean ± SD	Mean ± SD
Baseline,	44.55 ± 9.93	46.23 ± 10.25	45.78±8.71
2 weeks,	38.53 ± 8.33#	38.41 ± 8.85#	39.27±4.53#
4 weeks,	33.64 ± 5.93##	25.73 ± 6.35##**	31.82±8.91##*
6 weeks,	25.37 ± 5.75##	22.57 ± 6.81##	25.2 ± 8.43##

- Significant dissemblance as compared to the baseline value ($p \leq 0.05$)
- Highly significant dissemblance as compared to the baseline value ($p \leq 0.001$)
* - Significant dissemblance from the group C ($p \leq 0.05$)
@ - Significant dissemblance between the group C and CC ($p \leq 0.05$)

0.04, p < 0.01)).[17]

Igarashi Akihito (2015) reported an increase in Schirmer I test, BUT and luciferin scores from 11.4 ± 9.0 mm, 2.2 ± 0.7 seconds and 4.3 ± 1.3 to 14.9 ± 0.7 in the rebamipide group found a significant improvement to ± 1.4 months and seconds to 1.9 ± 1.0 (P = 0.006, P < 0.001, Wilcoxon signed test).[18]

Sangeeta Shah (2017) conducted a study to evaluate the effectiveness of topical carboxymethylcellulose 0.5% and cyclosporine A 0.05% in dry eye and found that topical CMC 0.5% and cyclosporine A 0.05% improved all visible facial features in 6 weeks. He found healing. However, the results of the two groups were not significantly different.[12]

5. Conclusion

Overall, all three treatment groups showed significant improvements in tear film stability (TFBUT), tear production (Schirmer's test score), and reduction in dry eye symptoms (OSDI scores) over the six-week of treatment time interval. The findings of this study suggest that Cyclosporine 0.1%, Rebamipide 2%, and the combination of Carboxymethylcellulose & Cyclosporine 0.05% eye drops are effective in managing dry eye cases in the Indian population. However, further research with bigger sample sizes and longer treatment durations is required to confirm and compare the long-term efficacy of these treatments.

6. Source of Funding

None.

7. Conflict of Interest

None.

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