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Original Article

A Comparative Study between Efficacy of Cyclosporine 0.1% and Rebamipide 2% Eye Drops in Moderate to Severe Dry Eye Cases

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ABSTRACT:
Introduction: Dry eye disease is one of the most common ocular surface diseases in India and worldwide ; particularly in the post-menopausal women and elderly. It occurs when there is inadequate tear volume or function resulting in an unstable tear film and ocular surface disease.(1) The early detection and timely management of this disease is important to prevent long term sequelae and sight threatening complications. Multiple approaches which include drugs like Cyclosporine and Rebamipide are required to manage cases of moderate to severe dry eye disease. **Objectives:** 1.To study socio demographic profile of patients with dry eye. 2. To compare the effectiveness of Cyclosporine 0.1% eye drops and Rebamipide 2% eye drops in treatment of dry eye. 3. To suggest suitable recommendations based on study finding. **Methodology:** The study subjects were divided into two groups one of which received Cyclosporine 0.1% while the other group got Rebamipide 2% eye drops. Both groups were assesed based on Schirmer's test, OSDI score and TBUT over a period of 6 months along with their demographic characteristics and a statistical analysis of the comparison of the two drugs was drawn. **Results:** Based on the Schirmer's score, OSDI score and TBUT, Rebamipide is showing more promising results with lesser side effects as compared to Cyclosporine. **Conclusion:** Rebamipide 2% eye drop can be safely used in the long term management of moderate to severe dry eye cases.
Key Words: Cyclosporine, Rebamipide, Schirmer's, OSDI, TBUT.

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INTRODUCTION

Dry eye disease (DED) is the most common form ocular surface disease; 5%–34% of the global population is affected. It is a multifactorial disease and is therefore largely difficult to manage. Also, it has problems concerning compliance of patients and has very limited tools for diagnosis. It requires prompt diagnosis and treatment as it's associated with sight threatening complications.

According to the Beaver Dam Eye Study, the prevalence of this disease was found to be larger in females than in males. Also, the prevalence was found to be around 8% in younger individuals and 19% in older age group.(2)

The clinical features of dry eye comprise of ocular discomfort, foreign body sensation, burning sensation, itching, redness, stinging, pain, and intermittent visual disturbances. Thus, it may interfere with the individuals' ability to carry out routine daily activities .

Even though it is usually a non blinding disease, these patients spend a significant amount of money per year to alleviate the anxiety associated with it. e.g the sale of artificial tears surpassed US$540 million in the year 2002.(2)

Dry-eye syndrome (DES), also known as keratoconjunctivitis sicca or keratitis sicca, is a multifactorial disease of the tears and ocular surface found both in humans and some domesticated animals, which is associated with either increased tear film evaporation on the surface of the eye or decreased tear production by the meibomian glands. It is followed by rise in the osmolarity of the tear film and inflammation of the ocular surface. The diagnosis of DES is usually based on the presence of

symptoms, but various tests are available for diagnosis in certain cases. For example, Schirmer's test quantifies the amount of moisture bathing the eye. Lysozyme concentrations associated with the tear film are also sometimes measured.(3)

Besides senility and female sex, some of the risk factors for DES include postmenopausal estrogen therapy, medications such as antihistamines, connective tissue disorders, LASIK and refractive laser surgery, low intake of omega-3 fatty acids, and radiation therapy. Manaviat et al. have linked DES with type 2 diabetes. In their study of 199 patients with type 2 diabetes, 108 patients (54.3%) had DES. The prevalence of DES was significantly related to duration of diabetes, but not to sex or age. However, the authors did not speculate as to an etiologic link. DES may also be exacerbated by environmental factors such as contact lens wear, low-humidity environments, smoking, use of various medications such as antidepressants, antihypertensives, and medications to treat benign prostatic hyperplasia, prolonged computer use, watching television, reading, living at higher elevations, and excessive wind or air conditioning.(3)

DES can seriously impair the affected individual's quality of life. Besides the negative effects of eye pain, DES can also show harmful effects on mental condition, such as depression and anxiety. Miljanovic et al. reported in a study of 690 participants that DES affected the ability to carry out routine activities, such as driving, television viewing, and computer work.(3)

Treatment for DES depends on the severity of the condition. Environmental conditions that increase tear evaporation and factors that may decrease tear production should be minimized or eliminated. Artificial tears or ocular lubricants (preservative free) are often successful in ameliorating symptoms, especially in mild cases. Nutritional supplementation with omega-3 fatty acids may be useful, but research in this area is limited and the results somewhat inconclusive to date. Inflammation plays a vital role in the cascade of this disease hence many anti-inflammatory agents are being used including corticosteroids, tetracyclines, and cyclosporine. Severe or prolonged dry-eye cases may require surgical procedures, such as lid surgery, tarsorrhaphy, or mucus membrane, salivary gland, or amniotic membrane transplantation.(3)

The best available modality for treating DED is eye drops. The first-choice of treatment in the US is Cyclosporine ophthalmic preparation, while the first choice in Japan is hyaluronate eye drop. Recently promoted in Japan, however, is Rebamipide ophthalmic solution. This ophthalmic solution induces mucin production.(4)

Among the plethora of available treatment options, cyclosporine A is the only prescription eye drop accepted by the US Food and Drug Administration (FDA) specifically for patients with DES and seems to be the most widely used current therapy for DES.(3)

Rebamipide was introduced in 1990. It's role was to produce mucin and thus repair gastric mucosa. Later on, experiments demonstrated that, Rebamipide increases the number of conjunctival goblet cells and keratoconjunctival epithelial cells in vitro and in vivo. Stable expression of mucin is a novel postulate put forth for treating dry eye. Recent studies have shown that its use can be exceedingly effective.(4)

Evidence regarding the safety and efficacy of available treatment options is needed to enable appropriate treatment decisions for individual patients. Henceforth our objective of the present study was to compare the efficacy of 2% Rebamipide ophthalmic suspension with that of 0.1% Cyclosporine ophthalmic solution in patients having moderate to severe dry eye.

MATERIALS & METHODOLOGY

Study place: Dr. D.Y. Patil Hospital And Research Institute, Kadamwadi, Kolhapur

Study design: Prospective Interventional Longitudinal Study

Study duration: July 2016 to August 2018

Sample size : 40 in each group i.e. total 80 (calculated using Slovin's formula under guidance of statistician)

INCLUSION CRITERIA

- Individuals of age groups 50 and older.
- Both genders.
- Presenting with signs and symptoms of dry eye for > or = 2months such as: ocular irritation, redness, mucous discharge, fluctuating vision.
- Cases satisfying the McMonnies's questionnaire and Dry eye grading scheme
- Individuals who have given written informed consent

EXCLUSION CRITERIA

- Individuals of age less than 50 years.
- Pregnant females
- Lactating females
- Females with child bearing potential.
- Active eye infections.
- Known allergies to ingredients of the two drugs.
- Using contact lenses.
- Currently using other topical medications.

METHODOLOGY

Approval from institutional ethics committee and research committee was taken. Patients presenting to the Ophthalmology OPD at D.Y Patil Medical College, with signs and symptoms of dry eye disease assessed according to the McMonnie's Questionnaire at the first visit. The patients were then graded according to the DEGS.

Total 80 patients i.e. 40 patients in each group with moderate to severe cases of Dry Eye Disease (DED) were included in the study as per the inclusion- exclusion

criteria after counseling, and a written informed consent was taken in their own language. Patient details were entered in the case record form.

As patients came to OPD they were divided into two groups randomly using the lottery method, one of which will received Cyclosporine 0.1% and the other received Rebamipide 2% eye drops in combination with 1% methylcellulose eye drops. Patients were followed first at 1st month after starting the respective drug and then at monthly intervals for 6 months. At the end of 6thmonth, DEGS grading was done and those who had benefits and tolerated the drug were managed as per standard of care. Patients at each follow up were investigated with following tests : Complete visual assessment.

- TBUT (Tear break up time) : <10 seconds is suspicious.
- Schirmer's Test – 1 and 2: repeated abnormal tests are highly supportive.
- Ocular surface disease index.
- Individual symptom score.(Mc Monnie's score)

Both the groups of patients were compared using TBUT, Schirmer's and OSDI and a data analysis of this comparison was established.

Additionally, the demographic characteristics and adverse effects of the two drugs were also studied.

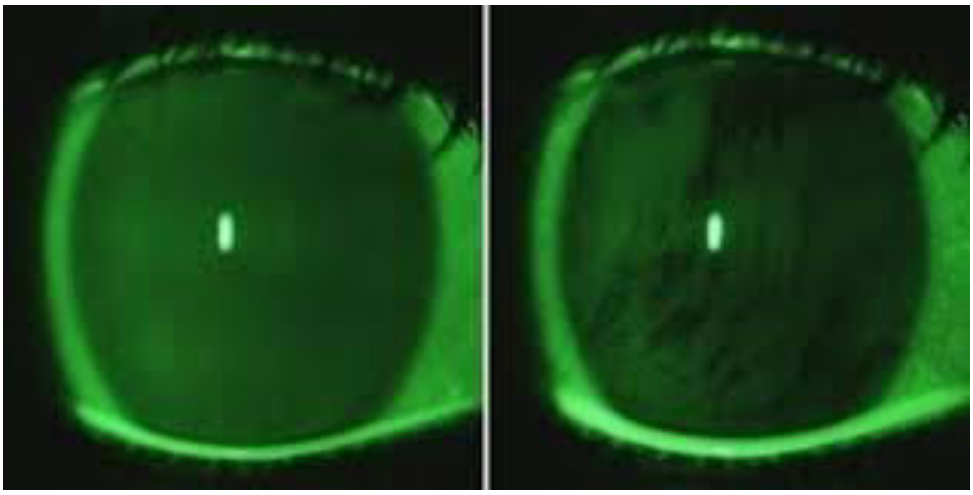


Fig 1 : Tear break up time

Fig 2 : Schirmer's test

STATISTICAL ANALYSIS

Data was analyzed using software Epiinfo version 7.2. Results were presented in the form of tables & graphs. Age, gender & various scores were compared in both groups. Mean values of scores was compared using unpaired T test. P value less than 0.05 was considered for significance.

RESULTS & OBSERVATIONS

Table 1: Distribution of study subjects according to type of drug used and demographic characteristics

Demographic characteristics	Type of drug used		P Value
	Rebamipide (n=40)	Cyclosporine (n=40)	
Male	28	32	
Female	12	8	0.30
Mean age in years	43.25 ± 8.65	46.76 ± 9.35	0.21

Table 1 shows that there were 40 study subjects in each group i.e. cyclosporine & Rebamipide group respectively. Out of total 40 study subjects 70% & 80% were males in Rebamipide and cyclosporine group respectively. There was no significant difference between mean ages of the two groups (p>0.5).

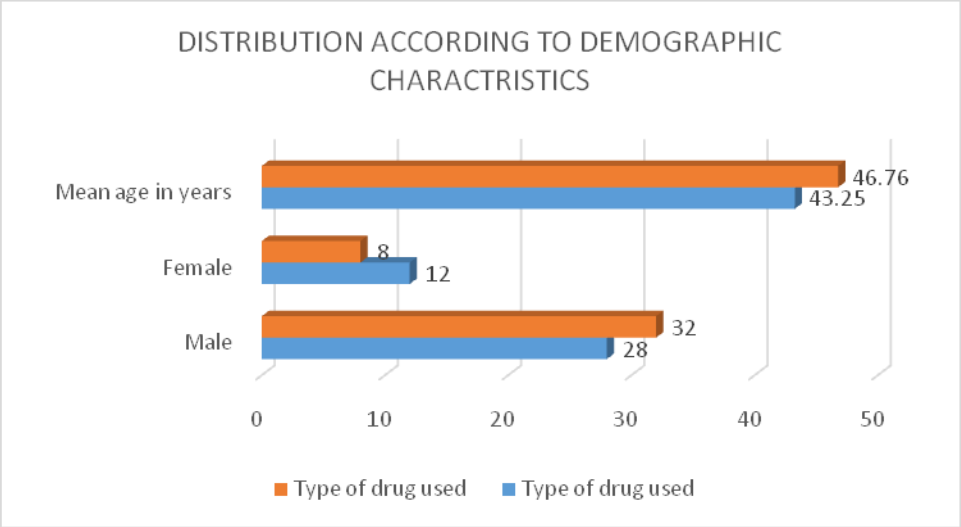


Table 2: Distribution of study subjects according to type of drug used and causes of dry eye

Demographic characteristics	Type of drug used	
	Rebamipide (n=40)	Cyclosporine (n=40)
Primary Sjögren's syndrome	0	0
Non-Sjögren's lacrimal disease	26	32
Meibomian gland disease	22	20
Lid surfacing/blinking abnormalities	08	12

In above table, it was observed that among causes of dry eye disease Non-Sjögren's lacrimal disease was most common cause of dry eye disease (65% & 80% in both groups). This was followed by Meibomian gland disease & lid surfacing/blinking abnormalities.

Table 3: Comparison of mean Schirmer score between two drugs during 6 month of follow up.

Period of follow up	Type of drug used		P Value
	Rebamipide (n=40)	Cyclosporine (n=40)	
	Mean ± SD	Mean ± SD	
1 month	5.78 ± 3.32	5.84 ± 2.75	0.94
2 month	7.47 ± 4.48	7.38 ± 5.16	0.95
3 month	9.36 ± 2.22	7.78 ± 2.67	0.04
4 month	10.62 ± 2.44	8.64 ± 2.18	<0.01
5 month	12.34 ± 2.82	10.44 ± 3.12	0.04
6 month	14.16 ± 2.45	11.96 ± 2.65	<0.01

In follow up period after treatment with drugs at 1 month & 2 months, there was no significant difference in mean Schirmer test score between Rebamipide and Cyclosporine groups. In both the groups, Schirmer score was found to increase gradually from 1 month to 6 months. At 3, 4, 5 & 6 months, Schirmer score was significantly more in Rebamipide group than Cyclosporine group (p<0.5).

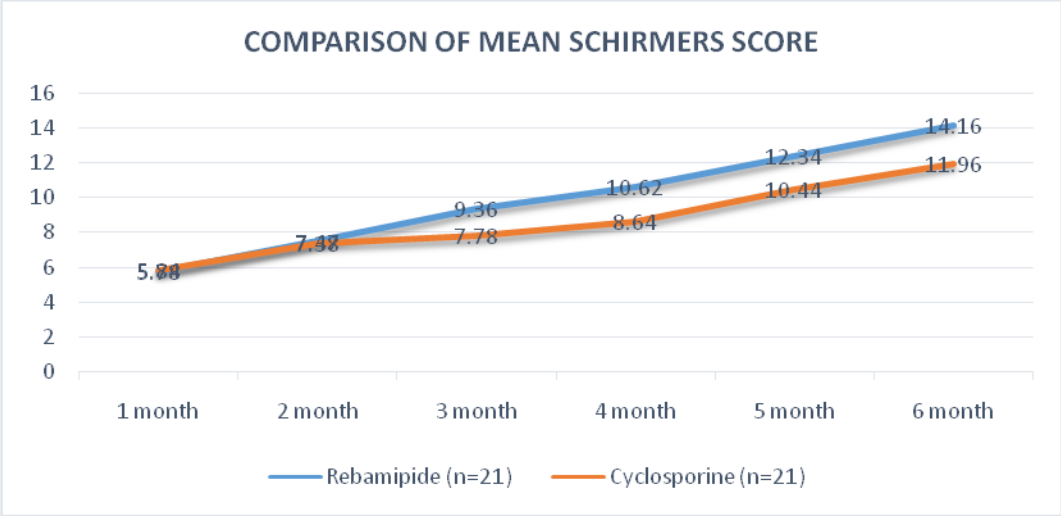


Table 4: Comparison of mean TBUT score between two drugs during 6 month of follow up.

Period of follow up	Type of drug used		P Value
	Rebamipide (n=40)	Cyclosporine (n=40)	
	Mean ± SD	Mean ± SD	
1 month	4.56 ± 3.42	4.78 ± 3.86	0.84
2 month	6.42 ± 2.44	5.88 ± 2.32	0.46
3 month	8.36 ± 2.78	6.78 ± 2.16	0.04
4 month	10.24 ± 3.14	8.12 ± 2.88	0.02
5 month	12.34 ± 3.44	9.54 ± 2.33	<0.01
6 month	13.28 ± 3.26	11.22 ± 2.84	0.03

In follow up period after treatment with drugs at 1 month & 2 month there was no significant difference in mean TBUT test score between Rebamipide and Cyclosporine groups. In both the groups TBUT score was found to increase gradually from 1 month to 6 month. At 3, 4, 5 & 6 months, TBUT score was significantly more in Rebamipide group than Cyclosporine group (p<0.5).

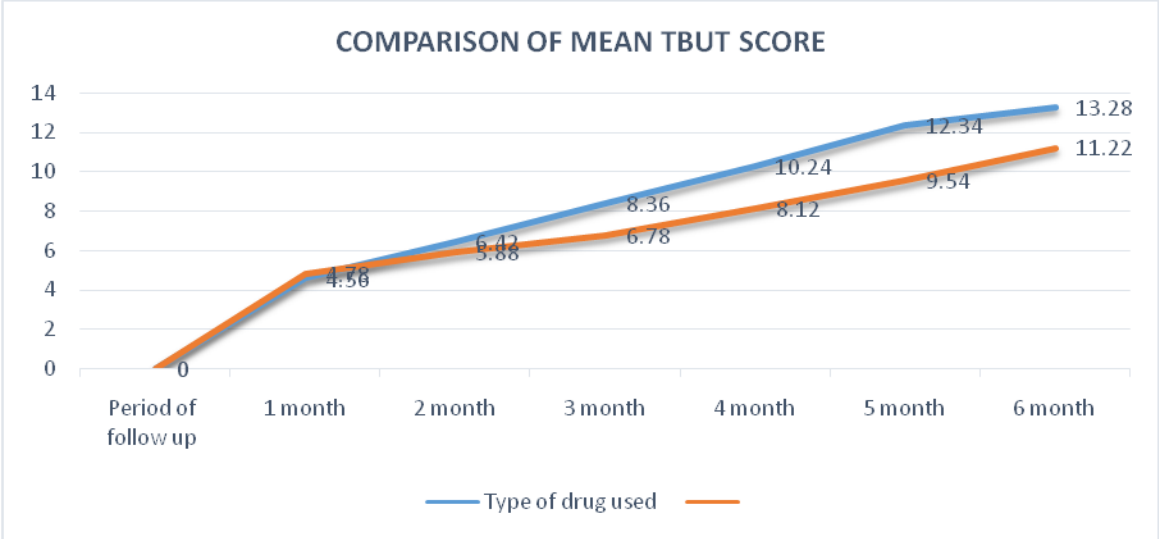
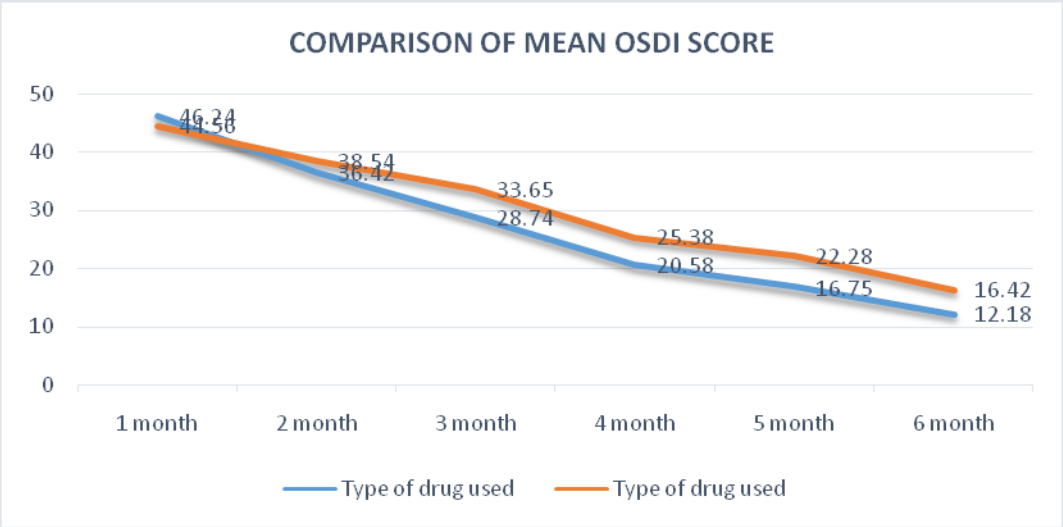


Table 5: Comparison of mean OSDI score between two drugs during 6 month of follow up.

Period of follow up	Type of drug used		P Value
	Rebamipide (n=40)	Cyclosporine (n=40)	
	Mean ± SD	Mean ± SD	
1 month	46.24 ± 10.25	44.56 ± 9.94	0.59
2 month	36.42 ± 8.86	38.54 ± 8.34	0.42
3 month	28.74 ± 6.36	33.65 ± 5.94	0.01
4 month	20.58 ± 6.82	25.38 ± 5.76	0.01
5 month	16.75 ± 5.88	22.28 ± 6.57	<0.01
6 month	12.18 ± 6.64	16.42 ± 5.96	0.03

In follow up period after treatment with drugs at 1 month & 2 month there was no significant difference in mean OSDI score between Rebamipide and Cyclosporine groups. In both the groups OSDI score was found to decrease gradually from 1 month to 6 month. At 3, 4, 5 & 6 month OSDI score was significantly less in Rebamipide group than Cyclosporine group (p<0.5).



DISCUSSION

In present study we compared efficacy and safety of Cyclosporine and Rebamipide in treatment of dry eye disease. As per our search of literature, there was no study showing comparison between these two drugs. So we discussed individual studies of each drug and compared those studies with our study.

Shigeru Kinoshita (2014) in their study found that of the 154 total patients, 15 patients (9.7%) were male and 139 patients (90.3%) were female. The mean age was 59.3 years (range: 24-86 years). Of the 154 patients, 26 patients (16.9%) had primary or secondary Sjogren syndrome and 5 patients (3.2%) had Stevens- Johnson syndrome as the underlying cause of dry eye.(5)

Shizuka Koh (2013) in their study on treatment with Rebamipide found significant increases in the tear film BUT at 2 and 4 weeks after initiating the treatment (P<0.001 for both comparisons) compared with baseline, significant changes were seen in the Schirmer test scores 4 weeks after the treatment (P = 0.033), although there was no significant (P = 0.889) difference at 2 weeks.(6)

Sahil E (2010) conducted study in which they found that before and after 6 months of the treatment with topical cyclosporine A, the median Schirmer test scores were found as 3.00 and 4.00 mm, respectively. The median BUT score at baseline was 4.00 seconds, and after treatment, the median score was 5.00 seconds. There were statistically significant differences in the median Schirmer and BUT values between, before, and after 6 months of treatment (P < 0.05).(7)

Yeon Woong Chung (2013) in their study they found significant improvement in the tear break-up time after treatment with cyclosporine 0.05% starting at 1 month and further increases were seen at 2 and 3 months (p = 0.04, p < 0.01, respectively).(8)

Igarashi Akihito (2015) found that in the Rebamipide group, the Schirmer I test, TBUT, and fluorescein score improved significantly, from 11.4 ± 9.0 mm, 2.2 ± 0.7 seconds, and 4.3 ± 1.3 to 14.9 ± 7.4 mm, 4.5 ± 1.7 seconds, and 1.9 ± 1.0, respectively (P = 0.006, P < 0.001, P < 0.001, Wilcoxon signed rank test).(9)

CONCLUSION

In present study we found that:

- Non-Sjögren's lacrimal disease was most common cause of dry eye disease. **(65% & 80% in both groups).**
- In both the groups Schirmer test score, TBUT score & OSDI score increased gradually from 1 month to 6 months.
- Response to Rebamipide was more as compared to cyclosporine in treatment of dry eye disease at 4, 5 & 6 months of follow up
- Rebamipide was superior to cyclosporine in long term treatment of dry eye disease.

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