



Original Research Article

Role of 2% rebamipide ophthalmic suspension in the management of dry eye disease

D.N Prakash¹, Sujata Sajjan^{1,*}, K Satish¹, Raghavendra R¹, Mohammed Abdul Kayoom¹¹Dept. of Ophthalmology, Mysore Medical College and Research Institute, Mysuru, Karnataka, India

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ABSTRACT

Objective: To study the therapeutic effects of 2% rebamipide ophthalmic suspension in dry eye disease.**Materials and Methods:** It was Prospective study of 80 patients diagnosed with dry eye syndrome from Jun 2016 to April 2017. After complete ophthalmic examination all were treated with 2% rebamipide suspension. Dry eye-related Symptom Score, anterior segment examination with slit lamp, Tear Film Break-Up Time, Fluorescein Ocular Surface Staining Score(FOS) & Schirmer test were used to collect data from patients at baseline & at 2, 4, 8 & 12 week visits.**Results:** Mean dry eye-related symptom score showed a significant improvement from baseline at 2, 4, 8 & 12 weeks (9.80, 7.20, 7.40 & 7.83 points). Median FOS also showed significant improvement from baseline (3.0 points) at 2, 4, 8 & 12 weeks (2.0, 2.0, 1.0 & 1.0 points respectively). TBUT & Schirmer test values also improved but were not significant after treatment.**Conclusion:** 2% rebamipide ophthalmic suspension is an effective in treating dry eye. It helps in improving both ocular & tear film stability.© 2019 Published by Innovative Publication. This is an open access article under the CC BY-NC-ND license (<https://creativecommons.org/licenses/by/4.0/>)

1. Introduction

TFOS DEWS II has redefined dry eye as: “ Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles”.

Dry eye is a very common disorder commonly affecting females in menopausal age group and elderly patients. Based on etiology dry eye has been divided into aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE). Aqueous deficiency encompasses Sjogrens and Non- Sjogrens syndrome The distinction between the two, however is less clear, and both subtypes eventually activate the same final common pathway leading to a dysfunctional tear syndrome. Other factors include age related dry eye, female gender, hormonal factor, lid abnormalities which

prevent the spread of an even tear film, environmental factors like air conditioners and low humidity, and of late- the rising trend of refractive surgeries like LASIK photorefractive keratectomy resulting in decreased corneal sensation and blink rate are recognized as precipitating causes of dry eye. The prevalence in dry eye according to few studies in America and Australia is 5- 16% were as in Asian countries it is 27-33%.¹ If dry eye is left untreated for long duration sometimes sight threatening complication can occur and it also has negative impact on quality of life.^{2,3}

Rebamipide is a newer drug with mucin secretagogue activity belonging to the class of quolinone derivatives. It has also been demonstrated to have gastropotective effects by enhancing gastric prostaglandins like PG E2 and PGI2 secretion. Rebamipide is marketed in the eastern countries like Japan as an oral agent for the treatment of gastric mucosal disorders and gastritis. Rebamipide acts as a scavenger for oxygen free radical s and also has additional anti inflammatory properties.⁴ Once the various effects

* Corresponding author.

E-mail address: drsujatasajjan1@gmail.com (S. Sajjan).

of rebamipide 2% on the tissues were discovered, then began its development for its use in dry eye disease, and subsequently rebamipide 2% ophthalmic suspension were approved in treating dry eyes. Rebamipide acts by increasing the secretion of conjunctival and corneal mucin, and also by reducing the amount of inflammatory mediators like IL 8, TNF- α and NFkB.⁵

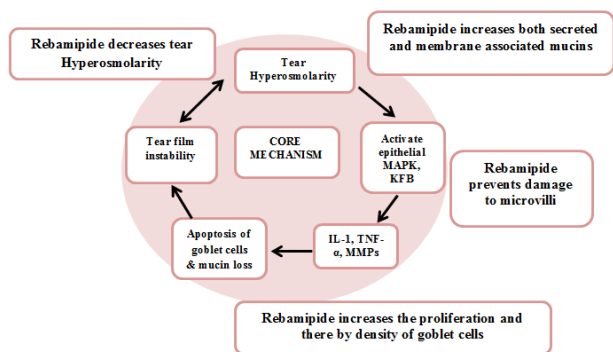


Diagram 1:

2. Objectives

To evaluate the therapeutic effects of 2% rebamipide ophthalmic suspension in dry eye disease

3. Materials and methods

3.1. Source of data collection

Primary source of information with observational methodology was used on the patients diagnosed to have Dry eye disease who attended Outpatient Department in tertiary eye care government hospital.

3.2. Sample size

Using Confidence Interval technique with level of significance 5% and Absolute Error 10% and Prevalence of 27% in Asian countries,¹ the inflated sample size was 80.

3.3. Inclusion criteria

All diagnosed cases of dry eyes for a minimum period of 6 months and willing to participate in the study.

3.4. Exclusion criteria

1. History of ocular surgery within 12 months.
2. Presence of infective pathologies on the ocular surface and adnexa.
3. Patients using other topically instilled ocular medications during study.
4. Use of contact lenses.

3.5. Method of study

Patients who attended OPD between from June 2016 to April 2017 and diagnosed to have Dry eye were included in this study.

The diagnosis of dry eye was based on the criteria of the Dry Eye Research group.⁸ Patients presenting with three essential problems were regarded as suffering from dry eye. These included the symptoms of dry eye, abnormality of tear film stability or secretion, and the amount of ocular surface damage. Patients were grouped as dry eye suspects if two out of these three problems were present. The tear secretion was considered abnormal when the SchirmerI test was equal to or less than 5 mm, and the tear stability is considered abnormal when the TBUT value is equal to or less than 5seconds. Van Bijsterveld system score of three or more points suggests presence ocular surface damage. Patients with two or three problems were enrolled for the study.

Detailed history and routine ophthalmic examination was carried out in all the enrolled patients. Questionaries' related to subjective dry eye symptoms were handed to all the patients and response noted. Complete ocular examination included measurement of best corrected visual acuity, Slit-lamp examination, fluorescein staining of ocular surface, TBUT measurement, Schirmer's test and retinal examination. Patients satisfying all inclusion and exclusion criteria were prescribed 2 % rebamipide eye drops. They were instructed to instil the drops 1 gtt. QID and were followed up. Follow up visits were scheduled at 2 weeks, 4 weeks, 8 weeks, and 12 weeks.

3.6. Assessment

The subjective dry eye symptom was assessed by questionnaire consisting of 11 symptoms. Each of the symptoms was scored by the patient with scores ranging from 0 to 3, which are as follows: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. Symptoms included were foreign body sensation, dryness, eye discomfort, photophobia, itching, eye pain, blurred vision, eye fatigue, heaviness, eye discharge and lacrimation.^{6,7}

3.7. FOS assessment

Fluorescein instillation was done in the eye by using a fluorescein strip wetted with a drop of proparacaine solution. After retraction of the patient's lower eyelid, the margin of fluorescein strip was touched to the conjunctiva.⁸ The patient is then told to blink multiple times so that the dye get spread throughout the ocular surface. The cobalt blue filter is used to evaluate the Fluorescein staining. According to the van Bijsterveld system, "the ocular surface was divided into three zones: nasal bulbar conjunctiva, temporal bulbar conjunctiva, and cornea".⁹ Each zone was

graded on a scale from 0 to 3. The maximum score in this system was 9. Score 0 which means no staining, score 1 suggesting few separated spots, score 2 suggesting many separated spots and score 3 meaning confluent staining.

3.8. Tear film break-up time (TBUT)

The TBUT was measured by applying a slightly moistened fluorescein strip to the bulbar conjunctiva and asking the patient to blink. Under a slit-lamp with a cobalt blue filter the tear film was analyzed. The patient during that time was instructed to not blink. The interval between the last blink and the appearance of the first randomly distributed dry spot in the corneal surface is known as the TBUT. Value of 5 or less is abnormal.

3.9. Schirmer test

The Schirmer test was used to measure the Tear production. This test measures the area of wet ability of a Whatman no. 41 filter paper which is 5 mm in breadth and 35 mm in length. Based on the use of topical anaesthesia, this test is classified as Schirmer 1 (without anaesthesia) or Schirmer 2 (with anaesthesia). In our study, the Schirmer test 1 was done. The filter paper strip was placed into the junction of medial 2/3rd and lateral 1/3rd of the lower lid margin (between the palpebral conjunctiva and the bulbar conjunctiva) without touching the cornea. After 5 min paper strip was removed and the wetted length of the strip was read. It is regarded as abnormal if wetted length is equal to or less than 5 mm.

4. Results

A total of 50 patients diagnosed with dry-eye syndrome were included in this study. The majority of the patients were between 51 to 60 years. The study included 61.3% women and 38.8% men.

Table 1: Distribution of patients according to age

Age	Frequency	Percent
<30Y	2	2.5
31-40Y	23	28.8
41-50	22	27.5
51-60Y	28	35.0
>60Y	5	6.3
Total	80	100.0

Table 2: Distribution of sex among patients

Sex	Frequency	Percent
M	31	38.8
F	49	61.3
Total	80	100.0

The dry eye symptom was evaluated by questionnaires covering 11 parameters. The most common complaints of the patients were Foreign body sensation and sensation of dryness, followed by itching, discomfort, watering. The means score at baseline was 10.8 ± 2.9 . Dry eye symptom score at 2 week, 4 weeks, 8 weeks, 12 weeks was 9.8 ± 2.6 , 8.2 ± 2.3 , 7.4 ± 2.0 and 6.8 ± 1.8 . Symptoms of dry eye improved significantly over 3 months in majority of the patients following treatment.

FOSS score at baseline 3.0 ± 2.5 . At 2week, 4week, 8week and 12week was 2.0 ± 2.3 , 2.0 ± 1.7 , 1.0 ± 2.4 and 1.0 ± 2.1 respectively. There was significant decreases in FOSS in eyes treated with rebamipide.

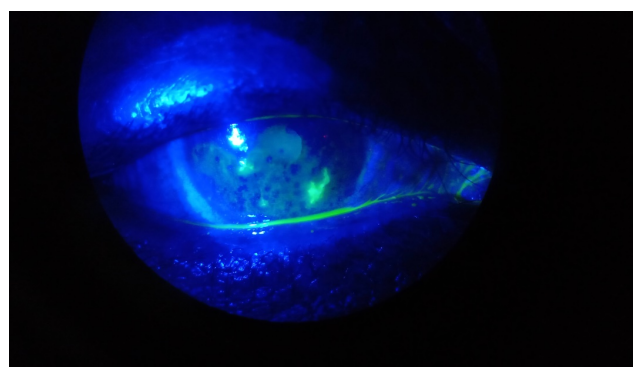


Fig. 1: Picture showing corneal and conjunctival staining

Schirmer's test before the beginning of the treatment showed a wetting of 6.0 ± 2.0 mm of the paper, and improved after 2 week, 4 week, 8 week and 12 week to 6.5 ± 1.5 , 6.5 ± 1.5 , 7.0 ± 1.5 and 7.5 ± 1.0 but statistically it was not significant

TBUT baseline 6.0 ± 1.4 , 6.3 ± 1.2 , 6.5 ± 1.5 , 7.3 ± 1.8 , 7.5 ± 1.3 improved from baseline but statistically not significant

Table 3: Score of parameters at baseline, 2, 4, 8 and 12 weeks

	DEWS	FOSS	ST	TBUT
BL	10.8 ± 2.9	3.0 ± 2.5	6 ± 2.0	6.0 ± 1.4
2week	9.8 ± 2.6	2.0 ± 2.3	6.5 ± 1.5	6.3 ± 1.2
4week	8.2 ± 2.3	2.0 ± 1.7	6.5 ± 1.5	6.5 ± 1.5
8week	7.4 ± 2.0	1.0 ± 2.4	7.0 ± 1.5	7.3 ± 1.8
12week	6.8 ± 1.8	1.0 ± 2.1	7.5 ± 1.0	7.5 ± 1.3

5 patients reported bitter taste, which was the most common adverse event observed. Followed by eye irritation and stinging sensation which were observed in one and two patients, respectively.

5. Discussion

The population under the study was patients aged 51-60 years and majorly comprised of females. This population was representative of dry eye patients amongst the general

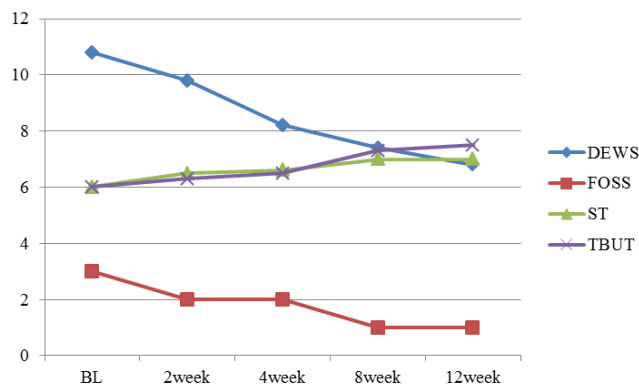


Fig. 2: Graph showing change in different parameter from baseline to 12weeks

population.¹⁰

Symptoms like foreign body sensation, feeling of dryness, photophobia showed improvement from baseline to 6 weeks. Study by ueda at el aslo showed similar results. Improvements in the symptoms of dry eye would contribute to improved quality of life.⁴

FOSS also improved from the baseline. Efficacy results have demonstrate d that when rebamipide is used to treat dry eye, there was improvement in both conjunctival and corneal parameters. Also, the study by Kinoshita et al¹¹ has reported that the fluorescein corneal staining score, lissamine green conjunctival staining score improved on treatment with rebamipide. These results were also similar to previous trials.¹¹ Rebamipide has been shown to increase the secretion of mucin like substances in the cornea and conjunctiva in a pre clinical trial.¹²

Evidence states that Rebamipide increases the number of conjunctival goblet cells⁴ and thereby enhances the mucin levels on the ocular surface.^{13,14} Decrease in the goblet cell density and reduced mucin levels have been observed in patients with dry eye, and the mechanism of action of rebamipide will aide in alleviating the symptoms in those suffering from dry eye.¹⁵

TBUT also showed improvement from baseline to 12 weeks. It was statistically significant only at 4 weeks but not at 12 weeks. Koh et al¹⁶ and Kinoshita et al¹¹ have both reported significant increases in the mean tear film break-up time in their studies. Study by Ude et al⁴ reported that TBUT was significantly improved only at 8 weeks.

No statistically significant improvement in schirmer test was shown by Kinoshita et al¹¹ and Ude el al⁴ in their studies comparing rebamipide and placebo groups.

Being preservative free, rebamipide 2% ophthalmic suspension, eliminates problem like the tear film instability, decrease in goblet cell density, loss of integrity of the corneal epithelial surface, squamous metaplasia of the conjunctiva and damage to the deeper ocular tissues. Of the extra ocular manifestations, dysgeusia (bitter taste) was

observed in 9.7% of the rebamipide group in the study conducted by Kinoshita et al.¹⁷

6. Conclusion

Rebamipide helps in improving the ocular surface condition in patients with dry eye, especially in severe conditions. It is well-tolerated and has a relatively safe clinical profile and hence it is a useful treatment option for dry eye.

7. Source of Funding

None.

8. Conflict of Interest

None.

References

- Gayton JL. Etiology, Prevalence, and Treatment of dry eye disease. *Clin Ophthalmol.* 2009;3:405–412.
- Friedman NJ. Impact of dry eye disease and treatment on quality of life. *Curr Opin Ophthalmol.* 2010;21:310–316.
- Reddy P, Grad O, Rajagopalan K. The economic burden of dry eye: a conceptual framework and preliminary assessment. *Cornea.* 2004;23(8):751–761.
- Ueda K, Matsumiya W, Otsuka K, Maeda Y, Nagai T, et al. Effectiveness and relevant factors of 2 % rebamipide ophthalmic suspension treatment in dry eye. *BMC Ophthalmol.* 2015;15. Available from: [58.D0I10.1186/s12886-015-0040-0](https://doi.org/10.1186/s12886-015-0040-0).
- Dorennavar L, Maurya RP, Singh VP, Singh MK, Sharma K, et al. The role of Rebamipide ophthalmic suspension in management of dry eye disease. *Indian J Clin Exp Ophthal.* 2015;1(4):191–196.
- Matsumoto Y, Ohashi Y, Watanabe H, Tsubota K. Efficacy and safety of diquafosol ophthalmic solution in patients with dry eye syndrome: a Japanese phase 2 clinical trial. *Ophthalmol.* 2012;119:1954–60.
- Hikichi T, Yoshida A, Fukui Y, Hamano T, Ri M, et al. A multicenter study on definite and probable dry eyes. *Jpn J Clin.* 1994;48:1621–1625.
- Kanaya Y, Hori Y, Muramatsu R, Deguchi Y, Shiba T, Maeno T. Comparison of Tear Meniscus Height after Different Methods of Fluorescein Staining. *J Eye.* 2013;30:1750–1753.
- Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol.* 1969;82:10–14.
- The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop. *Ocul Surf.* 2007;5:93–107.
- Kinoshita S, Awamura S, Oshiden K, Nakamichi N, Suzuki H, et al. Rebamipide Ophthalmic Suspension Phase II Study Group. Rebamipide (OPC-12759) in the treatment of dry eye: a randomized, double-masked, multicenter, placebo-controlled phase II study. *Ophthalmol.* 2012;119(12):2471–2478.
- Urashima H, Okamoto T, Takeji Y. Rebamipide increases the amount of mucin-like substances on the conjunctiva and cornea in the N-acetylcysteine-treated in vivo model. *Cornea.* 2004;23:613–619.
- Urashima H, Takeji Y, Okamoto T. Rebamipide increases mucin-like substance contents and periodic acid Schiff reagent-positive cells density in normal rabbits. *J Ocul Pharmacol Ther.* 2012;28:264–270.
- Takeji Y, Urashima H, Aoki A, Shinohara H. Rebamipide increases the mucin-like glycoprotein production in corneal epithelial cells. *J Ocul Pharmacol Ther.* 2012;28:259–263.
- Rivas L, Oroza MA, Perez-Esteban A, Murube-Del-Castillo J. Morphological changes in ocular surface in dry eyes and other disorders by impression cytology. *Graefes Arch Clin Exp Ophthalmol.* 1992;30:329–334.

16. 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.
17. Kinoshita S, Oshiden K, Awamura S, Suzuki H, Nakamichi N, et al. Rebamipide Ophthalmic Suspension Phase 3 Study Group A randomized, multicenter phase 3 study comparing 2% rebamipide (OPC-12759) with 0.1% sodium hyaluronate in the treatment of dry eye. *Ophthalmol*. 2013;120(6):1158–1165.

Sujata Sajjan PG Resident

K Satish Professor and HOD

Raghavendra R Assistant Professor

Mohammed Abdul Kayoom PG Resident

Author biography

D.N Prakash Associate Professor

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