To study the effect of Rebamipide 2% ophthalmic suspension in Dry eye

Agarwal R.[1], Vohra M.[2], Gupta P.[3], Rohatgi S.[4]

[1]Dr. Ruchika Agarwal, Associate Professor, Rama Medical College and Research Centre, Mandhna, Kanpur, [2]Dr. Malini Vohra, Assistant Professor, Rama Medical College and Research Centre, Mandhna, Kanpur (U.P), [3]Dr. Preeti Gupta, Dr. Ram Manohar Lohiya Combined Hospital, Lucknow (U.P), India, [4]Dr. Sanjeev Rohatgi, Professor, Rama Medical College and Research Centre, Mandhna, Kanpur (U.P), India.

Corresponding Author: Dr. Malini Vohra, 126/16, Block R, Govindnagar, Kanpur (U.P), India. Email-drmalinivohra@gmail.com

Abstract

Purpose: Current available therapies such as lubricants and anti-inflammatory drugs alleviate symptoms and reduce signs of dry eye. Various drugs have been developed to treat the underlying cause of disease .One such drug is Rebamipide 2% ophthalmic suspension. Our study aims to study the efficacy of Rebamipide 2% ophthalmic suspension in treating dry eye. **Material and methods:** It was a Prospective interventional study in which 60 patients were divided into two groups. Group A included those 30 cases which were subjected to rebamipide 2% (q.i.d) and 0.3% Hydroxypropylmethyl cellulose (q.i.d). Group B included those 30 cases, which were subjected to 0.3% Hydroxypropylmethyl cellulose (q.i.d) alone. Follow up was done at an interval of two weeks till twelve weeks. Beside recording improvement in symptoms following tests were performed at each visit - Schirmer's test, Fluoresce in staining test, Fluoresec in tear break up time (TBUT). **Results:** Cases treated with Rebamipide 2% eye drops showed a statistically significant improvement in both subjective and objective measures.There was a significant improvement in grittiness besides significant improvement in schirmers ($p<0.001$)), TBUT ($p<0.01$) and Fluorescien staining of cornea ($p<0.001$). The control group showed no significant difference compared to baseline. **Conclusion:** Our data suggests that rebamipide 2% ophthalmic suspension is effective in treating dry eye.

Keywords: Rebamipide, Schirmer's test, Tear film break up time.

Introduction

Dry eye syndrome (DES) is a disorder of the preocular tear film that results in damage to the ocular surface and is associated with symptoms of ocular discomfort. DES is a common disorder of eyes affecting a significant percentage of the population, especially those older than 50 years of age. Despite affecting millions and substantially altering the productivity and quality of life, treatment modalities for dry eye disease have been palliative, at best consisting of lubricating eye drops or punctal occlusion procedures, which focus either on tear replacement or tear preservation and provide only temporary and incomplete symptomatic relief.

But recently the understanding of underlying pathophysiological process of the disease has been discovered. It is now known that dry eye disease occurs as a result of underlying immune-mediated inflammatory process that affects the lacrimal gland and the ocular surface not only in Sjogrens but also Non-Sjogrens KCS. This inflammatory process ultimately disrupts the normal homeostatic functional unit responsible for normal tear production. With this emerging new concept, interesting advances in the treatment of dry eye diseases are being introduced to control the underlying pathogenesis of the disease. One such modality of treatment is the use of topical Rebamipide.

Current available therapies such as lubricants and anti-inflammatory drugs alleviate symptoms and reduce signs of DED; however the underlying cause of disease remains unattended. Recently, a new mucin-related drug. have been approved for treating dry eye rebamipide (Mucosta ophthalmic suspension UD2%; Otsuka Pharmaceutical. Co) Rebamipide is a mucosal

Manuscript received: 4th August 2018
Reviewed: 14th August 2018
Author Corrected: 20th August 2018
Accepted for Publication: 25th August 2018

protective medicine [1,2]. It increases gastric endogenous prostaglandins E2 and I2 to promote gastric epithelial mucins, which scavenge oxygen free radicals and have other anti-inflammatory actions. Rebamipide's biological effects include cytoprotection, wound healing, and inflammation prevention in a variety of tissues as well as gastrointestinal mucosa [1,2,3,4]. With respect to dry eye, rebamipide promotes the healing of corneal and conjunctival injuries by increasing secretion of both membrane-associated and secreted-type mucins. Rebamipide has been approved for treatment of dry eye in Japan since January 2012 and is being developed for this use in the United States.

The present study was undertaken to investigate the efficacy of topical Rebamipide ophthalmic emulsion for treatment of patients with dry eyes.

Material and Methods

Type of study- Prospective interventional case study was conducted

Place of study- Cornea Clinic of Department of Ophthalmology, Rama Medical College and Research centre Mandhna, Kanpur.

The study included 60 patients attending the OPD and Cornea Clinic of the Department of Ophthalmology, Rama Medical College and Research centre Mandhna, Kanpur.

Inclusion criteria- Persistence of signs and symptoms of dry eye disease despite the conventional management, which may have included - artificial tear: drops, gels and ointments, topical non – steroid anti-inflammatory, topical steroids, topical antibiotics, parasympathomimetic agents or punctual occlusion.

Schirmer's test reading of less than 10mm after topical instillation of 4% xylocaine (schirmer's two test) was considered significant for the diagnosis of Dry eye.

Exclusion criteria-Any external ocular disease including active ocular infection, Contact lens wearers, Previous history of herpetic keratitis, Degenerative corneal diseases,Pregnant and lactating females and those on systemic drugs like Beta-blockers, Anticholinergics, and Halothane etc.

All medications both systemic and local (except topical HPMC 0.3%) were stopped for two weeks before taking the baseline readings. Although required data from both the eyes of each case was collected but the data from the worse eye was included in the study. In cases of similar data on both sides the right eye was chosen for the study.

Statistical method– Paired t test was used for comparing the efficacy of two treatment protocols given.

Study Procedure- Before the commencement of treatment in each case it was ensured that no topical or systemic medicine was being used and if it was being used they were instructed to discontinue all medicines for two weeks. During this washout period they were allowed to use HPMC 0.3% (q.i.d). Observations at the end of this wash out period served as the baseline reading.

Efficacy was evaluated with both objective and subjective measures. Objective measures of efficacy included the degree of fluorescein staining, volume of tear secretion as measured by Schirmer's test; tear film quality as assessed by fluorescein tear break up time (FTBUT). Subjective measures of efficacy included a dry eye symptom questionnaire. Safety was assessed via adverse events, any systemic side effects, adverse haematological event, vital signs, physical examination, visual acuity, intra ocular pressure, ophthalmoscopy and slit lamp examination. Two groups comprising of 30 cases each were enrolled for the present study. Group A included those 30 cases which were subjected to rebamipide 2% (q.i.d) and 0.3% Hydroxypropylmethyl cellulose (q.i.d). Group B included those 30 cases, which were subjected to 0.3% Hydroxypropylmethyl cellulose (q.i.d) alone.

An informed consent was obtained from each case at the initial visit followed by a detailed history, examination and investigations. Observations were noted in a standard proforma. Follow up was done at an interval of two weeks till twelve weeks. The following tests were performed in the following sequence: Schirmer's test (To assess tear volume or Secretion), Fluorescein staining test (To assess ocular surface damage), Fluoresecin tear break up time (FTBUT) (To assess tear film stability).

The following tests were performed in the following sequence:

Schirmer's test (To assess tear volume or Secretion)

Schirmer's Strip (Whatman filter paper no. 41) was used (length = 35mm, width = 5mm). A drop of topical anesthetic was instilled. After 2 minutes Schirmer's

strips were folded and placed at the junction of the middle and lateral one thirds of the inferior cul-de-sac. The patient was instructed to look straight ahead and was allowed to blink normally during the test. After 5 minutes the strip was removed and the length of moistened part measured.

Interpretation: Normal: > 10mm, Mild: 5-10mm, Moderate: 3-5mm, Severe: <3mm

Fluorescein staining test (To assess ocular surface damage) Temporal conjunctiva touched with a 1mg fluorescein strip wetted with a drop of sterile saline. Excess fluid was taken off the strip before application. Patient was asked to blink several times and now examined under cobalt blue filler on a slit lamp. Presence of Inter palpebral punctate or confluent corneal and conjunctival staining was looked for and recorded. Fluoresecin tear break up time (FTBUT) (To assess tear film stability) Patient was seated comfortably before a slit lamp, 1mg of fluorescein impregnated strip was wetted with a drop of sterile isotonic saline. It was then introduced gently in the inferior cul-de-sac, the patient was instructed to take several blinks, and the blue exciter filter turned on, 10 x magnification. The patient was now asked to keep eyes open without blinking. The time interval from the last blink to the first appearance of dark spot in fluosescein stained film was noted.

Interpretation: Normal: >10 seconds, Mild: 5-10 seconds, Moderate: 3-5 seconds, Severe: <3 seconds

Results

As the cases were randomly selected the population under the study was predominantly middle aged in both the groups. 41-50 years was the most common age group (38.33%) followed by the age group 31-40 years (25%). The percentage of females (55%) was slightly more than males (45%).

Although the cases presented with a complex symptomatology but the most common symptom at presentation was foreign body sensation in the cases of both the groups (Table 1&2).

With due course of time over a period of three months the cases in Group A showed statistically significant improvement (p value <0.01) in all the symptoms especially foreign body sensation and grittiness. The rate of improvement was slow in the first month but was rapid in the last few weeks of study. While in Group B no significant improvement was noticed and the symptoms remained almost static.

Table-1: Symptoms in Group A.

Symptoms	0wk	2 wks	4 wks	6wks	8wks	10 wks	12wks	p value
Itching	15	14	10	8	6	4	4	<0.01
Burning	10	9	8	7	4	3	1	<0.01
FB sensation	22	17	14	11	7	5	2	<0.001
Redness	14	12	8	7	6	5	3	<0.01
Photophobia	10	11	10	9	4	2	1	<0.01

Table-2: Symptoms in Group B.

Symptoms	0wk	2 wks	4 wks	6wks	8wks	10 wks	12 wks	p value
Itching	16	15	12	11	12	10	12	>0.05
Burning	9	9	9	7	7	6	7	>0.05
FB sensation	24	22	21	18	20	17	19	>0.05
Redness	16	15	13	13	12	12	12	>0.05
Photophobia	10	9	8	7	8	8	7	>0.05

As per the inclusion criterion all the cases in the study group had schirmer's less than 10 mm with a mean reading of 4.30mm (S.D=1.49) in Group A and 4.47mm (S.D=1.59) in Group B at the start of the study (Table 3).

In Group A as the therapy was started the mean increased to 4.57mm (S.D=1.55) at the end of one month, 5.47mm (S.D=1.48) at the end of second month and became 5.83mm (S.D=1.6) at the end of the study. The increase in mean value was found to be statistically highly significant (p value <0.001) after application of paired student 't' test

In Group B after one month mean schirmer's was 4.47 mm (S.D=1.59), 4.53mm (S.D=1.68) at the end of second month and 4.58 (S.D=1.75) mm at the end of third month and so the mean value remained almost static over the study period and the increment seen was not significant

Table-3: Schirmer's test (mm).

Group	0wk mean (S.D)	2wks mean (S,D)	4wks mean (S.D)	6wks mean (S.D)	8wks mean (S.D)	10wks mean (S.D)	12wks mean (S.D)	P value
A	4.30 (1.49)	4.50 (1.55)	4.57 (1.55)	5.00 (1.70)	5.47 (1.48)	5.83 (1.60)	5.83 (1.60)	<0.001
B	4.47 (1.59)	4.47 (1.59)	4.47 (1.59)	4.50 (1.66)	4.53 (1.68)	4.57 (1.68)	4.58 (1.75)	>0.05

At initial visit in Group A BUT ranged from 5 to 12 seconds with a mean of 7.80 seconds (S.D=1.45) while it ranged from 5 to 10 seconds with a mean of 7.63 seconds (S.D=1.30) in Group B(Table 4).

The mean BUT progressively increased in Group A from 7.80 seconds to 8.07 seconds at the end of first month, 9.17 seconds at the end of second month and 9.93 seconds and the end of third month and this increment was found to be statistically significant. While in Group B the mean BUT did not show any significant increment during the study period.

Table-4: Tear film break up time (seconds)

Group	0wk mean (S.D)	2wks mean (S,D)	4wks mean (S.D)	6wks mean (S.D)	8wks mean (S.D)	10wks mean (S.D)	12wks mean (S.D)	P value
A	7.80 (1.45)	7.80 (1.45)	8.07 (1.44)	8.63 (1.38)	9.17 (1.26)	9.83 (1.29)	9.93 (1.39)	<0.001
B	7.63 (1.30)	7.63 (1.30)	7.65 (1.25)	7.43 (1.30)	7.60 (1.45)	7.67 (1.49)	7.79 (1.28)	>0.05

At the initial visit, 21 cases in Group A and 20 cases in Group B stained positively for fluorescein. After one month, 19 cases in Group A and 20 cases in Group B stained positively. After two months of therapy the number of stain positive cases reduced to 14 in Group A but remained 20 in Group B. At the end of therapy only 4 cases in Group A stained positively while in Group B 18 cases still remained stain positive (Table 5).

All the changes in Group A were stastically significant (P< 0.001) while in Group B no significant improvement was observed.

Table- 5: Fluorescein staining of the cornea and conjunctiva.

GROUP	0wks	2wks	4wks	6wks	8wks	10wks	12wks	'P'value
A	21	20	19	15	14	11	4	<0.001
B	20	21	20	20	19	19	18	>0.05

Discussion

Dry eye syndrome is the most common ophthalmic manifestation and untreated dry eye can cause increased risk of ocular infection, corneal ulcer, and blindness.

Current available therapies such as lubricants and anti-inflammatory drugs alleviate symptoms and reduce signs of DED; however the underlying cause of disease

remains unattended. The treatments of kerato conjunctivitis are varied. The goals of treatment are to relieve the symptoms of dry eye, improve the patient's comfort, return the ocular surface and tear film to the normal state, and, whenever possible, prevent corneal damage [5]. Treatment may range from education, environmental or dietary modifications, artificial tear substitutes, punctal plugs, and topical and/or systemic anti-inflammatory medications to surgery. The drug rebamipide was launched for the treatment of dry eye syndrome in Japan in 2012 as Mucosta ophthalmic suspension UD2%. It increases the level of mucin in the tear film covering the conjunctiva and cornea. In addition to increasing the proliferation of cultured rat conjunctival goblet cells, suppression of inflammation such as T cell activation and Th1 cytokine production has been reported [6,7]. Ophthalmic rebamipide suspensions are sterilized, single-use disposable therapeutics that lack preservatives to prevent secondary pollution. Thus, rebamipide is expected to have a beneficial effect on the ocular surface. Therefore, we attempted to evaluate its efficacy in dry eye disease.

Corneal staining is the hallmark of dry eye disorder and is believed to warrant treatment even without accompanying symptoms to prevent complications of infection, corneal scarring and blurred vision. A significant decrease in corneal and conjunctival staining is of particular clinical relevance because it indicates an improvement in the integrity of the ocular surface and tear film. In the present study, we found a statistically significant decrease in the fluorescein staining of cornea in eyes treated with rebamipide after 8 weeks, as compared to Group using lubricant eye drops only.

Another group recently demonstrated that rebamipide increases barrier function in a human corneal epithelial cell line, as measured by transepithelial electrical resistance [8]. Therefore, it is likely that rebamipide can increase corneal barrier function in vivo and in vitro. The in vitro study also demonstrated the anti-inflammatory effects of rebamipide because rebamipide inhibited increases in interleukin- (IL-) 6 and IL-8 induced by tumor necrosis factor (TNF) [8].

A comparison of 2% rebamipide ophthalmic suspension with 0.1% sodium hyaluronate in a randomized multicenter Phase 3 study showed marked improvement in signs and symptoms of DED as compared to sodium hyaluronate [9]. Otsuka Pharmaceutical Co., Ltd. in partnership with Acucela Inc. has initiated Phase 3 clinical trial to determine the efficacy and safety of 2% rebamipide ophthalmic suspension in US patients with DES [10].

TBUT is widely used as a parameter to noninvasively evaluate the stability of the tear layer [11]. In a report by Kinoshita et al ophthalmic rebamipide suspensions were administered in patients with dry eye, resulting in a significant increase in TBUT versus the placebo group [12]. In the present study, we found that there was a statistically significant increase in TBUT time in the group using Rebapimide eye drops. These results suggest that ophthalmic rebamipide suspensions may have beneficial effect in dry eye syndrome. Koh et al reported finding significant increases in the tear film break-up time, and there were significant upward curves from the baseline in terms of the total corneal higher-order aberrations, coma-like aberrations, and spherical-like aberrations after the application of rebamipide[13].

Schirmer's test is done to assess tear volume and secretion. In our study there was a significant increase in schirmers's value in the rebapimide treated group. In a study using cultured human corneal epithelial cells, rebamipide inhibited IL-6 and IL-8 production induced by tumor necrosis factor alpha (TNF-α) [8]. Anti-inflammatory effects such as inhibition of cytokine production and infiltration of inflammatory cells by rebamipide can result in an improvement of this type of dry-eye condition.

The limitations of the current study include a small sample size and a relatively short follow-up duration.

Conclusion

Our findings confirm our belief that adding topical rebamipide to the treatment of patients with dry eye is highly beneficial. Besides providing symptomatic relief it corrects the underlying disease process also. It provides significant improvement in patients symptoms like itching and burning. It also improves the amount and quality of tears in cases of dry eye which is evident in various tests like Schirmer's test, Cornealstaining. It will be of special help in immune mediated dry eye disorders like Sjogren's syndrome.

Current study Added to the existing Knowledge- Usage of Rebamipide drops in patients of Dry eye in combination with conventional lubricants is highly effective

Contribution from Various authors

Dr.Ruchika Agarwal– Designing of study and manuscript preparation.

Dr. Malini Vohra– Maintenance of data and follow up of patients.

Dr.Preetigupta– Statistical analysis and collection of reverences.

Dr.Sanjeev Rohatgi– Critical analysis of the whole study.

Funding: Nil, **Conflict of interes**t: Nil
Permission from IRB: Yes

References

1. Tanaka H, Fukuda K, Ishida W, Harada Y, Sumi T, Fukushima A. Rebamipide increases barrier function and attenuates TNF alpha-induced barrier disruption and cytokine expression in human corneal epithelial cells. Br J Ophthalmol 2013jul; 97(7): 912–6.

2. Ueta M, Sotozono C, Yokoi N, Kinoshita S. Rebamipide suppresses Poly I: C-stimulated cytokine production in human conjunctival epithelial cells. J Ocul Pharmacol Ther 2013 Sep; 29(7): 688–93.

3. Kimura K, Morita Y, Orita T, Haruta J, Takeji Y, Sonoda KH. Protection of human corneal epithelial cells from TNF-alpha-induced disruption of barrier function by rebamipide. Invest Ophthalmol Vis Sci 2013 Apr 17; 54 (4): 2572–760.

4. Kashima T, Akiyama H, Miura F, Kishi S. Resolution of persistent corneal erosion after administration of topical rebamipide. Clin Ophthalmol 2012; 6: 1403–6.

5. "Methodologies to diagnose and monitor dry eye disease: report of the diagnostic methodology subcommitteeof the internationaldryeyeworkshop. The Ocular Surface 2007 Apr;5(2):108-52.

6. Rios JD, Shatos M, Urashima H, Tran H, Dartt DA. OPC-12759 increases proliferation of cultured rat conjunctival goblet cells. Cornea 2006jun; 25(5): 573–81.

7.Sugai S, Takahashi H, Ohta S, Nishinarita M, Takei M, Sawada S, Yamaji K, Oka H, Umehara H, Koni I, Sugiyama E, Nishiyama S, Kawakami A. Efficacy and safety of rebamipide for the treatment of dry mouth symptoms in patients with Sjogren's syndrome: a double-blind placebo-controlled multicenter trial. Mod Rheumatol 2009; 19 (2): 114–24.

8. H. Tanaka, K. Fukuda, W. Ishida, Y. Harada, T. Sumi, and A. Fukushima. Rebamipide increases barrier function and attenuates TNFα- induced barrier disruption and cytokine expression in human corneal epithelial cells. Br J Ophthalmol. 2013;97 (7) :912–916.

9.S. Kinoshita, K. Oshiden, S. Awamura, H. Suzuki, N. Naka- michi, and N. Yokoi. A randomized, multicenter phase 3 study comparing 2% rebamipide (OPC-12759) with 0.1% sodium hyaluronate in the treatment of dry eye. Ophthalmology. 2013 Jun; 120(6): 1158-65.

10. "Acucela and Otsuka Pharmaceutical Announce the Initiation of a Phase 3 Clinical Trial to Evaluate Rebamipide Ophthalmic Suspension in Patients with Dry Eye Syndrome," http://www .acucela.com/Read-About-Us/Press-Releases.

11. M. S. Norn. Desiccation of the precorneal tear film, corneal wetting time. Acta Ophthalmologica.1969;47 (4) : 865–880.

12. S. Kinoshita, S. Awamura, K. Oshidenetal. Rebamipide (OPC-12759) in the treatment of dry eye: a randomized, double-masked, multicenter, placebo-controlled phase II study. Ophthalmology. 2012 Dec; 119 (12): 2471–2478.

13 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 Sep;32(9):1219–1223.

……...

How to cite this article?

Agarwal R, Vohra M, Gupta P, Rohatgi S. To study the effect of Rebamipide 2% ophthalmic suspension in Dry eye. Trop J Ophthalmol Otolaryngol.2018;3(3):45-50.doi:10.17511/jooo.2018.i03.07

……