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Efficacy of 2% Rebamipide Eyedrops in Patients with Superior Limbic Keratoconjunctivitis

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Abstract: Rebamipide, an oral mucosal protective agent approved in Japan for gastric mucosal disorders and gastritis has been recently introduced as an ophthalmic solution. Being a mucin secretagogue along with a goblet cell protective property, rebamipide has been proved to relieve symptoms of dry eye. Amongst its various uses implicated, superior limbic keratitis, a rare chronic inflammatory condition is also sited. To investigate the efficacy of 2% Rebamipide eye drops in patients of Superior limbic keratitis (SLK). In a prospective study, 32 eyes from 26 patients with SLK were treated with 2% Rebamipide, instilled as 1 drop in the affected eye, Qid for 4 weeks. Signs and symptoms were evaluated at the beginning of treatment and at 4 weeks. Objective signs were evaluated by fluorescein staining, Tear film breakup time (TBUT), Schirmer's test and conjunctival impression cytology. Symptoms were evaluated by the ocular surface disease index (OSDI) score on a scale of 0 to 100. 27 eyes showed disappearance of SLK, and 5 eyes showed residual fluoroscein staining. TBUT improved for 25 eyes (78.12%) and there was improvement in the schirmer's test results in 22 eyes (68.75%). OSDI score improved in 24 eyes (75%).No adverse effects seen. Conjunctival Goblet cell count increased in 23 (71.8%) eyes. Remission of symptoms was seen in significant no of cases. Study shows that 2% Rebamipide is effective and safe in improving both signs and symptoms of SLK.
Keywords: Rebamipide eye drops, superior limbic keratoconjunctivitis, conjunctival goblet cell, OSDI

INTRODUCTION

Superior limbic keratoconjunctivitis is an uncommon chronic inflammation of the superior limbus and superior bulbar and tarsal conjunctiva. It affects one or both eyes and is most commonly seen in middle aged women. The etiology is largely unknown. However a large number, that is over 50 % of patients of SLK have abnormal thyroid function (mostly hyperthyroidism). 3% of patients with thyroid disease have SLK [9]. Keratoconjunctivitis sicca is seen in 25 % of patients with SLK. Other associations of SLK are contact lens wear, host vs graft reactions. This condition occurs when there is tear film insufficiency and an excess or lax conjunctival tissue which leads to friction between the eye lid and conjunctiva leading to blink related micro trauma. This induces an inflammatory response which in turn leads to conjunctival edema and redundancy, and hence a self- perpetuating cycle is created.

Histopathologically, SLK is characterized by keratinization of epithelial cells with dyskeratosis, acanthosis and nuclear balloon degeneration. Stromal infiltration by polymorphonucear leukocytes, plasma cells, mastocytes and lymphocytes is seen. Decreased level of mucin like glycoprotein is seen which is responsible for interaction of epithelium and mucin of conjunctiva.

The symptoms consist of foreign body sensation, burning, mild photophobia, mucoid discharge, frequent blinking, and are often intermittent. Signs in the conjunctiva are papillary hypertrophy of the superior tarsal plate, hyperemia of superior bulbar conjunctiva, limbal papillary hypertrophy. In cornea superior punctate corneal erosions and superior filamentary keratitis can be seen.

Treatment of SLK consists of lubricants that reduce friction, acetylcysteine 5% or 10% to break down filaments, mast cell stabilizers and steroids to

reduce inflammation, cyclosporin. Soft contact lens and supratarsal steroid injection can also be used. Surgically, temporary superior and/or inferior punctual occlusion, resection of superior limbic conjunctiva and conjunctival ablation by silver nitrate can be done. One of the new modalities of treatment which has shown promising results is topical rebamipide.

Rebamipide, is a mucosal protective agent with mucin secretagogue activity and is approved in Japan as an oral drug for the treatment of gastric mucosal disorders and gastritis. It has been reported that rebamipide increases production of mucin like substance in the cornea and conjunctiva of a rabbit model in which ocular mucin was decreased by N-acetylcysteine [6]. Rebamipide increased MUC1 and MUC4 gene expression in human corneal epithelial cells, promoting glycoconjugate production, an indicator of mucin like glycoprotein. It has been found in various studies that rebamipide is effective in improving objective signs(fluorescein corneal staining score, lissamine green conjunctival staining score, and tear film break up time) and subjective signs (foreign body sensation, dryness, photophobia, pain, and blurred vision) in patients of dry eye. It has been shown that rebamipide increases conjunctival goblet cell number, protects corneal and conjunctival microvilli, increase mucin like glycoprotein production, upregulates memberane associated mucins, prevents ocular surface inflammation and antagonizes effects of TNF alpha on barrier functions and cytokine expression[7]. In a retrospective study in japan, it was shown that rebamipide had definite role in improving symptoms and signs of SLK in thyroid eye disease.

Aim and Objectives

The objective of this study is to evaluate the efficacy of2% rebamipide eye drops, instilled QID for 4 weeks in patients of SLK.

METHODS AND MATERIALS

It is a prospective observational study including 26 patients, male 16 (61.53%), female 10 (38.46%), in the age group of 15- 75, attending Regional Institute of Ophthalmology, SCB medical college, Cuttack during July 2015- May 2016. After a thorough history was taken, the signs and symptoms were evaluated and the patients meeting inclusion criteria were started on 2% rebamipide ophthalmic suspension QID in the affected eye for four weeks. A total of 32 eyes from these 26 patients were studied. The patients were evaluated at a weekly interval. The signs evaluated were fluorescein corneal staining, tear film break up time, schirmers test and conjunctival impression cytology. The symptoms were evaluated on basis of the Ocular surface disease index (OSDI) score where the patients were asked a series of 12 questions, according to the answers the score was obtained on a scale of 0-100 and patients were accordingly graded into normal, mild ,moderate and severe dry eye disease.

Inclusion criteria

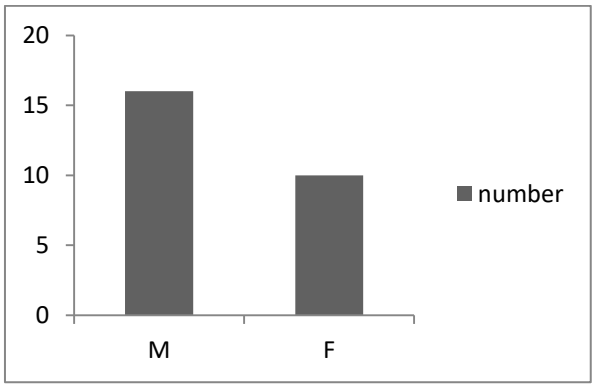
- Patients having symptoms and signs which are confirmtory to the diagnosis of Superior limbic keratoconjunctivitis.
- Patients in the age group of 15- 75.

Exclusion criteria

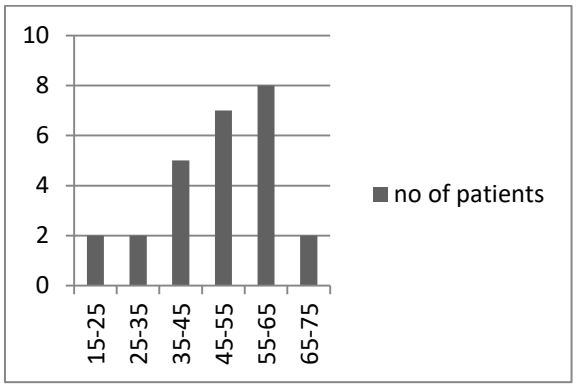
- One eyed patients
- Contact lens wearers
- Patients having other active inflammatory conditions or anterior ocular disorders like blepharitis or blepharospasm.
- Patients having known allergy to any of the components of the eye drop.
- Operation to ocular surface within 12 months or intaocular surgery within 3 months.
- Patients with continued use of eye drops.
- Patients having a punctal plug or had it removed within 3 months.

RESULTS

Demographic profile



Sex distribution



Age distribution

Efficacy evaluation
Signs
Fluorescein corneal staining

	No of patients Fl stain positive	Percentage of total with residual staining.	Percentage of total with no residual staining.
At baseline	32	100%	0
Week 1	24	75%	25%
Week 2	16	50%	50%
Week 3	9	28.12%	71.88%
Week 4	5	15.62%	84.38%

At the end of 4 weeks, only 5 patients (15.62%) showed residual fluorescein staining, and 27 patients (84.38%) showed no residual fluorescein staining.

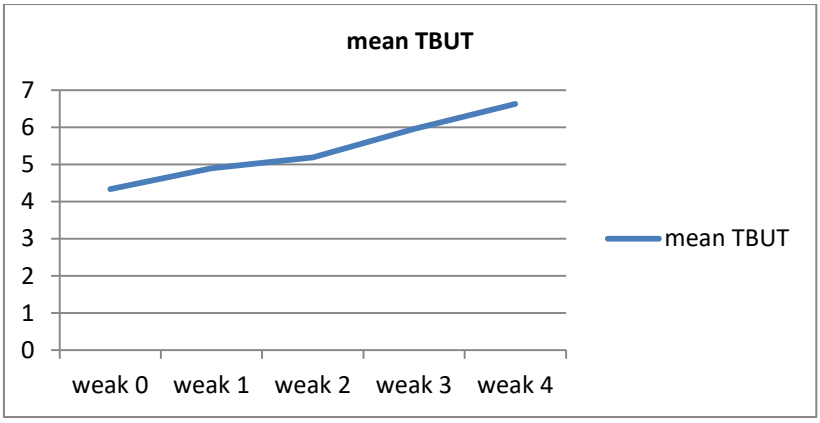
Tear film break – up time-

	No of patients showing improvement in TBUT	Percentage of patients showing improvement in TBUT
Week 1	11	34.38%
Week 2	17	53.12%
Week 3	21	65.62%
Week 4	25	78.12%

78.12% of patients showed improvement in TBUT at the end of 4 weeks.

Mean TBUT

	Mean TBUT
Baseline	4.34
Weak 1	4.90
Weak 2	5.19
Weak 3	5.96
Weak 4	6.63



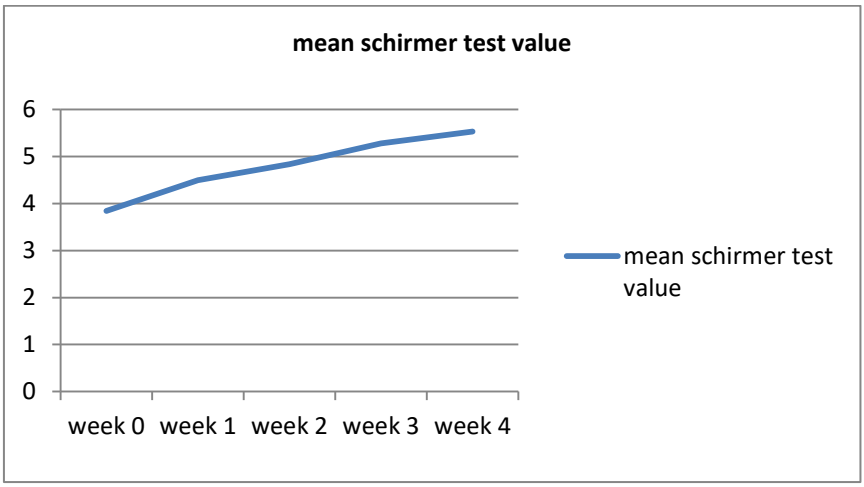
The mean TBUT improved from 4.34 seconds at baseline to 6.63 seconds at 4 weeks.

Schirmer test evaluation

	No of patients showing improvement in schirmer test results	Percentage of patients showing improvement in schirmer test results
Week 1	8	25%
Week 2	15	46.88%
Week 3	19	59.37%
Week 4	22	68.75%

Mean schirmer test reading

	Mean schirmer test reading in mm at 5 minutes
Baseline	3.84
Week 1	4.50
Week 2	4.84
Week 3	5.28
Week 4	5.53



The mean schirmet test value at 5 minutes improves from 3.84 mm to 5.53 mm at the end of 4 weeks.

Conjunctival goblet cell count

The conjunctival goblet cell count was done at baseline and at the end of 4 weeks, by impression cytology.23 patients (71.8 %) patients showed improvement in conjunctival goblet cell count.

Symptoms

According to the OSDI scores patients are divide as having normal, mild, moderate and severe dry eye disease.

	No of eyes			
	normal	Mild	moderate	Severe
Baseline	8	4	9	11
Week 1	8	6	10	8
Week 2	10	5	9	8
Week 3	17	3	6	6
Week 4	25	2	3	2

Total of 24 eyes (75 %) shows some improvement in the grade of OSDI scores. The number of eyes having severe OSDI score decreased from 11 (34.37%) to 2 (6.25%).The above table shows a definite improvement in the OSDI scores. Side effects- No side effects were recorded in all 26 patients studied.

DISCUSSION

32 eyes from 26 patients (16 male,10 female) were evaluated for symptoms and signs of SLK at the initiation of treatment with 2% rebamipide ophthalmic suspension instilled at a dose one drop four times daily in the affected eye. Follow up was done at the end of week 1,2 ,3 and 4. Definite, improvement was seen for both signs and symptoms of SLK. The fluorescein corneal staining improved for 27 eyes (84.38%) and only 5 eyes (15.62%) showed residual fluorescein staining at 4 weeks. The TBUT improved in 25 eyes (78.12%) at the end of 4 weeks and the mean TBUT improved to 6.63 seconds at 4 weeks from 4.34 seconds at baseline. The schirmer test value improved in 22 eyes (68.75%) at the end of 4 weeks and mean schirmer test value improved from 3.84 mm at baseline to 5.53 mm at the end of 4 weeks. The conjunctival goblet cell count increased in 23 eyes (71.8%) at the end of 4 weeks. 24 eyes (75 %) showed some improvement in the OSDI score grading with the number of eyes having severe dry eye disease decreasing from 11 (34.37%) to 2 (6.25%). A study conducted by shigera kinishita et al comparing the effect of 1% and 2% rebamipide over placebo in dry eye syndrome showed similar effects [1]. Studies have established the superiority of 2% rebamipide on sodium hyaluronate [2] and its usefulness in coditions like VKC/AKC has also been studied with positive outcomes [3]. Takayashi *et al*. studied the effect of 2% rebamipide solution in SLK with thyroid disease and showed improvement in both signs and symptoms [8]. Other studies have evaluated rebamipide in keratoconjunctivitis sicca and corneal refractive surgeries with encouraging results [4,5].

CONCLUSION

2% rebamipide ophthalmic suspension is effective and safe in improving both signs and symptoms of SLK and can be considered in the management of SLK.

REFERENCES

1. Kinoshita S, Awamura S, Nakamichi N, Suzuki H, Oshiden K, Yokoi N, Rebamipide Ophthalmic Suspension Long-term Study Group. A multicenter, open-label, 52-week study of 2% rebamipide (OPC-12759) ophthalmic suspension in patients with dry eye. American journal of ophthalmology. 2014 Mar 31;157(3):576-83.
2. Kinoshita S, Oshiden K, Awamura S, Suzuki H, Nakamichi N, Yokoi N, 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. Ophthalmology. 2013 Jun 30;120(6):1158-65.
3. Ueta M, Sotozono C, Koga A, Yokoi N, Kinoshita S. Usefulness of a new therapy using rebamipide eyedrops in patients with VKC/AKC refractory to conventional anti-allergic treatments. Allergology International. 2014;63(1):75-81.
4. Arimoto A, Kitagawa K, Mita N, Takahashi Y, Shibuya E, Sasaki H. Effect of rebamipide ophthalmic suspension on signs and symptoms of keratoconjunctivitis sicca in Sjögren syndrome patients with or without punctal occlusions. Cornea. 2014 Aug 1;33(8):806-11.
5. Igarashi A, Kamiya K, Kobashi H, Shimizu K. Effect of rebamipide ophthalmic suspension on intraocular light scattering for dry eye after corneal refractive surgery. Cornea. 2015 Aug 1;34(8):895-900.
6. Urashima H, Okamoto T, Takeji Y, Shinohara H, Fujisawa S. Rebamipide increases the amount of mucin-like substances on the conjunctiva and cornea in the N-acetylcysteine-treated in vivo model. Cornea. 2004 Aug 1;23(6):613-9.
7. Tanaka H, Fukuda K, Ishida W, Harada Y, Sumi T, Fukushima A. Rebamipide increases barrier function and attenuates TNFα-induced barrier disruption and cytokine expression in human corneal epithelial cells. British Journal of Ophthalmology. 2013 Jul 1;97(7):912-6.
8. Takahashi Y, Ichinose A, Kakizaki H. Topical rebamipide treatment for superior limbic keratoconjunctivitis in patients with thyroid eye disease. American journal of ophthalmology. 2014 Apr 30;157(4):807-12.
9. Kanski JJ, Bowling B. Clinical ophthalmology: a systematic approach. Elsevier Health Sciences; 2011 Apr 28.