Topical Rebamipide Treatment for Dry Eye Syndrome in Thyroid Ophthalmopathy

Prasanta Kumar Nanda[1], Bishnu Prasad Rath[2], Jayaram Meher[3]

[1]Professor and HOD, Department of Ophthalmology, SCB Medical College, Cuttack, Odisha. [2]Postgraduate Resident, Department of Ophthalmology, SCB Medical College, Cuttack, Odisha. [3]Postgraduate Resident, Department of Ophthalmology, SCB Medical College, Cuttack, Odisha.

ABSTRACT

BACKGROUND

Thyroid eye disease (TED) is prevalent in patients with thyroid abnormality and usually in hyperthyroid state. Dry eye disease in TED is multifactorial with a significant component being the inflammatory processes due to involvement of the lacrimal gland, goblet cells in the conjunctival microvilli etc. The effect of Rebamipide tablet on the gastric mucosa for healing of gastric ulcer has already been proved by many studies. Rebamipide acts on the goblet cells, microvilli functions and decrease the inflammatory process.

METHODS

42 eyes of 33 patients having thyroid eye disease were included in the study. They were evaluated with TBUT and Schirmer test using Whatman-41 stripes and using dry eye scoring system. They were diagnosed as dry eye if TBUT < 10 secs and Schirmer <5 mm/ 5 mins and dry eye score >6. These eyes were treated with eye drop Rebamipide 2% and reassessed at 8 wks. and 16 wks.

RESULTS

38 and 39 eyes showed significant improvement of dry eye state as evaluated by means of TBUT (>10 secs) and Schirmer's test (> 5 mm/ 5 mins) and decrease in the dry eye score at 8 weeks and 16 weeks of follow up respectively. No serious adverse events were reported during follow up.

CONCLUSIONS

Topical Rebamipide significantly improved the dry eye condition in patients of thyroid eye disease.

KEYWORDS

Thyroid Eye Disease, Dry Eye Disease, Rebamipide, TBUT, Schirmer's Test, OSDI

Corresponding Author:
Dr. Bishnu Prasad Rath,
1B/58, Sector-8,
Dr. D. B. Tonpe Road, CDA,
Cuttack- 753014, Odisha, India.
E-mail: rathbishnuprasad@gmail.com
DOI: 10.18410/jebmh/2019/686

Financial or Other Competing Interests: None.

How to Cite This Article:
Nanda PK, Rath BP, Meher J. Topical rebamipide treatment for dry eye syndrome in thyroid ophthalmopathy. J. Evid. Based Med. Healthc. 2019; 6(52), 3275-3279. DOI: 10.18410/jebmh/2019/686

Submission 05-12-2019,
Peer Review 08-12-2019,
Acceptance 25-12-2019,
Published 30-12-2019.

BACKGROUND

Thyroid Ophthalmopathy / Thyroid eye disease is a group of disorders affecting the eye in patients having thyroid abnormalities mostly in hyperthyroid states (Graves's disease) but can be seen in patients with hypothyroid and euthyroid states.[1] The main pathophysiology behind the development of TED is the autoantibody against the thyroid gland also act on the fibroblasts of ocular tissue.

Due to antibodies against the ocular fibroblasts, it initiates an inflammation cascade by secretion of inflammatory mediators like IL-6, IL-8, prostaglandins and GAGs. These agents cause tissue oedema of the orbital fat, extra ocular muscles, interstitial tissue and lacrimal glands. They present with epibulbar hyperaemia, swelling, tear insufficiency and instability, signs due to lid retraction, proptosis, corneal signs due to lid retraction, lack of lubrication and optic nerve compression signs.

The tear film stability is due to the action of both membrane-associated mucin present on the corneal and conjunctival microvilli and secretory mucin secreted by conjunctival goblet cells.[2,3] In TED there is decrease in both the membrane associated and secretory mucin due to the inflammatory process. TED also affects the tear secretion by affecting the lacrimal glands leading to tear insufficiency. There is also increase evaporation due to lid retraction, lid lag and proptosis. All these mechanisms may lead to development of dry eye in TED. The dry eye condition should be addressed to prevent symptoms arising from dry eye and prevent complication arising from this.

The quality of life on the basis of symptoms of patients of dry eye disease is evaluated using many different questionnaires. Among them the Ocular Surface Disease Index (OSDI) is frequently used to assess the severity of DED. The diagnosis of both symptomatic and asymptomatic DED patients can be made using tear film break up time (TBUT) and Schirmer test.

Rebamipide is a novel quinolinone derivative which act as a secretagogue for mucin and also has cytoprotective, anti-inflammatory action.[4] It up regulates the gene expression of MUC1, MUC4, MUC16, thus increases membrane associated mucin. It increases the secretory mucin level in the damaged eye by increasing secretion of mucin from goblet cells and by increasing the no of goblet cells. It attenuates the production of inflammatory cytokines like IL-6, IL-8.[5] It restores the microvilli present on the apical surface of corneal and conjunctival epithelium.

We wanted to evaluate the efficacy of 2% topical Rebamipide ophthalmic solution for treatment of dry eye disease in patients of thyroid eye disease.

METHODS

Patients with thyroid eye disease were evaluated for dry eye disease and diagnosed cases were included in the study. The patients were explained about the study in their understandable language. Consents were obtained from the patients. Patients with other ocular comorbidities, who fail to follow up, and who fail to adhere to the study were excluded from the study. It was a tertiary care hospital based prospective study conducted between April 2019 - October 2019. 42 number of eyes of 33 number of patients having thyroid ophthalmopathy and dry eye disease were included in the study. Age range of patients was 30-70 years. Patients with thyroid ophthalmopathy and dry eye disease were started with commercially available 2% Rebamipide ophthalmic suspension four times a day in the affected eye for 16 weeks and were evaluated at 8 weeks interval. The patients who were using any artificial tear preparation previously were allowed to use the same along with Rebamipide. The signs evaluated were tear film break up time and Schirmer's test (Whatman-41 stripes).

TBUT was measured by means of sodium fluorescent stripes. The stipes were wetted with the tear film without any prior eye drop or procedure in the eye. The corneal surface was observed using blue filter of the slit lamp. The time calculated till appearance of 1st break in tear film. Those who had TBUT less than 10 secs were included in the study. Schirmer's test was performed using Whatman-41 stripes. On seated position the stripes were placed in lower lid after folding at appropriate place. The length of wet stripe was noted after 5 mins. The value below 5 mm were included in our study.

OSDI Questionnaire-

Have You Experienced Any of The Following During the Last Week-						
		All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time
1	Eyes that are sensitive to light?	4	3	2	1	0
2	Eyes that feel gritty?	4	3	2	1	0
3	Painful or sore eyes?	4	3	2	1	0
4	Blurred vision?	4	3	2	1	0
5	Poor vision?	4	3	2	1	0

Table 1a

Have Problems with Your Eyes Limited you Performing any of the Following During the Last Week-							
		All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time	
6	Reading?	4	3	2	1	0	N/A
7	Driving at night?	4	3	2	1	0	N/A
8	Working with a computer or a bank machine (ATM)?	4	3	2	1	0	N/A
9	Watching TV?	4	3	2	1	0	N/A

Table 1b

Have Your Eyes Felt Uncomfortable in Any of the Following Situations During the Last Week-							
		All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time	
10	Windy conditions?	4	3	2	1	0	N/A
11	Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12	Areas that are air conditioned?	4	3	2	1	0	N/A

Table 1c

The symptoms were evaluated on basis of Ocular surface disease index (OSDI) score, a 12-questionnaire system. The 12 items were graded on a scale of 0 to 4, where 0 indicates none of the time, 1; some of the time, 2;

half of the time, 3; most of the time, 4; all the time. The total score was then calculated on the basis of a formula: OSDI = [(sum of scores of all the questions answered) × 100] / [(total number of questions answered) × 4]. So, it is a scale of disability from 0-100, with higher the score showing greater the disability. Score above 5 was taken as abnormal and were accordingly graded into normal, mild, moderate and severe dry eye disease.

RESULTS

The distribution of age and sex in the studied patients were shown by the charts below. There were 20 males and 13 females in our study. The highest percentage of patients in the age group of 30-39 yrs. (39.3%).

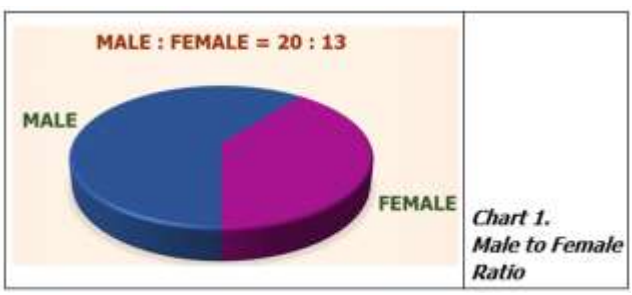

Chart 1. Male to Female Ratio

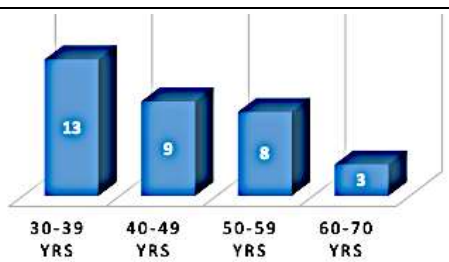

Chart 2. Age Distribution

The TBUT finding in seconds at the baseline level were compared with the TBUT at 8th and 16th week by means of number of eyes showing improvement from the baseline score. There is significant improvement in the TBUT values at both 8th week (p=0.000) and in 16th week (p=0.000).

No. of Eyes Showing Improvement at 8th wk.	%	No. of Eyes Showing Improvement at 16th wk.	%
23	54.76%	38	90.48%

Table 2. No. of Subjects Showing Improvement in TBUT

Mean Baseline TBUT	Mean TBUT at 8th Wk.	Mean TBUT at 16th Wk.
5.5714±1.63	6.857±1.68	9.5952±1.30

Table 3. Improvement in Mean TBUT in Seconds

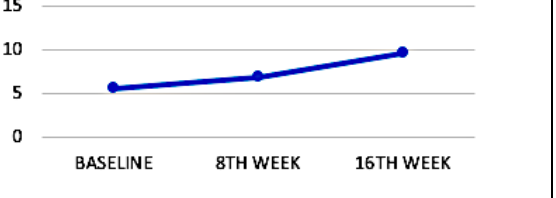

Chart 3. Mean TBUT Graph Showing Improvement

The mean TBUT values at both 8th (6.857±1.68) and 16th (9.5952±1.30) week were also compared with the base line value (5.5714±1.63) showing a significant increase in the TBUT score at 16th week.

The Schirmer's test value in terms of mm in 5 mins were compared at 8th and 16th week by means of number of patients showing improvement from baseline value. They so an increase in Schirmer test value both at 8th week (p=0.001) and 16th week (p=0.000). The mean Schirmer value also showed an increase at 16th week.

No. of Eyes Showing Improvement at 8th Wk.	%	No. of Eyes Showing Improvement at 16th Wk.	%
23	54.76	39	92.86

Table 4. No. of Subjects Showing Improvement in Schirmer's Value

Mean Baseline Schirmer's Value	Mean Schirmer's Value at 8th Week	Mean Schirmer's Value at 16th Week
3.4524±1.76	4.4286±2.29	7.9286±1.56

Table 5. Improvement in Mean Schirmer's Value

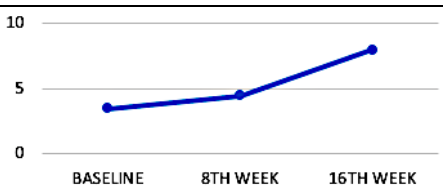

Chart 4. Graph Showing Improvement in Mean Schirmer's Value

They showed a significant improvement in symptoms by means of decrease on OSDI score both at 8th and 16th week. The number of patients who were severe group at baseline (20) as per OSDI decreased to 11 at 8th week and to 2 at 16th week. There was an increase in mild and normal cases during the study. The moderate group remained almost same throughout the study as number in the severe group decreased.

Time	Normal	Mild	Moderate	Severe
Baseline	2	8	12	20
At 8th week	12	9	10	11
At 16th week	35	3	2	2

Table 6. OSDI Score

DISCUSSION

Rebamipide is a novel quinolinone derivative synthesised and developed by a Japanese company. Initially it was developed to be used for gastric ulcer.[6,7,8,9] Its use was 1st established by animal experimental models.[10,11,12,13] In 1990, it was marketed in the form of tablet for gastric ulcer.

Many studies were done to know its effect on gastrointestinal mucosa in terms of cytoprotection, wound healing, and anti-inflammatory action.[14,15] These action on gastrointestinal mucosa is universal.[16,17] Similar to gastric mucosa the eye contains goblet cells on its surface which help in lubrication and tear film stabilisation.[2,3,18,19] So, use of Rebamipide on ocular surface diseases specially in dry eye diseases was thought. In vivo results of Rebamipide on

goblet cells of conjunctiva,[20,21,22,23] microvilli maintenance[24,25,26] and its anti-inflammatory properties[20] were encouraging.[27,28,29] In 2012 Rebamipide 2% eye suspension was lunched in Japan. Our study showed a significant improvement in dry eye condition with the use of rebamipide 2% ophthalmic suspension in dry eye diseases of TED patients in terms of TBUT. Nakashima H, et al[28] in their study on mucin removed rabbit eye model showed effect of rebamipide ophthalmic solution. Rebamipide also subsides the inflammation of lacrimal gland along with the surface epithelium. Our study showed there was significant improvement in the Schirmer test value. Kinosita et al[30,31] reported improvement in fluorescent corneal staining score, lisamine green conjunctival staining and TBUT score in DED patients treated with rebamipide ophthalmic suspension at 2 weeks and 52 weeks. But their study showed no significant improvement in Schirmer test value contrary to our study which showed a significant improvement.

Koh et al[32] found a significant increase in TBUT with application of rebamipide similar to our study. They also found improved tear stability leading to improved optical quality with rebamipide in patients of dry eye. No specific study was found for rebamipide use in thyroid eye disease with dry eye disease after search of Google scholar and Pubmed. But studies were done on the effects of rebamipide ophthalmic suspension on superior limbic keratopathy (SLK),[33] lagophthalmos,[34] lid wiper epitheliopathy[35] and persistent corneal erosion.[36] Takahashi et al reported that thyroid eye disease patients with SLK after using topical rebamipide showed an improvement and complete disappearance of SLK in 84.8% of patients after treatment. They suggested rebamipide as first line of treatment in such patients. We used OSDI scoring system to assess the quality of life of the subjects and to classify them with respect to dry eye. It has a simple 12 questions mainly concentrating on symptoms on last week.

Use of this questionnaire for DED was validated by many studies. Our study showed there is reduction in severe group and increase in normal and mild group during the study period. The moderate group showed almost no change as the severe group subjects became moderate group. Our study showed a positive effect of rebamipide ophthalmic 2% suspension on dry eyes of TED patients. The limitations of our study that it included lesser number of subjects and all signs of DED were not taken into account and also done for a shorter interval. Larger studies should be performed with special importance to TED and for longer period.

CONCLUSIONS

Our study showed a significant improvement in signs of dry eye disease in patients of thyroid eye disease in terms of TBUT and Schirmer's test at 8th and 16th week of treatment with 2% Rebamipide ophthalmic suspension. There was also improvement in the quality of life of these patients measured by OSDI questionnaire. We suggest use of Rebamipide in patients of TED may be along with other lubricating solutions.

ACKNOWLEDGEMENTS

We are thankful to Prof Dr. Sumita Mohapatra for her insights and support. Special thanks to Kankotree Rath for helping in data compilation.

REFERENCES

[1] Thyroid eye disease. British Thyroid Foundation, Revised 2019.
[2] Mantelli F, Argüeso P. Functions of ocular surface mucins in health and disease. Curr Opin Allergy Clin Immunol 2008;8(5):477-483.
[3] Gipson IK, Argueso P. Role of mucins in function of corneal and conjunctival epithelia. Int Rev Cytol 2003;231:1-49.
[4] Haruma K, Ito M. Review article: clinical significance of mucosal protective agents: acid, inflammation, carcinogenesis and rebamipide. Aliment Pharmacol Ther 2003;18 Suppl 1:153-159.
[5] Ueta M, Sotozono C, Yokoi N, et al. Rebamipide suppresses polyI: C-stimulated cytokine production in human conjunctival epithelial cells. J Ocul Pharmacol Ther 2013;29(7):688-693.
[6] Yamasaki K, Ishiyama H, Imaizumi T, et al. Effect of OPC-12759, a novel antiulcer agent on chronic and acute experimental gastric ulcer, and gastric secretion in rats. Jpn J Pharmacol 1989;49(4):441-448.
[7] Uchida M, Tabusa F, Komatsu M, et al. Studies on 2(1H)-quinolinone derivatives as gastric ulcer active agents. 2-(4-Chlorobenzoylamino)-3-(2(1H)-quinolinone-4-yl) propionic acid and related compounds. Chem pharm Bull 1985;33(9):3775-3786.
[8] Nebiki H, Higuchi K, Arakawa T, et al. Effect of rebamipide on helicobactor pylori infection in patients of peptic ulcer. Dig Dis Sci 1998;43(9 Suppl):203S-206S.
[9] Kobayashi M, Takeuchi M, Hashimoto S, et al. contributory factors to gastric ulcer healing after endoscopic submucosal dissection including the promoting effect of rebamipide. Dig Dis Sci 2012;57(1):119-126.
[10] Ro JY, Kim JY, Kim KH. The inhibitory mechanism of rebamipide on the mediator release in the guinea pig lung mast cells activated with specific antigen- antibody reactions. Pharmacology 2001;63(3):175-184.
[11] Saad SY, Najjar TA, Al-Sohaibani MO. The effect of rebamipide on cisplatin induced nephrotoxicity in rats. Pharmacol Res 2000;42(1):81-86.
[12] Hong KW, et al. Effect of rebamipide on liver damage and increased tumour necrosis factor in a rat model of endotoxin shock. Dig Dis Sci 1998;43(9 Suppl):154S-159S.

[13] Kishimoto S, Haruma K, Tari A, et al. Rebamipide an anti-ulcer drug, prevents DSS induced colitis formation in rats. Dig Dis Sci 2000;45(8):1608-1616.
[14] Naito Y, Yoshikawa T, Tanigawa T, et al. Hydroxyl radical scavenging by rebamipide and related compounds: electron paramagnetic resonance study. Free Radical Boil Med 1995;18(1):117-123.
[15] Yoshikawa T, Naito Y, Tanigawa T, et al. Free radical scavenging activity of novel anti-ulcer agent rebamipide studied by electron spin resonance. Arzneimittelforschung 1993;43(3):363-366.
[16] Arakawa T, Higuchi K, Fujiwara Y, et al. 15th anniversary of rebamipide: looking ahead to new mechanism and new application. Dig Dis Sci 2005;50 Suppl 1:S3-S11.
[17] Matsuda T, Ohno S, Hirohata S, et al. Effect of rebamipide as adjunctive therapy in treatment of recurrent oral aphthous ulcers in patients with Behcet's disease: a randomised, double-blind, placebo-controlled study. Drugs R D 2003;4(1):19-28.
[18] Arugueso P, Balaram M, Spurr-Michaud S, et al. Decreased level of goblet cell mucin MUC5AC in tears of patients with Sjogren syndrome. Invest Ophthalmol Vis Sci 2002;43(4):1004-1011.
[19] Cennamo GL, Del Prete A, Forte R, et al. Impression cytology with scanning electron microscopy: a new method in the study of conjunctival microvilli. Eye (Lond) 2008;22(1):138-143.
[20] Urashima H, Okamoto T, Takeji Y, et al. Rebamipide increases the amount of mucin like substances on the conjunctiva and cornea in the N-acetylcysteine-treated in vivo model. Cornea 2004;23(6):613-619.
[21] Yasuhiro T, Hideo N, Yoto K, et al. Effect of rebamipide ophthalmic suspension on capsaicin induced corneal epithelial damage in rats. Journal of the Eye 2013;30(9):1309-1313.
[22] Rios JD, Shatos M, Urashima H, et al. OPC-12759 increases proliferation of cultured rat conjunctival goblet cells. Cornea 2006;25(5):573-581.
[23] Rios JD, Shatos MA, Urashima H, et al. Effect of OPC-12759 on EGF receptor activation, p44/p42 MAPK activity, and secretion in conjunctival goblet cells. Exp Eye Res 2008;86(4):629-636.
[24] Takeji Y, Urashima H, Aoki A, et al. Rebamipide increases the mucin-like glycoprotein production in corneal epithelial cells. J Ocul Pharmacol Ther 2012;28(3):259-263.
[25] Uroshima H, Okamoto T, Takeji Y, et al. Rebamipide increases the amount of mucin-like substances on the conjunctiva and cornea in the N-acetylcysteine treated in vivo model. Cornea 2004;23(6):613-619.
[26] Takeji Y, Urashima H, Aoki A, et al. Rebamipide increases the mucin-like glycoprotein production in corneal epithelial cells. J Ocul Pharmacol Ther 2012;28(3):259-263.
[27] Itoh S, Itoh K, Shinohara H. Regulation of human corneal epithelial mucins by rebamipide. Curr Eye Res 2014;39(2):133-141.
[28] Nakashima H, Urashima H, Takeji Y, et al. Therapeutic effect of rebamipide ophthalmic suspension of cornel and conjunctival damage in mucin removed rabbit eye model. Atarashii Ganka 2012;29:1147-1151.
[29] Tanaka H, Fukuda K, Ishida W, et al. 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.
[30] Kinoshita S, Awamura S, Oshiden K, et al. Rebamipide (OPC-12759) in the treatment of dry eye: a randomized, double-masked, multicenter, placebo-controlled phase II study. Ophthalmology 2012;119(12):2471-2478.
[31] Kinoshita S, Oshiden K, Awamura S, et al. A randomized, multicenter phase 3 study comparing 2% rebamipide (OPC-12759) with 0.1% sodium hyaluronate in the treatment of dry eye. Ophthalmology 2013;120(6):1158-1165.
[32] Koh S, Maeda N, Ikeda C, et al. Effect of instillation of eyedrops for dry eye on optical quality. Invest Ophthalmol Vis Sci 2013;54(7):4927-4933.
[33] Takahashi Y, Ichinose A, Kakizaki H. Topical rebamipide treatment for superior limbic keratoconjunctivitis in patients with thyroid eye disease. Am J Ophthalmol 2014;157(4):807-812.e2.
[34] Itakura M, Itakura H, Kashima T, et al. Topical rebamipide improves the ocular surface in mild lagophthalmos. Clin Ophthalmol 2013;7:1333-1338.
[35] Itakura H, Kashima T, Itakura M, et al. Topical rebamipide improves lid wiper epitheliopathy. Clin Ophthalmol 2013;7:2137-2141.
[36] Kashima T, Akiyama H, Miura F, et al. Resolution of persistent corneal erosion after administration of topical rebamipide. Clin Ophthalmol 2012;6:1403-1406.