Topical Rebamipide Treatment for Dry Eye Syndrome in Thyroid Ophthalmopathy

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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

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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. 94 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 strips).

TBUT was measured by means of sodium fluorescent strips. The strips 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 strips. 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-

<table>
<thead>
<tr>
<th>Have You Experienced Any of The Following During the Last Week:</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>Half of the Time</th>
<th>Some of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Eyes that are sensitive to light?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2 Eyes that feel gritty?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3 Painful or sore eyes?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4 Blurred vision?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5 Poor vision?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Have Problems with Your Eyes Limited you Performing any of the Following During the Last Week:</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>Half of the Time</th>
<th>Some of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Reading?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7 Driving at night?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8 Working with a computer or a bank machine (ATM)?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9 Watching TV?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Have Your Eyes Felt Uncomfortable in Any of the Following Situations During the Last Week:</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>Half of the Time</th>
<th>Some of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Windy conditions?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11 Places or areas with low humidity (very dry)?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12 Areas that are air conditioned?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
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%).

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).

The mean TBUT values at both 8th (6.857±1.68) and 16th (9.595±1.30) week were also compared with the base line value (5.571±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 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.

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.

DISCUSSION

Rebamipide is a novel quinolinone derivative synthesised and developed by a Japanese company. Initially it was developed to be used for gastric ulcer. Its use was 1st established by animal experimental models. 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. These action on gastrointestinal mucosa is universal. Similar to gastric mucosa the eye contains goblet cells on its surface which help in lubrication and tear film stabilisation. 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[28] 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[30] 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. Kinostita et al[30,31] reported improvement in fluorescent corneal staining score, lissamine 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.

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REFERENCES


