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ORIGINAL ARTICLE

Comparison of 2% Rebamipide and 0.1% Sodium Hyaluronate in the Treatment of Dry Eye

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Abstract

Background: Dry eye disease is a multifactorial disease with varying presentations ranging from minor discomfort to sight threatening complications. Different drugs are used to treat dry eye and act on different layers of the tear film. Rebamipide is a new emerging drug that specifically addresses mucin deficient dry eye. ***Purpose:*** To evaluate the efficacy of 2% rebamipide and to compare it with 0.1% sodium hyaluronate in the treatment of dry eye disease. ***Material and Methods***: 130 patients visiting the eye OPD of a tertiary care hospital in North India with dry eye disease were enrolled and divided randomly into two groups of 65 patients each. One group was prescribed 2% rebamipide eye drops 4 times a day and the other was prescribed 0.1% sodium hyaluronate 6 times a day for 6 weeks. Schirmer's test values, tear film breakup time (TBUT), Lissamine green staining score and a dry eye related questionnaire were evaluated at 2, 4 and 6 weeks. ***Results:*** The difference between the results of the two groups was found to be statistically significant (p value <0.05) at 6 weeks of therapy. ***Conclusion:*** Rebamipide proved to be better than sodium hyaluronate in reducing the symptoms and improving clinical signs like Schirmer's values, TBUT and lissamine staining score when used for up to 6 weeks and may emerge as 1st line treatment for dry eye disease in near future.

Key Words

Dry eye disease, Sodium hyaluronate, Rebamipide, Schirmer's test

Introduction

Dry eye is a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film and is accompanied by ocular symptoms in which tear film instability and hyperosmolarity play a major etiological role (1). Its prevalence increases with age and is more prevalent in women than men (2). The prevalence of dry eye disease in north India is 32% in the age group of 21-40 years (3). The tear film volume decreases with advancing age to become 10% of the adult value by the age of 70 years (4).

Schirmer's test, tear film breakup time and lissamine staining are the tests routinely performed in such patients. Schirmer's test measures the tear production i.e. the aqueous component whereas TBUT measures the tear film stability i.e. the lipid component. Impression cytology is a minimally invasive procedure that helps detect goblet cell loss and can be used in diagnosing mucin deficient dry eye. Sodium hyaluronate is a novel lubricating agent that has flow and deformation characteristics comparable to those of the aqueous layer. It protects and promotes healing of corneal epithelium, is anti inflammatory, lowers tear viscosity and retains water. It thus stands as the best-known lubricant for dry eye disease.

Rebamipide is a quinolinone derivative which induces cyclooxygenase 2 (COX2) synthesis that results in an

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increase in endogenous prostaglandin synthesis (E_2 and I_2) in the gastric mucosa and was thus used in gastric ulcers. Lately, in 2012, it was found to increase mucin production in the tear film also. It increases the production of both membrane associated and secreted type mucins. Moreover, it didn't just improve symptoms in patients with mucin deficient dry eye but also in those with aqueous deficiency due to the fact that rebamipide has additional anti-inflammatory action on the ocular surface that reduces the inflammation in aqueous deficient dry eye. It also maintains the microvillous structure of the corneal epithelium conferring stability to the tear film. The only reported side effect of the drug is dysgeusia in 9.7% of the patients using the drug (5). The present study was undertaken to compare the efficacy of 2% rebamipide with 0.1% sodium hyaluronate in the treatment of dry eye disease.

Material and Methods

This prospective, longitudinal, hospital-based, randomized, analytical, observational study was conducted in the Department of Ophthalmology, Govt. Medical College, Jammu over a period of one year from November 2018 to October 2019. The clearance for conducting this study was taken from the 'Institutional Ethics Committee'. Patients with symptoms of dry eye attending the eye OPD or referred from other specialties for ocular examination were enrolled in the study. The cases were non-selective with regards to age, sex, ethnic origin and occupation.

Sample size was calculated by using G*Power software for windows version 3.1.9.4. The parameters used were – á error probability 0.05 (two tailed), power 80% and ratio of sample size between two groups as 1. The mean and standard deviation for rebamipide and sodium hyaluronate were taken from the previous study as 10.57 ± 1.74 and 9.65 ± 2.32, respectively for the effect size (6). After calculation, the sample size was found to be 65 in each of the two groups. A total of 130 patients were enrolled in the study. Patients were randomly divided into two groups of 65 each based on Random number table prepared by using GraphPad random number generator.

Inclusion criteria include a) Patients with symptoms of dry eye disease; b) Patients with Schirmer test values below 10 mm; c) Patients with TBUT score of less than 10 seconds; and d) Patients willing to participate**.**

Exclusion criteria were a) Patients allergic to fluorescein dye; b) Patients with Schirmer test values more than 10 mm; and c) Patients with TBUT score more than 10 seconds.

After taking an informed written consent from the patients, a detailed history and ocular examination were done. The patients were then subjected to tests for dry eye disease, namely, Tear film break up time (TBUT), Schirmer test, and lissamine green staining. They were also asked to fill up a dry eye related questionnaire. 65 patients were prescribed 2% rebamipide eye drops and the other 65 were prescribed 0.1% sodium hyaluronate eye drops. The patients were followed up at 2, 4 and 6 weeks. At each follow up visit, the patients were subjected to Schirmer's test, tear film break up time and lissamine green staining and also filled up the dry eye symptom score chart.

Statistical Analysis was done using IBM SPSS statistics for windows version 25.0 (IBM Corp. Released 2017, Armonk, NY, USA). Categorial variables were presented as number and percentage whereas continuous variables as mean ± standard deviation. Comparison of qualitative variables between two groups was done using Chi square test and quantitative variables with independent-samples t-test. All the tests were done at 5% level of significance and $p \leq 0.05$ was considered to be statistically significant.

Results

The study consisted of 130 patients with dry eye disease. They were randomly divided into two groups of 65 each. 34 patients (52.3%) in rebamipide group were males and 31 (47.7%) were females. 32 patients (49.23%) in sodium hyaluronate group were males and 33 (50.77%) were females. The difference between the sex composition of both the groups was insignificant with a p value of 0.726. The mean age of the patients was 66.55 ± 11.739 years in rebamipide group and 65.20 ± 11.071 years in sodium hyaluronate group. The difference in the age distribution in both the groups was not statistically significant (p=0.779).

The symptom score improved significantly from baseline to 6 weeks in both rebamipide and sodium hyaluronate group. The improvement in the symptom score was statistically significant in both groups with a p value < 0.001. However, the symptom scores were better in sodium hyaluronate group in the initial weeks but rebamipide group had better symptom score after around 4 weeks of the initiation of therapy with a p value of 0.033 as shown in *Table 1*. The difference in the Schirmer's value of both groups were insignificant at baseline, 2 weeks and 4 weeks, but became statistically significant at 6 weeks with p value of 0.019 as shown in

Table 1: Symptom Score of Each Group

Symptom Scores						
Assessed at	**Group**	**Number**	**Mean**	**Std. Deviation**	**Std. Error of Mean**	***p*-value**
0 weeks	Rebamipide	65	2.58	.527	.065	.093
	Sodium hyaluronate	65	2.42	.610	.076	
2 weeks	Rebamipide	65	1.72	.857	.106	.126
	Sodium hyaluronate	65	1.51	.732	.091	
4 weeks	Rebamipide	65	.72	.718	.089	.033
	Sodium hyaluronate	65	1.00	.750	.093	
6 weeks	Rebamipide	65	.38	.550	.068	.001
	Sodium hyaluronate	65	.75	.708	.088	

Table 2: Schirmer's Value of Each Group

Schirmer's Value						
Assessed at	**Group**	**Number**	**Mean**	**Std. Deviation**	**Std. Error of Mean**	***p*-value**
0 weeks	Rebamipide	65	8.09	1.400	.174	.820
	Sodium hyaluronate	65	8.15	1.660	.206	
2 weeks	Rebamipide	65	9.38	1.791	.222	.117
	Sodium hyaluronate	65	9.89	1.880	.233	
4 weeks	Rebamipide	65	11.43	1.776	.220	.923
	Sodium hyaluronate	65	11.46	1.829	.227	
6 weeks	Rebamipide	65	13.57	1.741	.216	.019
	Sodium hyaluronate	65	12.69	2.423	.301	

Table 3: Tear Film Breakup Time of Each Group

TBUT Value						
Assessed at	**Group**	**Number**	**Mean**	**Std. Deviation**	**Std. Error of Mean**	***p*-value**
0 weeks	Rebamipide	65	8.03	1.250	.155	.103
	Sodium hyaluronate	65	8.38	1.208	.150	
2 weeks	Rebamipide	65	9.58	1.424	.177	.170
	Sodium hyaluronate	65	10.00	1.969	.244	
4 weeks	Rebamipide	65	10.37	1.547	.192	.085
	Sodium hyaluronate	65	10.89	1.872	.232	
6 weeks	Rebamipide	65	12.35	1.292	.160	.007
	Sodium hyaluronate	65	11.57	1.895	.235	

Table 4: Lissamine Green Staining Score of Each Group

Lissamine Green Staining Score						
Assessed at	**Group**	**Number**	**Mean**	**Std. Deviation**	**Std. Error of Mean**	***p*-value**
0 weeks	Rebamipide	65	4.68	1.371	.170	.079
	Sodium hyaluronate	65	4.25	1.403	.174	
2 weeks	Rebamipide	65	3.66	1.004	.125	.272
	Sodium hyaluronate	65	3.45	1.212	.150	
4 weeks	Rebamipide	65	2.22	1.125	.140	.531
	Sodium hyaluronate	65	2.34	1.108	.137	
6 weeks	Rebamipide	65	.95	1.192	.148	.007
	Sodium hyaluronate	65	1.54	1.251	.155	

Table 2.

The difference in the tear film breakup time of both groups were insignificant at baseline, 2 weeks and 4 weeks, but became statistically significant at 6 weeks with *p* value of 0.007 as shown in *Table* 3. Similarly, the difference in lissamine staining score of both groups were insignificant at baseline, 2 weeks and 4 weeks, but became statistically significant at 6 weeks with *p* value of 0.007 as shown in *Table* 4.

Discussion

The term Lacrimal Functional Unit (LFU) refers to the whole system comprising of the lids, ocular surface (cornea, conjunctiva and meibomian glands) and lacrimal glands, and the nerves, both sensory and motor that supply them. Dry eye could result from any disturbance in this system (7). The function of the tear film is to maintain the transparency of the cornea, and hence the quality of the image that is formed on the retina. Thus, the tear film has a major role in determining the quality of vision that the patient has (8).

Food and Drug Administration provided a drug monograph containing various agents that could be useful for treating dry eye disease (9). The monograph included ophthalmic astringents, demulcents, emollients, hypertonic agents and vasoconstrictors. Inflammation also plays a role in the pathophysiology of dry eyes. A number of treatment options are available for dry eye but none of the known drugs can be called the first line treatment for dry eye disease of all types. A novel drug, rebamipide is being used in various parts of the world for dry eye treatment and showing promising results (5,6).

In our study, the mean age of the patients was 66.55 ± 11.739 years in rebamipide group and 65.20 ± 11.071 years in sodium hyaluronate group. The difference in the age distribution in both the groups was not statistically significant (*p*=0.779). Kinoshita *et al.* (6) included 188 patients and the mean age of the patients was 56.6 ± 17.4 years. So, our study is comparable to them in terms of age.

In our study, 52.3% patients in rebamipide group were males and 47.7% were females, whereas, 49.2% patients in sodium hyaluronate group were males and 50.8% were females. There was no statistically significant difference in the sex composition of both the groups (p=0.728). Kinoshita *et al.* (6) in his study had 13.2 % males and 86.7% females, while Tokuda *et al.* (10) had 52.5% males and 47.5% females, whereas Kase *et al.* (11) reported 19.2% females and 80.7% males. Our study is comparable to the study by Tokuda *et al.* (10) but not to the studies by Kinoshita *et al.* (6) and Kase *et al.* (11). Although females are known to be predisposed to dry eye but in our study, dry eye was found equally in both the genders.

In our study, the symptom score improved significantly from baseline to 6 weeks in both rebamipide and sodium hyaluronate group. The improvement in the symptom score was statistically significant in both groups with a *p* value <0.001. The difference in the improvement of the symptom scores in both the groups was not statistically significant at 2 weeks but became significantly better in rebamipide group at 4 (*p* value=0.033) and 6 weeks (*p* value=0.001). Kinoshita *et al.* (6) reported that foreign body sensation reduced with both rebamipide and sodium hyaluronate and the difference between the two groups in the reduction of foreign body sensation was not statistically significant (*p*=0.686). Similarly, difference in the reduction in photophobia, eye pain and blurred vision was not statistically significant in the groups with *p* value of 0.126, 0.312 and 0.900 respectively. Dryness, however, showed better improvement with sodium hyaluronate than rebamipide with a *p* value of 0.046. Ueda *et al.* (12) showed reduction in dry eye symptom score from 14.5 at baseline to 7.83 at 12 weeks with prescription of 2% rebamipide ophthalmic solution.

The Schirmer's test value in our study improved with both rebamipide and sodium hyaluronate. The increase in schirmer's value in rebamipide group was significantly better than sodium hyaluronate group at 6 weeks with a *p* value of 0.019. In a study by Kinoshita *et al.* (6) schirmer's test values increased in both rebamipide group and sodium hyaluronate group, but the difference between the two was not statistically significant (*p* value=0.229). Dhawan *et al.* (13) reported an increase in schirmer's value from 10.5 at baseline to 19. 5 at 7 weeks of treatment with 2% rebamipide eye drops.

The tear film breakup time improved in our study with both the use of rebamipide and sodium hyaluronate. The difference between the improvement in both the groups was statistially not significant at 2 weeks and 4 weeks (*p* value=0.107, 0.85, respectively) but became significantly better at 6 weeks in rebamipide group (*p* value=0.007). Similar to our study, Kinoshita *et al.* (6) reported improvement in tear film breakup time with both rebamipide and sodium hyaluronate with insignificant difference between the two groups at 4 weeks (*p* value=0.218).

Lissamine green staining score in our study showed improvement with both rebamipide and sodium

hyaluronate. The difference between the decrease in the score in both the groups was statistially not significant at 2 weeks and 4 weeks (*p* value=0.272, 0.531, respectively) but became significantly better at 6 weeks in rebamipide group (*p* value=0.007). Simsek *et al.* (14) also reported that rebamipide eye drops significantly improved the lissamine green staining score when compared with sodium hyaluronate eye drops (*p* value=0.025). Similarly, Mori *et al.* (15) found lissamine staining score to improve with rebamipide eye drops (*p* value=0.001).

Thus, it can be said that similar to previous studies, our study also noted that sodium hyaluronate and rebamipide eye drops were equally good at reducing signs and symptoms of dry eye. Rebamipide, however, was better than sodium hyaluronate after 6 weeks of therapy. This is attributable to the fact that in addition to the effects produced by sodium hyaluronate in treating dry eye, rebamipide has additional mucin enhancing activity. Since the results of both the drugs were comparable, rebamipide can be considered as a very good alternative to sodium hyaluronate for dry eye. It may also be used as first line drug in the treatment of dry eye disease. Further studies are required to confirm our findings.

There were certain limitations in our study. First, the schirmer's test was conducted without anaesthesia, so reflex tearing was included in the recording. Secondly, the patients were not followed up after stopping the drugs, so the wearing off time of the drugs cannot be commented upon. Lastly, the degree of irritation or stinging sensation on instillation of the drugs was not compared among the groups.

Conclusion

Rebamipide has shown comparable results to the best-known lubricant, sodium hyaluronate. It can be used in all forms of dry eye disease and, thus has a potential to stand out as the first line treatment for dry eye disease in near future.

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Conflicts of Interest

There are no conflicts of interest.

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