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The Effect of a New Tear Substitute Containing Glycerol and Hyaluronate on Keratoconjunctivitis Sicca

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ABSTRACT

The purpose of this study was to evaluate the efficacy of LO2A, a newly developed tear substitute containing glycerine and sodium hyaluronate, in the treatment of dry eyes. Twenty-five informed consent patients suffering from keratoconjunctivitis sicca were included. Patients were treated for one week with LO2A in one eye, and with their current tear substitute in the other eye. Rose bengal staining was evaluated on a scale of 0 to 3. Patient satisfaction was graded on a scale of 1 to 5. The average satisfaction score for LO2A was significantly higher compared to the control preparations at 1 week ($p=0.0003$) and at 2 weeks ($p=0.0232$). A highly significant reduction in rose bengal staining was demonstrated following 1 week of treatment with LO2A ($p<0.0001$). The LO2A treated eyes had significantly less staining than control eyes at 1 week ($p=0.021$) and at 2 weeks ($p=0.023$). An inverse correlation was found between patient grading and the rose bengal scoring (spearman rank coefficient $= -0.49$, $p<0.001$). LO2A showed a beneficiary effect on dry eye patient satisfaction and on rose bengal test, as compared to other tear substitute preparations currently used by these patients.

INTRODUCTION

Dry eyes in form of conjunctivitis sicca or keratoconjunctivitis sicca is a condition in which the eye is insufficiently covered by the tear film. It may be asymptomatic, but usually patients do suffer from a variety of symptoms. It becomes symptomatic when the epithelium of the conjunctiva or of both the conjunctiva and the cornea becomes abnormal as manifested by various tests. It rarely may affect vision. Dry eyes is one of the most common conditions seen by the ophthalmologist.

The major therapeutic approach to dry eyes is tear fluid supplementation by various eye drops. These eye drops are based on one of several materials, such as cellulose derivatives (methylcellulose, ethylcellulose, hydroxyethycellulose etc.), polyvinyl derivatives (polyvinylalcohol, polyvinylpyrolidone, polyvinylcarboxylic acid) and fatty substances (lanolin, white petrolatum) (1,2). More recently, chondroitin sulfate, sodium hyaluronate (3,4) and an acrylic polymer (5) were also tried and proved effective. However, most patients with dry eyes continue to complain and remain symptomatic in spite of using these tear substitutes. This lack of optimal effect can result from the short-time effect of any of

the available tear substitutes, the possible toxic effect of frequently used preservative containing eye drops or from the lack of effect of any artificial tear preparation on the symptom causing eye changes. No available tear substitute was proved to be significantly effective on the conjunctival signs as detected by the rose bengal test, or on the tear film integrity as detected by the tear break-up time (B.U.T.) and the non-invasive break-up time (N.I.B.U.T.) (6). Therefore, the search for an ideal tear substitute continues (6).

LO2A eye drops is a new, recently developed and patented (7) tear substitute containing hyaluronate with glycerol, a very powerful humectant (8). The humectant action of glycerol, combined with hyaluronate, makes it suitable to function as a tear substitute.

MATERIALS AND METHODS

The eye drops (LO2A) were manufactured and supplied by Laboratories H. Faure from France. The drops were supplied in uni-dose units without any preservative. Each uni-dose contained ingredients as outlined in Table 1.

TABLE 1
The Composition of the Preparations

1. The ingredients of the LO2A uni-dose:
   Glycerine isotonic
   Carbomer
   Sodium hyaluronate
   Purified water q.s.

2. The viscosity forming agents in the control preparations:
   Cellulose derivatives
   PVP + hydroxyethylcellulose
   Isotonicity is adjusted by salts.

The study was performed in accordance with the Helsinki declaration and approved by the Intramural and National Ethical Committees. Each patient signed an informed consent form prior to inclusion to the study. Inclusion criteria for patients included typical symptoms of dry eyes (dryness or sand sensation, burning, tearing) manifesting for at least one year, a current regular treatment with a known tear substitute for a minimum of one drop three times a day, and a positive rose bengal stain of +2 or +3 (as described below).

After inclusion, patients had a slit-lamp biomicroscopy, to exclude any ocular surface diseases causing dry eyes. Patients were excluded if any abnormality of the ocular surface was found. Patients were also excluded if any other topical treatment apart from a tear substitute was used on a regular basis during the preceding year.

Following an informed consent, one eye was randomized for topical treatment with LO2A drops (study eye), and the other eye for the same preparation that was used by the patient prior to the study (control eye). The various preparations used in the control eyes are shown in Table 1. In each eye one drop of either LO2A or the control preparation was instilled three times a day. Patients were instructed to use the two preparations at the same time.

Twenty-five patients were included in the study. The study was performed in two stages. In the first stage, 15 patients were included for a period of one week. In the second stage, 10 additional patients participated for a period of two weeks. Follow up visits were performed at the beginning of the study, after one week, and in the last 10 patients after two weeks as well. All the follow-up examinations were performed by an independent observer, who was masked as to the specific treatment given to each eye.

Rose bengal test was performed by first applying one drop of 0.4% benoxinate hydrochloride, followed by one drop of 1% rose bengal given one minute later, into the lower fornix. The patient was asked to blink several times to distribute the dye evenly. One minute following the application of rose bengal, the staining of rose bengal was determined by counting the number of spots, and then turned into a score of 0 to 3. A negative result was scored 0, a number of up to 50 spots was given a score of 1, 50-100 spots were given a score of 2, and over 100 spots - a score of 3.

Patient's satisfaction was based on the improvement in symptoms and on the lack of stinging or burning by the medication. The symptoms accounted for were itching, burning, sensation of dryness or foreign body sensation. Each patient was asked to express his or her general satisfaction with the drug for each eye separately, on a scale of 1 to 5, with a score of 1 indicating lowest satisfaction and 5 the highest satisfaction.

Statistical analysis of the results included the Wilcoxon signed rank test for comparison between scores for the same eye at different times, and Mann-Whitney test for comparison between scores of study versus control eyes.

RESULTS

Rose bengal staining scores and patient satisfaction scores are presented in Table 2. The median scores for the study eyes and for the control eyes of the different examinations are shown in Table 3.

Rose Bengal Score

The median rose bengal score for the control eyes was similar at baseline and following 1 week ($p=0.19$). However, there was a highly significant difference between baseline and 1 week rose bengal staining for the study (LO2A) eyes: 2.8 compared to 1.9 ($p<0.0001$).

At the beginning of the study, both eyes had similar initial rose bengal staining: 2.6 versus 2.8 ($p=0.29$). After one week, the rose bengal staining was significantly lower for the eyes treated with LO2A: 2.4 versus 1.9 ($p=0.02$).

Significant reduction in rose bengal staining was also demonstrated at 2 weeks (The median score was 2.7 for the control eyes and 1.9 for the study eyes, $n=10$, $p=0.0232$).

The rose bengal positive staining was seen usually in the interpalpebral exposed zones of the bulbar conjunctiva, nasal and temporal to the limbus. In some patients the lower conjunctiva was also affected.

Subjective Evaluation

Patient satisfaction from LO2A was significantly higher compared with their current tear substitute. After one week of treatment the mean score for the study eyes was 3.36, compared to 2.24 for the control eyes ($p=0.0003$). After 2 weeks, the study eyes received a score of 3.3, compared to 2.4 for the controls ($p=0.023$).

Eleven patients felt that LO2A was subjectively more satisfying by 1 or 2 grades, while 4 patients felt it to be better by 3 to 4 grades. One patient felt that the current preparation was better by 2 grades. Nine patients claimed that both preparations were equal (Table 4).

TABLE 2

Rose Bengal and Subjective Evaluation at 1 and 2 Weeks

No	Baseline - rose bengal		1 wk - rose bengal		1 wk - subjective		2 wks- rose bengal		2 wks - subjective	
	control	study	control	study	control	study	control	study	control	study
1	3	3	2	1	1	4				
2	1	3	1	1	2	4				
3	3	3	1	2	2	4				
4	2	3	3	1	1	3				
5	3	3	3	2	3	3				
6	2	3	2	2	3	3				
7	3	3	3	2	2	3				
8	2	3	2	2	1	4				
9	3	3	2	2	4	4				
10	3	3	3	3	4	2				
11	3	2	3	1	1	4				
12	2	2	2	2	1	5				
13	3	3	3	3	1	3				
14	2	2	1	1	3	4				
15	2	2	3	2	3	3				
16	3	3	3	1	3	4	3	2	3	4
17	2	3	2	2	3	3	2	1	3	4
18	3	3	3	2	1	3	3	2	2	3
19	2	2	2	2	3	3	3	2	3	3
20	3	3	3	1	2	4	2	1	2	4
21	3	3	3	3	2	2	3	3	2	2
22	3	3	3	3	2	2	3	3	2	2
23	3	3	2	1	3	4	2	1	2	4
24	3	3	3	3	2	2	3	2	2	3
25	3	3	2	2	3	4	3	2	3	4

TABLE 3

Comparison of Mean Scores for Study and Control Eyes

	CONTROL EYES		LO2A		
Rose Bengal Score					
Baseline	2.6	}p=0.19	2.8	}p<0.0001	p=0.29
1 week	2.4		1.9		p=0.021
2 weeks	2.7		1.9		p=0.023
Subjective Score					
1 week	2.24		3.36		p=0.0003
2 weeks	2.40		3.30		p=0.0232

Table 4

Summary of Subjective Results

	Number of patients
Both preparations equal	9
LO2A better by 1 grade	5
LO2A better by 2 grades	6
LO2A better by 3 grades	3
LO2A better by 4 grades	1
LO2A worse by 2 grades	1

Correlation between Rose Bengal Score and Patient Satisfaction

We analyzed the correlation between the change of rose bengal scoring and the change in patient satisfaction for the 10 patients for whom a follow up of two weeks was available. This correlation was significant (Spearman rank coefficient = -0.57, corrected for ties, p=0.02, Figure 1). The final patient scoring for all 25 patients (at one week or at two weeks) was also found to be well correlated with the final change in rose bengal (Spearman rank coefficient = -0.49, corrected for ties, p<0.001, Figure 2).

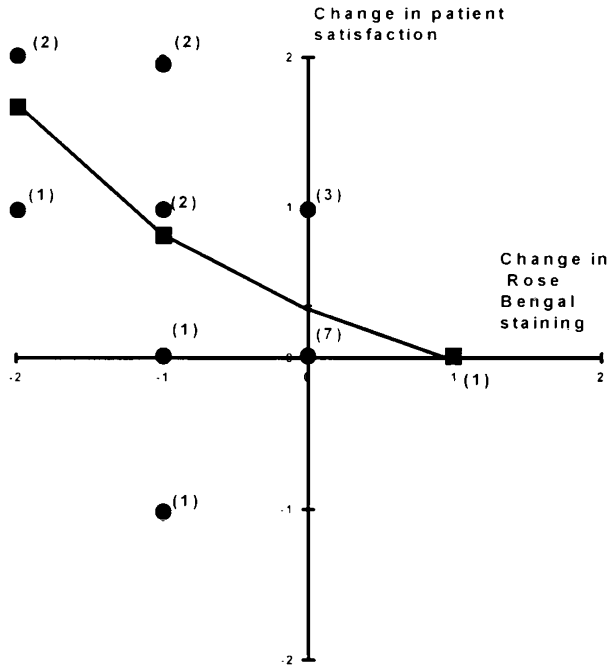

FIGURE 1. The Relation Between the Change in Patient Subjective Scoring and the Change in Rose Bengal Staining During Two Weeks of Treatment in the Study Eyes and the Control Eyes of 10 Patients. Spearman rank coefficient = -0.57 (p=0.02). ■ indicates means of patient satisfaction for a given change in rose bengal staining. ● indicates number of patients for each point (shown in parenthesis).

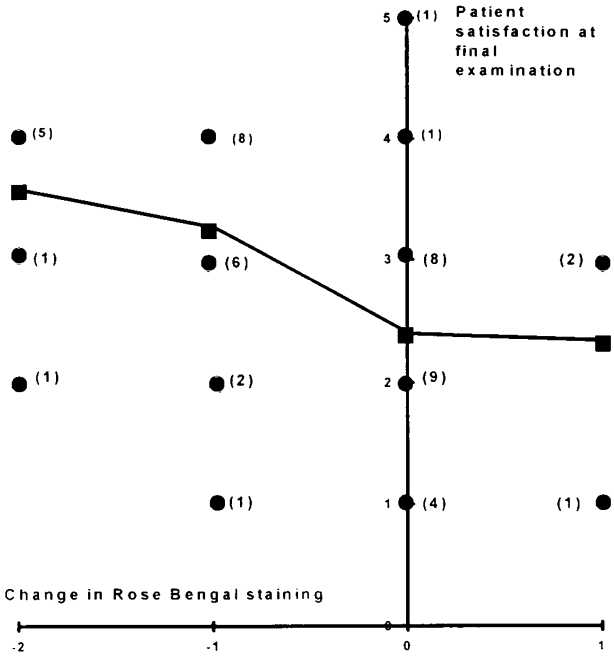

FIGURE 2. The Relation Between the Final Patient Subjective Scoring at 1 Week or at 2 Weeks, and the Change in Rose Bengal Staining During that Period. The points show study eyes and control eyes of 15 patients at 1 week, and of another 10 patients at 2 weeks. Spearman rank coefficient = -0.49 ($p<0.001$). ■ indicates means of patient satisfaction for a given change in rose bengal staining. ● indicates number of patients for each point (shown in parenthesis).

DISCUSSION

Four preliminary studies performed in Italy (9-12) indicated the superiority of LO2A in treatment of dry eyes as regards patients' satisfaction and the results of rose bengal tests. Our study confirms these results.

We evaluated the rose bengal test in a different way from the scoring of 1 to 9 suggested by van Bijsterveld (13), which included also corneal staining. We evaluated only conjunctival staining and counted the number of rose bengal staining spots on the conjunctiva in a score of 0 to 3. This is a more objective form of evaluating rose bengal results (14). It was our impression that the rose bengal test expresses better than other tests the subjective feelings of dry eye patients and that rose bengal scoring is highly associated with symptomatology (Fig. 1).

Previous investigators (9-12) assumed that the beneficial effect of LO2A results from the hyaluronic acid. We believe that it is the combination with the humectant action of glycerol that causes the effect of LO2A. A humectant absorbs fluid and holds it, thus prolonging the coverage of the ocular surface by the tear film. In contrast, cellulose derivatives and polyvinyl derivatives are not humectants. Mannitol was shown not to be humectant at all. Their beneficial effect on dry eyes results from both supplementation of a tear-like fluid and the increase in viscosity of the tear film. This is a different mode of action from that of a humectant. Moreover, the viscosity profile of LO2A is non-newtonian, which means that the viscosity is high when the lids are open, but during lid movement, the viscosity decreases. The implication of the non-newtonian properties of this solution is more convenience to the patient during lid movement.

Other clinical tests for dry eyes, such as the Schirmer test and the tear break-up time were found by different investigators to be unrelated to either the mode of treatment or to the symptoms of patients with dry eyes. A previous study showed that in normal subjects there is a poor correlation between these two tests and little or no influence of temperature, relative humidity, air pollution, barometric pressure or a combination of some or all factors on these two tests (15).

The relative effect of the drops being preservative free on our results is not clear. The possible cytotoxicity of ophthalmic preservatives has been known for many years (16), and it may be enhanced in patients using drops very frequently. This matter will be the subject of a future study.

In conclusion, LO2A, a new preparation for treatment of dry eyes, based on a combination of a humectant and hyaluronate, was tested on 25 patients. This study indicates a beneficial effect of this preparation on both symptoms and objective count of rose bengal spots.

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