

Clinical Investigations

SODIUM HYALURONATE EYEDROPS ENHANCE TEAR FILM STABILITY

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Summary: Sodium hyaluronate eyedrops can relieve various dry eye symptoms by prolonging the stability of the precorneal tear film. To determine the most effective concentration of sodium hyaluronate, we studied the concentration-dependent effects of sodium hyaluronate eyedrops on the precorneal tear film breakup time (BUT) in 12 volunteers. These subjects had a BUT of 10 seconds or less and a low tear volume determined with the phenol red thread test. They received four different concentrations of sodium hyaluronate eyedrops (0, 0.05, 0.1 and 0.3%). BUT was measured noninvasively using a non-contact specular microscope before the sodium hyaluronate eyedrop instillation and again after 5, 15, 30, 60, 120 and 180 minutes. The tear film stability period was prolonged significantly with 0.1% and 0.3% eyedrops at all measurement times ($P < 0.05$), while the eyes treated with 0% and 0.05% eyedrops showed no significant prolongation of tear film stability at any measurement times. The findings of this study confirm that sodium hyaluronate at a concentration of at least 0.1% is required to delay the breakup of the precorneal tear film.

Key Words: Dry eye, eyedrops, non-contact specular microscope, precorneal tear film breakup time, sodium hyaluronate

Introduction

Sodium hyaluronate eyedrops were recently developed as a therapeutic agent for the treatment of dry eyes⁴⁻¹⁰. Sodium hyaluronate is clinically effective because it stabilizes the tear film⁶, which results in delay of the precorneal tear film breakup time (BUT). However, the minimal concentration of sodium hyaluronate for delaying BUT for a long period remains to be accurately defined.

Previously the effect of sodium hyaluronate eyedrops on dry eyes was evaluated only by the degree of staining with either sodium fluorescein or Rose Bengal. To objectively evaluate the effects of sodium hyaluronate on the stability of the tear film, we measured BUT using a non-contact specular microscope^{2,3}. This technique allows

noninvasive assessment of tear film stability and monitoring of BUT. As a result, we could accurately determine the best sodium hyaluronate therapeutic regimen for alleviating some of the symptoms of dry eye.

Subjects and Methods

Twelve female volunteers with BUTs of 10 seconds or less and with low tear volumes (15 mm or less in the phenol red thread test¹) participated in this study after giving written informed consent. The eye with shorter BUT in each subject was analyzed in this study. Background data are shown in Table 1.

Each eye underwent four separate study periods, randomly receiving 0.05, 0.1 and 0.3% w/v sodium hyaluronate (MW: about 1 000 000) solution or the vehicle alone (Table 2). Instillation of the eyedrop was done with the usual single dose eyedrop container. The volume of one drop was approximately 50 μ L. To avoid any residual effects, there was a recovery interval of at least one week before applying another eyedrop regimen.

The precorneal tear film at the 6 o'clock

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Table 1. Data of subject eyes

Eye No.	Age (y)	Eye	BUT* in target eye (s)	Tear volume† in target eye (mm)
1	38	R	6	15
2	24	R	3	13
3	27	R	2	15
4	28	L	4	15
5	25	R	3	15
6	35	L	1	15
7	25	L	8	13
8	20	R	3	11
9	22	R	5	15
10	22	R	2	6
11	25	R	9	13
12	26	R	6	11
Mean $\pm$ SD	26.4 $\pm$ 5.2		4.3 $\pm$ 2.5	13.1 $\pm$ 2.7

*Tear film breakup time measured after instillation of sodium fluorescein

†Wet length in phenol-red thread test at 15 seconds

Table 2. Components and properties of vehicles

Item	Element/Value
Sodium hyaluronate (purified from rooster comb)	600 000~1 200 000 (MW)
Isotonic agent	Sodium chloride Potassium chloride
Buffering agent	α -aminocaproic acid
Stabilizer	Disodium edeta
Preservative	None
pH	6.0-7.0
Osmotic pressure ratio	0.9-1.1

position on the cornea near the limbus was monitored through a non-contact specular microscope (Konan S 580, Tokyo) with modified lens system and TV camera to non-invasively measure the intervals between tear film breakup times (NIBUT). Video images of a normal tear film and the multiple breakups in an unstable tear film are shown in Figures 1 and 2. The time of the first dry spot appearance was measured using a stopwatch with 0.1 second steps. The NIBUT measurements were performed before and 5, 15, 30, 60, 120 and 180 minutes after an eyedrop instillation.

To eliminate any bias in the data, the individuals who measured NIBUT were not the same as those who opened the envelopes

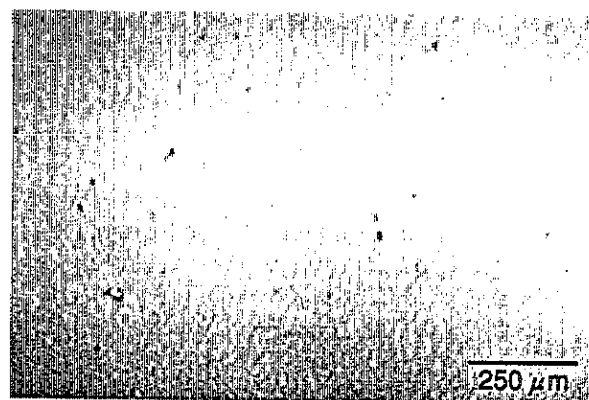


Figure 1. Video image of normal precorneal tear film.

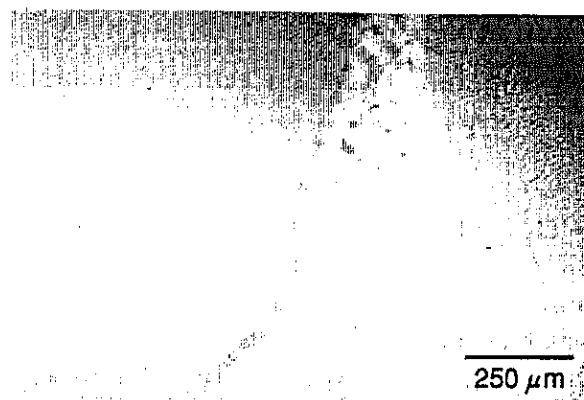
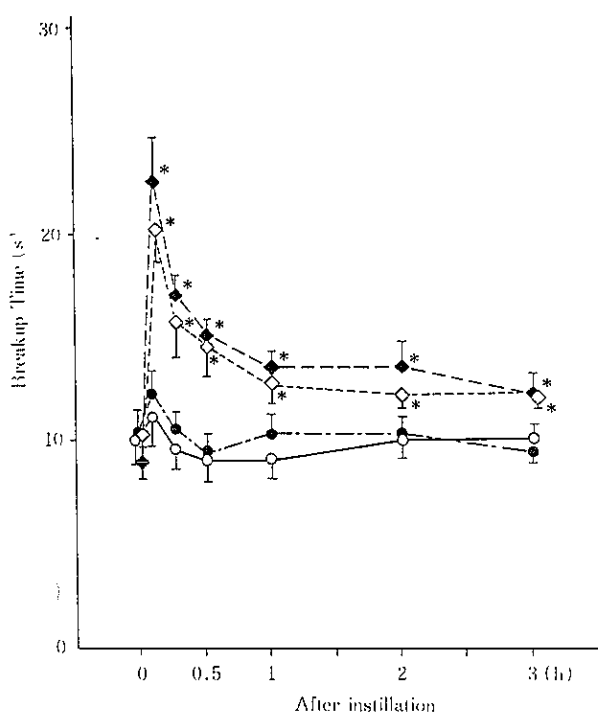


Figure 2. Video image of breakup of unstable tear film.



(Mean $\pm$ SE, $n=12$)
 (* < 0.05)

Figure 3. Concentration-dependent effects of sodium hyaluronate eyedrops on breakup of precorneal tear film. Relative to vehicle treatment, there was significant delay ($P < 0.05$) of breakup after treatment with eyedrops of 0.1% and 0.3% sodium hyaluronate concentration.

---◆--- 0.3% ---◇--- 0.17%
 ---●--- 0.05% ---○--- vehicle

bearing a particular sodium hyaluronate concentration. Thus, all data were recorded and analyzed without any prior knowledge of the sodium hyaluronate concentration applied to the eyes of the subjects.

The statistical significance of the results was determined using the Duncan's multiple-range test.

Results

The effect of sodium hyaluronate eyedrops on the delay of breakup of the tear film is shown in Figure 3. No delay in NIBUT was recorded at any measurement times in the eyes given the vehicle alone or a sodium hyaluronate eyedrop of 0.05% concentration. On the other hand, NIBUT was delayed significantly ($P < 0.05$) with 0.1% and 0.3%

sodium hyaluronate eyedrops at all measurement times for at least 3 hours after the instillation of the eyedrop.

Discussion

Sodium hyaluronate topical application has been reported to be effective in the treatment of dry eyes^{5,9}. In another study, it was also reported that 0.1% sodium hyaluronate could effectively delay NIBUT⁶. We have extended this initial finding by determining the dose-dependent effects on the breakup time of sodium hyaluronate in concentrations between 0.05% and 0.3%, as measured over a 3-hour period after eyedrop instillation. Our results clearly showed that there is a significant delay in NIBUT for at least 3 hours in the eyes treated with 0.1% and 0.3% concentrations of sodium hyaluronate. The effects of sodium hyaluronate were completely different between 0.05% and 0.1%. The concentration of 0.05% sodium hyaluronate had no tear film stabilizing effect even just 5 minutes after instillation. The reason is uncertain. However, the viscosity of the solution of a visco-elastic material such as sodium hyaluronate may increase rapidly from a certain point of concentration. The cause of the different behavior between 0.05% and 0.1% concentrations of sodium hyaluronate may be explained by such a phenomenon.

In summary, we determined that 0.1% and 0.3% sodium hyaluronate eyedrops were effective in delaying the breakup of the tear film in 12 volunteers. These results suggest that the concentration of sodium hyaluronate in eyedrops must be at least 0.1% for effective treatment of dry eye.

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