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# Effect of sodium hyaluronate (0·1%) on break-up time (NIBUT) in patients with dry eyes

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SUMMARY We evaluated the effect of 0·1% sodium hyaluronate (unpreserved) in 10 patients with dry eyes. The precorneal tear film break-up time was assessed by the non-invasive technique, and the severity of symptoms was recorded before and after treatment on a 0 to +3 scale. It was found that the tear film stability was significantly increased ($p<0·05$) in eyes treated with sodium hyaluronate. The symptoms of grittiness and burning were also significantly alleviated in the treated eyes.

Dry eyes may be caused by inadequacy of one or more of the major tear fluid components. Causes include deficiency of meibomian lipid, aqueous fluid, and mucus glycoprotein[1-3] and also inadequate blinking, poor lid-globe apposition, abnormal surface elevations, and breakdown in the wettability of the conjunctival and corneal epithelial surface cells.

Dry eyes give rise to chronic ocular discomfort. Patients complain of burning, itching, photosensitivity, and grittiness. The last is the most frequent symptom in 88% of the cases.[4] The diagnosis of dry eyes is also based on the results of a battery of clinical tests, notably Schirmer's test, tear film break-up time (BUT),[5] vital staining with fluorescein and/or rose Bengal.[5-6] In recent years a number of other tests such as thread Schirmer's,[8] kinetic wetting,[9] osmolarity,[10] cytology of ocular surface,[11] and contact specular microscopy[12] have been added. Haematological investigations, for example autoantibodies, are also conducted to distinguish between primary and secondary Sjögren's syndrome.[13,14] The mainstay of dry eye treatment is tear supplementation with solutions containing hydrophilic polymers such as substituted methyl ethers or cellulose, polyvinyl alcohol, or polyvinylpyrrolidone. These solutions lubricate the eye during blinking and prevent the eye from drying when open.[15]

The efficiency of tear substitutes is measured by relief of symptoms, decrease in tear film BUT, decrease in fluorescein and rose Bengal staining intensity, and improvement in Schirmer paper wetting.[16] Since stability of the tear film is thought to contribute to the relief of symptoms, break-up time provides the simplest short-term index of efficiency. However, the conventional break-up time test is invasive and requires the instillation of fluorescein, which has been shown itself to shorten the break-up time.[17] Fluorescein could also modify the effect of the drop being investigated. Since repeated measurements of stability are required to assess the efficacy of the drop over a time interval, the non-invasive technique provides an alternative method without the use of fluorescein.

Solutions of sodium hyaluronate have biophysical properties like those of mucus glycoprotein and native tears. Such solutions have non-newtonian properties and 'shear thin' at high shear rates (Kaura R, Tiffany JM, unpublished).

In this paper the efficacy of unpreserved 0·1% sodium hyaluronate is evaluated in dry eye patients in: (i) increasing the tear film stability by means of the non-invasive break-up time; (ii) alleviating ocular symptoms.

## Materials and methods

Eleven dry-eye patients (7 female, age range 25–74 years; 4 male, age range 37–74 years) with a varying duration of keratoconjunctivitis sicca for between one and 40 years were recruited after informed consent from a pool of over 100 patients currently receiving treatment for dry eyes at the Oxford Eye Hospital. Ten dry-eye patients were accepted into the study. Eighteen eyes (90%) had Schirmer tear test values (without topical anaesthesia) <5·5 mm,

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one eye had 6 mm, and the remaining eye had 8 mm of wetting in 5 minutes; a typical staining pattern with fluorescein and a non-invasive tear film break-up time (NIBUT) of less than 30 seconds were observed in the least affected eye. We excluded dry eye patients with a history of other ocular disease, past anterior segment surgery, iritis, contact lens wearers, and those on topical therapy other than artificial tears.

The participants were requested not to use their existing artificial tears at least 12 hours prior to their appointment. One eye of each patient was randomly chosen to receive one drop of unpreserved sodium hyaluronate (0·1%), this being the test eye. The fellow eye received one drop of unpreserved sodium chloride (0·9% saline), this being the control eye. Both the solutions were dispensed from identical dropper bottles labelled A and B.

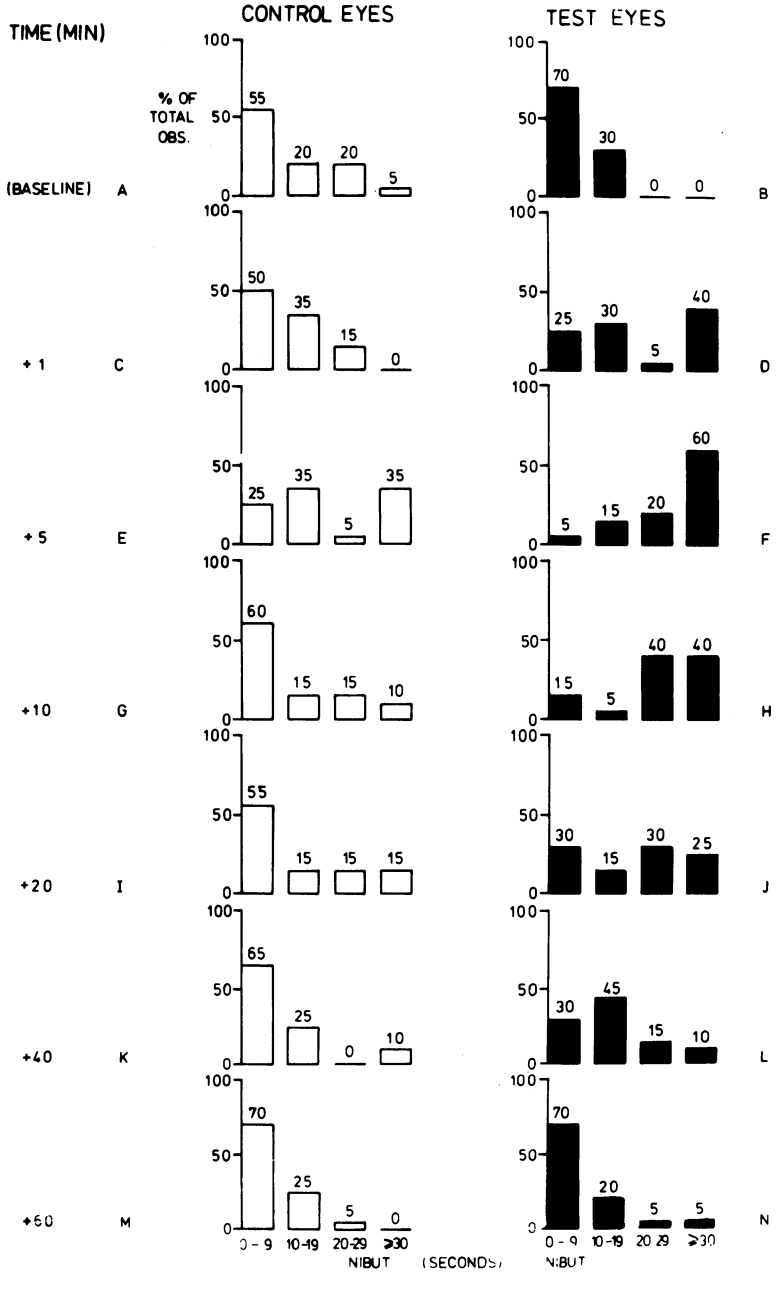


Fig. 1 *Frequency distribution of the non-invasive break-up time of control and test eyes before and after treatment with normal saline and unpreserved sodium hyaluronate (0·1%)*

0·1% Sodium hyaluronate tears were prepared by injecting 1·2 ml of 1% proprietary Healonid into 10·8 ml of unpreserved balanced salt solution, in a laminar flow cabinet.

Prior to treatment, subjective symptoms of grittiness, burning, itching, and photosensitivity for each eye at the time of assessment were recorded on a 0 to +3 scale (0=absent, +1=mild, +2=moderate, and +3=severe) by one of the investigators.

The precorneal tear film stability (NIBUT) was measured by a non-invasive instrument which avoids the use of fluorescein.[18] All observations were made in a masked manner by a separate observer uninvolved with drop instillation and history taking. The NIBUT was determined twice for each eye, alternating between eyes for each measurement. The eye having its NIBUT assessed first was randomly chosen, but for a given patient the sequence of testing

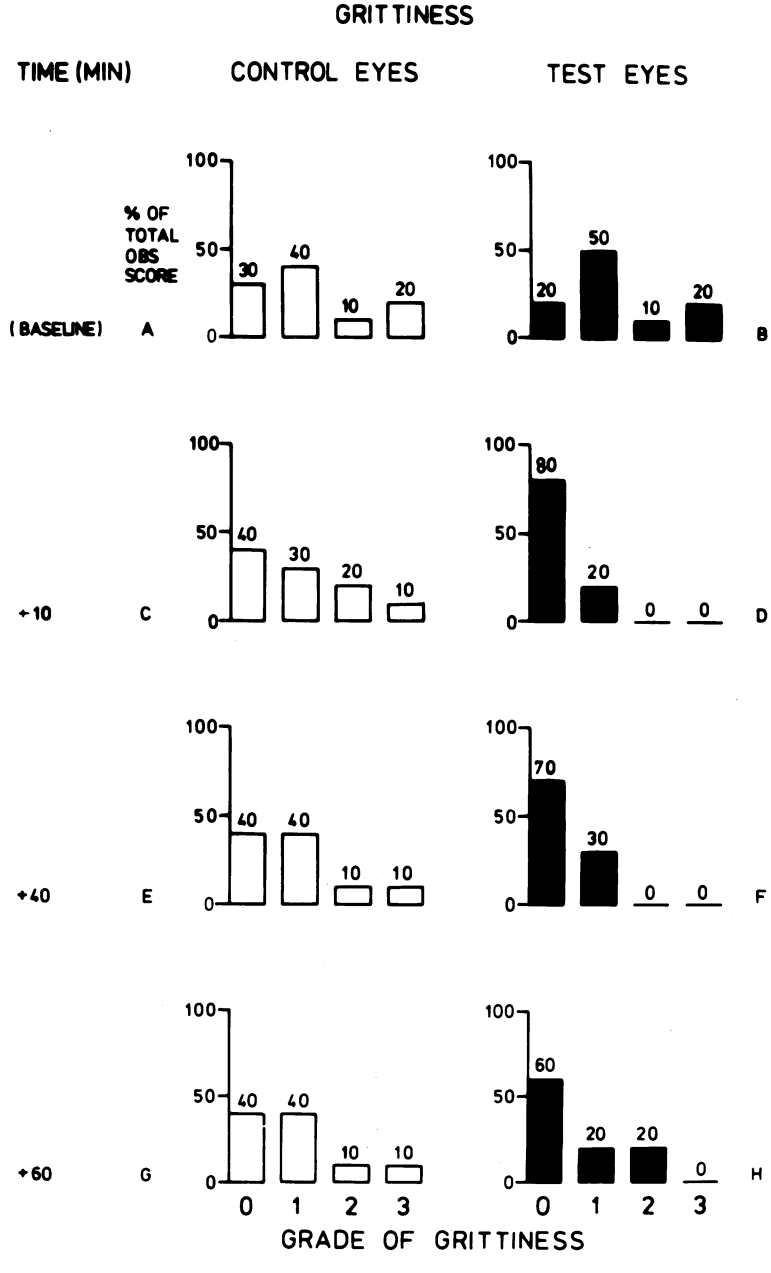


Fig. 2 *Frequency distribution of the grittiness in the control and test eyes before and after treatment.*

was rigidly adhered to throughout the study.

The study began by one drop of either sodium hyaluronate (0·1%) or sodium chloride (0·9%) being placed in the lower fornix temporally in the test and control eye[19] with a minimum of delay between drop instillations. The patient blinked in order to mix the applied drop with the conjunctival fluid.

Measurement of NIBUT began one minute after the last drop. The patient while positioned at the instrument was requested to make a complete unforced blink. The time taken in seconds between the last complete blink and the appearance of the first randomly located break(s) in the reflected grid pattern was taken to be the NIBUT. If the tear film remained intact for 30 seconds or longer, the reading was terminated.

The tear film stability was assessed at the following times: +1, +5, +10, +20, +40, and +60 minutes.

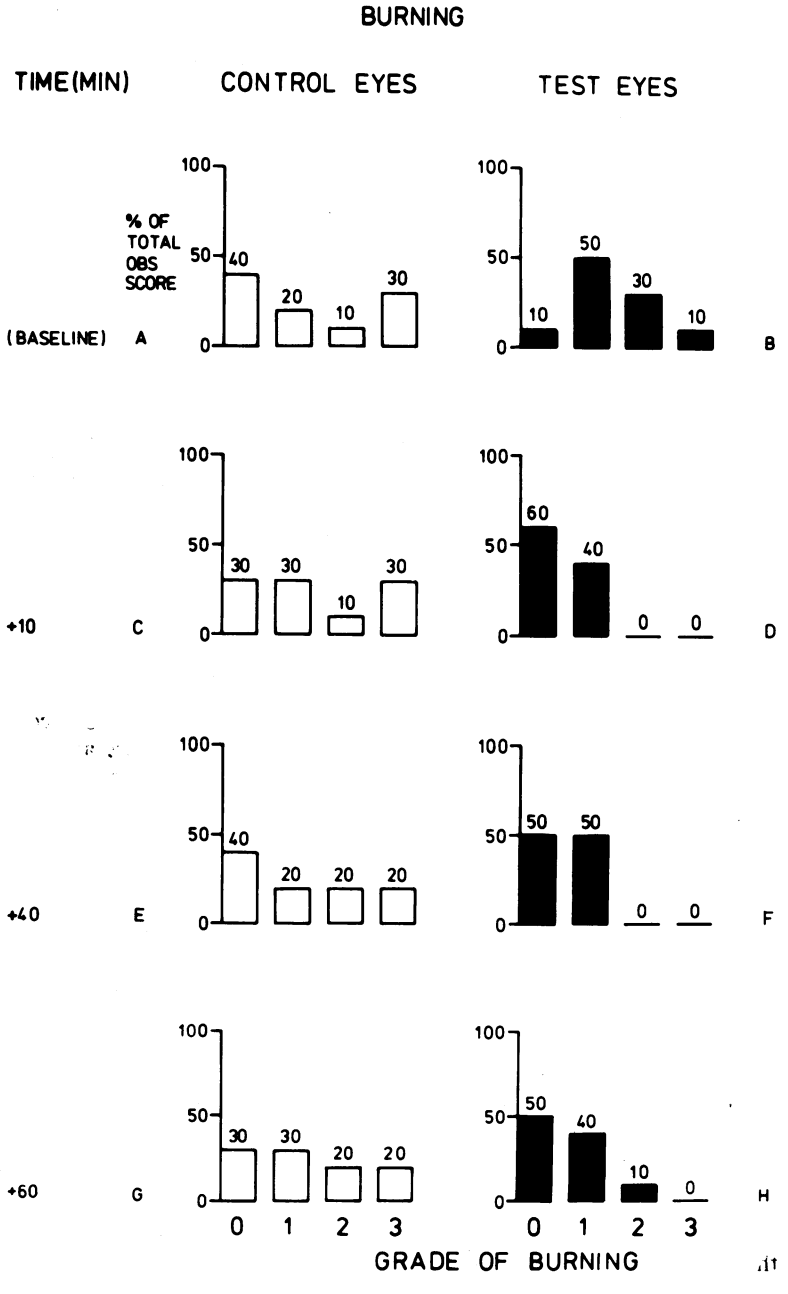


Fig. 3 *Frequency distribution of burning in the control and test eyes before and after treatment.*

Table 1 *Inter- and intragroup comparison of NIBUT in control (0·9% saline) and test (0·1% sodium hyaluronate) dry eyes*

| *Test* | *Control (min)* | *Baseline* | *+1* | *+5* | *+10* | *+20* | *+40* | *+60* |
|---|---|---|---|---|---|---|---|---|
| Baseline | NS | NS | NS | NS | NS | NS | NS | NS |
| +1 | | 0·0001 | 0·004 | | | | | |
| +5 | | 0·00001 | | 0·04 | | | | |
| +10 | | 0·00001 | | | 0·003 | | | |
| +20 | | 0·0003 | | | | 0·049 | | |
| +40 | | 0·01 | | | | | 0·047 | |
| +60 | | NS | | | | | | NS |

NS=not significant (p>0·05).
Diagonal values indicates intergroup comparison. Horizontal and vertical values indicates intragroup comparison.

Table 2 *Inter- and intragroup comparison of subjective score of grittiness in control (0·9% saline) and test (0·1% sodium hyaluronate) dry eyes*

| *Test* | *Control (min)* | *Baseline* | *+10* | *+40* | *+60* |
|---|---|---|---|---|---|
| Baseline | | NS | NS | NS | NS |
| +10 | | 0·01 | NS | | |
| +40 | | 0·03 | | NS | |
| +60 | | 0·01 | | | NS |

NS=not significant (p>0·05)
Diagonal values indicates intergroup comparison. Horizontal and vertical values indicates intragroup comparison.

Table 3 *Inter- and intragroup comparison of subjective score of burning in control (0·9% saline) and test (0·1% sodium hyaluronate) dry eyes*

| *Test* | *Control (min)* | *Baseline* | *+10* | *+40* | *+60* |
|---|---|---|---|---|---|
| Baseline | | NS | NS | NS | NS |
| +10 | | 0·01 | NS | | |
| +40 | | 0·03 | | NS | |
| +60 | | 0·05 | | | NS |

NS=not significant (p>0·05)
Diagonal values indicates intergroup comparison. Horizontal and vertical values indicates intragroup comparison.

The symptoms score were assessed at +10, +40, and +60 minutes following treatment.

## Results

The frequency distribution in the non-invasive break-up time and the subjective scores of grittiness and burning are shown in Figs. 1 to 3. The data was analysed by the non-parametric Mann-Whitney U test for both inter- and intragroup variations of the test and control eyes. The results are presented in Tables 1 to 3.

The baseline distribution of the NIBUT in the control and test eyes is shown in Fig. 1. In the control eyes 55% of the NIBUT measurements were in the 0–9 seconds interval, 20% were in each of the 10–19 and 20–29 seconds intervals. Only 5% of the NIBUT were greater than 30 seconds. In the test eyes 70% of the NIBUT values were in the 0–9 seconds interval and 30% in the 10–19 seconds interval. None of the values were greater than 30 seconds. These baseline distributions were not significantly different (p>0·05).

After instillation of a drop of 0·1% sodium hyaluronate there was a significant increase in tear film stability at one minute in comparison with normal saline (p<0·05; Fig. 1C, D; Table 1). This stabilising effect persisted for at least 40 minutes (p<0·05; Fig. 1; Table 1). Sodium hyaluronate treated eyes showed, over their baseline readings, a highly significant increase in the NIBUT (p=0·0001 at 1 minute, p=0·01 at 40 minutes; Table 1) as well.

Figs. 2 and 3 show frequency distributions of subjective scores for the following symptoms: (i) grittiness (Fig. 2); (ii) burning (Fig. 3).

Fig. 2 represents the variations in the scores of grittiness, which were not significantly different (p>0·05; Table 2). After treatment with sodium hyaluronate there was an immediate relief of grittiness, which lasted for 60 minutes. Table 2 shows the inter- and intragroup significance levels for both the test and the control eyes.

Fig. 3 shows the variation in score for 'burning'. These base line distributions were comparable (p>0·05). On treatment with sodium hyaluronate there was a significant relief from burning, which was present at 10 minutes (p=0·01), 40 minutes (p=0·03), and 60 minutes (p=0·05); Table 3).

The frequency distributions of the symptom scores for itchiness and photosensitivity before and after treatment are omitted, as the symptoms were not significantly alleviated (p>0·05).

## Discussion

Sodium hyaluronate unlike other available tear substitutes is a non-newtonian fluid which shear thins and rapidly regains its original viscosity (Kaura R, Tiffany JM, unpublished; Pharmacia, personal communication, 1985). It has been shown to adhere to corneal epithelium, and thus it is useful in the management of patients with severe dry eye.[20]

In this study the NIBUT and symptoms were used as criteria to assess the usefulness of 0·1% sodium hyaluronate (unpreserved) in the treatment of keratoconjunctivitis sicca. The topical application of 0·1% sodium hyaluronate significantly increased the NIBUT in comparison with the control eye (saline treated) for up to at least 40 minutes (Fig. 1, Table 1).

The subjective relief of the most frequently presented sympton, grittiness,[4] was alleviated immediately and lasted up to 60 minutes. Grittiness was significantly reduced only on intragroup analysis (Fig. 2, Table 2). Similarly burning was also alleviated. This relief persisted for up to 60 minutes, and it was also significant on intragroup comparison (Fig. 3, Table 3). Pollack and McNiece[22] showed that the relief of 'pain', a chronic symptom, at least in the severe dry eyes was obtained only after prolonged use of sodium hyaluronate.

In this 'acute' study itchiness and photosensitivity failed to respond to the treatment with sodium hyaluronate.

In conclusion it has been shown, both objectively and subjectively, that 0·1% sodium hyaluronate (unpreserved) could have a role in the management of dry eyes. The beneficial effect of sodium hyaluronate is most likely attributed to its viscoelastic properties, which are akin to those of natural tears.

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