ORIGINAL ARTICLE

SODIUM HYALURONATE EYE DROPS IN THE TREATMENT OF DRY EYE DISEASE: AN OPEN LABEL, UNCONTROLLED, MULTI-CENTRE TRIAL

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Background: Dry eye disease (DED) is one of the most frequently encountered ocular morbidities. The objective of this study was to assess the performance of sodium hyaluronate eye drop for eight weeks in patients with DED. **Patients and Methods:** This was a multi-centre, open-label, uncontrolled clinical trial carried out at different centres of Pakistan, from August 2009 to November 2010. A total of 250 diagnosed patients of Dry Eye who met the inclusion criteria were included in the study. After informed written consent, all patients having at least 2 of the Dry Eye symptoms, and at least 1 of the tests (Tear Film Break-up time (TBUT) ≤10 second, Schirmer's test ≤6 mm/5 min, and positive corneal staining) were enrolled. Tolerability/safety assessments consisted of monitoring and recording of adverse events and physical examinations at baseline, 4th week and 8th week. **Results:** Out of 250 allocated patients 13 dropped out. The mean age of the patients was 47.6±13.8 year and out of 237 patients 86 (36.3%) were men and 151 (63.7%) were women. At the initial visit the foreign body sensation was 80%, itching 68%, burning 58%, watering 38%, photophobia 38%, and feeling of dryness was 16%. At the 3rd visit the foreign body sensation decreased to 32%, itching to 32%, burning to 20%, watering to 12%, photophobia to 18%, and feeling of dryness to 14%. **Conclusion:** Sodium hyaluronate has a beneficial effect on the conjunctival epithelium in a well-defined and homogeneous population of patients with dry eye and can be considered useful for the treatment of dry eye.

Keywords: Fluoresce in eye stain, Tear Break up Time, Schirmer's test, Dry Eye Disease

INTRODUCTION

Dry eye disease (DED) is among the most common complaints reported to ophthalmologists. Dry eye disease is one of the most frequently encountered ocular morbidities. Twenty-five percent of patients who visit ophthalmic clinics report symptoms of dry eye, making it a growing public health problem and one of the most common conditions seen by eye care practitioners.[1] In 2007, the International Dry Eye Workshop (DEWS) revised the original definition and classification scheme of DED and developed a new definition as well as a three-part classification of DED based on aetiology, mechanism, and severity of the disease.[2]

Several risk factors for the development of DED have been identified repeatedly in epidemiological studies such as increasing age and female gender (particularly postmenopausal women), Aging, dry environment, hormonal changes, contact lens, blepharitis, auto-immune disease, pollution, extensive computer use, preservatives in topical medications. DED can have a considerable impact on visual function, daily activities, social and physical functioning, workplace productivity, direct and indirect cost of the disease, and quality of life (QOL).[3,4]

The Beaver Dam population-based study found DED prevalence to be 14% in adults of 48 to 91 years of age.[5] The study also found that DED affects more women than men (16.7% versus 11.4%, respectively). Reliable epidemiological studies from the large Women's Health Study and Physician's Health Study indicate that the prevalence of symptomatic dry eye in the United States is about 7% in women and 4% in men over the age of 50 years.[6] These numbers translate into approximately 3.2 million women and 1.05 million men with DED in the United States.[7] The frequency of dry eye syndrome in adult patients attending the eye clinic of Military Hospital Rawalpindi was 16%.[8]

The use of ocular lubricants provides comfort and supports the natural healing process, thereby leading to a better quality of life. For individuals with dry eye, the preservative used in ocular lubricant formulations is particularly critical as ocular surface inflammation may be aggravated by preservative use. Sodium hyaluronate products are considered to provide a preservative-free environment for the ocular surface as they contain GenAqua, a preservative and buffering system releasing low amounts of germicidal hydrogen peroxide, which is enzymatically broken-down completely and very rapidly upon contact with the eye into additional moisturising water and nutrient oxygen. The objective of this study was to assess the performance of sodium

hyaluronate eye drops for 8 weeks in patients with Dry Eye Disease.

MATERIAL AND METHODS

A total of 250 diagnosed patients of Dry Eye (who met the inclusion criteria) at 10 different centres were included in this study. After informed written consent, all patients were assessed as per following criteria: Presence of at least 2 of the symptoms (Foreign Body Sensation, Itching, Burning, Watering, Photophobia and Feeling of Dryness in the eye), and at least 1 of the 3 tests (Tear Film Break-up time ≤10 seconds, Schirmer's Test ≤6 mm/5 min, and Positive Corneal Staining).

Tolerability/safety assessments consisted of monitoring and recording of adverse events and performance of physical examinations at baseline, 4th week, and 8th week. The primary endpoint for efficacy was the change in Fluorescein and Rose Bengal staining scores from baseline at the 4-week endpoint. Safety evaluation included adverse events, clinical laboratory tests and ophthalmologic examinations using slit-lamp biomicroscopy.

Demographic and baseline variables were described by summary statistics. For continuous data Mean±SD, and for categorical data frequency and percentages were calculated. Extended Mantel-Haenszel Chi-square for linear trend and ANOVA were performed, and $p<0.05$ was considered significant.

RESULTS

Out of 250 patients 13 dropped out. The mean age of the patients was 47.6±13.8 year, and out of 237 patients 86 (36%) were men and 151 (64%) were women. Mean duration of symptoms was 8.9±8.5 months. Photophobia (38%) was the main ocular history, followed by ocular surgery (24%), and concomitant eye medication (22%). Systemic history revealed menopause (28.3%), diabetes mellitus (16.0%), and smoking 12.0%.

Exacerbating conditions for dry eye symptoms are tabulated in Table-1. Changes in ocular symptoms and signs in DED patients are shown in Table-2, and results of slit lamp biomicroscopy and fluorescein staining are tabulated in Table-3.

Table-1: Exacerbating conditions for Dry Eye symptoms (n=237)

Conditions	n	%
Not any reason	131	55.3
Summer or hot days	38	16.0
Light	19	8.0
Contact lens	14	6.0
Dry weather	14	6.0
Morning	9	4.0
Computer work	5	2.0
Summer or hot days	5	2.0
Whole day	1	0.4
Winter	1	0.4

Table-2: Changes in ocular symptoms and signs from baseline to visit-3 (n=237) [n (%)]

Ocular History	Visit-1	Visit-2	Visit-3	*p*
Foreign body sensation	190 (80)	166 (70)	76 (32)	<0.001
Itching	161 (68)	109 (46)	76 (32)	<0.001
Burning	137 (58)	85 (36)	47 (20)	<0.001
Watering	90 (38)	52 (22)	28 (12)	<0.001
Photophobia	90 (38)	76 (32)	43 (18)	<0.001
Feeling of dryness	38 (16)	24 (10)	33 (14)	0.45

Table-3: Slit-lamp Biomicroscopy (Mean±SD) (n=237)

Parameter	Visit-1	Visit-2	Visit-3	*p*
TBUT (sec)	6.6±2.8	6.7±3.2	8.3±2.3	<0.001
Schirmer's Test (No Anaesthesia)	6.9±5.4	6.6±3.5	7.8±3.7	<0.01
Corneal staining [n (%)]				
Fluorescein	180 (76)	76 (32)	38 (16)	<0.001
Rose Bengal	9 (3.4)	0 (0)	0 (0)	<0.001

DISCUSSION

Treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. The efficacy of sodium hyaluronate in patients with dry eye was evaluated by Nelson[9] following a treatment period of 8 weeks. Results have shown that treatment with sodium hyaluronate promotes corneal and conjunctival epithelial healing.

It was recently reported that sodium hyaluronate significantly improves signs and symptoms in patients with moderate to severe dry eye independently of the saline composition of ophthalmic solutions.[10] Hyaluronan is a natural polymer and its concentration increases in response to ocular damage and during corneal wound healing.[11] Troiano *et al*[12] in their study reported that treatment with 0.4% hyaluronic acid hypotonic solution gave better results in relieving symptoms, along with a statistically significant improvement ($p<0.001$) in the state of corneo-conjunctival epithelium, than the isotonic solution. At the end of their study, 60.7% of the patients declared that they preferred hypotonic solution and only 10.7% preferred isotonic solution; the remaining 28.6% did not notice any difference between the 2 treatments.[12] Present study suggests that subjective symptoms like foreign body sensation, itching, burning, watering and photophobia much improved ($p<0.001$), suggesting sodium hyaluronate as effective regardless of its chemical properties.

In vitro hyaluronate promotes cell migration and can stabilise ocular surface epithelial barrier[13,14] suggesting that it may be directly involved in the process of epithelial repair by activation of the CD44 (the hyaluronate receptor). Sodium hyaluronate significantly ($p<0.05$) decreased CD44 values compared with carboxymethylcellulose (CMC). Comfort was significantly ($p<0.05$) better in the sodium hyaluronate group than that in the CMC group. Recovery in keratitis

(type, extent and depth) and symptoms was faster in the sodium hyaluronate group than in the CMC group.[15]

This study found the decrease in Flourescin and Rose Bengal staining while TBUT was increased from 6.6 to 8.3 seconds and also Schirmer's test increased from 6.9 to 7.8. Sand *et al* found significantly decreased Rose Bengal staining and increased break-up time following 0.2% treatment compared to placebo. No significant difference was found in the Schirmer's test values and the cornea sensitivity. The patients significantly preferred sodium hyaluronate treatment.[16]

Hyaluronate may play a part in controlling the localised inflammation often present in patients with keratoconjuctivitis sicca.[17] Hyaluronate increases the stability of the pre-corneal tear film, which protects the ocular surface from environmental agents[17] and it has water retentive properties, which improve ocular surface wettability.[18] Hyaluronate may contribute to a favourable microenvironment during ocular repairing processes.

Hyaluronate has visco-elastic properties that can lubricate the ocular surface reducing friction during blinking and ocular movements. We found no adverse events during the study period. In a previous study safety evaluations also showed that the incidence of mild adverse drug reactions, eye discharge and eye irritation were higher in the diquafosol group than in the sodium hyaluronate group.[19]

CONCLUSION

Sodium hyaluronate products are particularly effective for eye dryness. Sodium hyaluronate eye drops seem to be a valuable new agent in the management of DED.

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