Original Article

A prospective contralateral eye comparison of the tolerability of two artificial tears with different physical properties in patients with dry eye disease

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ABSTRACT

Background: Artificial tears (ATs) are widely used in ophthalmic practice with various formulations, mainly as a treatment for dry eye, owing to their rapid ability to alleviate the signs and symptoms of this condition. We aimed to investigate drop comfort and subjective ocular symptoms after instillation of the following ATs with different physical properties: Optive® non-preservative (OUD) and Systane® Hydration non-preservative (SHUD).

Methods: This was a prospective, double-blind, randomized, contralateral eye comparison study. A rheometer and a digital pH meter were used to evaluate the viscosity and pH of both ATs prior to instillation. We recruited 36 patients with dry eye disease. Single standardized AT volumes were set using a micropipette for all patients. Ocular discomfort was assessed using the Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire (OOD4SQ; 0 – 5 scale) before and 60 min after instillation. Drop comfort was assessed using the Ora Calibra™ Drop Comfort Scale (0 – 10 scale) immediately after AT instillation. The difference in the drop comfort score (DCS) between the two ATs and ocular discomfort scores using OOD4SQ before and 60 min after instillation of each AT were recorded and compared.

Results: The viscosities and pH of SHUD and OUD were 32.73 centipoise (cP) and 7.74 and 14.42 cP and 7.19, respectively. The mean (standard deviation) DCS was higher in the SHUD group than in the OUD group (1.83 [1.21] versus 1.67 [1.12]); however, the difference was not statistically significant ($P > 0.05$). There was a significant reduction in all parameters of OOD4SQ including overall discomfort, burning, dryness, grittiness, and stinging 60 min after OUD instillation (all $P < 0.05$), while a significant difference was only noted in dryness ($P < 0.05$) in the SHUD group.

Conclusions: OUD, which has a lower viscosity and pH compared to SHUD, provides less subjective sensation and better ocular comfort 60 min after instillation. Further randomized clinical trials including patients with dry eye disease of different severities, larger sample sizes, and longer follow-up periods are required to verify our findings.

KEYWORDS

artificial tears, viscosity, dry eye disease, ophthalmic absorption, treatment, clinical efficacy, prospective study

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INTRODUCTION

Artificial tears (ATs) are widely used in ophthalmic practice with various formulations, mainly as a treatment for dry eye, owing to their rapid ability to alleviate the signs and symptoms of this condition [1, 2]. The formulation used in AT production alters the physical properties of ATs, such as viscosity, pH, osmolality, and density, which affect the bioavailability of the products [3, 4]. In addition, manufacturers should consider the tolerability and stability of the final production of ATs to ensure that the main goal of treatment can be achieved [5].

Highly viscous ATs are more effective in relieving ocular discomfort, as they prolong the residence time owing to the slower drainage rate of tears from the ocular surface and increase the adhesive capacity of macromolecules with the mucin layer [6]. This, in turn, improves ocular surface hydration, maintains the osmolarity of the tear film, and reduces the risk of ocular surface inflammation. However, high-viscosity formulations are likely to cause ocular discomfort, blurred vision, stickiness, and crusty residue formation after AT instillation [7].

In addition to viscosity, pH is a physical property that affects AT formulation, as its buffer system stabilizes the chemical composition of ATs to extend their shelf life and simultaneously protects the ingredients against decay [8]. However, inappropriate pH values of ATs may affect ocular sensation after instilling drops. The pH values of ATs outside the ocular comfort range or deviating far from the pH of natural tear may cause irritation, stinging sensation, or ocular discomfort [9, 10].

The physicochemical properties of ATs should be at the optimum level, as alteration of these factors would compromise patient compliance and reduce the bioavailability of ATs owing to excessive tearing, resulting in rapid flushing of the instilled ATs [10, 11]. We aimed to evaluate the patients' subjective response to Optive® non-preservative lubricant eye drops (OUD) (0.5% carboxymethylcellulose sodium, 0.9% glycerin) and Systane® Hydration non-preservative lubricant eye drops (SHUD; 0.1% sodium hyaluronate) based on the drop comfort after instillation and overall ocular symptoms before and 60 min after instillation.

METHODS

This prospective, double-blind, randomized, contralateral eye comparison study recruited 36 patients with dry eye disease. The study procedures adhered to the tenets of the Declaration of Helsinki. The study protocols were approved by the International Islamic University Malaysia (IIUM) Research Ethics Committee (IREC 2019-125). The first phase of this study (testing the physical properties of ATs) was conducted at the Kulliyyah of Pharmacy, IIUM, while the second phase was conducted at the IIUM Optometry Clinic. Before data collection, all patients were informed of the study steps, and written consent was obtained.

All patients underwent a comprehensive optometric examination before recruitment [12, 13] and fulfilled the following inclusion criteria: good ocular and general health, aged 20 – 40 years, non-contact lens wearer, and developed dry eye disease. All included patients had a tear break-up time < 5 s [14], ocular surface disease index score ≥ 13 [15], and Schirmer test I ≤ 10 mm / 5 min [2]. Patients with a history of ocular trauma, evidence of active ocular infection in either eye, or significant underlying ocular pathology affecting the ocular surface were excluded [16-18]. We enrolled 36 patients, including 10 (28%) men and 26 (72%) women, with a mean (standard deviation [SD]) age of 27.47 (6.91) (range: 20 – 40) years. Table 1 outlines the demographic and baseline characteristics of the study patients. Figure 1 summarizes the allocation of patients.

Two marketed non-preservative ATs, OUD (Allergan Inc., Irvine, California, USA) and SHUD (Alcon Laboratories Inc., Fort Worth, TX, USA), were used. For the first phase of the study, the physical properties (viscosity and pH) of both ATs were measured before application to the patients' eyes. Viscosity was measured using a Thermo Scientific rheometer (HAAKE RheoWin, Version 3.61.0004, Thermo Fisher Scientific Inc., Massachusetts, US), and pH was determined using a compact pH meter (LAQUAtwin pH-meter pH33, Horiba Advanced Techno Co., Ltd., Shiga, Japan).

Table 1. Demographic and baseline characteristics of study patients with dry eye disease

Variables	Value
Age (y), Mean ± SD	27.47 ± 6.91
Sex (Male / Female), n (%)	10 (28) /26 (72)
TBUT (s), Mean ± SD	2.64 ± 2.21
OSDI, Mean ± SD	15.75 ± 2.15
Schirmer 1 (mm), Mean ± SD	3.75 ± 0.86

Abbreviations: y, years; SD, standard deviation; n, number of participants; %, percentage; TBUT, tear break-up time; s, seconds; OSDI, ocular surface disease index; mm, millimeter.

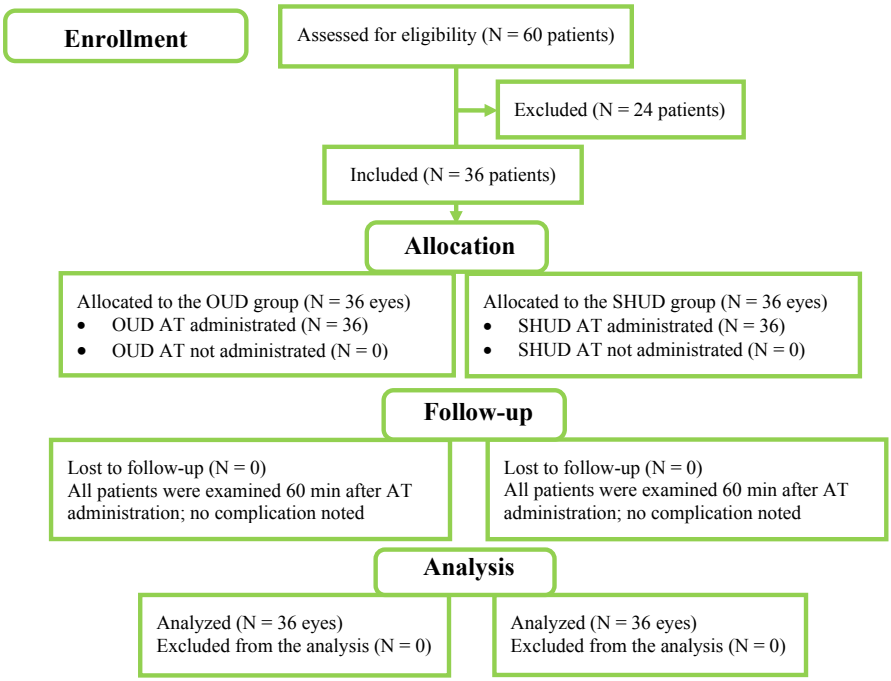

Figure 1. Allocation of the study patients to the OUD or SHUD group. Abbreviations: N, numbers; OUD, Optive® non-preservative lubricant eye drop (%0.5 Carboxymethylcellulose, %0.9 glycerin); SHUD, Systane® Hydration non-preservative lubricant eye drop (%0.1 Sodium hyaluronate); AT, artificial tears.

The ATs were prepared off-label, and the time taken by the rheometer to measure the viscosity of each AT was approximately 5 min. AT (1 mL) was applied to the lower measuring plate of the rheometer before the instrument automatically standardized the temperature to 25°C. Before the measurement, the upper plate of the rheometer was lowered to a gap size of 1000 µm and rotated according to the speed set by the examiner [19]. The torque applied on the upper plate of the rheometer exerted a rotational shear stress on the AT placed between the upper and lower plates. The shear rate was set from 10 to 100 s^{-1} in a single sweep, and the rate of shear stress at each interval was automatically determined using the rheometer [19]. Based on the viscosity law, the viscosity of the ATs was calculated using the built-in software of the rheometer. Viscosity at the highest shear rate (100 s^{-1}) was recorded for the analysis using the viscosity equation [19].

Before the pH measurement, two-point calibration was performed using two standard solutions, with pH of 4 and 7 [20]. A drop of AT (0.2 mL) was applied evenly on the flat sensor until the AT covered the entire surface of the sensor. Subsequently, the compact pH-meter automatically measured the pH of ATs. Three measurements were obtained for each AT, and the average pH was recorded for the analysis. The pH meter sensor was cleaned using distilled water before measuring the pH of the next sample to avoid sample crossover contamination [20].

The study participants and the optometrist who conducted the procedures were blinded to the ATs used. To determine the subjective ocular symptoms, before AT administration, the patients were asked to answer the Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire (OOD4SQ), and the severity of ocular symptoms was recorded. For this questionnaire, patients were required to grade overall discomfort, burning, dryness, grittiness, and stinging, with regard to how their eyes felt at the time. This questionnaire consists of six points (0 [none] to 5 [worst]) [21, 22]. After answering the questionnaire, a single drop of 60 µL of ATs was instilled into the patients' eyes using a micropipette [23]. The order of AT instillation (OUD or SHUD) and eye order of the AT instillation were randomized using randomization software (Research Randomizer, Version 4.0) [24].

Immediately after AT administration, the patients were asked to rate the drop comfort of ATs instilled according to the Ora Calibra™ Drop Comfort Scale (ODCS) on a scale of 0 (most comfortable) to 10 (most uncomfortable) [21, 22]. After AT instillation in both eyes, the patients were requested to remain in the examination room, where temperature and humidity maintained at 20°C – 24°C [3] and 40% – 50% [23], respectively, for 60 min. After 60 min, the patients were asked to answer the OOD4SQ again to obtain their feedback on ocular symptoms after AT instillation. Both eyes with different ATs instilled in each eye were measured for both OOD4SQ before and 60 min after AT instillation and ODCS scoring immediately after AT administration.

Table 2. Comparison of the severity of ocular symptoms using OOD4SQ between baseline and 60-min post-AT instillation

Type of ATs	Time of measurements	Overall discomfort (Mean ± SD)	Burning (Mean ± SD)	Dryness (Mean ± SD)	Grittiness (Mean ± SD)	Stinging (Mean ± SD)
OUD (n = 36)	**Baseline**	1.25 ± 0.97	0.89 ± 0.89	1.03 ± 0.81	0.83 ± 0.85	0.61 ± 0.69
	60 min	0.58 ± 0.65	0.58 ± 0.50	0.28 ± 0.62	0.28 ± 0.62	0.19 ± 0.40
	***P*-value**	**< 0.001**	**0.006**	**< 0.001**	**< 0.001**	**< 0.001**
SHUD (n = 36)	**Baseline**	0.81 ± 0.92	0.42 ± 0.69	0.78 ± 0.87	0.39 ± 0.65	0.39 ± 0.49
	60 min	0.61 ± 0.73	0.17 ± 0.38	0.50 ± 0.66	0.19 ± 0.58	0.22 ± 0.54
	***P*-value**	0.228	0.083	**0.039**	0.051	0.110

Abbreviations: OOD4S, Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire (0-5 scale; 0 = no discomfort, 5 = worst); ATs, artificial tears; SD, standard deviation; OUD, Optive® non-preservative lubricant eye drop (0.5% Carboxymethylcellulose, 0.9% glycerin); n, number of included eyes; SHUD, Systane® Hydration non-preservative lubricant eye drop (0.1% Sodium hyaluronate); min, minutes. Note: *P*-values < 0.05 are shown in bold.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y., USA). The normality of data distribution was assessed using the skewness and kurtosis of the distribution [25]. Data are expressed as mean (SD) or frequency (percentage). A descriptive analysis was employed to obtain the mean drop comfort score from the ODCS of both ATs. The independent *t*-test was used to compare the mean drop comfort score between the two ATs. To compare the ocular symptoms scored by the OOD4SQ before and 60 min after AT instillation, a paired-samples *t*-test was conducted. Statistical significance was set at a *P*-value < 0.05.

RESULTS

The physical properties showed that SHUD was more viscous compared to OUD, with viscosities of 32.73 and 14.42 centipoise (cP), respectively. In addition, pH measurement results revealed that both ATs were alkaline, with SHUD having a more basic pH (7.74) compared to OUD (7.19).

Based on the patients' drop comfort score using ODCS, OUD had a lower but comparable ($P = 0.546$) drop comfort score compared to SHUD, with mean (SD) drop comfort scores of 1.67 (1.12) and 1.83 (1.21), respectively, recorded immediately after AT instillation.

Table 2 shows a comparison of the mean ocular symptoms before and 60 min after AT instillation. The overall and mean scores of each ocular symptom changed significantly between baseline and 60-min post-OUD instillation (all $P < 0.05$; Table 2).

In the SHUD group (Table 2), only dryness had significantly reduced 60 min after SHUD instillation ($P < 0.05$). The mean scores for other ocular symptoms, including overall discomfort, burning, grittiness, and stinging, were comparable between the two measurement time points (all $P > 0.05$), although the mean values had reduced (Table 2).

DISCUSSION

OUD, which has a lower viscosity and pH compared to SHUD, provides less subjective sensation and better ocular comfort 60 min after instillation.

OUD and SHUD [23, 26-28] have been widely used by eye care practitioners and patients to treat dry eye disease, owing to their over-the-counter availability. We found a higher viscosity for SHUD, which was slightly alkaline compared to OUD. The final viscosity of ATs should be <30 cP to avoid discomfort, blurred vision, and irritation, which may lead to faster drainage of ATs caused by reflex tears and blinking [29, 30]. Our results suggested that SHUD, with viscosity > 30 cP (SHUD: 32.73 cP) had a higher mean but comparable drop comfort score compared to OUD, with mean (SD) drop comfort scores of 1.83 (0.21) and 1.67 (0.12), respectively. This finding was in line with a previous report [29, 30], in which higher-viscosity ATs were more likely to affect ocular comfort after instillation. However, both ATs were well tolerated, with a comparable drop comfort score.

Regarding the pH of ATs, Garcia-Valldecabres et al. [31] and Tong et al. [32] suggested that the pH of ATs should range from 6.6 – 7.8 (ocular comfort range) to avoid any discomfort after instillation. Both OUD and SHUD showed pH within the suggested ocular comfort range, i.e., 7.19 and 7.74, respectively. However, the pH of ATs should be adjusted to the physiological parameters of natural tears [33], as it can affect the ocular surface by changing the homeostatic balance of the tear film, which may result in epiphora, irritation, stinging sensation, or ocular discomfort [9, 10, 34] and decreased drug bioavailability [34]. While the mean (SD) tear pH of dry eye

was 7.46 (0.24) [35], we found the pH values of both OUD and SHUD to be slightly far from the natural tear pH in the patients with dry eye, which could cause irritation after instillation.

Generally, both formulations showed a reduction in the mean score of OOD4SQ for all parameters (overall discomfort, burning, dryness, grittiness, and stinging) when compared between baseline and 60 min after AT administration. However, significant improvements were noted in all parameters of the OOD4SQ in the OUD group. Only dryness had significantly improved 60 min after SHUD instillation. This finding is in line with previous studies conducted by Markoulli et al. [23], who reported better ocular comfort after instillation of the Optive eye drop throughout the 1-h observation period.

Although many studies have associated the viscosity of ATs with prolonged ocular retention time [3, 36, 37], which indirectly improves ocular symptoms because of prolonged contact with the ocular surface, contradictory findings were observed in this study. OUD, which has a lower viscosity compared to SHUD, efficiently reduced the ocular symptoms of dry eye owing to the active ingredient used in its formulation, in which anionic characteristic of carboxymethylcellulose sodium might play a greater role in improving the ocular symptoms, because viscosity alone may not completely explain the prolonged ocular retention time [3, 38].

This study showed less subjective sensation and better ocular comfort 60 min after instillation of OUD compared to SHUD, despite having a lower viscosity and pH compared to SHUD. However, the both ATs used in this study were non-preservatives. Thus, the drop comfort score and changes in ocular symptoms might differ in preservative ATs, which requires further investigation. Additionally, the effects of ATs on ocular symptoms were observed after a 60-min interval with a single instillation, in which the long-term effect of ATs with multiple instillations could be evaluated to determine the effectiveness of the treatment. We did not classify the patients based on the severity of dry eye disease. Future randomized clinical trials with various spectra of dry eye disease, larger sample sizes, and longer follow-up periods are required to verify our findings.

CONCLUSIONS

The results of this study demonstrated that both ATs were well tolerated and provide effective relief from ocular discomfort, even after a short observation period. OUD with low viscosity and pH provides markedly better drop comfort score and significantly improves all ocular discomfort symptoms. Future randomized clinical trials with various spectra of dry eye disease, larger sample sizes, and longer follow-up periods are required to verify our findings.

ETHICAL DECLARATIONS

Ethical approval: The study procedures adhered to the tenets of the Declaration of Helsinki. The study protocols were approved by the International Islamic University Malaysia (IIUM) Research Ethics Committee (IREC 2019-125). Before data collection, all patients were informed of the study steps, and written consent was obtained.

Conflict of interest: None.

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