IMMEDIATE EFFECTS OF ARTIFICIAL TEARS VISCOSITY AND PH ON OCULAR SIGNS AND SYMPTOMS

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ABSTRACT

Purpose: To evaluate the short-term effects of artificial tears (ATs) with different viscosity and pH; Systane® Hydration preservative (SH) and non-preservative (SHUD), Optive® preservative (O) and non-preservative (OUD) on patients' signs and symptoms in normal and dry eye (DE) groups.
Methods: 120 participants (55: DE group, 65: normal group) involved in this prospective, double-masked randomized study. Rheometer and digital pH-meter were used to evaluate the viscosity and pH of all ATs. Ocular discomfort between pre and post-instillation (after 60 minutes interval) was evaluated using Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire (OOD4SQ). Drop comfort immediately assessed after ATs instillation using Ora Calibra™ Drop Comfort Scale (ODCS). Tear break-up time (TBUT) and tear meniscus height (TMH) were measured at baseline, 5, 15 and 60 minutes after instillations. Tear ferning pattern (TFP) were observed and compared at baseline and 60 minutes after instillation.
Results: Viscosity of all ATs were; SHUD: 32.73cP, SH: 26.7cP, OUD: 14.42cP and O: 13.88cP with pH of 7.74 (SHUD), 7.85 (SH), 7.19 (OUD) and 7.24 (O). Highest DCS was found in SH for both DE (2.00±1.042) and normal group (1.84±0.963). Significant reduction ($p<0.05$) in all parameters of ocular symptoms (OOD4SQ) were found after instillation of OUD in both groups. TBUT and TMH for both groups increased significantly ($p<0.05$) from baseline at all time-interval (except TBUT for O in normal group at 5 minutes post-instillation). TFP improved significantly after 60 minutes instillation of all ATs in both groups.
Conclusion: All ATs improved TBUT, TMH and TFP in both groups, regardless their viscosity and pH. OUD showed better ocular symptoms improvement and less subjective sensation compared to other tested ATs.

Keywords: artificial tears, ocular symptoms, pH, viscosity

INTRODUCTION

Artificial tears is one of the favorable treatment modalities among eye care practitioners to treat ocular surface problems such as dry eye (Asiedu et al., 2016) due to their availability in the market with affordable price, easy to use with simple steps and proven to improve and rejuvenate the ocular surface affected from dry eye (Torkildsen et al., 2017). Furthermore, artificial tears is available over-the-counter, in which the patient can easily buy the products, even without the prescription from medical personnel. Despite being the preferable treatment among eye care practitioner in managing dry eye, it is quite difficult for the eye care practitioner to prescribe the most effective artificial tears that can improve both signs and symptoms of dry eye as there are variety of brands and formulations available in the market.

Different artificial tears are formulated with different chemical components such as lubricants, polymers, solutes, electrolytes and with or without preservatives (Torkildsen et al., 2017; Che Arif et al., 2020; Che Arif et al., 2021). All these components have their own functions that contribute to the efficacy of artificial tears, and at the same time will affect the physical properties, which is also an important factor that may affect the bioavailability of artificial tears (Aragona et al., 2019; Araújo et al., 2016). Hyaluronic acid (HA) and carboxymethylcellulose (CMC) are the common lubricants used in artificial tears formulation due to their great ability in alleviating both subjective and objective signs and symptoms of dry eye (Song et al., 2017; Cagini et al., 2017; Salzillo et al., 2016; Che Arif et al., 2023).

However, it is still unclear on what factors actually lead to the improvement in term of signs and symptoms of ocular discomfort; chemical component, physical components, or both factors. While chemical components usually being listed on the leaflet, information on physical properties of artificial tears rarely being disclosed by the manufactures even though this information may be beneficial in guiding the eye care practitioners and patients in choosing the suitable artificial tears based on ocular conditions. Viscosity and pH are among physical properties of artificial tears which worth to be investigated thoroughly as viscosity anecdotally known to be associated with tear retention time, while pH was believed to affect the ocular sensation after instillation in the case of large discrepancy in pH unit between artificial tears and natural tear pH (Salzillo et al., 2016; Baranowski et al., 2014; Che Arif et al., 2023). As these factors seem to affect the performance of artificial tears in improving the signs and symptoms of dry eye, hence this study would like to observe if artificial tears with different viscosity and pH will performed differently in improving signs and symptoms of dry eye.

MATERIALS AND METHODS

This prospective, double-masked randomized study conducted at International Islamic University Malaysia Eye Specialist Clinic (IESC). A total of 55 mild to moderate dry eye

participants, along with 65 normal participants were recruited in this study. Written informed consents were obtained from all participants prior to study procedures. The study procedures were reviewed and approved by the International Islamic University Malaysia (IIUM) Research Ethics Committee (IREC 2019-125).

Inclusion criteria for this study were; participants who were having good ocular and general health, aged between 20 to 40 years old, have no known sensitivity or intolerance to any of the products used in this study, and non-contact lens wearer. Meanwhile those having these criteria; history of previous ocular trauma (Garcia-Lázaro et al., 2011), evidence of active ocular infection in either eye (Lambiase et al., 2017), significant underlying of ocular pathology affecting cornea and ocular surface such as recurrent pterygium (Hilmi et al., 2019; Hilmi et al., 2017), corneal opacity or irregularity (Hilmi et al., 2020; Che Azemin et al., 2016; Hilmi et al., 2019) and under treatment of drug affecting tearing (Torkildsen et al., 2017) were excluded from this study. For female participants who were in menstrual cycle, the data collection process was not conducted during that period as tear production and stability were affected due to hormonal changes in menstrual cycle (Gibson et al., 2017; Versura et al., 2007).

Measurement of artificial tears' viscosity and pH

Four artificial tears were used in this study; Systane® Hydration preservative (SH), Systane® Hydration non-preservative (SHUD), Optive® preservative (O) and Optive® non-preservative (OUD). Physical properties of artificial tears; viscosity and pH were measured using rheometer and compact pH meter, respectively. Thermo Scientific Rheometer (Model HAAKE RheoWin Version 3.61.0004, Thermo Fisher Scientific Inc, Massachusetts, US) was utilized to measure the viscosity of artificial tears while automated compact pH-meter (LAQUAtwin pH-meter pH33, Horiba Advanced Techno Co., Ltd., Shiga, Japan) was used for pH measurement.

Sample of artificial tear (1ml) was applied on the lower measuring plate of rheometer and upper plate was lowered until the gap between upper and lower plate was 1.000mm. The temperature of each sample was standardised to 25°C and measurement started as the upper plate started to rotate due to the torque applied (Che Arif et al., 2020). For this study, viscosity of each artificial tear was measured from shear rate of $10s^{-1}$ to $100s^{-1}$ using a 35mm plate sensor (ThermoFisher Scientific, 2017).

For pH measurement, a small amount of artificial tears (0.2ml) was dropped on the flat sensor of pH meter until it covered the entire surface. After pressing the measurement button, the instrument would automatically measure the pH of artificial tear. The average pH from three measurements for each sample was taken for analysis and prior to next measurements; the sensor of pH meter was cleaned using distilled water to avoid sample cross-contamination.

Evaluation of signs and symptoms before and after the instillation of artificial tears

All participants were required to answer the Ocular Surface Disease Index (OSDI) questionnaire (Allergan Inc, Irvine, CA, USA) and the score obtained from this questionnaire was used as the main reference to divide the participants into two groups, which were normal group; OSDI score < 13, and dry eye group ; OSDI score ≥ 13 (Doguizi et al., 2019; Wolffsohn et al., 2017; Che Arif et al., 2021). The other parameters involved in classifying the participants under dry eye group were; TBUT < 5 seconds (Li et al., 2018) and Schirmer test I ≤ 10 mm/5 minutes (Shah et al., 2017). Those participants who were having TBUT ≥ 5 seconds and Schirmer test I > 10 mm/5 minutes were classified under normal group and if there was any parameter that did not tally with the listed criteria, the main reference, OSDI score was used to determine the group.

Prior to baseline measurement, participants were asked to answer Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire (OOD4SQ) (Ora Inc, Andover, MA, USA). This questionnaires comprise of five points; overall discomfort, burning, dryness, grittiness and stinging, with 0 to 5 scales in which 0 indicates no discomfort and 5 is the worst discomfort. Participants were asked to rate the severity on how their eyes felt at these two specific time; pre and 60 minutes post-artificial tears instillation.

Next, tear breakup time (TBUT), tear meniscus height (TMH) and tear ferning pattern (TFP) were assessed at baseline. The temperature and humidity of the examination room were kept constant at 20°C-24°C (Dutta et al., 2019) and 40%-50% (Markoulli et al., 2018), respectively. TBUT was recorded with a video camera mounted on digital high-definition slit-lamp biomicroscopy (Model SL 990, SLB Mega Digital Vision HR, Costruzione Strumenti Oftalmici, Italy). TBUT determination was later conducted by playing back the video recordings and TBUT was measured using stopwatch. Three measurements were taken and the mean value was recorded for analysis.

TMH measurement was conducted using Zeiss Visante ™ Optical Coherence Tomography (OCT) (Zeiss Meditec, Inc, Dublin, USA) in a dim-illuminated room. From the image obtained, TMH was defined as tear film height between the edge of the lower eyelid and the cornea (Rosmadi et al., 2019). 'All scans' protocol with 'Raw Image Mode High Resolution Corneal Scan' was selected in order to capture the image of tear film by focusing on lower eyelid at '6 o'clock' and the corneal refraction as reference (Rosmadi et al., 2019). The images captured from OCT were saved in Tagged Image File Format (TIFF), and being transferred to image analysis software, Image J Software (National Institutes of Health, USA) to quantify the TMH values by converting the known pixels of the image to unit of millimeter (mm); 1 pixel = 1.126 mm.

For TFP assessment, a sample of unstimulated tears was collected from temporal, lower tear meniscus of participant's eye using the glass microcapillary tube and allowed

to dry by evaporation for 5-10 minutes (Sharanjeet-Kaur et al., 2016). Microscopic appearance of the dried tear was observed under the light microscope (Ken-α-Vision Manufacturing, Inc., Missouri, USA) by using 10X magnification (Alanazi et al., 2019) and TFP observed were classified into four groups according to Rolando's tear ferning classification (Rolando et al., 2984). For the statistical analysis, the grading of TFP were based on the numerical-converted TFP grading with type I = 1.0, type II = 2.0, type III = 3.0 and type IV = 4.0 (Versus et al., 2007; Sharanjeet-Kaur et al., 2016).

After baseline measurements of TBUT, TMH and TFP, a drop of different artificial tears was instilled into the right eye, followed by the left eye for the other brand of artificial tears using a pipette with a constant volume of 60µl (Markoulli et al., 2018). Right after artificial tears instillation, participants graded the drop comfort using Ora Calibra™ Drop Comfort Scale (ODCS) (Ora Inc, Andover, MA, USA) based on 0-10 scale, in which 0 indicating very comfortable and 10 is very uncomfortable. After the instillation, TBUT and TMH were re-measured at 5, 15 and 60 minutes, while TFP was observed at 60 minutes post-artificial tears instillation.

Lastly, after 60 minutes artificial tears administration, participants were again required to answer the OOD4SQ in order to observe for any significant improvement in ocular symptoms after the artificial tears instillation. As there were four artificial tears used in this study, each participant were required to attend two visits, with at least 24 hours wash-out period between the visits (Markoulli et al., 2018; Rosmadi et al., 2019). Research randomizer software (https://www.randomizer.org/) was used to randomise the eyes and artificial tears to be used at each visit.

IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA) was used to execute the statistical calculations, with p-value of 0.05 was set as the level of significance. Normality assumption for all the data was assessed using skewness and kurtosis of the distribution (Kim, 2013). Differences between pre and time-interval after the instillation (5, 15 and 60 minutes for TBUT and TMH, 60 minutes for TFP) of all artificial tears and differences of ocular symptoms (OOD4SQ) between baseline and after 60 minutes artificial tears administration were compared using Paired Sample T-test, while Repeated Measures One-way analysis of variance (RM-ANOVA) was employed to compare the TBUT and TMH between instillations of all the tested solutions at each time-interval. Descriptive analysis was employed to obtain the mean of drop comfort score of ODCS for each artificial tear.

RESULTS

Physical properties of artificial tears

Based on the findings, SHUD was found to have the highest viscosity (32.73 cP), followed by SH (26.7 cP) and OUD (14.42 cP), while O had the lowest viscosity (13.88 cP). pH measurements showed that pH of all artificial tears were alkaline; SHUD: 7.74, SH: 7.85,

OUD: 7.19 and O: 7.24. The viscosity and pH for all artificial tears were summarised in Table 1.

Table 1 Physical properties of artificial tears

Artificial tear brand	Manufacturer	Lubricants	Preservative	Viscosity (cP)	pH
Systane® Hydration	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate, Hydroxypropyl guar	Polyquaternium®-1 0.0011%	26.70	7.85
Systane® Hydration UD	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate, Hydroxypropyl guar	None	32.73	7.74
Optive®	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5%, Glycerin 0.9%	Purite	13.88	7.24
Optive® UD	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5%, Glycerin 0.9%	None	14.42	7.19

Signs and symptoms after artificial tears instillation

TBUT increased significantly in both groups for all artificial tears, except O in normal groups at 5 minutes of instillation (p= 0.135). For dry eye group, TBUT of all artificial tears kept increased up to 60 minutes of observation period, with highest values of TBUT was noted at this period. Meanwhile for normal group, highest increment of TBUT was observed at 15 minutes post-instillation. RM ANOVA analysis showed that mean TBUT differed significantly across the measurements after the instillation of all artificial tears, as shown in Table 2.

Table 2 Comparisons ofTBUT at different times between all artificial tears in dry eye and normal groups

Artificial tears	Groups	PRE Mean ± SD (sec)	5 min Mean ± SD (sec)	15 min Mean ± SD (sec)	60 min Mean ± SD (sec)	p value (RM ANOVA)
SH	Dry eye	4.14 ± 1.15	4.81 ± 0.82	4.69 ± 1.12	5.14 ± 1.20	**<0.001**
p value*		-	**<0.001**	**<0.001**	**<0.001**	
	Normal	6.00 ± 0.94	6.20 ± 0.77	6.27 ± 0.76	6.16 ± 0.83	**0.016**
		-	**0.037**	**0.002**	**0.033**	
SHUD	Dry eye	4.06 ± 1.07	4.78 ± 0.80	4.89 ± 0.95	5.28 ± 1.30	**<0.001**
p value*		-	**<0.001**	**<0.001**	**<0.001**	
	Normal	5.95 ± 0.96	6.16 ± 0.71	6.23 ± 0.83	6.11 ± 0.90	**0.014**
		-	**0.027**	**0.001**	**0.033**	
O	Dry eye	4.00 ± 1.12	4.69 ± 0.92	4.89 ± 1.12	5.08 ± 1.44	**<0.001**
p value*		-	**<0.001**	**<0.001**	**<0.001**	
	Normal	6.02 ± 0.88	6.16 ± 0.78	6.27 ± 0.79	6.18 ± 0.84	**0.032**
		-	0.135	**<0.001**	**0.033**	
OUD	Dry eye	4.17 ± 0.94	4.78 ± 0.80	4.86 ± 1.05	5.31 ± 1.24	**<0.001**
p value*		-	**<0.001**	**<0.001**	**<0.001**	
	Normal	5.86 ± 1.11	6.09 ± 0.86	6.23 ± 0.89	6.23 ± 0.83	**<0.001**
		-	**0.031**	**<0.001**	**<0.001**	

* p-value analysed using Paired sample T-test

Paired sample T-test in both dry eye and normal groups revealed that TMH values were significantly higher after the instillation of all artificial tears compared to baseline at every time points as demonstrates in Table 3. Higher TMH post-instillation indicated that all artificial tears were effective in increasing tear volume in both groups of participants. RM ANOVA findings indicated significant differences in TMH values after the instillation of SH, SHUD, O, as well as OUD at all-time intervals.

Table 3 Comparisons of TMH at different times between all artificial tears in dry eye and normal groups

Artificial tears	Groups	PRE Mean ± SD (mm)	5 min Mean ± SD (mm)	15 min Mean ± SD (mm)	60 min Mean ± SD (mm)	P-value (RM ANOVA)
SH	Dry eye	0.176 ± 0.040	0.200 ± 0.058	0.201 ± 0.042	0.198 ± 0.037	**<0.001**
P-value*		-	**0.002**	**<0.001**	**<0.001**	
	Normal	0.224 ± 0.037	0.238 ± 0.055	0.237 ± 0.043	0.234 ± 0.035	**<0.001**
		-	**0.001**	**<0.001**	**<0.001**	
SHUD	Dry eye	0.191 ± 0.056	0.213 ± 0.068	0.211 ± 0.054	0.216 ± 0.057	**<0.001**
P-value*		-	**<0.001**	**<0.001**	**0.001**	
	Normal	0.221 ± 0.034	0.242 ± 0.050	0.241 ± 0.048	0.235 ± 0.036	**<0.001**
		-	**<0.001**	**<0.001**	**<0.001**	
O	Dry eye	0.181 ± 0.042	0.201 ± 0.051	0.200 ± 0.043	0.201 ± 0.046	**<0.001**
P-value*		-	**<0.001**	**<0.001**	**<0.001**	
	Normal	0.223 ± 0.036	0.238 ± 0.053	0.240 ± 0.049	0.233 ± 0.038	**<0.001**
		-	**<0.001**	**<0.001**	**<0.001**	
OUD	Dry eye	0.185 ± 0.038	0.208 ± 0.051	0.216 ± 0.051	0.213 ± 0.048	**<0.001**
P-value*		-	**<0.001**	**<0.001**	**<0.001**	
	Normal	0.226 ± 0.038	0.248 ± 0.059	0.238 ± 0.045	0.238 ± 0.044	**<0.001**
		-	**<0.001**	**<0.001**	**0.002**	

* p-value analysed using Paired sample T-test

As for TFP, significant improvement was observed 60 minutes post-artificial tears instillation in both dry eye and normal groups in Table 4. However, dry eye group portrayed greater improvement compared to normal group. Lower baseline in normal

group might be the reason for the discrepancy between normal and dry eye group, with much improvement was noted in dry eye group as compared to normal group.

Table 4 Comparisons of TFP between baseline and after 60 minutes instillation of all artificial tears in dry eye and normal group

Artificial tears	Groups	Time of measurement	TFP (Type) Mean ± SD	P-value*
SH	Dry eye	Baseline	2.39 ± 1.050	**<0.001**
		Post-instillation	1.58 ± 0.692	
	Normal	Baseline	1.45 ± 0.548	**0.024**
		Post-instillation	1.34 ± 0.479	
SHUD	Dry eye	Baseline	2.36 ± 1.046	**<0.001**
		Post-instillation	1.44 ± 0.504	
	Normal	Baseline	1.43 ± 0.545	**0.044**
		Post-instillation	1.34 ± 0.479	
O	Dry eye	Baseline	2.33 ± 1.014	**<0.001**
		Post-instillation	1.47 ± 0.560	
	Normal	Baseline	1.45 ± 0.548	**0.024**
		Post-instillation	1.34 ± 0.479	
OUD	Dry eye	Baseline	2.36 ± 1.046	**<0.001**
		Post-instillation	1.47 ± 0.560	
	Normal	Baseline	1.43 ± 0.545	**0.024**
		Post-instillation	1.30 ± 0.509	

* p-value analysed using Paired sample T-test

In term of symptoms, participants in normal group rated all the artificial tears drops as comfortable, with low drop comfort score given for all artificial tears in both groups. However, for each artificial tear, higher drop comfort score was recorded in dry eye group compared to normal group, except for OUD. The highest mean score was observed after the instillation of SH, in both normal and dry eye groups. Table 5

summarizes the mean drop comfort score right after the instillation of all artificial tears in both groups.

Table 5 Drop comfort score determine using Ora Calibra™ Drop Comfort Scale (0-10 scale; 0 = most comfortable, 10 = most uncomfortable) in dry eye and normal groups

Artificial tears	Groups	Drop comfort score (mean±SD)	P-value*
SH	Dry eye	2.00±1.042	**<0.001**
	Normal	1.84±0.963	
SHUD	Dry eye	1.83±1.207	**<0.001**
	Normal	1.55±0.761	
O	Dry eye	1.83±0.775	**<0.001**
	Normal	1.68±0.674	
OUD	Dry eye	1.67±1.121	0.286
	Normal	1.68±0.909	

* p-value analysed using Independent T-test

The pre- and post-instillation analysis of ocular symptoms revealed significant improvement in all artificial tears except O (normal group) and SHUD (dry eye group) for overall discomfort. Symptom of dryness significantly decreased after the instillation of all artificial tears in both groups. Burning and grittiness showed improvement after 60 minutes instillation of SH and OUD in both groups. As for stinging, only OUD displayed significant improvement when comparing the score from baseline and 60 minutes post-instillation in both groups. Table 6 shows the comparison of ocular symptoms score at baseline and 60 minutes post-instillation for all artificial tears in both groups.

Artificial tears	Groups	Time of measurement	Overall discomfort†	Burning†	Dryness†	Grittiness†	Stinging†
SH	Dry eye	Baseline	1.14±0.990	0.22±0.422	0.92±0.770	0.22±0.540	0.22±0.591
		60 min	0.42±0.500	0.06±0.232	0.36±0.487	0.00±0.000	0.14±0.351

		p-value*	**<0.001**	**0.012**	**<0.001**	**0.019**	0.324
	Normal	Baseline	0.91±0.741	0.16±0.370	0.70±0.701	0.20±0.553	0.20±0.408
		60 min	0.68±0.639	0.02±0.151	0.48±0.549	0.00±0.00	0.16±0.526
		p-value*	**0.049**	**0.013**	**0.003**	**0.018**	0.533
	Dry eye	Baseline	0.81±0.920	0.42±0.692	0.78±0.866	0.39±0.645	0.39±0.494
		60 min	0.61±0.728	0.17±0.378	0.50±0.655	0.19±0.577	0.22±0.540
		p-value*	0.228	0.083	**0.039**	0.051	0.110
SHUD							
	Normal	Baseline	0.68±0.800	0.27±0.451	0.70±0.734	0.27±0.624	0.27±0.451
		60 min	0.48±0.664	0.16±0.370	0.45±0.548	0.09±0.291	0.14±0.347
		p-value*	**0.037**	**0.024**	**0.003**	**0.031**	0.083
	Dry eye	Baseline	0.86±0.798	0.14±0.351	0.89±0.747	0.08±0.280	0.17±0.561
		60 min	0.36±0.487	0.06±0.232	0.39±0.494	0.00±0.000	0.14±0.351
		p-value*	**<0.001**	0.083	**<0.001**	0.083	0.661
O							
	Normal	Baseline	0.64±0.750	0.11±0.321	0.75±0.781	0.14±0.462	0.14±0.510
		60 min	0.48±0.590	0.02±0.151	0.25±0.488	0.07±0.334	0.11±0.321
		p-value*	0.070	**0.044**	**<0.001**	0.083	0.660
	Dry eye	Baseline	1.25±0.967	0.89±0.887	1.03±0.810	0.83±0.845	0.61±0.688
		60 min	0.58±0.649	0.58±0.500	0.28±0.615	0.28±0.615	0.19±0.401
		p-value*	**<0.001**	**0.006**	**<0.001**	**<0.001**	**<0.001**
OUD							
	Normal	Baseline	0.50±0.699	0.34±0.479	0.48±0.664	39.0±0.618	0.41±0.583
		60 min	0.25±0.438	0.16±0.370	0.14±0.409	0.16±0.428	0.20±0.408
		p-value*	**0.015**	**0.003**	**<0.001**	**0.011**	**0.018**

Table 6 OOD4SQ (0-5 scale; 0 = no discomfort, 5 = worst) in dry eye and normal groups

* p-value analysed using Paired sample T-test
† Data displayed in mean ± standard deviation
OOD4SQ: Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire

DISCUSSION

Physical properties of artificial tears

Previous studies had suggested that the final viscosity of artificial tears should be < 30 cP in order to avoid discomfort, blurred vision, as well as irritation (Aragona et al., 2019; Pires et al., 2013; Che Arif et al., 2023). This is because, higher viscosity artificial tears may affect the ocular bioavailability due to faster drainage of artificial tears caused by reflex tears and blinking (Pires et al., 2013; Che Arif et al., 2023). However, the shear rate were not specified in these studies. Therefore, the exact viscosity could be different depending on the shear rate applied by the rheometer. In this study, all artificial tears had a viscosity < 30 cP (at highest shear rate measured), except for Systane Hydration UD (32.73 cP).

As for pH, previous literatures reported that the pH of normal tears ranged from 6.5 to 8.06 (Iyamu and Enobakhare, 2019; Yamada et al, 1996; Norn, 1988; Abelson et al., 1981; Carney and Hill, 1976), while study comparing pH between control groups and dry eye patients showed that the mean pH of dry eye patients was slightly higher (7.46 ± 0.24) as compared to normal group (7.45 ± 0.23) (Khurana et al., 1991). Meanwhile, pH of artificial tears was suggested to be in the range of 6.6 to 7.8 pH unit in order to avoid any discomfort after instillation (Carney and Hill, 1976; Garcia-Valldecabres et al., 2004; Che Arif et al., 2023). The range of pH for all artificial tears in this study was in between 7.19 to 7.85, with 3 artificial tears having pH within ocular comfort range, while SH having pH beyond the recommended ocular comfort rate (7.85).

Ocular signs after artificial tears instillation

In term of signs after the instillation of artificial tears, for both dry eye and normal groups; significant improvements of TBUT (except for O in normal group; p=0.135) were noted at every measurement taken for all artificial tears, even with different pH and viscosity. This results suggested that both hyaluronic acid (HA)-based artificial tears (SH and SHUD) and carboxymethycellulose (CMC)-based artificial tears (O and OUD) were effective in managing tear film instability. These findings were in good agreement with previous studies, which reported that these two formulations were beneficial in improving ocular surface integrity (Song et al., 2017; López-De La Rosa et al., 2017; Wallerstein et al., 2018; Md Rejab et al., 2018).

TMH measured in this study increased significantly in both groups at every time interval after the instillation of all artificial tears, regardless of their viscosity and pH. We found a different trend of TMH between normal and dry eye group. TMH in normal group for all artificial tears reaching maximum values at 5 minutes, before starting to drop at 15 and 60 minutes post instillation, except for O, which showed maximum TMH values at 15 minutes post-instillation before started to decrease at 60 minutes. This is not

the case happened in dry eye group, where maximum values of TMH vary for each artificial tears; 5 minutes for O, 15 minutes for SH and OUD, and 60 minutes for SHUD.

Above all, in dry eye group, SHUD which was the most viscous artificial tear among all seemed to perform well compared to other artificial tears as it maintained the maximum value of TMH for up to 1 hour. This result suggested that highly viscous solution tends to remain longer in the ocular surface (Rosmadi et al., 2019; Akiyama-Fukuda et al., 2016). However, this finding was not consistent with the results for normal group as all artificial tears showing much similar performance in improving TMH. Thus, we hypothesized that viscosity alone may not fully explained the extension of retention time, but the ingredients used in the formulation of artificial tears might influence their clinical performance in improving tear volume of ocular surface (Karaca et al., 2019).

Electrolytes such as potassium chloride, sodium chloride and magnesium chloride hexahydrate added in the formulation of artificial tears lead to the improvement in TFP as electrolytes were able to maintain or lower the osmolarity of ocular surface (Masmali, 2019). This reflects the findings from this study in which the type of TFP in all artificial tears, regardless of their viscosity and pH, significantly improved after 60 minutes instillation. The electrolytes used in the formulation of SH, SHUD, O and OUD, together with the improvement in tear volume (Garcıa-Resua et al., 2014) following artificial tears instillation were believed to improve the tear quality of the participants in this study.

Ocular symptoms after artificial tears instillation

Following instillation, all artificial tears were well tolerated (Torkildsen et al., 2017; Torkildsen et al., 2018; Ousler et al., 2015), with low drop comfort score; ranged from 1.55 to 2.00 observed in both groups. SH resulted in the least comfort for both dry eye (2.00±1.042) and normal (1.84±0.963) groups. This could be due to its high viscosity and pH which lie outside ocular comfort range. Meanwhile, SHUD (1.55±0.761) and OUD (1.67±1.121) had the lowest drop comfort score in normal and dry eye groups, respectively.

All artificial tears tested in both groups decreased the symptoms after 60 minutes. However, only certain symptoms significantly improved post-artificial tears instillation. It could be seen that OUD performed better in both normal and dry eye groups in all parameters observed. Even with the same active and inactive ingredients in OUD and O, OUD was more effective in improving ocular symptoms compared to O. This could be related to the preservative (Purite®) added in O that might affect the findings. This is supported by previous study conducted by Nasser et al., (2018) which demonstrated significant improvement in ocular symptoms (OSDI score) after switching from preserved to non-preservative artificial tears, proving the clinical benefits of preservative-free artificial tears in relieving dry eye symptoms.

Even though there were two preservative-free artificial tears (OUD and SHUD) used in this study, OUD demonstrated effective symptomatic relief compared to SHUD. This could be due to ingredients used in OUD were more tolerable and contribute to the sustainability of comfort even after 60 minutes instillation. Carboxymethylcellulose (CMC) as one of the lubricants used in OUD formulation was reported to hydrate and lubricate the ocular surface, resulting in alleviation of patient-reported symptoms of dry eye (Labetoulle et al., 2017).

CONCLUSION

TBUT, TMH and TFP in both normal and dry eye groups significantly improved after 60 minutes instillation of all artificial tears, regardless of their viscosity and pH. Besides, all artificial tears were well tolerable with low drop comfort score recorded in both groups. Ocular symptoms before instillation of artificial tears improved after all artificial tears instillation, but only OUD significantly improved all the ocular symptoms observed.

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