ORIGINAL ARTICLE

Comparison of Immediate Effects on Usage of Dual Polymer Artificial Tears on Changes in Tear Film Characteristics

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ABSTRACT

Introduction: This study aimed to evaluate the short-term efficacy of two comparable formulation of dual-polymer artificial tears: Systane Hydration preservative (SH) and non-preservative (SHUD) in 60 minutes observation period compared to normal saline. **Methods:** Fifty participants involved in this prospective, double-masked randomised study. Viscosity and pH of artificial tears were evaluated using rheometer and digital pH-meter prior to tear film assessment. Tear break-up time (TBUT) and tear meniscus height (TMH) were measured at baseline, 5, 15 and 60 minutes after instillation. Tear ferning pattern (TFP) were compared between baseline and 60 minutes after instillation. One-way analysis of variance (ANOVA) and Independent T-test were used to evaluate the effects of SH and SHUD after instillation and comparison between each specific time-interval respectively. P-value of 0.05 was set as the level of significance. **Results:** The viscosity of SH and SHUD was 26.7cP and 32.73cP re-spectively with pH of 7.85 (SH) and 7.74 (SHUD). Both artificial tears showed significant increment in TBUT between baseline and 15 minutes (SH:5.82±1.063, p=0.01; SHUD:6.02±0.979, p<0.001), and 60 minutes (SH:6.22±0.616, p<0.001; SHUD:6.34±0.658, p<0.001). SHUD demonstrated significant increment in TMH at every measurement taken (0.1996±0.02449, p<0.001 at 5min, 0.2038±0.02276, p<0.001 at 15min and 0.2068±0.02094, p<0.001 at 60min). Likewise, in SH group, significant increment in TMH at 15 minutes (0.1994±0.02325, p<0.001) and 60 minutes (0.2012±0.02379, p<0.001) were noted. Both groups revealed improvement in TFP (both, p<0.001) at 60 minutes. No significant im-provement was noted in control group. **Conclusion:** Improvement in TMH was prominently faster in SHUD than SH, although both TBUT and TFP revealed comparable tears quality between both artificial tears.

Keywords: Artificial tears, Systane Hydration, Tear film quality, Tear film quantity

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INTRODUCTION

Tear film is the outermost layer that surrounds the anterior ocular surface in which it plays a significant role in providing clear vision as well as maintaining the health of the eye (1). Tear film serves as a primary refracting surface of the light entering the eye and at the same time promoting the health of the avascular cornea by providing nutrition and protecting the cornea from any infection (2). One of the common problems related to tears is dry eye in which it occurs due to reduction in tear film volume, more rapid breakup of tear film due to disturbance in stability of tears and increase in rate of evaporation of tears from the ocular surface (1).

One of the most preferable first-line treatments for dry eye is artificial tears (3,4). This is due to several reasons. Firstly, its ease of use with only required very minimal steps. Secondly, artificial tears are now commonly available over-the-counter with affordable range of price. Lastly, artificial tears have been proven to improve both ocular symptoms and its clinical signs in patient with mild to moderate dry eye (5). Thus, it is not surprising that artificial tears are now the first choice treatments and solutions for both clinicians and patients respectively.

Artificial tears are specifically formulated solutions with combination of ocular lu-bricants and active ingredients, such as carboxymethylcellulose (CMC), hydroxypropyl methylcellulose (HPMC), sodium hyaluronate (SH), polyethylene glycol (PEG) and glycerin with common aims which are to alleviate ocular discomfort and rejuvenate the ocular sur-face affected by dry eye (6). Currently, two ocular lubricants known as Hyaluronic acid (HA) and Hydroxypropyl guar (HPG) are being used in artificial tears formulations due to its viscoelastic and hydrating properties which can prolong the ocular residence time, provide optimum lubrication and better distribution of tear to the ocular surface (7,8). Both HPG and HA in artificial tears formulation have been proven to alleviate ocular discomfort (7,8). However, contradictory findings were found with some studies suggested HA is a better compound than HPG (9) and vice versa (10). Not to mentioned, previous study reported that combination of HA-HPG provides greater effect on ocular hydration and lubrication, with prolonged retention time as compared to single polymer-based artificial tears formulation (11). Apart from types of ocular lubricants used in artificial tears production, efficacies of artificial tears are primarily depending on its physical properties such as viscosity and pH. Previous work by Salzillo et al. (12) suggested that a higher viscous artificial tear would provide better relieve for ocular discomfort as it improved tears retention time, reduced rates of tear drainage and enhancing the macromolecules adhesive capability of mucin layer, hence, improving the ocular sensation. Thus, this study aimed to evaluate the initial treat-ment responses in term of tear stability (tear break-up time; TBUT), tear quantity (tear me-niscus height; TMH) and tear quality (tear ferning pattern; TFP) after the instillation of dual polymer artificial tears with different physical properties.

MATERIALS AND METHODS

Hundred eyes from 50 participants comprised of 23 male and 27 female with mean age of 28.4 ± 5.5 (age range: 20-40 years) were recruited in this prospective, double-masked randomised study using convenience sampling. Sample size calculation was based on statistical significant difference at 95% confidence, with 80% power and mean of TBUT; 3.62 ± 1.54 and 4.47 ± 1.13 (23). Prior to study procedures, consent by all participants was obtained after been briefed thoroughly regarding the benefits and risks pertaining to this study. This study adhered to the tenets of Declaration of Helsinki, and the study procedures were reviewed and approved by the International Islamic University Malaysia (IIUM) Research Ethics Committee (IREC 2019-125).

Inclusion criteria set includes participants who were having good ocular and general health, aged between 20 to 40 years old, having no known sensitivity or intolerance to any of the products used in this study, and non-contact lens wearer. As this study observed the effect of dual polymer artificial tears on normal tear film, all the participants were having; TBUT > 5 seconds (13,37-39), ocular surface disease index (OSDI) score < 13 (14) and Schirmer test I > 10 mm/5 minutes (15). History of previous ocular trauma, evidence of active ocular infection in either eye, significant underlying of ocular pathology affecting ocular surface (16–18) or under treatment of drug affecting tearing were excluded from this study (5). 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 (19,20).

Physical properties of Artificial Tears

Three ophthalmic solutions were used in this study, which were two dual-polymers artificial tears; Systane® hydration (SH) (Alcon Laboratories Inc, Fort Worth, TX, USA) and Systane® hydration unit dose (SHUD) (Alcon Laboratories Inc, Fort Worth, TX, USA), and one control solution; Opticare Normal saline solution (Excel Pharmaceutical Sdn. Bhd., Selangor, Malaysia). For the first phase of this study, physical properties (viscosity and pH) for all three ophthalmic solutions were measured before being tested on the participant's eye.

Viscosity and pH of all solutions used in this study was measured by rheometer and compact pH meter respectively. Thermo Scientific Rheometer (HAAKE RheoWin, Version 3.61.0004, Thermo Fisher Scientific Inc, Massachusetts, US) was used to measure the viscosity of both artificial tears and normal saline. The viscosity of each solution was measured one by one; with viscosity measurement was completed in 5 minutes for each sample. All ophthalmic solutions were prepared off-labeled, and was noted as solution A, B and C before being applied (approximately 1ml) on lower measuring plate of the rheometer. The rheometer would automatically standardised the temperature of 25°C for all tested sample. Before measurements were taken, the upper plate of rheometer lowered to a gap size of 1000 microns and rotated according to the speed set by the examiner (21,40).

Torque applied on the upper plate exerted a rotational shear stress on the sample that was placed in between upper and lower plate. As for this study, shear rate was set from 10s-1 to 100s-1 in a single sweep, while the rate of shear stress at each interval was automatically determined by the rheometer (21,40). With known shear rate and shear stress, viscosity of tested solution was calculated by the built-in software of rheometer according to viscosity law as stated in equation 1.
Equation 1: Viscosity

$$\text{Viscosity} = \frac{\text{Shearstress}(\tau)}{\text{Shearrate}(\gamma)}$$

pH measurement of both artificial tears and normal saline was conducted using compact pH-meter (LAQUAtwin pH-meter pH33, Horiba Advanced Techno Co., Ltd., Shiga, Japan). Before measuring the pH, two-point calibration was performed using two standard solutions; pH 4 and pH 7. Approximately 0.2ml sample of each solution was dropped on the flat sensor until the solution covered the entire surface of the sensor. Three measurements were conducted for each sample, with the average pH was recorded for analysis. Before measuring the pH for the next sample, the sensor was cleaned using distilled water in order to avoid sample crossover contamination.

Measurement of tear break-up time (TBUT), tear meniscus height (TMH) and tear ferning pattern (TFP)
As the study design was a comparative bilateral eye study with three ophthalmic solutions used, each participant was required to attend two visits, in which for each visit, a single drop of either SHUD, SH or normal saline was randomly applied to one eye and a single drop of other solution was applied to the other eye. Another solution was applied during the next visit, with at least 24 hours wash-out period between the visits (14,22). Research randomizer software (https://www.randomizer.org/) was used to randomise the eyes and solutions to be used at each visit. All procedures were conducted in the same examination room, with temperature and humidity were kept constant at 20°C-24°C (14) and 40%-50%, respectively (22). Both participant and optometrist conducting the procedures were blinded to the ophthalmic solutions used at each visit.

For TBUT measurement, participant's TBUT was recorded using a video camera mounted on digital high-definition slit-lamp biomicroscopy (Model SL 990, SLB Mega Digital Vision HR, Costruzione Strumenti Oftalmici, Italy). Tear break-up time was defined as the time taken for the first black spot to appear on the stained ocular surface after the last complete blink observed using cobalt-blue filter of the slit lamp (23). Three consecutive measurements were acquired and the mean value was calculated and recorded. Tear break-up time for each participant was measured at baseline and after 5, 15 and 60 minutes instillation of ophthalmic solutions.

Anterior segment Zeiss Visante TM optical coherence tomography (OCT) (Zeiss Meditec, Inc, Dublin, USA) was used to measure the TMH at baseline and after 5, 15 and 60 minutes instillation of ophthalmic solutions. Tear meniscus height was defined as the tear film height between the edge of the lower eyelid and the cornea (14,41,42). In order to capture the image of tear film, 'all scans' protocol with 'raw image mode high resolution scan' was used at 270° orientation, focusing on lower eyelid at '6 o'clock' and the corneal refraction as reference (14). The procedure was conducted in dim illuminated room. Each participant was instructed to focus on the target while maintaining spontaneous blinking, and they will be asked to blink once before the TMH measurement was done. The image obtained was in Tagged Image File Format (TIFF), in which were then transferred to image analysis software (ImageJ, version 1.51j8, National Institute of Health, Bethesda, MD, USA) to quantify the TMH values by converting the known pixels of the image to unit of millimeter (mm). Three measurements were taken at each time interval and the mean was calculated and recorded. Tear meniscus height for each participant was also being measured at baseline and after 5, 15 and 60 minutes instillation of ophthalmic solutions.

For tear ferning patterns, tear samples were collected from each participant at baseline and after 60 minutes of instillation in order to observe if there was any improvement in TFP after the instillation of both artificial tears and normal saline. A small sample (1-2μl) of tear was collected from temporal, lower tear meniscus using the glass microcapillary tube and allowed to dry by evaporation for 5-10 minutes on microscope slides (24). Microscopic appearance of the dried tear was observed under the light microscope (Ken-□-Vision Manufacturing, Inc., Missouri, USA) using 10X magnification (25) and TFP observed were classified into four groups according to Rolando's tear ferning classification (26).

Data analysis
The data were analysed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, N.Y., USA). Normality of all the data was assessed using skewness and kurtosis of the distribution (27). The differences in all variables pre and post-instillation (Baseline vs. 5 min, Baseline vs. 15 min, Baseline vs. 60 min) were examined using paired sample T-test. One-way analysis of variance (ANOVA) was used to determine the differences in TBUT, TMH and TFP between groups at specific time interval. Paired t-test was employed in order to compare the immediate effects of SHUD and SH on all intended tear film characteristics. The significance level was set at $P < 0.05$.

RESULTS

Physical properties of SH, SHUD and normal saline
The study findings revealed that SHUD was the most viscous solution among the tested oph-thalmic solutions, with viscosity of 32.73 cP followed by SH with 26.70 cP, and normal normal saline with 0.71 cP. Based on pH measurements, both artificial tears were alkaline with SH slightly basic (pH = 7.85) compared to SHUD (pH = 7.74). Meanwhile, pH for nor-mal saline was 6.64, which was slightly acidic. The physical properties for all three tested ophthalmic solutions were summarised in Table I.

Tear film characteristics
In this study, tear film characteristics were based on TBUT, TMH and TFP. For TBUT, the result showed no significant difference in TBUT for all groups at baseline. Although there were increments noted at 5 minutes after instillation in both SH and SHUD groups, the dif-ference was not significant ($P = 0.110$ for both groups). Tear break-up time increased signifi-cantly after 15 and 60 minutes instillation of SH ($P < 0.001$) and SHUD ($P < 0.001$). Howev-er, TBUT measured using normal saline decreased 15 and 60 minutes following instillation. Generally, changes in TBUT for each group for 60

Table I: Physical properties of artificial tears and normal saline

Brand name	Manufacturer	Lubricant	Viscosity (cP)	pH
Systane® hydration	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate (SH) 0.1%, Hydroxypropyl Guar (HPG) (HA-HPG)	26.70	7.85
Systane® hydration UD	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate (SH) 0.1%, Hydroxypropyl Guar (HPG) (HA-HPG)	32.73	7.74
Opticare Normal saline solution (0.9% NaCl)	Excel Pharmaceutical Sdn. Bhd., Selangor, Malaysia	-	0.71	6.64

minutes evaluation showed significant difference at 15 and 60 minutes post-instillation. Comparison of TBUT assessment between SH, SHUD and normal saline are shown in Table II.

For TMH assessment, at baseline, there were no significant differences between SH, SHUD and normal saline. However, at 5 minutes and onwards after instillation of SHUD, TMH was statistically higher compared to baseline. The increment was remained significant up to 15 and 60 minutes of observational period. The same trend was observed for SH at 15 minutes and onwards after instillation. However, no significant changes was noted in normal saline group (P = 0.092). These findings showed that higher viscosity would leads to higher TMH values. Comparison of TMH assessment between SH, SHUD and normal saline are shown in Table II.

For tear ferning pattern (TFP), the grading 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 (20,22). This study finding revealed that both SH (P < 0.001) and SHUD (P < 0.001) significantly im-proved TFP after 60 minutes instillation of artificial tears. However, TFP in normal saline remain unchanged even after 60 minutes post-instillation. Summary of TFP findings com-parison between baseline and 60 minutes are shown in Table II. This study also found that there were no significant difference between both SH and SHUD groups at each interval measured, as summarised in Table III.

DISCUSSION

This study was conducted to compare the short-term efficacy after installation of two dual-polymer artificial tears to improve tear film characteristics. This is important as artificial tears are commonly prescribed as the first-choice treatment in relieving ocular discomfort. Although artificial tears are generally safe, previous study had reported several side effects in isolated such as blurred vision, sticky sensation and foreign body sensation (28). Formu-lation of artificial tears is crucial in determining the efficacy of artificial tears as different formulation work differently, with some of artificial tears

Table II: Comparison of tear breakup time, tear meniscus height and tear ferning pattern between Systane Hydration (SH), Systane Hydration unit dose (SHUD) and normal saline

Parameters	Artificial tears	Baseline	5 min	15 min	60 min
TBUT (sec)	**SH**	5.62 ± 1.139	5.74 ± 0.965	5.82 ± 1.063	6.22 ± 0.616
	p-value*	-	0.110	**0.010**	**<0.001**
	SHUD	5.64 ± 1.141	5.76 ± 0.965	6.02 ± 0.979	6.34 ± 0.658
	p-value*	-	0.110	**<0.001**	**<0.001**
	Saline	5.46 ± 1.092	5.66 ± 1.136	5.34 ± 1.136	5.32 ± 1.077
	p-value*	-	0.086	0.083	0.181
	p-value†	0.714	0.904	**0.005**	**<0.001**
TMH (mm)	**SH**	0.1924 ± 0.02536	0.1920 ± 0.02458	0.1994 ± 0.02325	0.2012 ± 0.02379
	p-value*	-	0.687	**<0.001**	**<0.001**
	SHUD	0.1948 ± 0.02501	0.1996 ± 0.02449	0.2038 ± 0.02276	0.2068 ± 0.02094
	p-value*	-	**<0.001**	**<0.001**	**<0.001**
	Saline	0.1928 ± 0.02588	0.1964 ± 0.03015	0.1916 ± 0.02402	0.1900 ± 0.02579
	p-value*	-	0.092	0.436	0.119
	P-value†	0.880	0.358	**0.033**	**0.002**
TFP (type)	**SH**	2.18 ± 0.941			1.66 ± 0.626
	p-value*	-			**<0.001**
	SHUD	2.18 ± 0.941			1.58 ± 0.499
	p-value*	-			**<0.001**
	Saline	2.18 ± 0.941			2.18 ± 0.941
	p-value*	-			1.000
	p-value†	1.000			**<0.001**

* p-value analysed using paired sample T-test (Baseline vs. 5 min, Baseline vs. 15 min, Baseline vs. 60 min)
†p-value analysed using One-way analysis of variance (ANOVA)
Bold values are significant, p<0.05

Table III: Comparison of TBUT, TMH and TFP between SH and SHUD

Parameters studied	Artificial tears	Baseline*	5 min*	15 min*	60 min*
TBUT (sec)	SH	5.62 ± 1.139	5.74 ± 0.965	5.82 ± 1.063	6.22 ± 0.616
	SHUD	5.64 ± 1.141	5.76 ± 0.965	6.02 ± 0.979	6.34 ± 0.658
	P-value†	0.789	0.918	0.330	0.349
TMH (mm)	SH	0.1924 ± 0.02536	0.1920 ± 0.02458	0.1994 ± 0.02325	0.2012 ± 0.02379
	SHUD	0.1948 ± 0.02501	0.1996 ± 0.02449	0.2038 ± 0.02276	0.2068 ± 0.02094
	P-value†	0.636	0.125	0.341	0.214
TFP (type)	SH	2.18 ± 0.941			1.66 ± 0.626
	SHUD	2.18 ± 0.941			1.58 ± 0.499
	P-value†	1.000			1.000

*Data displayed in mean ± standard deviation
†p-value analysed using Independent t-test

were designed to improve one or more layers of tear film (29). The usage of dual polymers artificial tears (HPG-HA) has been studied for its effectiveness in promoting desiccation protection, recovery and lubricity in models of corneal epithelium (11).

This study found that both HPG-HA artificial tears showed significant increment in TBUT values at 15 minutes and onwards. TMH values were significantly increased at all intervals for SHUD, while SH was found significantly improved after 15 and 60 minutes instillation. It is worth to note that TFP showed improvement after 60 minutes of artificial tears administration. These findings were in agreement with previous work by Labetoulle et al. (30). Combination of these two polymers in a single formulation have been proven to increase corneal wettability and decrease friction during blinking due to their viscoelastic properties and strong water retention, which would then lead to the improvements in tear film stability, quality and quantity (30).

Previous literatures have proven that viscosity has a significant role in tear retention on the ocular surface (31,32). Likewise, this study results suggested both artificial tears ex-hibit a shear-thinning behavior, which means a higher viscosity was observed at low shear stress and vice versa. Thus, this also indirectly indicates that the efficacy of artificial tears is higher in high viscosity at low shear rate, as in case of opened eye, in which it can increase the retention time by reducing the rate of evaporation. While in low viscosity at high shear rate (during blinking), artificial tears can provide better ocular comfort and prevention of excessive friction or stressed to the ocular surface during blinking (33,34,).

Previous researchers suggested a cut-off viscosity of < 30 cP for artificial tears is crucial to avoid ocular discomfort, blurred vision and ocular irritation after immediate instillation (12,35,43,44). This is important as ocular irritation would in turn leads to immediate drainage of artificial tears due to reflex tears and blinking, thus affecting the efficacy of arti-ficial tears. Likewise, this study findings support the previous research (35) as SHUD which has higher viscosity (32.73cP) showed greater improvement in all parameters observed compared to SH (26.70cP). However, it is worth to note that the difference in all parameters observed between these two artificial tears was not significant. This could happen due to another factor, which are the inactive ingredients or other lubricants in the formulation.

Determination of artificial tears pH is important as variation in pH which does not mimic the natural tears (6.5 to 7.6) could cause ocular irritation, stinging sensation or ocular discomfort right after instillation. This in turn would affect the artificial tears' bioavailabil-ity due to excessive tearing (36). pH values of both artificial tears were found slightly higher than 7.6 (SHUD: 7.74 and SH: 7.85), in which this could lead to the presence of ocular irrita-tion right after drop. However, in this current study, no attempt has been done to observe the patient's response after the instillation of these two artificial tears.

This study would like to highlight that the effects of dual polymers artificial tears evaluated were only observed within 60 minutes interval after single instillation. Thus, the long term effects usage of these artificial tears, alongside with multiple instillations needs further investigation. Furthermore, participants for this study were all normal. Thus, further studies need to be done on suspected dry eye or fully diagnosed dry eye patients in order to have better insights on the impact usage of dual polymer artificial tears in terms of im-provement of tear film characteristics and as treatment of dry eye. Apart from physical properties, ocular symptoms such as blurred vision and foreign body sensation right after instillation; should be evaluated in order to determine the effectiveness of the treatment.

CONCLUSION

Improvement in TMH was prominently faster in SHUD than SH, although both TBUT and TFP revealed comparable tears quality between both artificial tears.

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