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Tear lipid supplement prophylaxis against dry eye in adverse environments

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ABSTRACT

Purpose: To compare the prophylactic efficacy of single application of lipid and non-lipid containing tear supplements, prior to exposure of symptomatic dry eye subjects to a simulated adverse environment.

Methods: Thirty subjects with mild-to-moderate dry eye symptoms participated in the prospective, randomised, double-masked, paired-eye trial. A lipomimetic drop (Systane® Balance) was applied to one eye (randomised), and a non-lipid containing drop (Systane® Ultra) applied simultaneously to the contralateral eye. Subjects were subsequently exposed to a validated simulated adverse environment model created by a standing fan directed towards the eye, at a distance of 1 m, for 2.5 min. Low contrast glare acuity, lipid layer grade (LLG), non-invasive tear break-up time (NIBUT), temperature variation factor (TVF), and tear meniscus height (TMH) were evaluated at baseline, following eye drop instillation and following simulated adverse environment exposure.

Results: Both therapies resulted in increased NIBUT (both $p < 0.001$), and prevented its decline below baseline with simulated adverse environment exposure (both $p > 0.05$). However, only the lipomimetic drop increased LLG ($p < 0.001$) and precluded its fall below baseline post-adverse environment exposure ($p = 0.15$). Furthermore, post-instillation and post-exposure LLGs and NIBUT were significantly higher in the lipomimetic group (all $p < 0.05$). No significant changes were observed in glare acuity, TVF and TMH (all $p > 0.05$). More subjects (67%) reported greater ocular comfort in the eye receiving the lipomimetic.

Conclusions: Single application of both lipid and non-lipid containing eye drops conferred protective effects against exposure to adverse environmental conditions in subjects with mild-to-moderate dry eye, although the lipomimetic demonstrated superior prophylactic efficacy.

1. Introduction

Adverse environmental conditions are recognised to exacerbate signs and symptoms of dry eye [1–7]. Low relative humidity and high airflow velocity can widen water vapour pressure gradients between the ocular surface and the surrounding environment, encouraging greater tear evaporation [2–5], and contributing to reduced tear film stability and ocular discomfort [1–7].

Artificial tear supplements are commonly used dry eye therapies, and both lipid and non-lipid containing formulations are available [8]. Non-lipid drops effect tear film aqueous augmentation, increase lubrication and reduce ocular surface desiccation [9]. Lipomimetic drops, consisting of an emulsion of mineral oils and phospholipids, seek to provide additional fortification to the lipid layer which inhibits tear film aqueous evaporation [9–12].

The potential protective effects of topical lipid, corticosteroid, and antioxidant formulations in low relative humidity environments have been reported independently in recent studies [4,13,14]. However, it has not yet been established whether differences exist in the efficacy of lipomimetic and non-lipid containing tear supplements in protecting against dry eye. The current study sought to compare the prophylactic efficacy of a single application of lipid and non-lipid eye drops, prior to exposure to a simulated adverse environment, in subjects with mild-to-moderate dry eye.

2. Methods

2.1. Subjects

This prospective, double-masked, randomised, paired-eye trial followed the tenets of the Declaration of Helsinki, and was approved by the University of Auckland Human Participants Ethics Committee (UAHPEC 2011/072). Subjects were required to be ≥18 years, with symptomatic dry eye, but with no other major ocular/systemic diseases, previous ocular surgery, or contact lens wear or use of topical/systemic medications known to affect the eye within the preceding 48 h. Mild-to-moderate dry eye symptoms were defined by a McMonnies Dry Eye Questionnaire score of ≥10. Eligible participants were enrolled after

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providing written consent.

Thirty eligible participants were recruited, satisfying sample size requirements calculated using PASS 2002. Multiplicity and non-parametric adjusted power calculations were made with lipid layer grade as the designated outcome, and showed that a minimum of 22 participants was required to detect a clinically significant difference of 1 grade, with 80% power ($\beta = 0.2$) and a two-sided significance level of 5% ($\alpha = 0.05$). The SD of normal values was estimated to be 1 grade [15].

2.2. Interventions

Participants were randomly assigned to simultaneously receive one drop (0.03 mL) of lipid-containing Systane® Balance (Alcon®, US) in one eye, and non-lipid-containing Systane® Ultra (Alcon®, US) in the contralateral eye. The eye drops were administered towards the lower tear meniscus while gently pulling down the lower eyelid. Following a 20-min period, subjects were exposed to a simulated adverse environment created by a 45 cm 55-W standing fan directed towards the eye, at a distance of 1m, for a period of 2.5 min. This simulated adverse environment was externally validated by an independent cohort of 5 healthy subjects (3 females, 2 males; age range, 21–44 years), and shown to reliably result in a reduction in non-invasive tear film break-up time by 2.5 ± 0.5 s following exposure ($p = 0.006$). All subjects were assessed in the same location, with a mean ± SD room temperature of 21.8 ± 0.5 °C and mean ± SD relative humidity of 47.3 ± 6.1%.

2.3. Measurements

Both the study participants and investigators conducting clinical assessments were masked to treatment randomisation. Measurements were conducted at baseline, 10 min post-eye drop instillation, and immediately following simulated adverse environment exposure. Measurements were performed in ascending order of invasiveness to minimise the impact on tear film physiology for subsequent tests: temperature variation factor, tear meniscus height, lipid layer grade, non-invasive tear film break-up time, and low contrast glare acuity.

Low contrast glare acuity (BEGAT, Tawa, NZ) was assessed at 1m. Lower tear meniscus height (TMH) was determined using high-magnification digital imaging with Image J software graticule calibration (NIH, US). Infrared thermography (Thermo TVS-200EX, Avio, Japan) allowed determination of temperature variation factor (TVF), calculated by averaging the temperature differences between the geometric centre of the cornea and the superior, inferior, nasal and temporal limbus (3, 6, 9 and 12 o'clock positions), respectively. Lipid layer grade (LLG) and non-invasive tear film break-up time (NIBUT) were assessed by the Tearscope Plus (Keeler, UK), with a fine grid inserted for break-up time measurements. LLG was assessed based on the modified Guillon-Keeler grading system [16]: grade 1, open meshwork; grade 2, closed meshwork; grade 3, wave/flow; grade 4, amorphous; grade 5, coloured fringes; grade 0, non-continuous layer (non-visible/abnormal coloured fringes) [15]. NIBUT was recorded as the time taken, following a blink, for the grid reflection to first show distortion, while the subject maintained fixation and refrained from blinking. Three consecutive NIBUT measurements were averaged. Subjectively, participants were requested to compare ocular comfort between the two eyes following simulated adverse environment exposure.

2.4. Statistics

Statistical analysis was performed with GraphPad Prism 6.02. The significance of overall treatment, time, and treatment-by-time interaction effects were assessed using repeated measures two-way analysis of variance (ANOVA) for continuous variables with normal distributions confirmed by Kolmogorov-Smirnov testing ($p > 0.05$). Non-normally distributed continuous data (NIBUT) were logarithmically transformed, and ordinal data (LLG) converted to rank-values before analysis. Multiplicity-adjusted post-hoc assessment of individual treatment and time effects were conducted using Sidak's test. Categorical data (treatment preference) were compared using Fisher's exact test. All tests were two-tailed and $p < 0.05$ was considered significant.

Table 1
Repeated measures analysis of variance of clinical measurements for treatment, time, and interaction (treatment-by-time) effects. Ordinal data were converted to rank-values prior to assessment. Data are presented as *p*-values. Asterisks denote statistically significant values ($p < 0.05$).

	p		
	Treatment	Time	Interaction
Best corrected visual acuity (logMAR)	0.57	0.52	0.99
Tear film lipid layer grade	< 0.001*	0.004*	0.02*
Non-invasive tear film break-up time (s)	0.008*	< 0.001*	0.17
Temperature variation factor	0.69	0.13	0.71
Tear meniscus height (mm)	0.53	0.12	0.10

3. Results

The mean ± SD age of the 30 enrolled subjects (17 female, 13 male) was 27 ± 9 years (range, 21–60 years), and the mean ± SD McMonnies score was 12.7 ± 4.4 (range, 10–25). Tables 1 and 2 illustrate the summary statistics of the clinical measurements at baseline, following eye drop instillation and following adverse environment exposure. Baseline clinical measurements did not differ significantly between the lipid and non-lipid drop treatment groups (all $p > 0.05$).

Repeated measures ANOVA demonstrated statistically significant effects of treatment, time, and treatment-by-time interactions for LLG (all $p < 0.05$). Multiplicity adjusted post-hoc analysis showed that lipid-containing drop instillation resulted in increased LLG ($p < 0.001$), which did not fall below baseline levels following provocative environmental exposure ($p = 0.15$). This contrasted with non-

Table 2
Clinical measurements of the eyes of subjects randomised to lipid and non-lipid containing eye drops at baseline, following eye drop instillation and simulated adverse environment exposure. Data are presented as mean ± SD, or median (IQR). Asterisks denote statistically significant differences ($p < 0.05$).

	Lipid drop (n = 30)	Non-lipid drop (n = 30)	p
Low contrast glare acuity (logMAR)			
Baseline	0.14 ± 0.09	0.15 ± 0.09	0.99
Post-instillation	0.12 ± 0.09	0.13 ± 0.09	0.97
Post-exposure	0.14 ± 0.10	0.15 ± 0.10	0.99
p	0.96	0.98	
Tear film lipid layer grade			
Baseline	2 (2-3)	2 (2-3)	> 0.99
Post-instillation	3 (3-4)	3 (2-3)	< 0.001*
Post-exposure	2 (2-3)	2 (1-2)	0.02*
p	< 0.001*	< 0.001*	
Non-invasive tear film break-up time (s)			
Baseline	5.2 (4.4–6.5)	5.1 (4.4–6.6)	> 0.99
Post-instillation	7.8 (6.4–9.1)	7.0 (5.5–8.1)	0.02*
Post-exposure	5.6 (4.7–7.1)	4.9 (4.1–6.3)	0.04*
p	< 0.001*	< 0.001*	
Temperature variation factor			
Baseline	0.30 ± 0.18	0.30 ± 0.20	> 0.99
Post-instillation	0.24 ± 0.14	0.25 ± 0.15	> 0.99
Post-exposure	0.33 ± 0.16	0.28 ± 0.21	0.75
p	0.23	0.57	
Tear meniscus height (mm)			
Baseline	0.18 ± 0.04	0.17 ± 0.03	0.38
Post-instillation	0.19 ± 0.03	0.19 ± 0.04	0.42
Post-exposure	0.19 ± 0.03	0.21 ± 0.03	0.30
p	0.74	0.08	