Abstract

Purpose: To investigate if the application of Blephagel, an eyelid cleansing gel, causes subjective and/or objective cooling effects by measuring ocular symptomology and temperature.

Methods: Twenty-five healthy subjects underwent baseline non-invasive temperature measurements on the closed upper eyelid (centrally, nasally, and temporally) and ocular surface temperature (OST) on both eyes using an infrared camera. A standard application of Blephagel was then applied to the closed upper eyelid and eyelashes with a sterile cotton-wool to one eye selected at random. Temperature measures were then repeated on both eyes after 30-60, 120-150, and 180-210 seconds. At each interval, subjects rated the comfort and any cooling sensation of each eye on a 0-10 scale.

Results: After application of the gel, there was a significant difference in temperature at all locations on the eyelid between the test and control eyes over time (F=9.322, p<0.001). Post hoc analysis revealed this was significant from 30-60 second interval (36.3 ± 1.1°C versus 37.2 ± 0.7°C; p<0.001) and the 120-150 seconds interval (36.8 ± 0.8°C versus 37.2 ± 0.6°C; p<0.001). There was no significant variation between the OST locations over time (F=3.350, p=0.07). With respect to symptoms, there was a significant increase in cooling sensation in the test eye compared to the control eye over time (F=10.438, p<0.001), that remained throughout the experiment.

Conclusions: Blephagel produces a reduction in temperature of the eyelids that is accompanied with a subjective cooling sensation.

Abstract word count: 233

Main Text

INTRODUCTION

Eyelid cleansing has been established as an effective long-term method to treat anterior blepharitis by removing debris from the eyelid margin [1, 2]. Typically, this process involves application of a warm compress [2], or solution impregnated wipes/eye pads [3, 4, 5]. However, compliance with treatment regimens is variable, particularly with combination therapies [6]. More recently, an eyelid cleansing gel, “Blephagel” (Thea Pharmaceuticals, Keele, UK), has been developed that may provide a cooling sensation and thus additional symptomatic relief, which may be beneficial when eyelids are inflamed. Indeed, inflammation is reflected by local increases in skin temperature due to blood vessel dilatation and increased blood flow as measured with infrared thermal imaging [7], including the ocular surface as observed in dry eye, scleritis, anterior uveitis, and Grave’s ophthalmopathy [7, 8, 9]. Hence reducing ocular temperature may help relieve the signs and symptoms of blepharitis. The aim of this study was to therefore investigate whether any subjectively reported cooling effect is experienced and if this could be measured objectively, in healthy subjects.

MATERIALS & METHODS

The study was designed as a contralateral eye comparison (one test eye, one control eye). The study was reviewed and approved by the Institutional Review Board; and complied with the Declaration of Helsinki and the UK Data Protection Act. All subjects were enrolled with written informed consent following a description of the study and any potential risks.

Experimental Protocol

Subjects (n=25) were recruited from Aston University. Inclusion criteria required subjects to be ≥18 years old, with no active ocular (confirmed with a slit lamp biomicroscope examination) or systemic disease, no medications, or contact lens wear. They were masked to the premise of the study.

Baseline temperature was measured on the closed upper eyelid centrally and along the upper eyelid margin (centrally, nasally, and temporally). Ocular surface temperature (OST) was also measured on the cornea (centrally) and of the bulbar conjunctiva (nasally and temporally) on both eyes using an infrared camera (Thermo Tracer TH7102; NEC Corporation, Tokyo, Japan) by measuring the average temperature within 5mm^2 area at each location, where a series of digital markers were used to ensure the same area was measured per subject [10]). Room temperature was consistent (mean 22.1±0.3°C, measured daily from digital thermometer in thermostat regulated room) and air flow minimised (doors closed with no windows) during data collection.

A single unit dose (one pump) of cleansing gel from the dispenser was then first applied to a sterile cotton-wool pad and then to the closed upper eyelid and along the eyelash line to one eye (selected at random via number generator). The researcher was masked as to the chosen test eye.

Closed eyelid temperatures and OST measures were then repeated on both eyes after 30-60, 120-150, and 180-210 seconds post application. Subjects were asked to rate the comfort and any cooling sensation of each eye on separate 0-10 scales for each symptom (0=poor comfort/no cooling sensation; 10=excellent comfort/strong cooling sensation) at the same time intervals.

Subjects were instructed to keep both eyes closed for the duration of the study, unless OST was being measured.

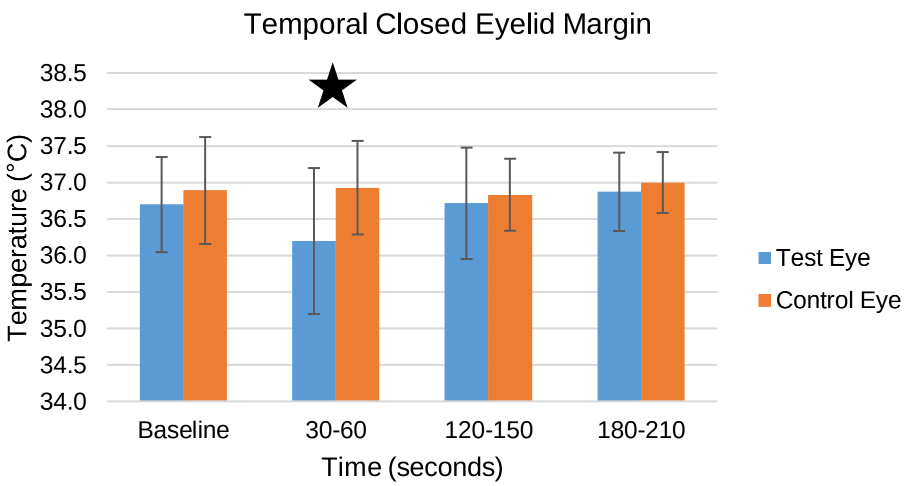
Statistical Analysis

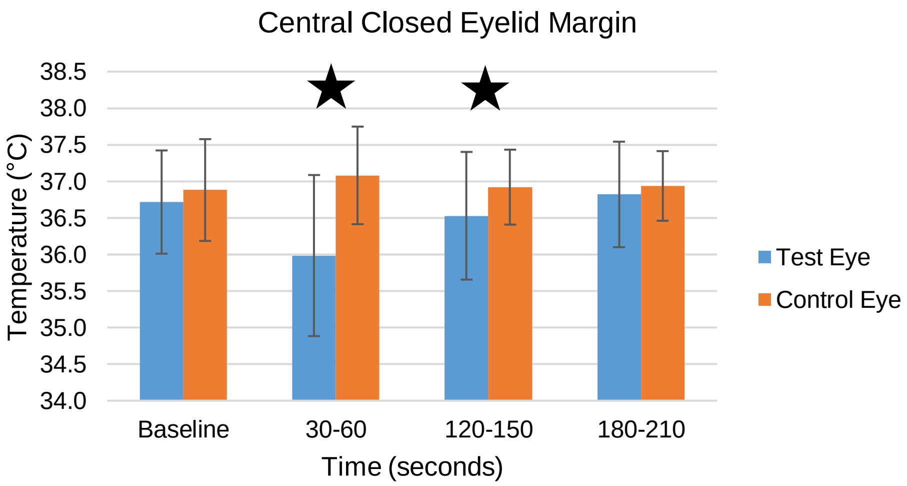
Data was assessed for normality using the Kolmogorov-Smirnov test. Temperature changes over time were evaluated by repeated measures analysis of variance (ANOVA), and where statistical significance was identified ($p<0.05$), post hoc analysis was performed using paired *t* tests.

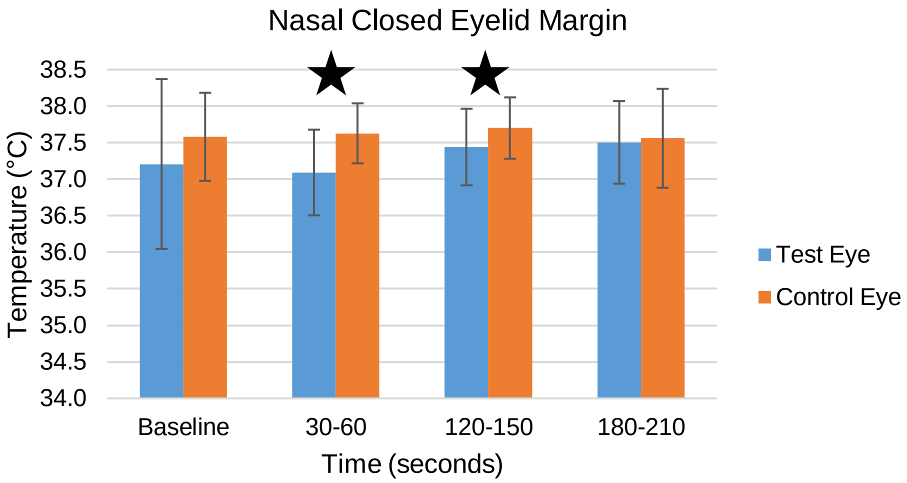
RESULTS

All 25 subjects (64% female; mean age (±1 standard deviation) = 20.8±1.3 years) completed the study without complications, and no adverse events or additional symptoms reported.

Temperature on Closed Eyelids







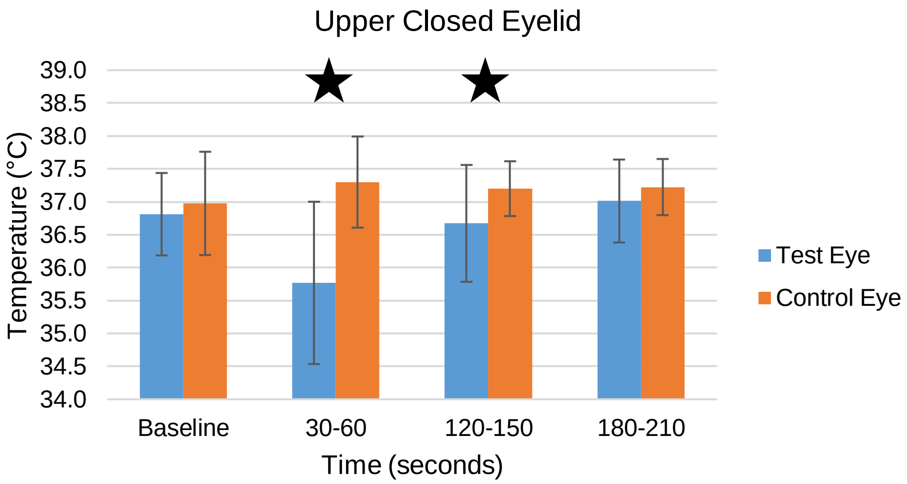
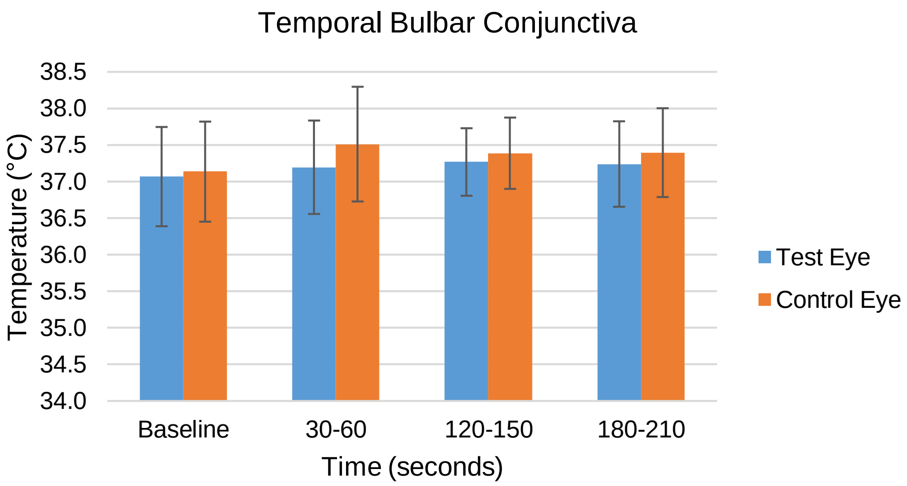


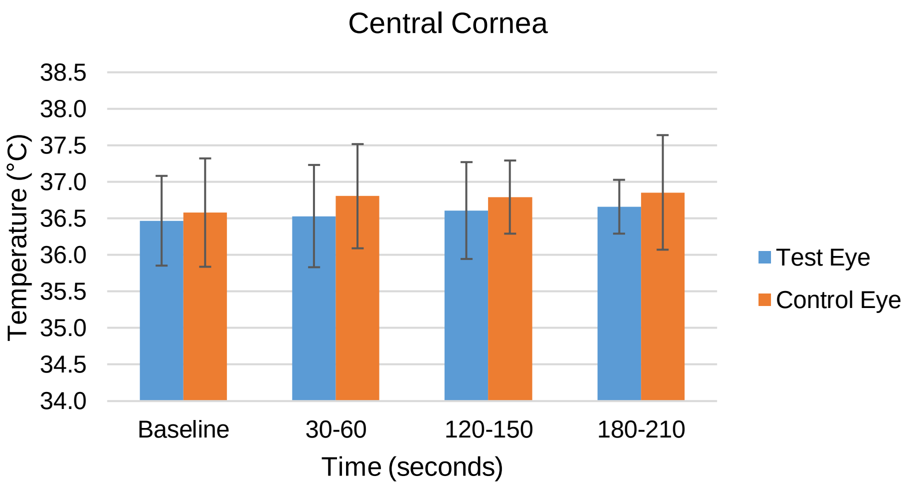
Figure 1: Mean temperature ±1 standard deviation (°C) at each closed eyelid location over time for test and control eyes. * = statistically significant difference ($p<0.05$) between test and control eyes as determined by post-hoc analysis.

At baseline, there was no (statistically) significant difference in temperature between the eyes at the same locations (Figure 1). After application of the gel, there was a statistically significant difference in temperature at all locations between the test and control eyes over time (F=9.322, p<0.001). The mean temperature across the entire eyelid surface reduced in the test eye, with post hoc analysis revealing this was significant from 30-60 second interval (36.3 ± 1.1°C versus 37.2 ± 0.7°C; p=0.00) to the 120-150 seconds interval (36.8 ± 0.8°C versus 37.2 ± 0.6°C; p=0.00); after 180-210 seconds there was no significant difference in mean eyelid temperature across the closed eyelid surface between test and control eyes (37.1 ± 0.7°C versus 37.2 ± 0.6°C; p=0.06). However, the temperature of the temporal location of the test eye was not significantly different compared to the control eye between 120-150 seconds post application (p=0.42).

Within eye comparisons show no significant change in temperature over time at any eyelid location in the control eye (F=2.076, p=0.136); but a significant change in temperature over time was observed in the test eye at all eyelid locations (F=9.902, p=<0.001). This temperature reduction was greatest between baseline and the 30-60 second interval, where temporal reduced by 0.5°C (p=0.003), central by 0.7°C (p<0.001), and upper by 1.1 °C (p<0.001), except for the nasal location which was not significantly reduced compared to baseline in the test eye (p=0.62). This difference compared to baseline in the test eye was no longer significant after the 120-150 second interval for all locations.

Temperature on Ocular Surface





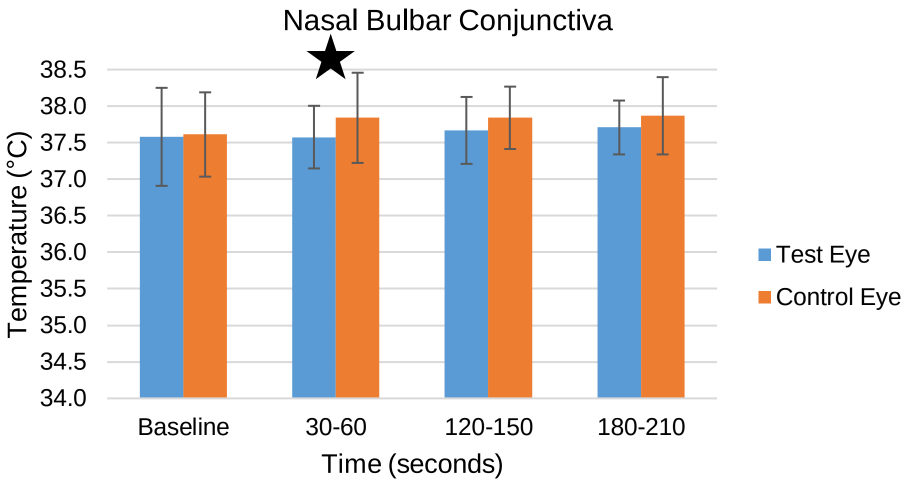
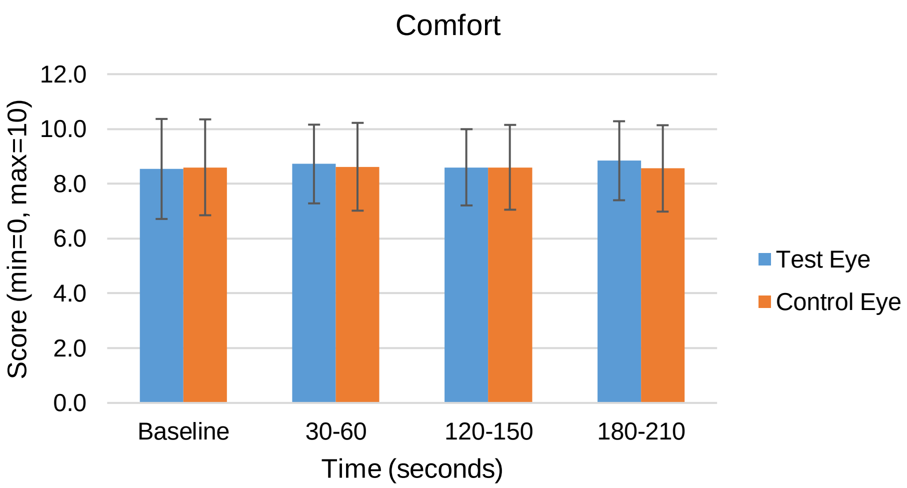


Figure 2: Mean temperature ±1 standard deviation (°C) at each ocular surface location over time for test and control eyes. * = statistically significant difference ($p<0.05$) between test and control eyes as determined by post-hoc analysis.

At baseline, there was no statistically significant difference in temperature between the same locations of the test and control eye (Figure 2). Although there was significant differences between the locations at each time interval per eye (F=50.916, p<0.001), these did not vary at the same locations between test and control eyes over time (F=3.350, p=0.07); except for the nasal location after 30-60 seconds (Figure 2;0.26°C cooler on test compared to control eye). Within eye comparisons also demonstrate no significant difference in temperature over time for control eyes (F=0.559, p=0.64) and test eyes (F=2.966, p=0.10) at all locations.

Symptoms



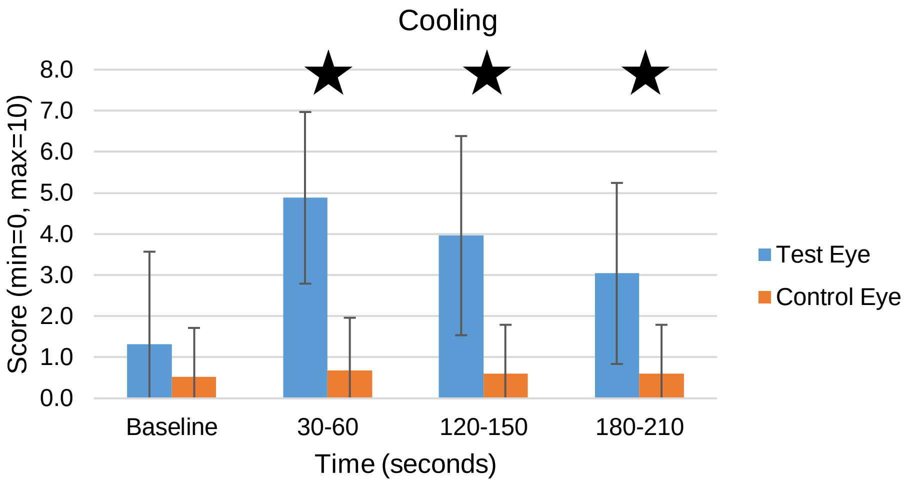


Figure 3: Mean (±1 standard deviation) comfort and cooling sensation scores over time for text and control eyes. * = statistically significant difference between test and control eyes as determined by post-hoc analysis.

There was no statically significant difference in comfort sensation between the test and control eyes at baseline (p=0.75) and over time (F=0.862, p=0.44). Within eye comparisons also demonstrated no significant difference in comfort over time for the control eye (F=0.279, p=0.84) and test eye (F=0.162, p=0.69).

For the cooling sensation, at baseline there was no statistically significant difference between the test compared to the control eye (Figure 3; p=0.11). However, after the application of the gel there was a statistically significant increase in cooling sensation in the test eye compared to the control eye over time (F=10.438, p<0.001). Post hoc analysis reveals that this cooling sensation remained through the course of the experiment between the test and control (Table 3), but the effect tapered significantly over time in the test eye (30-60 versus 120-150 p=0.01; 120-150 versus 180-210 p=0.04). Within eye comparisons show the control eye remained unchanged with respect to cooling sensation over time (F=0.359, p=0.98), whereas for the test eye this was significant compared to baseline at all time intervals (F=9.830, p=<0.001).

DISCUSSION

The eyelid cleansing gel (Blephagel) produced a statistically significant reduction in temperature across the eyelid surface and margin, by approximately 1°C (actual 0.97°C) in the test eye compared to the control eye after 30-60 seconds post application. This reduction in temperature remained statistically significant up to 120-150 seconds (2 to 2.5 minutes) between the test and control eye, albeit at a smaller difference (0.33°C). This reduction in temperature is accompanied by a statistically significant increase in subjective cooling sensation between the test and control eyes, peaking at a score of 4.9 out of 10 after 30-60 seconds. This effect was sustained for the duration of the experiment, suggesting the cooling sensation remains through to 180-210 (3 to 3.5 minutes); despite being no statistically significant difference in temperature between test and control eyes at any eyelid location at the 180-210 interval.

The gel produces a small effect on temperature of the ocular surface, with only the nasal bulbar conjunctiva decreasing significantly- this was not unexpected due to the direct application to the eyelid skin only to reflect the anatomical location where anterior blepharitis presents. However, cooling effects on the ocular surface (cornea and conjunctiva) have been reported following application of a gel mask on the closed eyelids in active allergic conjunctivitis [10] – here, the gel mask was applied for 5 minutes and was considerably cooler as it was refrigerated (to 2-4°C), whereas no such prior cooling was applied in this study. In this study by Bilkhu et. al (2014), the cooling effect was associated with improvement in ocular symptoms of allergic inflammation and reduction of conjunctival hyperaemia, likely due to induced vasoconstriction and subsequent reduced conjunctival blood flow [10]. Other studies have reported lowering of ocular surface temperature in eyes with scleritis and Grave's ophthalmopathy following topical steroid therapy, which was associated with improvements in signs and symptoms [9, 11]. Therefore, the cooling effect produced by the gel may help improve signs of inflammation in blepharitis by inducing vasoconstriction. Moreover, the application/removal process of an eyelid cleansing gel can help remove any crusting/debris than often presents in anterior blepharitis [1, 2]. Much like solution impregnated eyelid wipes, this simple treatment method may help serve to aid compliance particularly in light of the concurrent cooling sensation [3, 4, 5], given that treatments with no immediate effect can lead to patient disengagement [12].

Limitations of the study were due to the open-label design where subjects were aware which eye the gel is applied and thus prone to overestimating subjective reports on comfort/cooling (subject bias). This may explain the persistent cooling sensation after 180 seconds while the temperature differential between the test and control eyes was insignificant. In addition, subjects were healthy volunteers with no active eye disease – although the results cannot extend to actual anterior blepharitis sufferers, given the inflammatory nature of this condition the observed cooling effect in the present study may help improve symptoms during active episodes, which can include burning and gritty sensation of the eyelids [13]. Randomised, active-controlled (i.e. test product vs test vehicle) masked trials in patients with confirmed anterior blepharitis are therefore required to investigate clinical efficacy of Blephagel while negating subject and experimenter bias. The use of healthy subjects is very likely to explain the lack of any treatment effect on comfort, where baseline levels were unsurprisingly high.

CONCLUSIONS

Application of Blephagel produces a statistically significant reduction in temperature of the eyelid surface that is accompanied by subjective cooling sensation, which may persist beyond objective temperature changes. These effects may help relieve burning and gritty symptoms frequently reported in anterior blepharitis; in addition to removing any debris/crusting of the eyelashes through the application and removal process. Further study with robust clinical trial design is required to determine treatment effects in anterior blepharitis patients.

References

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