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Treatment of contact lens related dry eye with antibacterial honey

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ABSTRACT

Aim: Contact lens induced dry eye affects approximately 50% of contact lens wearers. The aim was to assess the effects of Manuka (Leptospermum sp.) honey eye drops (Optimel, Melcare, Australia) on dry eye in contact lens wearers. The safety of the honey eye drops in contact lens wear and contact lens wearers' compliance were also evaluated.

Design: Prospective, randomised, cross over study, examiner masked, pilot treatment trial.

Methods: Twenty-four participants aged 20 to 55 years with contact lens related dry eye were recruited and randomised to two treatment groups; 20 completed the study. One group used Optimel eye drops twice a day for two weeks followed by conventional lubricant (Systane Ultra, Alcon) therapy for two weeks; the other group completed the treatments in the reverse order. Before and after each treatment dry eye symptomology, ocular surface inflammation, and tear quantity and quality were assessed. Participants completed a daily log detailing their usage of treatments and any issues.

Results: Dry eye symptoms improved significantly after Optimel treatment. Patients with more severe symptoms at baseline showed a greater improvement in symptoms. No significant differences were observed in the objective signs of dry eye; presumably because of the short treatment duration. Seventy-five% of contact lens wearers reported good adherence to Optimel treatment and 95% reported no issues using this product.

Conclusions: Optimel Eye Drops reduce the symptoms of dry eye in contact lens wearers and are safe to use. A longer treatment period to assess the effect on clinical signs of dry eye is required.

1. Introduction

Although contact lens wear is generally considered safe, it is not uncommon for patients to develop contact lens related problems. Depending on the study, up to 21% of contact lens wearers will develop a contact lens related complication each year, ranging from mild corneal epitheliopathy to vision threatening microbial keratitis [1]. The most common problem associated with contact lens wear is contact lens related dry eye [2]. The primary reasons for contact lens intolerance are discomfort and dryness, with up to 50% of contact lens wearers reporting dry eye symptoms [3–6]. Studies report that between 12% and 51% of lens wearers "drop out" of contact lens wear, with contact lens discomfort being the primary reason for discontinuation [7]. Contact lens wear disturbs the delicate homeostatic balance of the ocular surface, decreasing tear film stability, increasing tear evaporation, reducing tear film turnover, and probably increasing tear osmolarity, and thus initiating an inflammatory cascade [7].

Optimel Manuka+ Dry Eye Drops (16% Leptospermum spp. honey, sodium chloride, benzoic acid; Melcare Biomedical, Australia) (Optimel) has regulatory approval in Australia (ARTG Identifier 199785) and Europe (CE marked). Current approved treatment indications are chronic dry eye, blepharitis, and sore irritated eyes and eyelids. The product contains a unique proprietary mix of honeys from the Australian and New Zealand Leptospermum species (commonly known as Manuka, Tea Tree or Jelly Bush). These honeys are selected for their highest and most consistent level of antibacterial activity, including activity against antibiotic resistant strains such as methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa,*and other exceptional physicochemical properties such as a high phenolic and flavonoid content [8–11], immunomodulatory effects [12–14], and anti-inflammatory, anti-oxidant and wound healing properties [11,14,15].

Honey has a long history in eye care and wound care [16]. Honey is a supersaturated solution of sugars with an acidic pH, high osmolarity and low water content. These characteristics inhibit the growth of microorganisms, reduce oedema and promote epithelialisation [15,17].

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Honey from a variety of floral sources and geographic locations, and in a range of concentrations, has been reported as an effective adjunctive treatment in the chronic management of ocular surface diseases, including post-operative corneal oedema and bullous keratopathy unsuitable for corneal grafting [18,19], Sjogren's and non-Sjogren's aqueous deficient dry eye [20–22], meibomian gland dysfunction [20,22], herpes zoster-related neurotrophic keratitis [23], vernal keratoconjunctivitis [24], contact lens-related bacterial keratitis [25] and as an antimicrobial prophylaxis for ocular surgery [26]. In animal models, unprocessed honeys were as effective as conventional antibiotic therapies in the management of bacterial conjunctivitis and keratitis caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* [27–29] and demonstrated efficacy in the management of corneal alkali burns [30] and a corneal abrasion inoculated with *Pseudomonas aeruginosa* toxin to induce immune mediated keratitis [31].

There are few published clinical studies on the efficacy of antibacterial honeys in eye care and none involving contact lens wearers with dry eye. The aim was to evaluate the efficacy of medically regulated antibacterial honey eye drops versus conventional lubricant eye drop therapy for management of dry eye symptoms and signs in symptomatic contact lens wearers. Both the safety of the product and contact lens wearers' compliance with its use were assessed.

2. Materials and methods

2.1. Participants

Twenty-four soft contact lens wearers aged 20 to 55 years, who reported experiencing symptoms of dryness during contact lens wear, were recruited from the Queensland University of Technology, Optometry Clinic. Soft contact lens wearers who were hypersensitive or allergic to honey or bee products were excluded from participation, as were those using topical or systemic medications. The study complied with the tenets of the Declaration of Helsinki and was approved by the University's Human Research Ethics Committee.

Four patients (17%) did not complete the trial for the following reasons: they acquired adenoviral conjunctivitis (n = 1), they developed contact lens acute red eye associated with increased contact lens wear (n = 1), or they did not complete the lubricant therapy treatment due to stated preference for Optimel Manuka+ (n = 2). Only the data of the 20 participants that completed both treatments were included in the analyses (Table 1). The mean ages of participants were 25.7 ± 9.2 years, 11 were female and 9 were male. All wore soft contact lenses: eleven wore daily disposables, 1 wore fortnightly replacement lenses and 8 used monthly replacement lenses. Most wore their lenses more than 5 h per day (n = 19) on more than 3 days per week (n = 13); some wore their lenses less due to their dry eye problem.

2.2. Treatments

Participants were randomised to two treatment groups. One group used Optimel Manuka+ Dry Eye Drops (Optimel Manuka +) twice a day for two weeks followed by lubricant (Systane Ultra, Alcon, USA) therapy for two weeks; the other group completed the treatments in the reverse order. Systane Ultra (Alcon Laboratories, Texas, USA) was chosen as the comparison due to its known effectiveness in treating contact lens related dry eye [32,33]. Before being given to the participants for at home use, the Optimel Manuka+ eye drops were instilled onto the eye's surface to determine if a sensitivity reaction was likely. Participants were instructed to use the eye drops twice a day; once in the morning at least 10 min before lens insertion and then once at the end of the day after contact lens removal. They were to use the drops daily regardless of whether they had worn contact lenses that day or not.

It was not possible to mask the participants as to which treatment they were using as the Optimel Manuka+ eye drops have a unique look, smell and taste with nasolacrimal drainage. Before and after each treatment period dry eye symptomology, ocular surface inflammation, and tear quantity and quality were assessed. The researchers taking the measurements were masked as to which of the two treatments had been used. During each treatment period participants completed a log detailing their usage of treatments and any issues experienced.

Table 1
Participant characteristics at baseline.

VARIABLE	PARTICIPANTS (n = 20)
Age (year)	25.7 ± 9.2
Gender (no. male/female)	9/11
Contact Lens Type (no. wearing daily/fortnightly/monthly)	11/1/8
Duration of Lens Wear per Day (no. wearing < 5/5-10/ > 10hours)	1/14/5
Wearing Schedule Days per Week (no. wearing < 3/3-5/ > 5 days)	7/5/8

2.3. Measurements

Participants attended three measurement sessions (baseline, after lubricants, after honey treatment). Validated dry eye questionnaires used to assess ocular symptoms included the Ocular Surface Disease Index (OSDI) [34] and Ocular Comfort Index (OCI) [35]. The scores of these questionnaires exhibit a positive correlation with each other with a high validity, reliability, specificity and sensitivity [34,36]. They were also asked to report their compliance with the Optimel Manuka+ eye drop treatment. The questionnaire had four choices Excellent (two drops per day nearly every day as recommended), Good (one or two drops per day most days), Fair (one drop per day most days), and Poor compliance (one or two drops when needed only), the participant chose one option.

Assessment of the tear film and ocular surface were performed using the Keratograph5 M (OCULUS Optikgeräte GmbH, Wetzlar, Germany). These assessments included limbal and bulbar conjunctival redness [37], non-invasive tear break up time (NIBUT) [38], and tear meniscus height [39]. The Schirmer 1 test of secretion [41] was also performed. All participants also underwent an anterior eye slit lamp examination. The presence of papillae upon lid eversion was graded using the Efron Scale [42]. Conjunctival fluorescein staining was graded using the Oxford Scale [43].

2.4. Data analysis

The data of the participant's most symptomatic dry eye at baseline was selected for data analysis. Descriptive data have been presented as mean ± standard deviations. Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Analysis of potential confounders showed that there was no impact of treatment order on the data and thus the data was collapsed to one group for analysis. A repeated measures analysis of variance (repeat measure ANOVA) was used for statistical analysis of crossover and treatment effects. Data of the participants with a baseline OSDI score of > 12 were also analysed separately; i.e. the sub-group with the more severe dry eye symptoms [36]. Pearson correlation analysis was performed to evaluate the relationship between Optimel Manuka+ treatment and clinical measures. P values < 0.05 were considered statistically significant.

3. Results

Compliance with Optimel Manuka+ treatment was excellent in 40%, good in 35%, fair in 20% and poor in 5% of participants (Fig. 1).

Fig. 1. Participant self-reported compliance with Optimel Manuka+ eye drop treatment. The questionnaire had four choices excellent, good, fair and poor compliance, the participant chose one option.

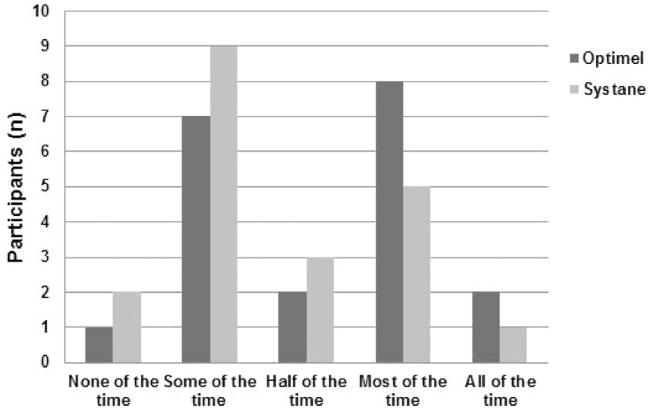

Fig. 2. Participant self-reported symptom control with Optimel Manuka+ and Systane Ultra eye drop treatments. The questionnaire had five choices, ranging from their symptoms were controlled none of the time to all of the time (with three intermediate choices). The participant chose which option was closest to their situation.

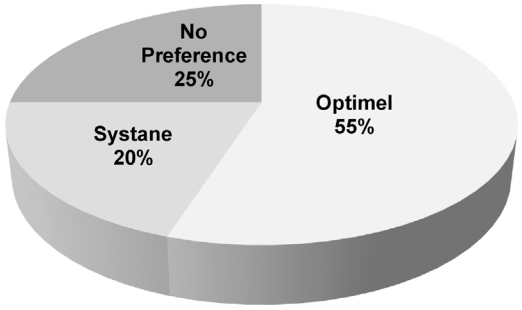

Fig. 3. Overall treatment preferences: 55% of participants favoured using Optimel Manuka+ eye drops over Systane Ultra eye drops to manage their contact lens-related dry eye. The questionnaire had three choices, they preferred Optimel Manuka+ eye drops, they preferred Systane Ultra eye drops or they had no preference.

Symptom control with Optimel Manuka+ treatment was reported to be achieved at least "most of the time" in 60% of patients (Fig. 2). Despite transient stinging and redness upon instillation, 75% of participants reported a "good" to "excellent" compliance with the Optimel Manuka + treatment. Optimel Manuka+ treatment was well tolerated by the majority of participants and 55% favoured using Optimel Manuka+ over Systane Ultra to manage their Contact Lens Induced Dry Eye (Fig. 3).

Both Optimel Manuka+ and Systane Ultra treatment produced a significant improvement in dry eye symptoms when symptomology was assessed using the OCI score: (Optimel Manuka+ difference = −6.2 ± 8.6, P = 0.01; Systane Ultra difference = −2.4 ± 5.0, P = 0.05) (Table 2).Whereas there was no statistical improvement based on symptoms as assessed using the OSDI score (Table 2)

Table 2
Comparison of dry eye assessment before (baseline) and following Optimel Manuka+ and Systane Ultra treatments.

MEASUREMENT	Baseline	After Optimel	P	After Systane	P
OSDI overall score (0 to 100)	19.2 ± 12.0	15.3 ± 12.5	0.15	22.3 ± 16.6	0.26
OCI value (0 to 100)	34.8 ± 5.9	28.6 ± 9.7	0.01*	32.4 ± 6.7	0.05*
Tear meniscus height (mm)	0.26 ± 0.08	0.22 ± 0.06	0.01*	0.24 ± 0.06	0.25
NIBUT (s)	10.7 ± 3.5	10.6 ± 4.9	0.91	10.8 ± 4.4	0.93
Schirmer I score (mm/5 min)	23 ± 11	20 ± 11	0.04*	20 ± 12	0.14
Bulbar redness score	0.94 ± 0.27	0.97 ± 0.35	0.67	0.96 ± 0.38	0.78
Limbal redness score	0.47 ± 0.15	0.55 ± 0.34	0.28	0.55 ± 0.29	0.13
Papillae grading (0 to 4)	1 ± 1	1 ± 1	0.19	1 ± 1	0.88
Fluorescein staining (0 to 4)	0.3 ± 0.4	0.5 ± 0.5	0.32	0.6 ± 0.6	0.06

Data are mean ± SD. *Data significantly different to baseline at P < 0.05.
OSDI = Ocular Surface Disease Index, OCI = Ocular Comfort Index, NIBUT = non-invasive tear break up time.

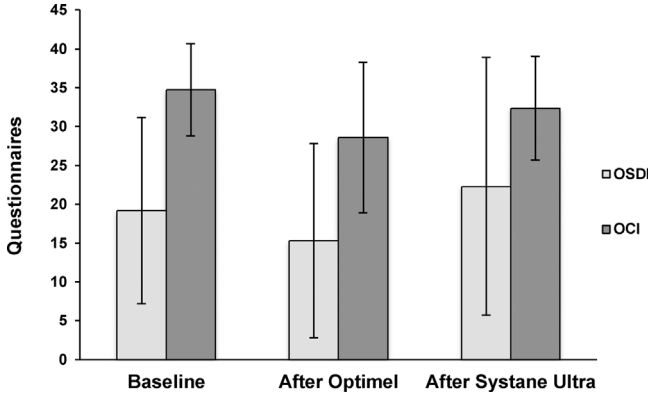

Fig. 4. Comparison of the Ocular Surface Disease Index (OSDI) and Ocular Comfort Index (OCI) before and after using Optimel Manuka+ and Systane Ultra eye drop treatments (data are mean ± SD). Improvements in the Ocular Surface Disease Index and Ocular Comfort Index following use of Optimel Manuka+ (a lower score means reduced symptoms) were statistically significant.

(Fig. 4).Tear meniscus height and Schirmer 1 test score significantly reduced following Optimel Manuka+ treatment (–0.05 ± 0.06 mm, P = 0.01; −3 ± 7, P = 0.04 respectively). None of the objective inflammatory signs (bulbar redness, limbal redness, papillae grading, fluorescein staining) showed a significant change with either treatment (Table 2).

The treatment effects of OptimelManuka + and Systane Ultra based on OSDI and OCI scores were significantly different (P = 0.02 and P = 0.05, respectively). The treatment effects of both agents were similar based on all other measures (Table 3).

When the data was reanalysed for just the participants with worst dry eye symptoms at baseline (OSDI score > 12; n = 13), the magnitude of the changes were greater (e.g. OSDI −6.9 ± 11.9 vs −3.9 ± 11.6) but the overall findings remained the same (Table 4).

The Optimel Manuka+ treatment effect on symptomology based on OSDI score was correlated to the measured effect on NIBUT, bulbar conjunctival redness and limbal conjunctival redness (P = 0.03, P = 0.01 and P = 0.02, respectively). Pearson correlation coefficients (r) were greater than ± 0.5 in these cases. There were no correlations between the remainder of the measurements.

Table 3
Comparison of Optimel Manuka+ and Systane Ultra eye drop treatment effects.

MEASUREMENT	After Optimel	After Systane	P
OSDI overall score (0 to 100) †	−3.9 ± 11.6	3.1 ± 11.7	0.02*
OCI value (0 to 100)	−6.2 ± 8.6	−2.4 ± 5.0	0.05*
Tear meniscus height (mm)	−0.05 ± 0.06	0.0 ± 0.08	0.23
Schirmer I score (mm/5 min)	−3 ± 7	−3 ± 8	0.78
NIBUT (s)	−0.14 ± 5.79	0.08 ± 3.95	0.83
Bulbar redness score	0.03 ± 0.30	0.02 ± 0.35	0.93
Limbal redness score	0.08 ± 0.33	0.08 ± 0.21	0.97
Papillae grading (0 to 4)	0 ± 1	0 ± 2	0.16
Fluorescein staining (0 to 4)	0.1 ± 0.5	0.3 ± 0.7	0.42

Data are after treatment values (Optimel or Systane) minus baseline values, mean ± SD.
*Optimel Manuka+ and Systane Ultra effect significantly different at $P < 0.05$.

Table 4
Comparison of Optimel Manuka+ and Systane Ultra eye drop treatment effects for participants with higher OSDI scores at baseline (n = 13).

MEASUREMENT	After Optimel	After Systane	P
OSDI overall score (0 to 100) †	−6.9 ± 11.9	1.9 ± 13.9	0.04*
OCI value (0 to 100)	−9.1 ± 9.1	−3.8 ± 5.3	0.08
Tear meniscus height (mm)	−0.06 ± 0.10	−0.04 ± 0.10	0.26
Non-invasive tear break up time (s)	−1.8 ± 5.7	−0.8 ± 3.8	0.49
Bulbar redness score	0.07 ± 0.30	0.06 ± 0.42	0.93
Limbal redness score	0.13 ± 0.39	0.12 ± 0.24	0.99
Schirmer I score (mm/5 min)	−5 ± 7	−3 ± 9	0.41
Papillae grading (0 to 4)	−1 ± 1	−1 ± 1	0.98
Fluorescein staining (0 to 4)	0.3 ± 0.6	0.4 ± 0.8	0.72

Data are after treatment values (Optimel or Systane) minus baseline values, mean ± SD.
*Optimel Manuka+ and Systane Ultra effect significantly different at $P < 0.05$.
OSDI = Ocular Surface Disease Index, OCI = Ocular Comfort Index, NIBUT = non-invasive tear break up time.

4. Discussion

At baseline participants had signs and symptoms of mild to moderate contact lens related dry eye. After only 2 weeks of treatment with Optimel Manuka+ improvements in symptoms were measured on the OCI (6.2 points, 18%). These improvements were greater in the subset of participants with greater OSDI dry eye symptom scores at baseline; improvements in this group were: OSDI 6.9 points (26%) and OCI 9.1 points (24%). The 6.9 point improvement on the OSDI in these more symptomatic participants is considered a clinically relevant improvement (the stated minimum clinically important change in OSDI is between 4.5 and 7.3) [36]. Despite improvements in symptomology no significant improvements occurred in the objective signs, presumably due to the short duration of use of the dry eye treatments.

The improvement in patient comfort levels with Optimel Manuka+ treatment may be attributable to the demonstrated antibacterial properties of Optimel Manuka+. Soft contact lens wear reduces tear exchange on the ocular surface, resulting in a decrease in antimicrobial defence mechanisms (reviewed in McDermott [44]). Aqueous tear enzymes such a lysozyme, lactoferrin and beta-lysin are reduced, not only resulting in increased ocular flora, but also increasing the risk of potential infection [45]. Studies demonstrate that there is a higher proportion of ocular surface flora in contact lens wearers, in particular coagulase negative *Staphylococcus*, *Propionibacterium acnes* and *Staphylococcusaureus* [46,47]. These bacteria have been implicated in the production of lipolytic enzymes, which destabilise the tear film resulting in dry eye symptoms. Albietz and Lenton [20] report that the number of colony forming units of coagulase negative *Staphylococcus* and *Staphylococcusaureus* were significantly reduced in eyes following treatment with antibacterial honey. One possibility is that Optimel Manuka+ may improve dry eye symptoms in contact lens wearers by preventing the overgrowth of commensal ocular flora.

Another possible mechanism of Optimel Manuka+ involves breaking the inflammatory cascade caused by tear film hyperosmolarity in soft contact lens wearers. Multiple studies demonstrate an increased tear osmolarity in contact lens wearers experiencing dry eye symptoms [40,48]. Tear film hyperosmolarity stimulates a cascade of inflammatory events in the ocular surface resulting in apoptotic death of conjunctival epithelium and goblet cells. A decrease in goblet cell density inevitably leads to increased tear film evaporation rates, exacerbating dry eye symptoms (reviewed in Doughty [49]). Several animal and human studies have demonstrated the active role of honey in the down regulation of inflammation on the ocular surface [20,24,30,31]. This would suggests that the tear film and state of the ocular surface is stabilised, improving patient comfort during lens wear.

The benefit of Optimel Manuka+ as long term antibacterial prophylaxis is important in contact lens wear. The prevalence of vision threatening microbial keratitis in daily wear soft contact lenses is 2.2-4.1/10,000 per year [50]. The antibacterial activity of Optimel Manuka+ is primarily due to the glucose oxidase enzyme, resulting in the slow release of hydrogen peroxide at very low but continuous levels when the honey is diluted. Hydrogen peroxide is an effective ocular antimicrobial agent even at very low concentrations [51]. The issue of antibacterial resistance occurring in Optimel Manuka+ is also unlikely as Leptospermum sp. honey has a minimum inhibitory concentration similar to the minimum bactericidal concentration of ocular flora [52]. Hence, the use of OptimelManuka+ in contact lens related dry eye provides long term prophylaxis against any potential ocular pathogens.

Temporary stinging and redness with honey application occurs in all patients, with the exception of those with neurotrophic corneas [23], this may impact uniform acceptance and ongoing patient commitment to treatment [20]. However, for the majority of participants improvements in overall symptomology must have been great enough for them to persevere with treatment; 75% reported good compliance with Optimel Manuka+ treatment. A limitation of this study was the relatively small study population (n = 20) and limited treatment duration. A longer treatment period of 2 to 3 months would provide a longer time frame over which to assess changes in clinical signs. Optimel Manuka+ in a randomised trial involving 114 participants and 2 months of treatment reduced by the symptoms, objective signs (e.g. Meibomian gland expressibility) and eyelid margin bacterial colony counts in patients with Meibomian gland disease [53]. As it is not possible to mask the treatment from the participants it is possible that some of the subjective improvement is due to a placebo effect however, placebo effect occur with all dry eye treatments and this is unlikely to account for a greater subjective improvement with a treatment that causes transient ocular redness and stings.

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Conflict of interest

No conflicting relationship exists for any author.

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