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Effects of a sea buckthorn oil spray emulsion on dry eye

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ABSTRACT

Purpose: To investigate the effects of a sea buckthorn oil and sodium hyaluronate-containing eyelid spray emulsion (SB spray) on dry eye.

Methods: A randomized controlled study was carried out. Adults (25–70 years) with Ocular Surface Disease Index (OSDI) ≥20 and moderate or severe dryness, burning or grittiness of the eyes were included. In study part one (n = 2), SB spray was used on both closed eyelids four times in one day. In part two (n = 10), SB spray was used on one randomized eyelid, and a commercial reference spray on the other for nine days. In part three (n = 40), eyes were randomized to one eye receiving SB spray and an untreated control for 1.5 months. Dry eye tests were carried out at baseline, during, and at the end of each study section. Symptoms were recorded in questionnaires and daily logs.

Results: In part one, the SB spray was well tolerated. In part two, OSDI decreased significantly (P = 0.022) in the SB spray eye compared to the reference spray, indicating a beneficial effect on symptoms. In part three, OSDI in the SB spray eye decreased significantly compared to the untreated control (P = 0.0007). The scores for dryness at the study end were lower in the SB spray eye compared to control (P = 0.0070). Symptom sums and frequencies of dryness (sum P = 0.0046, frequency P = 0.0016) and watering (sum P = 0.0003, frequency P = 0.013) in the daily logs were lower in the eye treated with SB spray.

Conclusions: SB spray on closed eyelids relieved the symptoms of dry eye.

1. Introduction

Dry eye is a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film, and accompanied by ocular symptoms [1]. There are two main mechanisms, which exist in a continuum and can reinforce each other. In evaporative dry eye, there is excess water evaporation from the tear film due to an unstable or deficient tear film lipid layer. In aqueous deficient dry eye, the lacrimal secretion is reduced, most commonly due to inflammatory infiltration of the lacrimal gland. Both mechanisms lead to hyperosmolarity of the tear film, which induces inflammation and damage to the ocular surface. The updated definition of dry eye includes contribution of neurosensory abnormalities to the symptoms [1–3].

Dry eye is among the most common reasons for patients to seek medical eye care. Prevalence ranging from 5 to 50% has been reported, depending on the population and the definition used [2,4]. The best-substantiated risk factors include aging, female sex, Asian ethnicity, Sjögren's syndrome, connective tissue diseases, and meibomian gland dysfunction, along with several modifiable factors (e.g. computer use, low environmental humidity, and certain medications) [4].

Dry eye can cause significant pain and limit everyday activities such as reading and using a computer [4]. The condition is commonly treated with artificial tears in an attempt to supplement the tear film. Lipid-containing products are considered a good alternative to traditional water-based formulations because they more closely resemble the composition of the tear film. During recent years, artificial tears sprayed on closed eyelids have been introduced as alternatives to eye drops [5,6]. The effects of oral sea buckthorn oil on dry eye have previously been investigated. Intake of 2 g sea buckthorn oil taken as four capsules per day for three months improved tear osmolarity and symptoms compared to placebo in a randomized, double-blind, placebo-controlled trial [7]. In the current study sea buckthorn oil was

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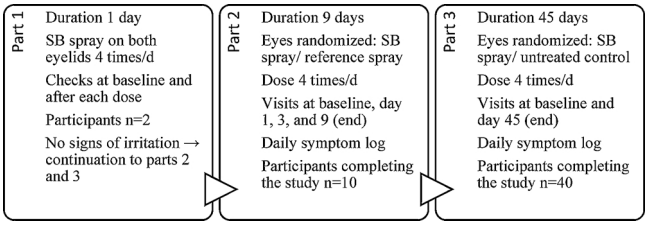

Fig. 1. Study design. Different participants attended each part of the study.

used as an active ingredient of a topical spray emulsion. The objective was to investigate the effects of this novel sea buckthorn oil - hyaluronic acid eyelid spray emulsion (SB spray) on dry eye.

2. Materials and methods

2.1. Study design

A randomized, controlled study was carried out at a private eye clinic Turun Silmäexpertit Ltd (Turku, Finland) between March and June 2016. The protocol followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital District of Southwest Finland, and Valvira - National Supervisory Authority for Welfare and Health. This study was registered in clinicaltrials.gov (identifier NCT02683382).

The protocol consisted of three parts, each attended by different participants (Fig. 1). In the first part, the safety and tolerability of SB spray were monitored for one day, before proceeding to observation periods of longer duration. The same tests and measurements were carried out as in the following parts of the study. Detailed results are not reported. In the second part, the eyes of each participant were randomized, and SB spray was compared to a commercial reference for nine days. In the third part, the effects of SB spray were compared to an untreated control eye during a study period of 45 days. Study participants, and the optician performing the measurements and symptom questionnaires at study visits were not blinded to the treatment. The study ophthalmologist scoring the signs of irritation from photographs taken at visits, did not know the treatment of the eye. The researchers analysing the data and outcome knew which eyes belonged to the same treatment but did not know what their treatment was.

2.2. Participants

The participants provided written informed consent, and they were informed of their right to withdraw at any time without giving a reason. Inclusion criteria were age 25–70 years, moderate or severe symptoms of dryness, grittiness/foreign body sensation or burning of eyes, and Ocular Surface Disease Index (OSDI) score ≥ 20. Exclusion criteria were: serious eye disease, known hypersensitivity to ingredients of the study sprays, or laser eye surgery within the previous 12 months. Participants were instructed to avoid local eye-care products during the study, and for at least five days prior to the beginning of the study. Otherwise they were asked to continue their normal routines and use of medication and personal care products, including eye cosmetics. The participants were instructed to come to the study visits without eye makeup or other eye-proximal cosmetics, including moisturizers.

2.3. Study products

The SB spray was an optically clear and preservative-free eyelid spray microemulsion containing sea buckthorn seed oil (0.4%) and hyaluronic acid (0.02%) as active ingredients in a hypo-osmolar and pH neutral buffer (Aromtech Ltd, Tornio, Finland, and Finnsusp Ltd, Lieto, Finland). The sea buckthorn seed oil, rich in α-linolenic acid (ALA, 18:3n-3) and linoleic acid (LA, 18:2n-6), was produced by supercritical CO_2 extraction with in-process control of oil colour (Aromtech Ltd). Hyaluronic acid was in the form of sodium hyaluronate and produced by bacterial fermentation. One dose of spray was administered to closed eyelids four times/d (in the morning, twice during the day, and in the evening).

The reference spray was a liposomal spray with soya lecithin (Tearsagain Sensitive, Optima Medical Swiss AG, Zug, Switzerland). It was administered to the closed eyelid four times/d (in the morning, twice during the day, and in the evening) according to the manufacturer's instructions. When applying the study spray(s), participants were asked to protect the other eye with their palm to avoid cross-contamination. For the visits following baseline assessment, participants were instructed to use the spray(s) about one hour before the appointment.

2.4. Tests and symptom evaluations

Dry eye tests were performed at each visit (Fig. 1) as follows: Tear osmolarity was measured using TearLab Osmolarity System (TearLab, CA; mOsm/L [8,9]). Tear film stability was measured as tear film breakup time (TBUT; seconds until breakup of fluorescein tear film [8,10]). Tear fluid secretion was measured using phenol red thread tear test (PRT) (Tianjin Jingming New Technological Development Co. Ltd, China; length of wetting the thread, mm/20 s [8,11]). To investigate the effect on skin around the eye, transepidermal water loss (TEWL), which indicates the integrity of the permeability barrier, was measured with a Vapometer device (Delfin Technologies Ltd, Kuopio, Finland; g/m^2h [12]). All measurements were performed in the same order and by the same person throughout the study.

Signs of irritation (corneal epithelial inflammation/corrosion, dilatation of blood vessels in the bulbar conjunctiva, conjunctival chemosis, dots on the margin of the cornea, oedema on the margin of the conjunctiva/cornea, eyelid irritation, and other possible signs of irritation) were evaluated and scored from photographs taken of the eyes and eyelids at study visits (TRC-NW7SF Retinal Camera, Topcon Corporation, Japan). The severity was scored, depending on the symptom, on a 3 or 4-point scale, in which each symptom corresponded to a verbal description (modified for this study from [13]).

Occurrence of dry eye symptoms was evaluated at each study visit by OSDI questionnaire [14] separately for the left and right eye. The questionnaire was translated into Finnish and modified for the study protocol. In the visits following baseline, participants were asked to report the symptoms experienced between the visits. Additionally, the symptoms of dryness, grittiness/foreign body sensation or burning of eyes were scored using a 4-point scale (0 = no symptoms to 3 = severe symptoms). Adverse effects, effect on periocular and eyelid skin, other user experience, and health and lifestyle information were monitored by questionnaires. In the second and third parts of the study, participants also kept daily symptom logs, where symptoms were reported using a 4-point scale (0 = no symptoms to 3 = severe symptoms).

2.5. Statistical analysis

Participants' eyes were randomized to SB spray eye and reference spray/control eye using randomly permuted blocks. Pre-study sample size estimation was based on the assumption that in part three the SB spray eye and the control eye would differ by one point or more (standard deviation 1.5) in the severity scores for eye dryness, burning, or grittiness/foreign body sensation. With a sample size of 40 participants, the study would have a power of 80% to detect the difference between the SB spray and control assuming a dropout rate of 10% (two-tailed tests, 0.05 significance level).

In the second and third parts of the study, the primary outcome was the difference of change between the SB spray and reference spray/control eye in OSDI, symptom scores at visits, TBUT, PRT, osmolarity, and TEWL. When analysing whether the mean changes between the SB

spray and reference spray/ control eye in OSDI, TBUT, osmolarity, or TEWL differed, the analysis of repeated measures was used, with two within-repeated factors: the eye and the visit. In this hierarchical linear mixed model, the UN@CS co-variance structure was used. If the overall significance level of the specific variables (time, time × treatment) was < 0.05, pairwise comparisons, their estimates, and confidence intervals were calculated for the differences at visits by using fitted means of the model. If the treatment × time interaction was significant, contrasts were programmed between two time-points and treatments. The normality assumption was tested visually together with Shapiro-Wilk test using residuals. If skewness was observed in the distribution, a square root transformation or a logarithm transformation was performed. The PRT measurements did not follow a normal distribution, and the comparison between treatment groups was made using the Wilcoxon signed-rank test.

Due to the small number of participants in study part two; treatment differences were not statistically analysed for the categorical variables except for the signs of irritation. In study part three, differences in the severity of symptoms, and in study parts two and three, signs of eye irritation between treatment groups at different points in time were analysed using the Stuart-Maxwell test or Wilcoxon signed-rank test.

The symptoms recorded in the logs (secondary outcome) were compared between the SB spray and reference spray/ control eye using the Wilcoxon signed-rank test. A symptom-sum variable was calculated to indicate the severity of symptoms. The percentage of symptom days was calculated for each symptom (percentage of days having a symptom score ≥1).

A significance level of 0.05 was used (two-tailed test). All participants were included in the statistical analyses (intention to treat). The software used was SAS® for Windows, version 9.4 (SAS Institute Inc, NC).

3. Results

In the first part of the study, no signs of irritation or adverse effects were observed (data not shown), and the study was continued to parts two and three.

3.1. Compliance and participants

In the first part, both participants completed the study according to the protocol. The majority of participants in the subsequent parts were women over 40 years of age who did not wear contact lenses (Table 1). In study part two, one participant dropped out because of an eye injury, not related to the study. In the logs, all participants reported using the SB and reference sprays as instructed for the majority of the study days. One participant reported not using the sprays on the final study day. On all other study days, all participants used at least part of the daily dose. Compliance in using SB and reference sprays was very similar. None of the participants reported using other local dry eye treatments during the intervention. All participants came to the study visits wearing no eye cosmetics.

Of the 45 participants beginning the third part of the study, 40 completed and attended the final visit. Two participants withdrew because they reported not benefitting from the SB spray. Other known reasons for withdrawal were unrelated to the study product. According to the logs, the SB spray was used according to the instructions on 97.6% of the days (median), and partly according to the instructions on 2.4% of the days. One participant reported the use of antihistamine eye drops in addition to the SB spray during two days of the study. Five participants reported the use of allergy or inflammation-relieving eye drops on their control eye on one to five study days. All participants followed the instruction not to wear eye cosmetics to the study visits.

Table 1
Baseline characteristics of participants[a].

	Part two n = 11	Part three n = 45
Women, n (%)	9 (82)	39 (87)
Age, years	53 (9)	60 (8)
Contact lens wearers, n (%)	2 (18)	0 (0)
Smokers, n (%)	2 (18)	5 (11)
Participants having an allergy, n (%)	4 (36)	19 (42)

[a] Values are means (SD), n (%).

3.2. Dry eye tests

In the second part of the study, the changes in tear film osmolarity (P = 0.91) or TBUT (P = 0.34) did not differ between the treatment eyes (Table 2). PRT at any visit did not differ between the SB spray and reference spray eyes (day 0, P = 0.66; day 1, P = 0.38; day 3, P = 0.15; day 9, P = 0.56; Table 2).

In the final part of the study, tear film osmolarity (P = 0.38) and TBUT (P = 0.11) did not differ between the SB spray and control eyes (Table 3). Results of the PRT test did not differ between the SB spray and control eyes at baseline (P = 0.25) or the end of the study (P = 0.74).

3.3. Dry eye symptoms

In the second part of the study, the mean change in OSDI differed significantly between the SB spray eye and reference eye (Fig. 2; treatment-by-time interaction, P = 0.045). OSDI lowered significantly more in the SB spray eye compared to the reference eye from baseline to study day 9 (P = 0.022, Fig. 2). Participants' scores regarding their experience of eye dryness, grittiness/ foreign body sensation or burning at study visits indicated lowering trends in the severity of all symptoms in both treatment eyes (data not shown). Symptom sums from the whole study period (**Supplementary Table 1**) and proportion of symptom days (**Supplementary Table 2**) calculated from the daily logs did not differ significantly between the treatments. A beneficial trend by SB spray compared to the reference (P = 0.094) was observed for watering of eyes (Supplementary Tables 1 and 2).

In the third part, OSDI in the SB spray eye was significantly reduced compared to the control eye with no treatment (P = 0.0007; Fig. 3). Participants' experience of eye dryness score was significantly lower in the SB spray eye compared to control at the study conclusion (P = 0.0070; **SupplementaryTable 3**). The scores for grittiness/ foreign body sensation (P = 0.11) and burning (P = 0.11) did not differ between the eyes (data not shown). Symptom sums of dryness (P = 0.0046) and watering (P = 0.0003) from the logs were significantly lower in the SB spray eye compared to control (**SupplementaryTable 4**). Furthermore, the proportion of symptom days was lower in the SB spray eye (dryness, P = 0.0016; watering, P = 0.013; **Supplementary Table 5**).

3.4. Skin

In the second part of the study, an overall increasing trend in skin TEWL from baseline to end was observed from the mean 15 (SD 6) to 27 (SD 7) and 16 (SD 8) to 30 (SD 9) g/m^2h in the SB and reference spray eyes, respectively. The changes in TEWL did not differ between the treatments (P = 0.71; **Supplementary Table 6**). In both treatments the experience of beneficial skin effects increased towards the end of the study (**Supplementary Table 7**). At the final visit, 8 of the 10 participants reported beneficial skin effects from SB spray and four participants from the reference spray. One person reported negative skin effects (feeling dryness) from the SB spray and three from the reference spray.

In the third part of the study, the baseline TEWL levels were higher compared to the baseline levels in the second part of the study, and there was no major difference in TEWL between the baseline and the

Table 2
Dry eye tests in study part two. Values are means (SD), or medians (Q1; Q3).

Day	Osmolarity (mOsm/L)[a]				TBUT (s)[b]				PRT (mm/20 s)[c]			
	SB spray		RF spray		SB spray		RF spray		SB spray		RF spray	
0	288.6	(10.6)	287.0	(5.7)	4.9	(1.1)	5.2	(1.6)	2.0	(1.0; 5.0)	3.0	(1.0; 5.0)
1	286.4	(6.1)	286.2	(6.9)	4.7	(1.4)	4.7	(1.8)	2.0	(1.0; 3.0)	2.0	(1.0; 5.0)
3	288.7	(10.2)	286.0	(7.2)	6.2	(1.5)	5.3	(1.6)	2.0	(1.0; 3.0)	4.0	(2.0; 6.0)
9	288.1	(10.2)	286.0	(7.0)	6.0	(1.2)	5.9	(1.6)	2.5	(1.0; 3.0)	3.5	(1.0; 5.0)

[a] Sea buckthorn oil (SB) spray n = 7–10, reference (RF) spray n = 9–11.
[b] SB spray n = 10–11, RF spray n = 10–11.
[c] SB spray n = 10–11, RF spray n = 10–11.

Table 3
Dry eye tests in study part three. Values are means (SD), or medians (Q1; Q3).

Day	Osmolarity (mOsm/L)[a]				TBUT (s)[b]				PRT (mm/20 s)[c]			
	SB spray		Control		SB spray		Control		SB spray		Control	
0	289.2	(9.9)	289.5	(9.3)	3.0	(1.6)	2.8	(1.4)	2.0	(1.0; 3.0)	2.0	(1.0; 3.0)
45	292.5	(8.8)	295.5	(17.4)	4.0	(1.7)	3.5	(2.2)	2.0	(1.0; 3.0)	2.0	(1.0; 3.0)

[a] Sea buckthorn oil (SB) spray n = 39–41, Control n = 38–42.
[b] SB spray n = 40–45, Control n = 40–45.
[c] SB spray n = 40–45, Control n = 40–45.

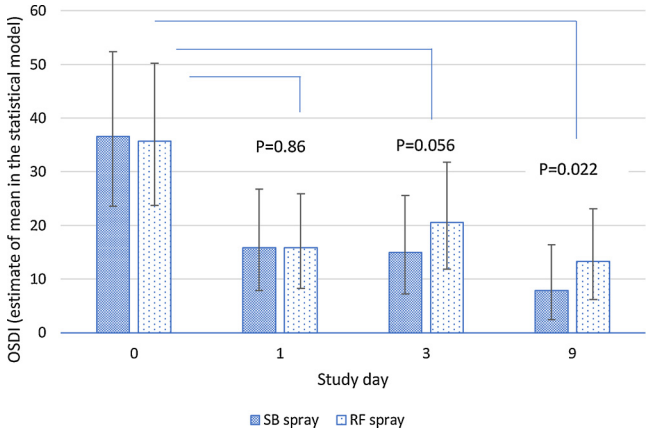

Fig. 2. OSDI scores in study part two. Values are estimates of the mean in the OSDI statistical model. Error bars describe the 95% CI. For statistical analyses, a square root transformation was performed on the data to fulfil the assumption of normal distribution. Estimates in the figure are back-transformed values. Sea buckthorn oil (SB) spray n = 10–11, reference (RF) spray n = 10–11. P-values represent the difference in change from baseline between the treatments.

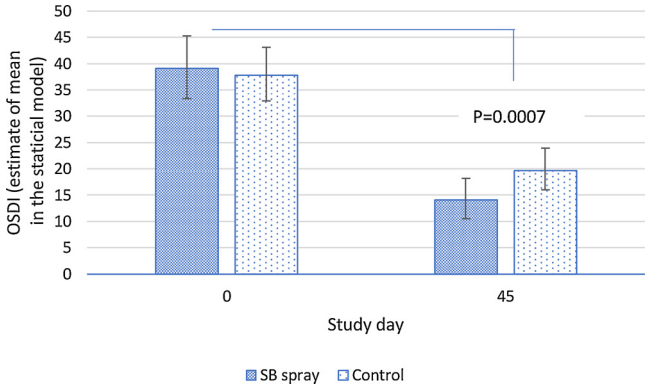

Fig. 3. OSDI scores in study part three. Values are estimates of the mean in the OSDI statistical model. Error bars describe the 95% CI. For statistical analyses, a square root transformation was performed on the data to fulfil the assumption of normal distribution. Estimates in the figure are back-transformed values. Sea buckthorn oil (SB) spray n = 39–45, Control n = 39-45. P-value represents the difference in change from baseline between the treatments.

end of the study for either the SB spray-treated or control eye. Changes in skin TEWL did not differ between the SB spray and the control eye (P = 0.45; **Supplementary Table 8**). At the final study visit, 18 (46%) of participants reported the spray had beneficial (e.g. hydrating, softening) effects on skin. Two participants (5%) felt negative skin effects.

3.5. Irritation

In the second part of the study, signs of corneal epithelial irritation/corrosion were significantly more severe in the reference spray eye than the SB spray eye after using the sprays for one day (P = 0.025; **Supplementary Table 9**). However, the irritation score was generally low, and lower at the last study visit compared to the baseline. After using the sprays for three days, signs of eyelid irritation were more severe in the SB spray eye compared to the reference spray (P = 0.046, **Supplementary Table 10**). Mild or local scaling/ redness was observed in five SB spray eyelids vs. one reference spray eyelid. At other visits, the treatment effects did not differ. At the end of the treatment, the number of participants not having signs of eyelid irritation was higher in both treatment eyes, compared to baseline, indicating the safety of the products. The other signs of eye irritation did not differ between the treatments at any time point (data not shown). In the final part of the study, none of the irritation signs differed significantly between SB spray and control eyes at baseline or the end of the study (data not shown).

3.6. Convenience of use

In the second part of the study, two participants used contact lenses. Both reported that the SB and reference sprays improved lens comfort. None of the participants felt that use of eye cosmetics affected the convenience of use of either spray. One participant reported the reference spray affecting the use of eye cosmetics. At the final study visit, all ten participants wanted to continue the use of SB spray and six participants wanted to continue the use of reference spray.

In the third part, all participants replying (n = 39) felt that use of

eye cosmetics did not affect the convenience of using the SB spray. One participant felt that SB spray affected the use of eye cosmetics by causing mild running of make-up. At the last visit, 26 participants (67%) would have liked to continue the use of SB spray.

4. Discussion

Beneficial effects were found with sea buckthorn oil and hyaluronic acid-containing eyelid spray for the symptoms of dry eye. The improvement of dry eye symptoms was significant compared to a commercial reference spray over a nine-day treatment period and when compared to the untreated control eye over a 45-day treatment period.

Hyaluronic acid is a polysaccharide naturally found in the vitreous body and extracellular matrix and commonly used in ophthalmologic formulations [15]. It has a high water-binding capacity, and several clinical studies have reported beneficial effects of hyaluronic acid, typically with ≥0.1% solutions, on signs and symptoms of dry eye and ocular damage [6,16–19]. However, in spray formulations, the concentration is restricted to appreciably lower concentrations to obtain a pleasant spray behavior on the eyelid.

Inflammation is an important contributor to dry eye [1,2]. Sea buckthorn seed oil is rich in essential fatty acids ALA and LA. In humans, a proportion of ALA and LA can be converted to very long-chain n-3 and n-6 fatty acids, respectively, in a series of enzyme catalysed reactions. These are precursors for eicosanoids, biologically active lipid mediators regulating inflammation. With the exception of dihomo-γ-linolenic acid (20:3n-6) derivatives, the n-6 fatty acid-derived eicosanoids are generally considered pro-inflammatory, whereas eicosanoids from n-3 fatty acids are anti-inflammatory or less inflammatory [20]. Very long-chain n-3 fatty acids are also precursors for resolvins and protectins, contributing to the resolution of inflammation [21]. A higher intake of n-3 fatty acids from the diet is associated with a lower risk of dry eye in women [22]. Clinical interventions suggest attenuation of dry eye by intake of combined LA and γ-linolenic acid (GLA, 18:3n-6) [23–27], n-3 fatty acids [28] and a combination of GLA and n-3 fatty acids [29].

Topical application n-3 fatty acids (0.2%) in mice attenuated several markers of dry eye-associated corneal damage, lipid peroxidation and inflammation [30]. ALA (0.2%) in eye drops relieved corneal damage and inflammation of dry eye in mice [31]. Topical ALA attenuated the release of inflammatory cytokines in stimulated human corneal epithelial cells via effects on the proinflammatory transcription factor nuclear factor-κB pathway [32]. Thus, it is justified to speculate that at least part of the clinical improvement observed in the present study may derive from the local activity of the sea buckthorn oil fatty acids in the SB spray.

Most previous studies of lipid-containing artificial tear sprays on closed eyelids have focused on the effect of a single dose, whereas there are fewer studies covering longer duration. The single-dose studies report beneficial effects on TBUT, tear film lipid layer thickness or grade, and subjective comfort from eyelid sprays containing phospholipids, sodium hyaluronate, plant extracts, and/or isoflavonoids from 10 to 90 min after application of the product [33–37]. Longer-term studies (from two to four-weeks duration) of phospholipid-containing eyelid sprays have reported beneficial effects on OSDI and markers of dry eye [38], modest changes in tear film lipid classes [39] or beneficial trends on TBUT and Schirmer test, but not significantly different compared to untreated controls [40].

In this study, a significant decrease in dry eye symptoms measured by OSDI was observed in response to SB spray compared to the reference spray or untreated control. In both in study parts two and three the effect on OSDI was in the range considered clinically important [41]. The improving symptoms were also recorded in the daily logs, whereas TBUT, PRT and tear osmolarity were not affected. These results may have been affected by the fact that participants were advised to use the study sprays about one hour before the scheduled study visits. The time interval between the tests and the application of the product was longer than in most similar studies published recently [33–37].

TEWL controlled by the *stratum corneum*, the outer layer of skin, is commonly used as a measure of barrier function of the skin. If the skin is damaged the barrier function is compromised and the TEWL increases [42]. Previous studies on the lipid-containing eyelid emulsions did not measure skin TEWL [33–40]. In this study the change in TEWL did not differ between the SB and reference spray or control eyes. Oil in water emulsions can improve *stratum corneum* hydration in healthy skin without affecting TEWL. However, effects on TEWL commonly need a more occluding film with water in oil emulsion [43] or pure plant oil [44].

This study has limitations. Due to the sensory properties of sea buckthorn oil an identical placebo was not possible to manufacture, and the participants could not be blinded to the treatments. It cannot be excluded that this may have affected the reporting of symptoms. However, using a commercial reference spray instead of a placebo allowed for a comparison between the SB spray and a spray with pre-existing efficacy studies [33–35,37–40]. It was expected that the participants' knowledge of getting active treatments (placebo effect) would be similar for the SB and reference sprays. It must also be acknowledged that the effects of different treatments observed in the contralateral eyes are not fully independent because of inter-eye signalling [45]. This may have equalized the differences in OSDI, especially at the end of part three, where the untreated eye showed only mild symptoms. On the other hand, comparing different treatments in contralateral eyes allows for less participant-related variation, and this design is commonly used to investigate dry eye treatments [33–35,37,46]. The inclusion criteria were experience of dry eye symptoms, and different dry eye types were included. Based on the median TBUT, PRT and OSDI, the participants at baseline had at least mild dry eye disease (TBUT < 10 s [2,8], PRT < 10 mm/20 s [8,11], OSDI ≥ 13 [8,14]). Mean tear osmolarities, however, were < 308 – 316 mOsm/L, commonly considered as the threshold values indicative of dry eye [2,8,9,47]. The poor correlation of the common diagnostic measures with symptoms of dry eye is well known, and each test reflects different aspects of dry eye disease [48].

In conclusion, a novel eyelid spray emulsion containing sea buckthorn oil and sodium hyaluronate relieved the symptoms of dry eye as measured by OSDI, visit questionnaires and by daily symptom logs. The beneficial effects were significant compared to a commercial reference spray and compared to an untreated control eye. The spray was well tolerated, and no significant adverse effects were observed.

Declaration of interest

Larmo P is an employee, and Kallio H is a partner of Aromtech Ltd (Tornio, Finland), manufacturer of SB oil and spray. Järvinen R is a partner and employee, Laihia J is an employee of Finnsusp Ltd (Lieto, Finland), manufacturer of SB spray. Other authors: no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clae.2018.11.011.

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