• Clinical Research •

Lid scrubbing with a gel combining natural extracts for dry eye treatment

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Abstract

● **AIM:** To evaluate the effect of lid scrubbing using a gel combining different natural extracts on ocular signs and symptoms of dry eye patients.

● **METHODS:** A retrospective study was performed on 19 dry eye patients (51.1±16.0y). Non-invasive tear break-up time, tear meniscus height, meibomian gland loss, lipid layer thickness, conjunctival redness, corneal staining, ocular surface disease index (OSDI), and ocular pain intensity were measured before (baseline), 1wk, and 2mo after lid scrubbing with a gel containing different natural extracts (okra extract, aloe vera leaf juice, hydrolysed soy protein, caffeine, citrus unshiu peel extract, and raspberry seed oil).

● **RESULTS:** Compared with the baseline, there was a statistically significant improvement in both first (P=0.048) and average (P=0.026) non-invasive tear break-up time 2mo after treatment, as well as in corneal staining (P=0.043, 0.012), OSDI (P<0.001), and ocular pain intensity (P<0.001) after 1wk and 2mo. In addition, there was no correlation between ocular signs and symptoms.

● **CONCLUSION:** The lid scrubbing with a gel combining different natural extracts show beneficial effects on tear film stability, corneal damage, and ocular symptoms, which is the reason why this therapeutic procedure is proposed as an alternative for dry eye management. However, it is not possible to attribute this beneficial effect solely to the presence of the natural extracts in the gel, primarily due to the absence of a negative control group.

● **KEYWORDS:** lid hygiene; natural extracts; okra; aloe vera; soy; dry eye
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INTRODUCTION

Dry eye is a multifactorial disease affecting ocular surface homeostasis, where patients manifest a broad range of ocular symptoms as well as tear film instability and hyperosmolarity, ocular surface damage and inflammation, and neurosensory abnormalities[1]. This condition represents a public health challenge since it affects a large part of the global population, reaching a prevalence of around 50% in some regions of the planet[2]. Due to the multifactorial nature of dry eye, there are several treatments available to patients depending on the disease's etiology and severity. These include tear substitutes, lid hygiene or warm therapy, anti-inflammatory drugs, secretagogue agents, autologous serum, or scleral lenses[3].

Natural extracts have been proposed as an alternative to dry eye treatments currently available, especially in recent years. These ophthalmic and oral formulations, which manifest anti-inflammatory, antioxidant, antimicrobial, and wetting properties, are based on several herbal extracts such as castor oil[4], traditional Chinese herbs[5], bilberry[6], green tea[7], saffron[8], lutein[9], quercetin[10], and different plant species (*Aster koraiensis*[11], *Camellia japonica*[12], *Chamaecyparis obtuse*[13], *Eurya japonica*[14], *Polygonum cuspidatum*[15], or *Rhynchosia volubilis*[16]). Treatments combining different herbal extracts[17-20] and derived from animals[21-23] have also been developed. However, only a few natural extracts have been translated to clinical studies, showing safety and efficacy for primary or adjuvant dry eye treatment[4-6,18,20,23-25].

In this regard, the purpose of the current study was to evaluate the effect of lid scrubbing with a gel combining different natural extracts on ocular signs and symptoms of dry eye patients. To the best of our knowledge, this is the first study to investigate the efficacy of lid scrubbing using a gel that

contains natural extracts for dry eye treatment. The gel contains okra extract, aloe vera leaf juice, hydrolyzed soy protein, caffeine, citrus unshiu peel extract, and raspberry seed oil as natural active ingredients. This proposed form of treatment involves a single in-clinic lid scrubbing and is suggested as an alternative to reduce the dosing frequency of most of the dry eye treatments, which typically require daily applications[3]. Therefore, lid scrubbing with this gel could be recommended as an adjuvant treatment in addition to the currently available treatments for dry eye patients.

SUBJECTS AND METHODS

Ethical Approval Ethical review and approval were waived for this study due to its retrospective design. However, informed consent was obtained retroactively from all subjects involved in the study.

Design of the Study and Patients A retrospective study was carried out in the Gran Vision (Madrid, Spain) Ophthalmology Clinic. The clinical database of this center was used. Data from nineteen patients were collected, whose demographic and clinical characteristics are summarized in Table 1.

Inclusion criteria were to be between 18 and 90 years of age and having a previous dry eye diagnosis based on the standardized criteria established in the TFOS DEWS II report[26]. Evaporative dry eye was diagnosed considering the presence of meibomian gland loss, while aqueous deficiency dry eye was diagnosed considering a tear meniscus height lower than 0.2 mm. This resulted in eight patients with evaporative dry eye and eleven with mixed dry eye. Exclusion criteria were any other ocular pathologies recorded in the clinic history and the use of systemic or ocular drugs affecting the ocular surface which could bias the results (*e.g.,* changes in medication during data collection).

Following the standardized recommendations of Armstrong[27] in his statistical guidelines for analyzing data obtained from one or both eyes, only one eye per patient was randomly selected for statistical analysis. This was done by flipping a coin, resulting in eight right eyes and eleven left eyes being analyzed. Measurements of the different variables were taken before (baseline) and after (1wk and 2mo) a single lid scrubbing with the gel containing natural extracts performed by an ophthalmologist. In each follow-up scheduled visit, ocular symptoms were evaluated before ocular signs. During the 2mo of data collection, the patients did not receive any other therapeutic procedures for dry eye. However, it should be noted that six patients had used tear substitutes for at least one month prior to lid scrubbing.

Treatment with the Gel Containing Natural Extracts The ZocuKit for ZEST® (Zocular Eyelid System Technology) is a commercially available medical device by Zocular LLC (Cypress, TX, USA), which contains the necessary material for lid scrubbing with an ocular gel based on different natural extracts. The gel's composition, provided by the manufacturer, included ultrapure water, naturally occurring compounds (okra extract, aloe vera leaf juice, hydrolyzed soy protein, caffeine, citrus unshiu peel extract, and raspberry seed oil), wetting agents (carboxymethyl cellulose and glycerin), preservatives (ethylhexylglycerin and phenoxyethanol), surfactants (decyl glucoside and disodium cocoamphodiacetate), a chelator (sodium phytate), and sodium chloride.

Table 1 Demographic and clinical characteristics of the patients included in the study

Parameters	Values
Patients (*n*)	19
Mixed dry eye	11
Evaporative dry eye	8
Age (range), y	51.1±16.0 (22 to 89)
Gender (female/male)	13/6
Country of origin	Spain
Medication taken before and during data collection	Enalapril (*n*=2); ebastine (*n*=1); paroxetine and norethisterone (*n*=1); duodart and sumial (*n*=1); flunarizine (*n*=1); atorvastatin and enalapril (*n*=1).

The treatment consisted of lid scrubbing with a swab impregnated in the gel containing natural extracts. Both eyes were treated, starting with the right eye. Following the manufacturer's instructions, the upper lid was scrubbed with the gel for 3min and the lower lid for another 2min using rotation and translation movements of the swab on the lid margin. Once the upper lid was treated, the excess gel was removed with a preservative-free saline solution (0.9% sodium chloride), and the procedure was repeated on the lower lid. After this in-clinic treatment, the patients were instructed to clean their lids with saline solution and gauze pads once a day for the first week. Patients did not receive any other therapeutic procedures for dry eye during the two months of data collection. Additionally, none of them reported any changes in medication during this period.

Measurement of Ocular Signs and Symptoms Ocular signs were measured using the Dry Eye Diagnostic System (MediWorks; Shanghai, China) incorporated into an S390L Firefly WDR slit lamp. Both first and average non-invasive tear break-up time were measured for a central corneal diameter of 8 mm by recording the Placido rings projection for 20s. The alterations in the tear film over the corneal surface are reflected as changes in the Placido rings' reflection pattern. The Dry Eye Diagnostic System software analyzes the distortion of the Placido rings to automatically calculate the tear break-up time values.

Tear meniscus height, meibomian gland loss of the upper lid by meibography, and conjunctival redness were automatically analyzed using the artificial intelligence identification system,

while lipid layer thickness and corneal staining were manually classified by comparing them to standard grading scales. Tear meniscus height is measured in the central region of the inferior eyelid. Meibomian gland loss was classified as none (grade 0), loss <1/3 (grade 1), loss 1/3–2/3 (grade 2), and loss >2/3 (grade 3). The lipid layer thickness was classified by comparing it to the software's standard grading template, resulting in <30 nm (grade 1), 30–60 nm (grade 2), 61–80 nm (grade 3), and >80 nm (grade 4). To the best of our knowledge, there are no studies in the scientific literature validating the relationship between the lipid layer thickness values and the scale of classification (grades 1 to 4). The severity of corneal staining and conjunctival redness was assessed using the Efron Grading Scale, which classifies severity as normal (0), trace (1), mild (2), moderate (3), and severe (4). Corneal staining was measured immediately after assessing the other ocular signs, using commercial fluorescein sodium.

Ocular symptoms were measured with the Ocular Surface Disease Index (OSDI) questionnaire[28] and the Eye Sensation Scale for pain intensity[29]. The OSDI questionnaire evaluates the frequency of ocular and visual symptoms in adverse environmental factors, as well as limitations in some daily activities, offering a score from 0 to 100. Regarding the Eye Sensation Scale, patients were asked to indicate their level of ocular pain intensity on a 10 cm line with 2.5 cm intervals between scores, ranging from 0 to 4. The intensity levels were classified as follows: none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3), and extreme (grade 4).

Statistical Analysis Statistical analysis was performed using the SPSS Statistics 23 software (IBM; Chicago, IL, USA). The normality of the variables was assessed with the Shapiro-Wilk test. The statistical comparison between the baseline and other measurements (1wk and 2mo) was carried out with the Wilcoxon signed-rank test, for cases of non-normality, or the Student's *t*-test for paired samples, for cases of normality. Additionally, the Pearson correlation coefficient between ocular signs and symptoms was calculated for each visit. A statistical significance of 95% (P<0.05) was established for all the tests.

The statistical variables were first tear break-up time, average tear break-up time, corneal staining, tear meniscus height, Meibomian gland loss, lipid layer thickness, conjunctival redness, OSDI, and ocular pain intensity. The results are expressed as mean±standard deviation (SD).

RESULTS

Figure 1 shows the results of non-invasive tear break-up time and corneal staining, while Table 2 summarizes the values and statistical comparison of the rest of the evaluated ocular signs. There was a statistically significant increase in both first (P=0.048) and average (P=0.026) tear break-up time two months after lid scrubbing with natural extracts compared to baseline. Regarding corneal damage, this treatment also improved corneal staining after one week (P=0.043) and two months (P=0.012). Furthermore, lipid layer thickness was reduced one week after treatment (P=0.034) but returned to

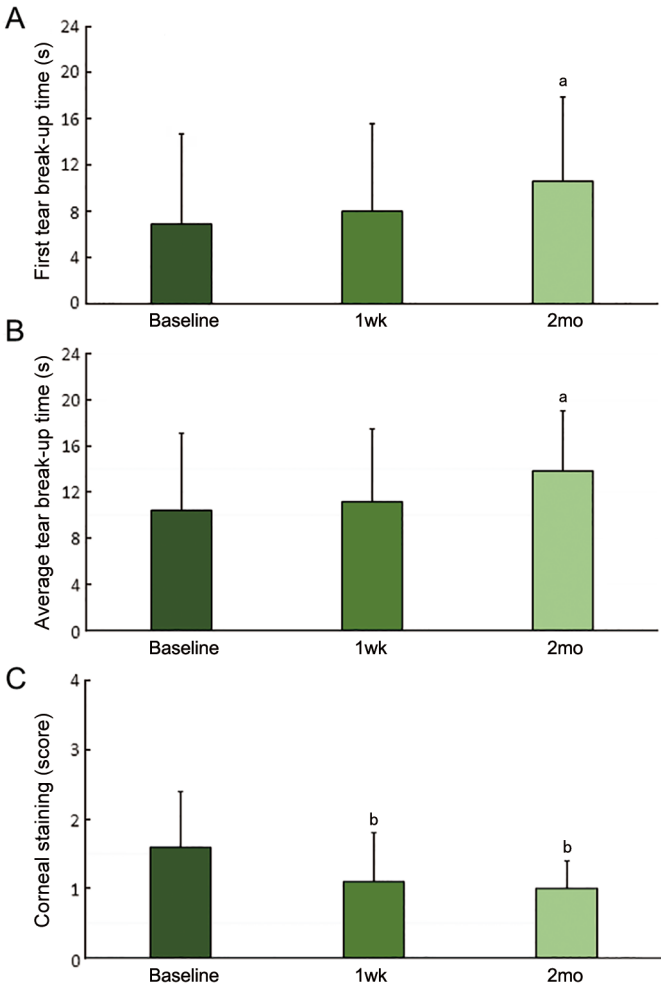

Figure 1 Results of the first tear break-up time (A), average tear break-up time (B), and corneal staining (C) at baseline, 1wk, and 2mo after treatment with the natural extracts [a]P<0.05, Student's *t*-test for paired samples (compared with the baseline). [b]P<0.05, Wilcoxon signed-ranked test (compared with the baseline).

Table 2 Values of tear meniscus height, meibomian gland loss, lipid layer thickness, and conjunctival redness at the baseline, 1wk, and 2mo after treatment with the natural extracts mean±SD

Variable	Measurement		
	Baseline	1wk	2mo
Tear meniscus height (mm)	0.21±0.09	0.21±0.08	0.20±0.07
P	-	0.844	0.536
Meibomian gland loss (score)	1.6±0.6	1.6±0.6	1.6±0.6
P	-	0.564	1.000
Lipid layer thickness (score)	3.4±0.5	3.1±0.7	3.4±0.6
P	-	0.034[a]	1.000
Conjunctival redness (score)	1.0±0.2	1.1±0.3	1.1±0.3
P	-	0.322	0.112

[a]P<0.05, Wilcoxon signed-ranked test (compared with the baseline).

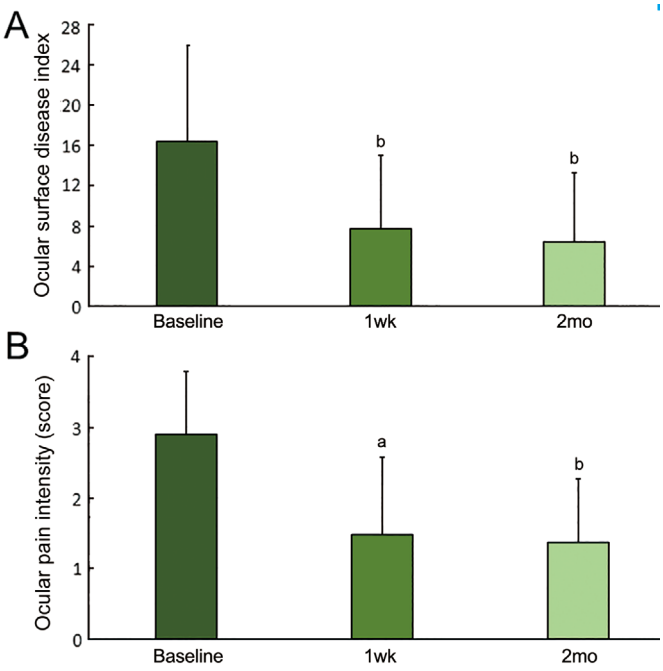

Figure 2 Results of the ocular surface disease index (A) and ocular pain intensity (B) at baseline, 1wk and 2mo after treatment with the natural extracts [a]P<0.01, [b]P<0.001, Wilcoxon signed-ranked test (compared with the baseline).

baseline values after two months. The rest of the ocular signs did not change significantly over time (P≥0.05).

In terms of ocular symptoms, Figure 2 shows the results of OSDI and ocular pain intensity. In both cases, there was a statistically significant reduction in ocular symptomatology 1wk and 2mo after treatment with the natural extracts (P<0.05). Nevertheless, there was no correlation between ocular signs and symptoms for any variable either one week or two months after treatment with the natural extracts (P≥0.05). Conversely, there was a positive correlation (P<0.05) between OSDI and ocular pain intensity at baseline (r=0.60) and after 1wk (r=0.73) and 2mo (r=0.61).

DISCUSSION

The current study found a beneficial effect of lid scrubbing with a gel containing natural extracts on tear film stability, corneal damage, and ocular symptoms, which could be presumed to be associated with the anti-inflammatory, antioxidant, and wetting properties that the different extracts of okra, aloe vera, soy protein, caffeine, citrus unshiu peel, and raspberry seed could have at the systemic level[30-35]. Despite the observed improvement in dry eye signs and symptoms after treatment with natural extracts, the underlying physiological mechanisms are not yet understood. This is mainly due to the lack of published basic research investigating the effects of these natural extracts on the ocular surface. Regarding this matter, it was only found one relevant study in the scientific literature. This was an *in vitro* study performed by Wozniak and Paduch[36], which demonstrated the anti-inflammatory effect of an extract of aloe vera on human corneal epithelial cells. They observed a reduction in the expression of cytokines [interleukin (IL)-1β, IL-6, IL-10, and tumor necrosis factor (TNF)-α] after adding the extract to the culture media.

Regarding tear film stability, there was an improvement in terms of increasing the first and average tear break-up time two months after treatment with the gel containing natural extracts (Figure 1). Considering that the lipidic layers of the tear film are responsible for tear film stability[37], the results of meibomian gland loss and lipid layer thickness, which suffered no changes 2mo after treatment (Table 2), would not explain the increase in tear film stability. However, this improvement could be also attributed to the stimulation of the mucinous component of tears after treatment. This could not be analyzed in this study since it requires specialized laboratory equipment such as a confocal microscope to quantify the density of goblet cells or mucin cloud height secreted by these cells, among other biomarkers[38]. However, the decrease in lipid layer thickness 1wk after treatment was not considered clinically relevant due to its low magnitude (0.3 score) and the recovery of basal values at 2mo.

In agreement with previous clinical studies involving dry eye patients, the current study reported an increase of around 3–4s in non-invasive tear break-up time 2mo after lid scrubbing with the gel containing natural extracts. In this regard, Maïssa *et al*[4] found that a single topical instillation of castor oil eye drops increased tear break-up time by around 3s for 4h. In addition, a one-month prospective (before and after) study performed by Tian *et al*[23] showed that the oral administration of animal-origin astaxanthin increased this time by only 1s. Finally, Nejabat *et al*[25] carried out a randomized, double-blind, and placebo-controlled study which showed an increase of 3s after the topical instillation of a green tea extract for four weeks. In contrast to the above, Huang *et al*[18], in another randomized, double-blind, and placebo-controlled study, reported no changes in tear break-up time after the oral administration of a formulation based on goji berry, *Cassiae semen*, *Ophiopogonis japonicus*, anthocyanosides, astaxanthin, and vitamins A, C, and E for 2mo.

With respect to corneal damage, the statistical results suggest that using the gel containing natural extracts for lid scrubbing could significantly improve corneal staining, reducing its mean score by more than 0.5 points (Figure 1). However, it is important to note that this treatment may not be equally effective for all patients with dry eye, as only half of the analyzed patients (9 out of 19) showed improvement in corneal staining after 2mo. The treatment was found to be effective for patients with mild to moderate corneal staining at baseline (9 patients with a baseline score of 2.2), but not for those with trace to mild corneal staining (10 patients with a baseline

score of 1.2). In the scientific literature, only one clinical study evaluating the effect of natural extracts on ocular surface damage has been found, conducted by Radkar *et al*[20]. In a randomized, double-blind, placebo-controlled trial involving dry eye patients, these authors found that the administration of an oral supplement containing extracts of marigold flower, curcumin, and an algal source for two months improved both corneal and conjunctival staining by approximately 0.5 points, which is consistent with the findings of the current study.

In terms of ocular symptoms, the decrease in OSDI and ocular pain intensity after treatment with the gel could not be attributed to the improvement of ocular signs (specifically tear break-up time and corneal staining) as there was no correlation between these. This lack of correlation between dry eye signs and symptoms agrees with a large number of studies published in the scientific literature, which assume a limitation for the diagnosis and management of the disease[39-40]. Most importantly, the improvement of ocular symptoms could have been biased by the influence of the placebo effect[41], in addition to the methodological limitations of a retrospective analysis. Thus, the absence of a control group would not allow assuming that the improvement of ocular symptoms was exclusively related to the lid scrubbing treatment with natural extracts. Other clinical studies, including some of those mentioned above, also demonstrated improvement in dry eye symptomatology after the topical instillation of castor oil by Maïssa *et al*[4], the oral administration of astaxanthin by Tian *et al*[23], and the topical instillation of green tea extract by Nejabat *et al*[25]. In a randomized and investigator-blind study involving patients with different forms of blepharitis, Muntz *et al*[24] also found an improvement in dry eye symptoms after the periocular application of a castor oil formulation for 1mo which was accompanied by a reduction in clinical signs of lid inflammation.

It should be noted that the current study was the only one which proposed lid scrubbing with natural extracts for dry eye treatment and showed promising results even two months after a single in-clinic treatment. The main advantage of this one-session procedure is that it would reduce the dosing frequency for dry eye patients and, therefore, lid scrubbing could be used as an adjuvant treatment to other daily treatments. However, there are still open questions as to whether this treatment could act synergistically with other treatments or as to what the most effective posology and administration method for the natural extracts studied is. Additionally, it is still not known if all the extracts present in the gel are beneficial for dry eye treatment. In general terms, the properties of the natural extracts evaluated in the current study did not differ from other natural extracts investigated for the treatment of dry eye in the clinical studies mentioned above[4-6,18,20,23-25], except for the route of administration and pharmaceutical form. The purpose of using these natural compounds is to utilize their anti-inflammatory and antioxidant properties to ameliorate oxidative stress and inflammatory processes on the ocular surface present in the pathophysiology of dry eye[42].

The main limitation of the current study was its retrospective design, which did not allow the establishment of a control group to determine whether the beneficial effect of lid scrubbing with the gel was solely due to the lid scrubbing procedure itself, the natural extracts, the wetting agents (carboxymethyl cellulose and glycerin), or on the contrary, it could be biased by environmental factors, particularly in the case of ocular symptomatology[41]. However, it should be noted that it was not possible to include a control group using a gel containing an identical formulation but without natural extracts, as such a product is not commercially available.

In conclusion, the lid scrubbing with a gel containing different natural extracts showed an improvement on tear film stability, corneal damage, and ocular symptoms, which is the reason why this therapeutic procedure is presented as an alternative for dry eye management. However, it was not possible to attribute this beneficial effect solely to the presence of the natural extracts in the gel, primarily due to the absence of a negative control group. Therefore, further prospective and controlled studies are needed to understand the clinical potential of this treatment as well as its synergistic effect together with other dry eye treatments already available.

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