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ORIGINAL RESEARCH

Impact of Improper Approach to Identify Lid Wiper Epitheliopathy (LWE)

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Purpose: Variability in the use of ophthalmic dyes to diagnose lid wiper epitheliopathy (LWE) has led to division in the literature and clinical practice. The principal aim of this study was to evaluate whether the use of a non-optimal methodology to identify LWE had a potential for false negatives; in which LWE was overlooked.

Patients and Methods: A total of 20 participants were initially categorized to not have LWE and were enrolled in this study. The protocol examined whether or not LWE would later be revealed through the use of optimized methodology. Semi-automated analysis was performed of images taken after two different drop instillations with varying post-dye viewing times for both lissamine green (LG) and sodium fluorescein (NaFl).

Results: There was a significant increase in area of staining revealed when an optimal methodology for LWE identification was used. Comparisons for every non-optimal condition were statistically significantly different against the optimal condition (all $p<0.01$). The use of a non-optimal methodology resulted in a 70% false-negative rate when using LG and a 95% false-negative rate when using NaFl.

Conclusion: The study demonstrated that using a double instillation of dye was statistically different from a single-dose, even with extended wait time for clinical observation. A single instillation did not offer adequate volume of dye for adequate lid margin uptake. A careful adherence to volume as well as a repeat administration is key to revealing the full area of LWE. A non-optimal approach to diagnose LWE can lead to false negatives.

Keywords: lid wiper, epitheliopathy, dry eye, lissamine green, sodium fluorescein, false negative

Introduction

The lid wiper is susceptible to insult and wear which can be visibly identified by vital dye staining to indicate lid wiper epitheliopathy (LWE). Lissamine green (LG), sodium fluorescein (NaFl), and rose bengal have all been used to detect the presence of LWE. The latter has not been used in recent years due to its propensity to stain healthy cells, adversely affect human corneal epithelial cell viability, and cause discomfort upon instillation.[1–3] Since 2002 a variety of approaches have been used to assess LWE.[4] Variability in the use of ophthalmic dyes in terms of concentration and the timing of observation has led to discordance in the literature.[5] The delivery of adequate vital dye volume appears to be key to uncovering the full extent of LWE. Korb et al[6–8] showed that the use of impregnated paper dye strips oftentimes does not provide an adequate concentration and volume of dye to disclose LWE staining. An optimized methodology to identify LWE has recently been described by Lievens et al[9] Though the relationship of LWE to other clinical

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signs and patient symptomatology has been questioned, the variation in approach to detect this condition creates confusion when comparing findings and/or establishing its presence. Of additional concern is the potential relationship between LWE and dry eye disease (DED). It has been theorized that compromise to the epithelium of the wiping system results in symptomatology akin to that of DED.[6,10–12] Consistent, repeatable and accurate testing for the signs of DED is critical given its growing incidence in the literature and its complexity to properly identify and manage.[6,10,13]

In addition to this, several challenges need to be considered when assessing for the presence of LWE. LWE must be distinguished from normal staining of the eyelid in the line of Marx. The line of Marx is a vital dye staining pattern that runs along the lid margin. It is located directly behind the mucocutaneous junction and extends from the outer canthi to the punctal region just behind the meibomian glands.[3,14] In vivo, the width of the line of Marx is reported to be 0.10 ± 0.09 mm.[15,16] The length of the lid margin has also been reported and measures 20.6 ± 1.9 mm.[17] Korb et al[8] used an assessment protocol that grades the horizontal length and width of the lid wiper staining (>10 mm is most severe). The inverted eyelid is curvilinear and mental estimations might make even approximate measurements very difficult. In line with this, Kunnen et al[18] observed that clinicians overestimated the height and underestimated the width of LWE staining. Based on the aforementioned measurements, the line of Marx should have an area that approximates 2.06 mm^2. A further challenge is that care must also be taken in a typical examination as to not mechanically induce staining through an improper technique of eyelid eversion. Repeated eyelid manipulation has been reported to affect lid margin staining.[19] Lastly, clinical efficiencies suggest that there is only a limited time afforded to examine a patient. Wolffsohn et al[20] found that eyecare practitioners took 7 minutes, on average, to assess the entirety of the anterior eye and only 26.2% routinely evaluated the lid wiper area.

A consistent approach to future research as well as clinical patient care is key to optimize patient care and diagnostic errors. The present study specifically examines the impact of LWE identification for the two most common dyes used in clinical practice, lissamine green (LG) and sodium fluorescein (NaFl), using a single-dose at 1-minute post-dye instillation (referred to short visual protocol) and comparing it to single-dose evaluations at 3- and 5-minute as well as an optimized methodology described by Lievens et al[9] (2-dose at 3-minute post-dye instillation, referred to optimal protocol). Thus, the principle aim of this study is to evaluate whether the use of a non-optimal methodology leads to a false-negative misdiagnosis of LWE.

Materials and Methods

Participants and Experimental Protocol

This paper reports previously unpublished data from excluded participants of a previous study by Lievens et al[9] Participants were recruited from the Southern College Optometry (SCO; Memphis, TN, USA) patient base. Participants were financially compensated for their time and travel expenses. The study was approved by the Institutional Review Board of SCO and conformed to the tenets of the Declaration of Helsinki. Ethical approval was additionally obtained from Anglia Ruskin University (Cambridge, United Kingdom). Written informed consent was obtained after explanation of the study and possible consequences of taking part.

The inclusion criteria included age ≥18 years and absence of LWE in both eyes using a short visual protocol in which LWE determination was made by visual inspection of the lid wiper region 1 minute after a single drop of LG was instilled in the right eye (RE) and a single drop of NaFl was instilled in the left eye (LE). Absence of LWE (no-LWE) was defined as no lid wiper staining in both eyes (with both respective dyes) at the 1-minute observation time. Candidates were excluded if they were contact lens wearers in an extended wear modality (routinely sleeping in lenses overnight). Candidates with any anterior segment infection, inflammation, disease, or abnormality (within the previous 7 days) and/or those currently using systemic or ocular medications that would typically contraindicate contact lens wear were also excluded. Finally, candidates who were monocular or had known allergies to the ophthalmic dyes used in this study were not enrolled. Fifty-seven participants were screened for enrollment and 37 were excluded due to the confirmed presence of LWE. Thus, 20 participants were categorized as no-LWE using the short visual protocol and were enrolled. The experimental protocol examined whether or not LWE might be revealed using a semi-automated analysis of images taken after two different drop instillations (1 vs 2 drops) and an increased post-dye viewing time (additional observations made at 3 and 5 minutes) for both LG and NaFl. LG was

Table 1 Summary of Experimental Protocol

Step	Description
1	Participant demographic data recorded
2	Medical history and ocular history recorded
3	Medication use recorded
4	LogMAR (RE/LE)
5	Biomicroscopy (slit lamp) anterior segment findings (RE/LE) • Examination of cornea, bulbar conjunctiva, palpebral conjunctiva, upper eyelid margin at (1) baseline and (2) conclusion of visit
6	Dosing of single-drop 1% LG (10 μL) in **RE** superior bulbar conjunctiva and photography at 1-, 3-, and 5-minutes post-LG instillation (termed LG1, LG3, and LG5, respectively)
7	Dosing of single-drop 2% NaFl (2 μL) in **LE** superior bulbar conjunctiva and photography at 1-, 3-, and 5-minutes post-NaFl instillation (termed NA1, NA3, and NA5, respectively)
8	Determination of no-LWE if no staining of the lid wiper noted at 1-minute observation times in both the RE and LE.
9	Dosing of 2-drops 1% LG (10 μL each), 1 minute apart, in **RE** superior bulbar conjunctiva and photography at 3-minutes post-LG instillation (termed LGLG3)
10	Dosing of 2-drops 2% NaFl (2 μL), 1 minute apart, in **LE** superior bulbar conjunctiva and photography at 3-minutes post-NaFl instillation (termed NANA3)

Abbreviations: RE, right eye; LE, left eye; LG, lissamine green; NaFl, sodium fluorescein.

used solely in the RE and NaFl was used solely in the LE as outlined in Table 1.

For each participant, all data were collected in a single visit. Baseline slit-lamp biomicroscopy and digital photography were performed on each eye using the same unit, BI900 LED Slit Lamp, with EyeSuite Imaging (Haag-Streit, Bern, SUI). Baseline assessments of the cornea, bulbar conjunctiva, palpebral conjunctiva were made for each eye (grade 2 and higher were excluded) on the Brien Holden Vision Institute Grading Scale (formerly referred to as the Cornea and Contact Lens Research Unit Grading scale). Comparisons among the 1 drop, 1-, 3-, and 5-minute conditions (LG1, LG3, LG5, NA1, NA3, NA5, respectively) and the 2-drop, 3-minute conditions (LGLG3 and NANA3, respectively) were made for both dyes.

Definition of Optimal LWE Assessment

Based on the optimal methodology described by Lievens et al[9] the 2-drop, 3-minute condition was used to confirm the presence of LWE with either LG (RE) or NaFl (LE) as compared to the short visual protocol described above. ADCIS (Advanced Concepts in Imaging Software, Saint Contest, FR) image software analysis was used to standardize the LWE area measurements for all groups.[9,21] A comparison of the area of lid wiper staining in the "no-LWE" versus the optimal methodology was used to assess the potential of a false-negative diagnosis. False-negative assessments can be identified when examining the change that took place in the optimal condition of LWE observation versus the investigator visual definition of "no-LWE" (single-dose of dye with a 1-minute observation wait time).

Dyes were instilled via a MicroPette Plus Single-Channel Variable Volume Pipettor, 2–20 μL volume (Scilogex, Rocky Hill, CT, USA), to assure exact dosages. Separate pipettors were used for LG and NaFl instillation. For single-drop instillation, 1% LG (10 μL applied RE) and 2% NaFl (2 μL applied LE) was applied to the superior bulbar conjunctiva.[22,23] The eyelid was carefully everted using a cotton-tipped applicator before each photograph (attention was made to not applanate the lid margin, causing iatrogenic staining). Photographs of the lid margin were taken after single-drop dosing (at 1, 3, and 5 minutes) and after double-drop dosing (at 3-minutes). Participants were instructed to blink normally after dye instillations. A washout period of 20–25 minutes was allotted between single-drop dosing and double-drop dosing in the same eye to allow for dye clearance.[24]

Analysis

Prior to image management and LWE detection, photographs of the everted lid (resolution of 2000*1000 digitized on 8 bits, 12× magnification, Haag-Streit BI900 LED Slit Lamp system and Canon EOS 60D digital camera) were captured in raw mode, and then converted into tiff-format images. The ADCIS software is designed to automatically detect LWE when using LG and NaFl vital dyes. Once this dyed area was detected, the software automatically segments the area and processes a series of computed measures (shape and intensity of the automatically detected regions). As LWE may have different presentations (continuous and non-continuous staining), the calculated area of lid wiper staining (mm^2) used for analysis includes all stained regions as well as the Line of Marx (mean area 2.06 mm^2). This approach is consistent with previous studies using alternative semi-automated methodologies.[9,17,18] Statistical analyses were performed using SAS software v9.4 (Cary, NC, USA). Tests for normality confirmed parametric data sets and the proper use of the paired Student's *t*-test.

Results

Agreement plots for both dyes demonstrate the differences when double instillation of dye was used (see Figure 1). Means and standard deviations for each of the conditions are presented in Table 2. There is an apparent significant shift in area of staining revealed when the optimal condition is chosen (LG1 1.76 mm^2 vs LGLG3 2.86 mm^2 and NA1 1.25 mm^2 vs NANA3 3.70 mm^2). Comparisons for every non-optimal condition are statistically significantly different against the optimal condition (all $p<0.01$). In the single-dose condition for both dyes, even when more time is allotted to dye uptake (3 and 5 minutes of wait time),

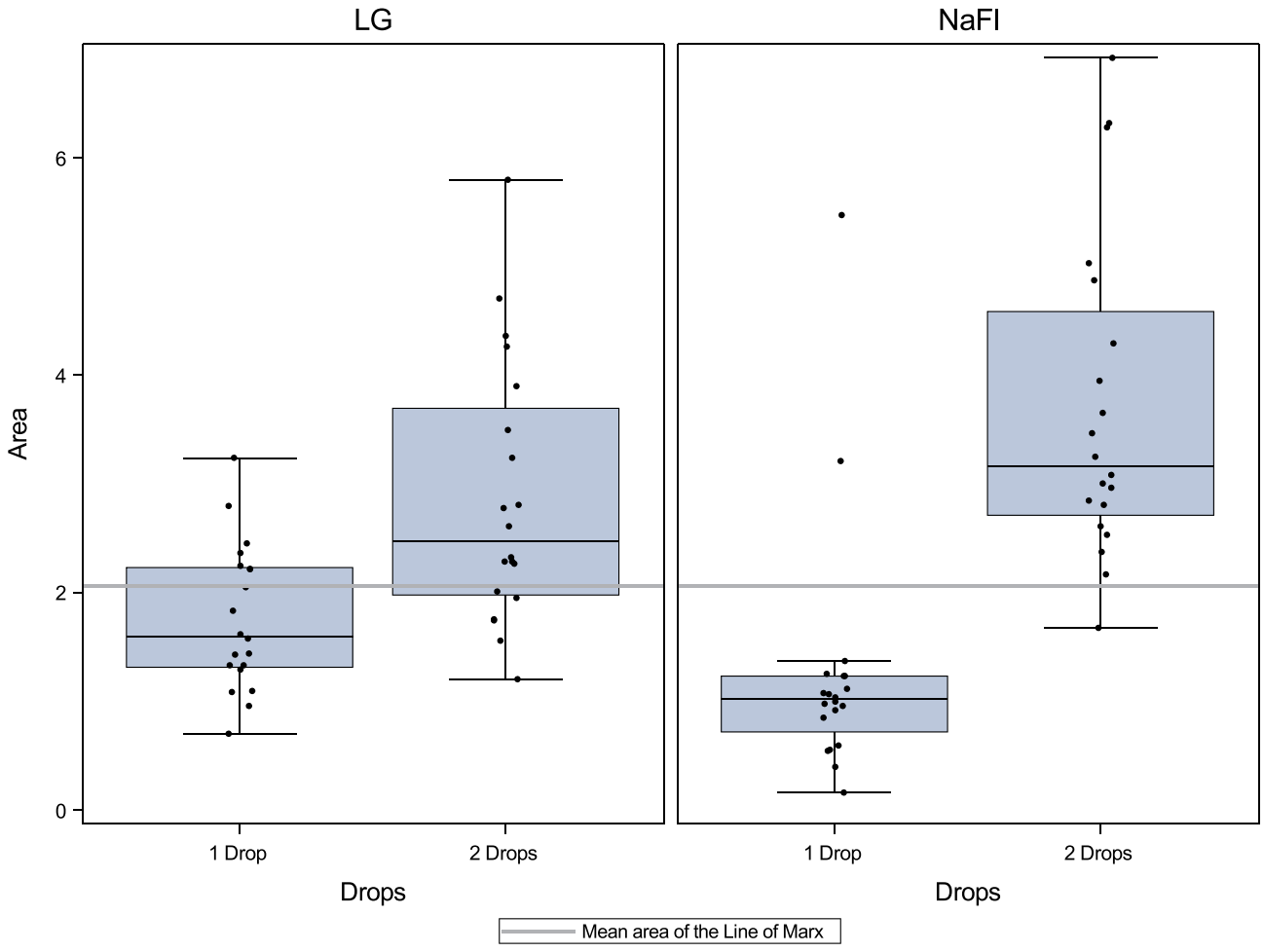

Figure 1 Plot of LWE area comparing the single-instillation LG and NaFl, respectively, with the short visual protocol versus double-instillation LG and NaFl, respectively, with the optimal methodology. Horizontal line across both graphs indicates the mean area for the line of Marx (2.06 mm^2).
Abbreviations: LG, lissamine green; NaFl, sodium fluorescein.

Table 2 *t*-Test Analysis of the LWE Area (mm2) of Using ADCIS for Each Dye and Dosing Condition

	RE				LE			
	LG1	**LG3**	**LG5**	**LGLG3**	**NA1**	**NA3**	**NA5**	**NANA3**
Mean LWE area (mm2)	1.76	1.92	1.28	**2.86**	1.25	2.25	2.54	**3.70**
SD	0.66	1.40	1.17	**1.21**	1.16	2.15	1.58	**1.48**
p-value comparing to optimal condition	p<0.0001	p=0.0043	p<0.0001		p<0.0001	p=0.0094	p=0.0029	

Note: Optimal methodology is noted as LGLG3 and NANA3, respectively.
Abbreviations: LG1, lissamine green 1 drop and 1-minute observation time; LG3, 3-minute observation time; LG5, 5-minute observation time; LGLG3, lissamine green 2 drops and 3-minute observation time; NA1, sodium fluorescein 1 drop and 1-minute observation time; NA3, 3-minute observation time; NA5, 5-minute observation time; NANA3, sodium fluorescein 2 drops and 3-minute observation time.

there still exists a significant difference when compared to the optimal condition. Image analysis of the LG optimal methodology revealed 14 participants (70% false negative) with greater area measurements than 2.06 mm^2 (Line of Marx only) as shown in Table 3. Similarly, in the NaFl optimal, condition, 19 participants measured greater than 2.06 mm^2 (95% false negative). Figure 2 illustrates a typical example of a false negative when using LG, the photograph shows the same eyelid margin with a single-instillation of dye (1 minute; short visual protocol) and double-instillation (3 minutes; optimal protocol). Similarly, Figure 3 illustrates a false-negative example when using NaFl.

Discussion

This study set out to investigate the potential rate of false negatives when using a non-optimal technique in the assessment of LWE. The mean area (mm^2) of LWE was assessed using imaging software and statistically significant differences were found between the means of each dosing and times conditions for both LG and NaFl dyes. The short protocol used a single drop of vital dye administered via pipettor. The dye amply covered the ocular surface and was akin to the typical amount administered in clinical practice through the usage of dye impregnated paper strips. Predictably, an underestimation of the area of LWE was observed for single-dosage (regardless of time evaluation) when compared to the optimal methodology described by Lievens et al.[9] More importantly, this study emphasizes the risk of false negatives if a non-optimal methodology is used for LWE evaluation. The present data suggest that with a single-instillation, there is a 70% risk of false negatives when using LG and a 95% risk of false negatives when using NaFl. Should ideal management of LWE be identified in the future, such therapy could only take place if the condition were to be correctly diagnosed. A false-negative diagnosis, however, would lead to an absence of intervention a risk of under-diagnosing LWE. Given the increasing prevalence of DED, and the potential connection for LWE and DED, all opportunities to reveal clinical signs are relevant for optimal clinical care.[6,10,13]

Korb et al[6] previously offered reasons why LWE can go unnoticed. Eyelids are not always everted during routine patient care and the lid margins are generally not fully inspected with the use of vital dye. Finally, as in the present report, the time of the vital dye to adsorb affected tissue is a critical factor to proper LWE detection. A premature observation of the lid wiper post-staining is an additional reason why LWE might have gone unnoticed in the past. Clinicians need to allow for the optimal evaluation time as recommended in recent reports.[9,23] This is particularly important, as very different approaches have been used to assess LWE[4] including single-instillation of vital dyes in recent investigations and that patients are frequently managed by multiple providers.[21–23]

A root cause analysis is a common approach to identify a given medical problem so that future issues do not take place. A medical decision, if corrected or avoided, would eliminate the undesirable consequence (such as in this case of an improper method of identifying patients).[25,26] Most medical errors are due to systems or process failures that lead to practitioners making mistakes.[25] Such would be the case with a non-optimal or premature approach to a clinical assessment is used. A false-negative clinical assessment can have a deleterious impact on healthcare.

In a strictly clinical observation of the lid wiper, the line of Marx has to be distinguished from LWE. This naturally occurring line appears to be the interface between lipids secreted from the meibomian glands and the aqueous (the leading edge of the lacrimal lake) and its size has been likely linked to meibomian gland dysfunction.[16,27] The line of Marx can shift as a factor of age and dry eye and remains to be a reasonable landmark

Table 3 LWE Initial Diagnoses Deemed "False Negative" According to the Short and Optimal Protocols Defined in the Study with the Use of Lissamine Green and Sodium Fluorescein Dyes

Vital Dye Used	Number of Participants Initially Classified as No-LWE	Number of Participants Determined to Have LWE When Optimal Methodology Used	Percentage of False Negatives
LG	20	14	70
NaFl	20	19	95

Abbreviations: LG, lissamine green; NaFl, sodium fluorescein.

on the lid margin as it takes up vital dye in nearly all patients.[4,16,28,29] Despite any line of Marx displacement, any vital dye staining proximal to the line of Marx is indicative of LWE. In the present analysis, epitheliopathy was generally very obvious when comparing the methodologies. To further illustrate this, examples of the false negatives for both dyes were shown in Figures 2 and 3. The margins in the photographs are starkly different. The initial image clearly outlines the line of Marx, whereas the adjacent image displays LWE. The overall mean for the line of Marx area was measured as 2.06 mm^2. It is acknowledged that the line of Marx can vary from one individual to another. A more precise assessment of false negatives might be to quantify each participant's line of Marx staining area individually in order to establish a unique anatomic baseline for later comparison. Challenges arise in attempting such an investigation in the precise identification of the full extent of the line of Marx, given the expected variability in terms of width and location among subjects[16] Therefore, in line with previous studies using alternative semi-automated methodologies,-[9,17,18] it was considered clinically appropriate to use average to provide a basis to detect false negatives in the present study.

Korb et al[6] reported the challenge of using paper impregnated strips to deliver adequate dye concentration and volume to uncover the full area of LWE staining. Paper impregnated strips, though, are readily available in clinical practice and research. It has been shown that the brand of paper strips could confound the volume of dye

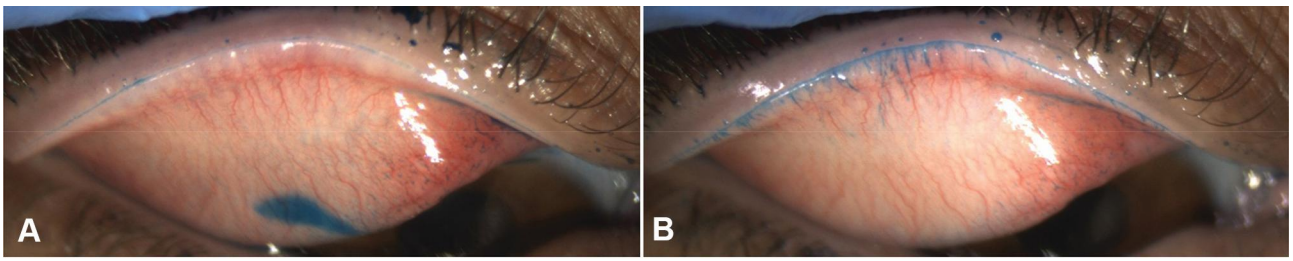

Figure 2 Images of the same participant. (**A**) Lid margin after 1 drop of LG instilled and photographed after 1 minute (line of Marx clearly evident). (**B**) Lid margin after 2 drops of LG instilled and photographed after 3 minutes (LWE present).
Abbreviation: LG, lissamine green.

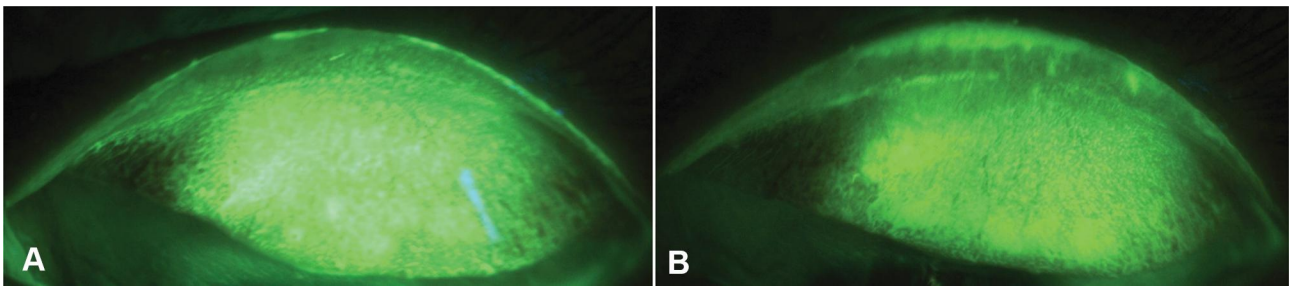

Figure 3 Images of the same participant (**A**) Lid margin after 1 drop of NaFl instilled and photographed after 1 minute (line of Marx clearly evident). (**B**) Lid margin after 2 drops of NaFl instilled and photographed after 3 minutes (LWE present).
Abbreviation: NaFl, sodium fluorescein.

administered as well. Lid wiper staining was reported to significantly differ between lissamine green strip brands, with GreenGlo showing the highest amount of staining, and Lissaver the least ($p > 0.009$).[30] Liquid dyes could offer the greatest consistency but have to be produced by a compounding pharmacy and have limited shelf life. The choice of dye to use, careful attention to adequate volume, and double instillation all appear to support reliable assessment of the lid wiper.

It is noted that only the upper lid wiper was assessed in the present work. Previous work has suggested that upper and lower lid LWE is from differing etiologies. Lower lid margin changes are thought to be due to hyperosmolar alterations in the tear meniscus rather than due to mechanical frictional wear.[31] Additionally, LWE of the upper lid has been linked to symptomatology whereas the lower lid LWE has not.[32,33] Mechanical manipulation of the eyelid with repeated eversions has also been suggested to increase staining patterns in LWE.[19] It is uncertain if changes to the lid wiper are strictly due to repeated eyelid eversions, alone, or also due to repeated instillations of vital dye. The present data reveal the significance of delivering additional dye volume to the lid margin with just one additional instillation. It is worth noting that there were significant differences between the present study and the report on repeated lid eversions and LWE.[19] Shaw et al did not control for the volume of dye instilled and a total of nine eversions (9 × 15 seconds) were carried out with 3-minute breaks.[19] In contrast, the present study controlled the delivery of dye, included a total of 6 eversions per eye, and allowed a longer interval between eversions. Additionally, the present study enrolled predominantly Caucasian participants whereas the other used mostly Asian participants (who have also been reported to have increased LWE).[19] Future investigations should further evaluate the role of ethnicity on LWE.

Sample size for enrollment in the present study was based on a previous study evaluating the temporal characteristics of NaFl in the tear meniscus.[34] No comparable studies existed for LG in the tear meniscus or other ocular depots. A sample size of 20 participants in the no-LWE group with only line of Marx projected staining was expected to deliver 80% power in order to detect a difference of 5 ± 8 staining intensity units. The no-LWE group was expected to identify the optimal methodology to uncover the full extent of the line of Marx. It was not expected to reveal LWE. Because LWE was present in a large percentage of these participants, it is understood that the rate of false negatives was relevant for this specific study group and specific assumptions for this rate might not transferable to a normal, larger population.

LWE is likely due to an increased sheer stress that can be initiated by eyelid anatomy, tear film instability, and contact lens wear. Conjunctival impression cytology and reductions in goblet cell count has been found to be significantly correlated to LWE.[29,35] The depth of lid wiper lesions is greater (with the presence of fissures and holes) in more severe LWE when compared to milder cases.[35] Additionally, insufficient tear volume, abnormal meibomian gland function (poor lipid layer), and abnormal mucins are also related to LWE.[35] Contact lens wear can alter many of the aforementioned conditions. One large study found that LWE was present in 85% of the contact lens wearers.[36] It is unsurprising that the present data confirm that the prevalence of LWE is very high and can be underestimated with improper technique. Unfortunately, once LWE is present, further aggravation of wear between the lid wiper and ocular surface is likely, which also may contribute to the high prevalence.[35]

Conclusion

Care should be taken to deliver adequate dye volume through a repeated administration in the observation of the lid wiper. It is possible that LWE has gone unnoticed or underestimated due to a premature observation of the lid wiper post-dye instillation.[6–8,33,37–40] Prior to the report to describe the optimal methodology to detect LWE, variability existed as to single[30,40,41] or double dosing of dye. The present report demonstrates that a double instillation of dye is statistically different than a single-instillation with extended wait times for clinical observation. A single instillation does not offer adequate volume of dye for adequate lid margin uptake. As mentioned, a careful adherence to volume as well as a repeat administration[21,23] is key to revealing the full area of LWE.

In symptomatic participants, LWE has been reported to be present 67%[42]–80%[7] of the time with the LWE width.[43] Adequately powered validation studies with large samples with optimal staining methodology should be performed to confirm these reports. Additionally, the present data were collected through the use of a semi-automated method to detect and measure LWE staining. Clinical grading in common use and investigation may not be able to accurately discriminate the minute cytologic lid margin differences between patients.[29] A renewed method of assessment to allow for reliable assessment of LWE in

common clinical practice would prove to be very useful and should be investigated.

Abbreviations

LG1, single-instillation LG with observation post 1-minute wait; LG3, single-instillation LG with observation post 3-minute wait; LG5, single-instillation LG with observation post 5-minute wait; LGLG3, double-instillation LG with observation post 3-minute wait (optimal condition); NA1, single-instillation NaFl with observation post 1-minute wait; NA3, single-instillation NaFl with observation post 3-minute wait; NA5, single-instillation NaFl with observation post 5-minute wait; NANA3, double-instillation NaFl with observation post 3-minute wait (optimal condition).

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