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Lid wiper epitheliopathy: The influence of multiple lid eversions and exposure time

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ABSTRACT

Purpose: To investigate the effect of multiple lid eversions on lid wiper epitheliopathy (LWE), along with the effect of cumulative lid exposure time and the patterns of associated staining.

Methods: The increase in area of lid wiper staining with lissamine green was compared by everting both the upper eyelids of each subject (i.e. contralateral design), with one eye being everted once for 45 s and the fellow eyelid everted three times, each time for 15 s. This pattern of contralateral eversion was repeated with a total of three eversions in one eye and nine eversions in the fellow eye, with each eye totalling 135 s cumulative exposure to eversion over about 9 min. The LWE area of staining was objectively quantified from slit lamp photography images captured at every lid eversion by 2 masked observers. Two-way repeated measures ANOVAs were used to determine the effect of number of lid eversions and cumulative exposure time on the amount of staining caused. Each image was also categorized into its primary LWE staining pattern, by a masked observer.

Results: The multiple eversions condition caused significantly greater LWE than the single eversion condition ($p < 0.001$), while cumulative exposure time did not have a significant effect on LWE ($p = 0.137$). Classification of the primary staining patterns revealed that with more eyelid eversions there was a shift from mostly 'no staining' to minor patterns ('short horizontal bands' and 'vertical streaks') and then to more extensive patterns ('broad horizontal bands' and 'comb-shaped').

Conclusions: The number of eyelid eversions is a confounding factor that should be controlled when investigating LWE, in particular when considering the link with dry eye or contact lens discomfort. However the cumulative exposure time did not appear to influence the LWE magnitude.

1. Introduction

The term 'lid wiper' (LW) refers to the region of the eyelid in contact with the ocular surface and is thought to be responsible for spreading the tear film during blinking. This region of the eyelid extends from the mucocutaneous junction (Marx's line) to the subtarsal fold over a width of between 0.3 to 0.6 mm [1,2] and laterally from the nasal to temporal canthus. Current histological understanding is that it is an epithelial thickening (8–12 layers, approximately 100 µm thick [3]), consisting predominantly of non-keratinised stratified squamous epithelial cells anteriorly, moving to parakeratinised (transitional) and cuboidal cells posteriorly [3]. Functionally, it has been reported that the lid wiper is the most sensitive region of the eyelid [4–6]. The term lid wiper epitheliopathy (LWE) refers to staining of the lid wiper after instillation of vital dyes such as fluorescein, rose bengal or lissamine green, and is generally thought to indicate epithelial disturbance due to friction-induced microtrauma [7–11].

Some studies have reported an association between LWE and contact lens related discomfort [7,8,12–15], while others have not [16–20]. A meta-analysis conducted on the data from six studies assessing soft contact lens wear, failed to demonstrate a significant relationship between the grade of LWE and comfort [21]. However complicating the interpretation of these studies are discrepancies in staining protocol, time of day of data collection, varying subject population characteristics and the use of subjective versus objective grading systems. More research is needed before a definite association between contact lens wear and LWE can be established.

However the association between dry eye and LWE is more clearly supported in the literature, with many studies, using adequate controls and various experimental designs, finding significant associations

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between LWE and dry eye indicators such as Ocular Surface Disease Index Score, non-invasive tear-break-up-time (NITBUT) and Schirmer values [7,8,15,22–24].

Despite the potential predictive usefulness of LWE, little is known about its cause. LWE for the upper lid can only be observed by eversion, and while this is a routine clinical procedure, everting the upper lid twice has been shown to significantly increase LWE [25]. As this is potentially a confounding factor in the assessment of LWE, this study aimed to examine the influence of multiple lid eversions and everted eyelid exposure time on LWE.

2. Materials and methods

2.1. Subjects

This study was approved by the Human Research Ethics Committee and followed the tenets of the declaration of Helsinki with informed consent being obtained from all participants. A total of 24 participants completed the screening visit to assess if they met the inclusion and exclusion criteria. Exclusion criteria included dry eye: Tear breakup time (TBUT) < 10 s, McMonnies Questionnaire > 14, Phenol red thread test < 10 mm in 15 s, systemic diseases associated with dry eye (including Sjogren's syndrome and rheumatoid arthritis) and medications with dry eye as a common side effect (including Roaccutane, oral contraceptives and antihistamines). Other exclusion criteria were frequent contact lens wear (more than once a week), contact lens wear in the week preceding the study and anterior ocular pathology (presence of more than mild LWE at screening, ocular surface or lacrimal diseases, lid and blinking abnormalities and previous ocular surgery). In total 12 participants were excluded: 10 due to failing the dry eye screening workup, 1 who had eyelids that were difficult to evert at the first attempt and another who had greater than mild LW staining at baseline. So after screening, 12 subjects completed the experimental data collection visit. These subjects ranged in age from 20 to 24 years (mean 21.8 ± 1.3 years) and consisted of 8 males and 4 females with an ethnic breakdown of 3 Caucasian and 9 Asian subjects.

2.2. Measurement techniques and protocol

Slit-lamp photography was used to take a reference image of each eye of each subject using 6.3× magnification with a millimetre ruler in frame to provide a scale reference for subsequent analysis. One drop of non-preserved unit dose saline (Reclens saline solution, Axis Pacific, NSW Australia) was used to wet the lissamine green strips (Green Glo 1.5 mg Lissamine Green Ophthalmic Strips, HUB Pharmaceuticals, Rancho Cucamonga, CA) prior to each eversion, with the dye being instilled on the inferior palpebral conjunctiva. The lid was everted within 30 s of instillation. The eversions were conducted by one of two 'everters' randomly assigned on a subject-by-subject basis. The same method to evert the eyelids was used by both 'everters'. The participant was asked to look down, the upper eyelid eyelashes were held (while being careful not to touch the lid margin) and the eyelid was pulled gently away from the globe. A cotton tip was placed on the upper lid and used to evert the eyelid. Baseline staining (Marx's line) was captured by slit lamp photography for both eyes.

Each eye of a participant was randomly assigned to the 'single eversion' or 'multiple eversion' condition. The single eversion condition involved everting the superior lid of that eye once for a duration of 45 s, while the multiple condition involved everting the superior eyelid three times for 15 s at each eversion, with slit lamp photography recorded for each lid eversion. This pattern of eversion was repeated 3 times (3 sessions) with 3 min break between each session. So in total the 'single' condition eyelid was everted a total of 3 times (exposure time 3 × 45 s = 135 s) and the 'multiple' condition eyelid was everted a total of 9 times (exposure time 9 × 15 s = 135 s), over about 9 min (Fig. 1). The exact duration of exposure upon each eversion was timed and recorded. The average duration of exposure for eversions designed to last 15 s was 15.7 ± 0.4 s while the eversions designated to last 45 s had a mean exposure time of 45.4 ± 0.4 s. It should be acknowledged that a lesser number of eversions, and shorter exposure times are the most clinically relevant, however the data collection was extended to more clearly investigate the underlying trends.

2.3. Statistical analysis

The area of staining (mm^2) present after each eversion was measured using ImageJ software (V1.51; National Institutes of Health, Bethesda, MD, http://rsbseb.nih.gov.ij/) (Fig. 2). The increase in area of staining was calculated for each eversion by subtracting the baseline staining (predominantly the area of Marx's line). Analysis was performed by two masked observers and the results of the two observers were found to be closely correlated. Bland-Altman and linear regression analysis comparing the results of the 2 observers (for all 168 photos analysed) revealed an average coefficient of determination (R^2) of 0.871 ($p < 0.001$) and an average linear regression slope of 0.837. Any image where the difference between the results of the two observers was three standard deviations away from the mean difference between the 2 observers, was identified as an outlier. The outlying images were re-analysed by a third observer and the two results (out of the 3) that were closest to each other, were then averaged and used for subsequent analysis. A total of 27 images out of 168 photos (16%) were analysed by the third observer.

A two-way repeated measures of analysis variance (ANOVA) was used to evaluate whether there was a significant difference in the measured staining area between the single and multiple eversion conditions and also between the three sessions of eversions. Pairwise comparisons from post hoc Bonferroni corrections were used to evaluate differences between each combination of pairings for each session. A second two-way repeated measures ANOVA was used to evaluate the effect of exposure time. A paired *t*-test was conducted on baseline staining (predominantly Marx's line) for the single condition versus the multiple condition to confirm whether the two eyes of the subjects had approximately equal staining at baseline. All data were checked for outliers, normality and sphericity in accordance with the assumptions of the statistical tests.

The eyelid photos were also classified by a masked observer based on the primary pattern of LWE staining, using the classification scheme which categorizes LWE into six patterns: no staining, short horizontal band, broad horizontal band, vertical streaks, comb-shaped and speckled [10].

3. Results

3.1. Effect of multiple lid eversions

The LWE staining area increased for each session of eversions with increasing exposure time and number of eyelid eversions (Table 1). Comparing the two conditions, the multiple eversion condition showed a greater increase in staining than the single eversion condition ($p < 0.001$) and the interaction between eversion condition and cumulative exposure time was also found to significantly affect the staining area ($p = 0.01$) (Fig. 3).

3.2. Effect of exposure time

To study the effect of exposure time, the mean increase in area of staining for the first three eversions of the two conditions were compared (Table 2 and Fig. 3). After the first three eversions, the mean increase in LW area of staining was very similar ($p > 0.05$) for the single eversion condition (5.52 ± 2.05 mm^2) and for the multiple eversion condition (4.68 ± 2.55 mm^2), even though the cumulative exposure time of the eyelids were quite different (135 s and 45 s

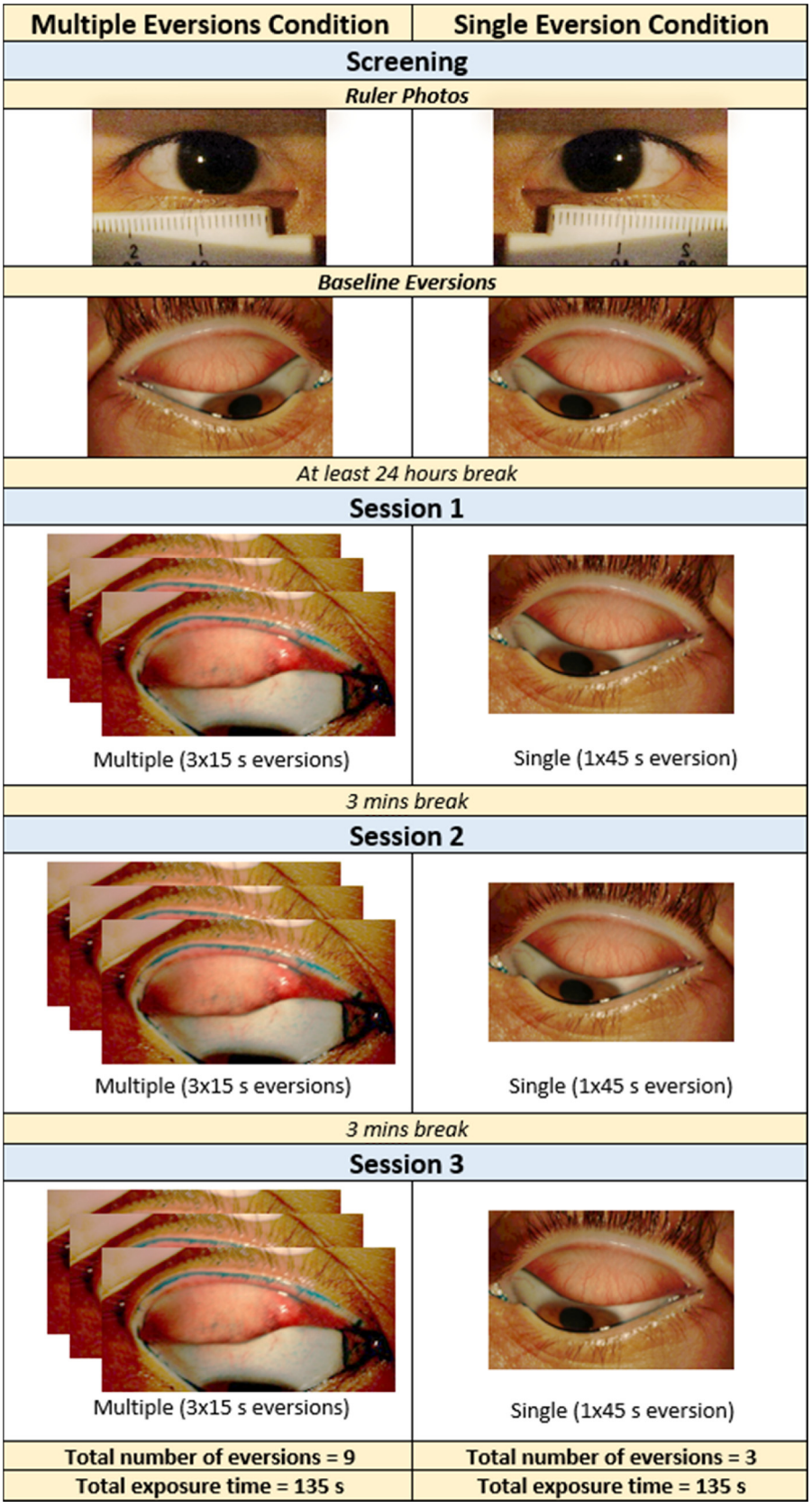

Fig. 1. Pictorial representation of methodology.

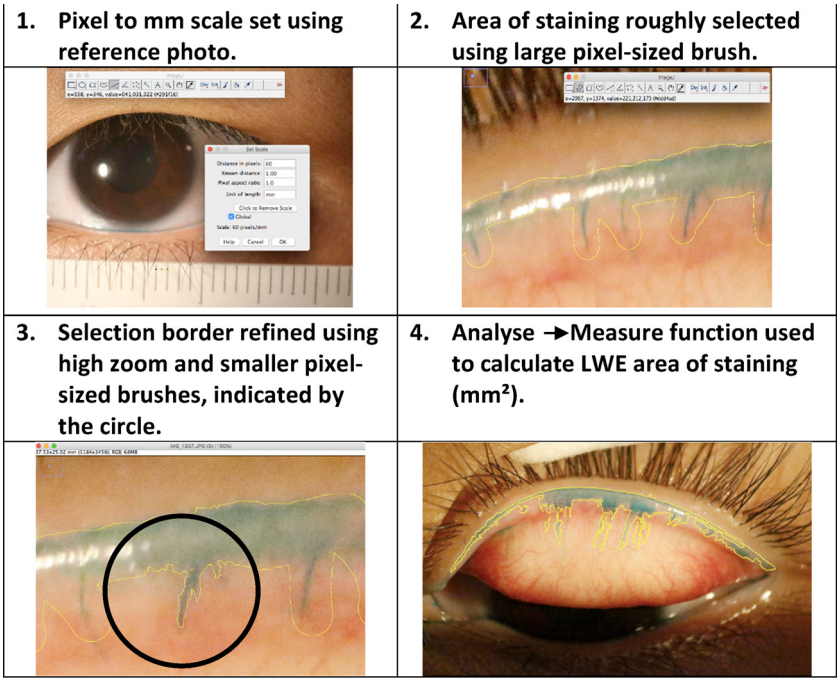

Fig. 2. ImageJ analysis procedure.

Table 1
Mean area increase in lid wiper staining where number of eversions differs but cumulative exposure time is equal between the single and multiple eversion conditions.

Cumulative exposure time (s)	Single eversion condition		Multiple eversion condition	
	Cumulative number of eversions	Mean increase in staining area from baseline (mm^2)	Cumulative number of eversions	Mean increase in staining area from baseline (mm^2)
45	1	2.91 ± 1.58	3	4.68 ± 2.55
90	2	4.13 ± 2.21	6	9.23 ± 3.02
135	3	5.52 ± 2.05	9	11.70 ± 3.35

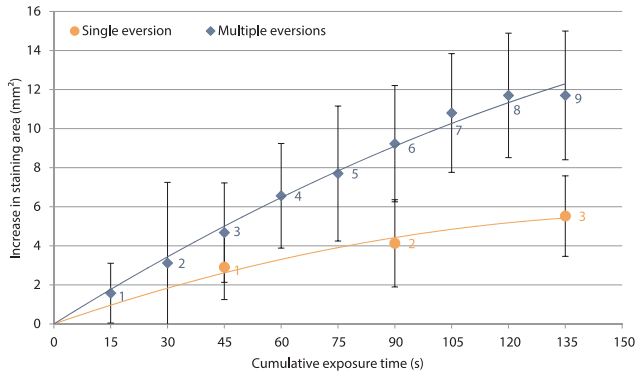

Fig. 3. Mean increase in staining area from baseline versus cumulative exposure time (s) and the cumulative number of lid eversions. Curves represent best polynomial fits.

respectively).

3.3. Baseline (Marx's line) staining

There was no significant difference in baseline staining area (predominantly Marx's line) at the initial lid eversion between the two eyes

Table 2
Mean area increase in lid wiper staining where the number of eversions is constant but cumulative exposure time differs between the single and multiple eversion conditions.

Cumulative number of eversions	Single eversion condition		Multiple eversion condition	
	Cumulative exposure time (s)	Mean increase in staining area from baseline (mm^2)	Cumulative exposure time (s)	Mean increase in staining area from baseline (mm^2)
1	45	2.91 ± 1.58	15	1.58 ± 1.8
2	90	4.13 ± 2.21	30	3.12 ± 1.87
3	135	5.52 ± 2.05	45	4.68 ± 2.55

for the single and multiple eversions conditions, with means of 3.06 ± 0.94 mm^2 and 2.98 ± 2.05 mm^2 respectively ($p = 0.872$).

3.4. Classification of primary LWE staining pattern

As exposure time and number of eversions increased, the primary staining pattern changed from mainly 'no staining' to predominantly 'short horizontal bands' and 'vertical streaks' for the next 3 eversions. For further eversions for the multiple eversions condition, the predominant patterns were the more extensive 'broad horizontal band' and 'comb-shaped' (Fig. 4). Similar frequencies of staining patterns can be seen when comparing the same eversion number between the single and multiple conditions (first 4 bars for each condition).

4. Discussion

Repeated eversion of the upper eyelid appears to lead to increased LWE, independently of the exposure time of the eyelid surface. This supports the findings of Delaveris et al. [25] who found that two lid eversions led to increased LWE. While the most accepted theory is that LWE is induced by excess friction between the lid wiper and ocular surface, the results of this study suggest that this may not be the only mechanism, since no friction is applied to the LW during eversion, yet LWE occurs. The act of everting the eyelid was a significant factor in

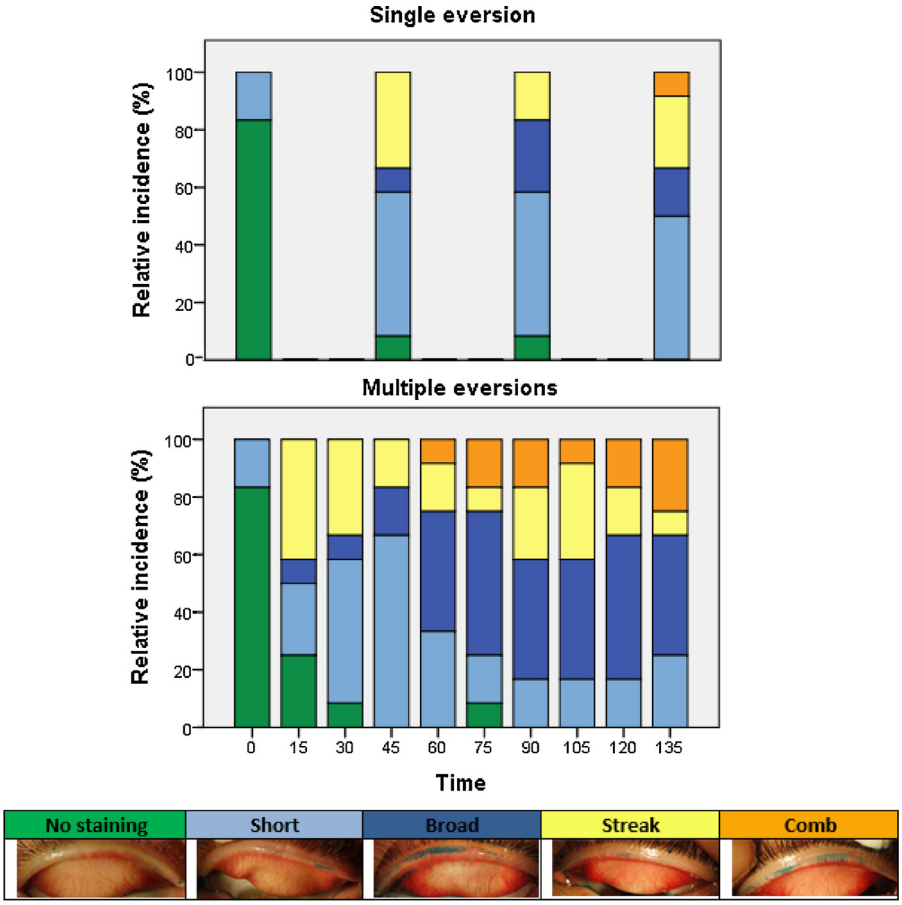

Fig. 4. Primary staining pattern distribution with accumulation of exposure time for the single eversion condition (top panel) and multiple eversion condition (lower panel).

LWE, while the exposure of the surface to air and potential dehydration (i.e. cumulative exposure time) was not a significant factor in LWE, for the exposure lengths considered in this study. There is a lack of knowledge concerning the underlying mechanism of LWE, partly because the staining properties of lissamine green are poorly understood [26]. This means that possible lid wiper staining mechanisms may include mucin staining, lipid staining or epithelial disturbance due to mechanical manipulation.

It is known that lissamine green stains mucous strands [26] and so it may be possible that excess mucin is expressed by the act of everting the lid. This theory is supported by the fact that goblet cells are present in lid wiper epithelium, singularly and in clusters. Some goblet cells are located on the surface while others are deep inside the epithelium and are connected to the ocular surface by cryptal epithelial infoldings [2,3]. The streaks of staining may correspond to the expression of deeper goblet cells, with multiple eversions leading to expansion of the cryptal infoldings and more mucin being secreted to the surface. Some linkages of mucins to LWE have been reported, with significantly greater LWE and reduced MUC5AC reactivity in symptomatic lens wearers [12] and some case reports of topical rebamipide (which enhances mucin secreted by goblet cells) improving LWE [27].

Alternatively, lissamine green may be staining lipid, and support for this hypothesis is the observation that lissamine green is often seen at the Meibomian gland orifices along the lid margin in close proximity to the lid wiper. It is also possible that the staining is due to lipid-mucin interaction with lipid excretion upon eversion, diffusing into the mucous-aqueous interface leading to the mucin-coated cells being lipid-contaminated and/or devitalised. The LWE streak patterns that are observed may represent areas of greater lipid concentration due to unequal amounts of lipid expressed from each gland. The use of Systane Balance (oil-in-water emulsion) has been shown to significantly improve LWE severity compared to baseline and compared to a control group using non-lipid rewetting drops [28].

The notion that epithelial disturbance due to mechanical manipulation may be involved is supported by the observation of tarsal vascular blanching during eversion, possibly indicative of force being applied to the lid. Iatrogenic LWE staining upon contact of the lid margin region with a finger prior to dye instillation has been reported [10] and suggests that the cells in the lid wiper region are sensitive to pressure and readily stain with light pressure disruption. It has been suggested that the LW may be in a state of sub-inflammation and be prone to damage [21]. Support for this theory is the discovery of keratinization-related proteins (filaggrin, transglutaminase1 and cytokeratin 1/10) in the lid margin epithelium [29]. These proteins are expressed in diseased tissues but are absent or only slightly expressed in normal ocular surface epithelium [30,31]. Confocal microscopy of the lid wiper has found increased Langerhan (immune) cell densities in subjects with contact lens related dry eye [32]. Other proinflammatory signs (hyperaemia and temperature) have been found to have significant (or close to) association with severe cases of LWE [7,17,33,34] and it has been claimed that corticosteriods are effective in minimizing or eliminating LWE signs and symptoms [35].

The LWE staining pattern distribution associated with silicone hydrogel contact lens wear has been reported to show a relatively even frequency distribution of the different staining patterns [10]. In contrast, this study found lid wiper staining patterns after multiple lid eversions gradually transitioned from the minor patterns (‘short horizontal band’ and ‘vertical streak’) to the more extensive patterns (‘broad horizontal band’ and ‘comb-shaped’).

The area of Marx’s line (mm^2) has been previously measured using a

similar digital analysis technique with a result of 2.7 ± 2.0 mm² [5], which is comparable to the baseline values found in this study of 3.06 ± 0.94 mm² and 2.98 ± 2.05 mm² for the single and multiple conditions respectively. A slightly larger area may have been observed in this study as on occasion some mild LWE staining was included in the baseline Marx's line area. Although another study using custom MATLAB software, reported a larger lid wiper staining area with a mean area of 3.36 ± 2.60 mm² [36].

While this study did not rigorously use identical volumes of lissamine green for each instillation, only one drop was applied prior to each lid eversion. A recent study did not find any significant difference in LWE staining when single versus double drops of lissamine green were used [25], so it is unlikely to have been a confounding factor in this work. However, more controlled delivery of the lissamine green would be preferable in future studies, since it is possible that repeated use over the 9 min timeframe may have contributed to greater uptake and an increased level of LWE. Another limitation of this study is that only lissamine green dye was used, whereas some previous studies have used a combination of dyes (usually lissamine green and fluorescein) [7,8]. However more recent work has found that the dual-dye method does not provide any diagnostic benefits over using lissamine green by itself [10,21].

Little is known about the time course of LWE including its development and resolution. Some parallels may be drawn with the cornea which is also richly innervated and predominantly non-keratinised stratified epithelium. The cornea responds in a matter of hours to minor surface damage with epithelial cells migrating to cover a breach [37]. Some have theorised that diurnal variations in LWE may occur with the staining being cumulative during the day and self-repairing overnight [18,21].

The participants in this study had no initial LWE, were infrequent or non-contact lens wearers, did not have dry eye and were aged between 20 and 24 years, and were predominantly of an Asian background so the results can only be interpreted for this group. In regards to ethnicity it is known that Asian eyelids have different geometries and have been reported to have increased lissamine green lid wiper epitheliopathy staining compared to Caucasian subjects. However in this study there were not enough subjects to analyse subgroups based on ethnicity, so it is unknown whether the effect of multiple eversions may differ depending on ethnicity. Future investigations of repeated lid eversions that may add further understanding of LWE might include interventions such as prior lipid expression or warm compresses, comparison between healthy, contact lens wearers and dry eye groups, young and older populations, Asian and Caucasian subgroups, diurnal variations and confocal microscopy to investigate cell morphological changes.

It seems likely that similar to corneal staining, there may be different forms of LWE. Contact lens-induced LWE (frictional effects between the lid wiper and anterior lens surface) may be different from dry-eye induced LWE (deficient tear film and shifts in tear osmolarity). Additionally only the upper eyelid was assessed in this study and it would be worthwhile investigating multiple eversions for the lower eyelid as it does not require full lid eversion to be viewed, and so would not be put under the same mechanical stress as the upper eyelid. Also in contrast to the upper eyelid, which has primarily vertical movement during blinking, the lower lid's primary movement is horizontal and the lower eyelid tear meniscus may have a higher osmolarity [38], which may produce different forms of LWE.

In conclusion, this study found a significantly greater area of LWE with additional lid eversions ($p < 0.001$), while increased exposure time had no significant effect on LWE staining ($p = 0.137$). Therefore multiple lid eversions must be considered to be a confounding factor that may lead to false positive results in studies investigating the link between LWE and conditions such as dry eye or contact lens discomfort. The different LWE pattern distribution we found compared to prior work, suggests that there could be different aetiological mechanisms involved in various forms of LWE. The possibility of LWE being multifactorial, with subtypes, should therefore be considered.

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The authors have no commercial or proprietary interest in any concept or product discussed in this article.

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