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Effect of lubricating eye drops on posterior-lid-margin sign in patients with dysfunctional-tear syndrome

ABSTRACT

Objective
This study compared the effect of lubricating eye drops on the posterior-lid-margin (PLM) sign and correlated the PLM sign with dry-eye symptoms among patients with dysfunctional-tear syndrome (DTS).

Methods
A double-masked, randomized clinical trial was conducted involving 30 eyes of 30 patients diagnosed with DTS who had the PLM sign. They were randomly assigned to receive one of the following: PEG 400 propylene glycol (Systane), hydroxypropylmethylcellulose (Genteal), or carboxymethylcellulose (Cellufresh). Primary outcome measure was the resolution time of the PLM sign after treatment with the eye drops. Secondary outcome measure was the correlation between ocular-discomfort grading and the PLM-sign severity grading.

Results
Ten patients in each group completed the study. The three groups were statistically equal \((p = 0.354)\) in terms of the mean resolution time of the PLM sign. The PLM sign had a positive moderate correlation with the subjective grading of ocular discomfort with a correlation coefficient of 0.74 at baseline.

Conclusion
Systane, Genteal, and Cellufresh were equally effective in resolving the PLM sign. The PLM-sign severity grading was also correlated with the subjective grading of ocular discomfort.

Keywords: Posterior-lid-margin sign, Lid wiper, Lid-wiper epitheliopathy, Dysfunctional-tear syndrome, Lubricating eye drops, Dry eye
Dry-eye syndrome (DES) or dysfunctional-tear syndrome (DTS) is a multifactorial disease involving the tears and ocular surface, resulting in subjective symptoms of ocular discomfort and visual disturbance and tear-film instability. It is associated with objective findings of tear hyperosmolarity and ocular-surface inflammation.

DES affects a person’s quality of life. According to the Women’s Health Study, patients with DES are three times more likely to have ocular complaints with common activities such as reading and watching television compared with those without the disease.

Patients, seen at the Dry Eye Clinic of the Department of Ophthalmology and Visual Sciences of the University of the Philippines– Philippine General Hospital (UP–PGH), generally presented with the following symptoms (in descending order of frequency): irritation/discomfort, foreign-body sensation, mild itchiness, tearing, dryness, burning/stinging, and eye strain/fatigue (Lim Bon Siong R, Sy E. Profile of patients in a tertiary hospital dry-eye specialty clinic in the Philippines, unpublished, 2007).

Because the symptoms are largely subjective, dry-eye disease is difficult to evaluate and manage. Although there are several clinical objective tests, including tear-film-breakup time, Schirmer tear test, and corneal and conjunctival vital staining to determine its presence and quantify severity, their correlation with the symptoms is inconsistent.

A recently recognized and very promising, albeit not widely popular, objective clinical assessment of dry-eye patients is the concept of lid-wiper epitheliopathy described by Korb in 2003. Independent of this study, the UP–PGH Dry Eye Clinic has been monitoring this clinical finding prior to 2003 and has been using the term posterior-lid-margin (PLM) sign. In a recent unpublished study by Sy and Lim Bon Siong evaluating the profile of dry-eye patients at the UP–PGH Dry Eye Clinic, 255 (79.69%) of the 320 subjects evaluated for lid-margin lissamine green staining had the PLM sign.

The lid wiper is located at the marginal conjunctiva of the upper eyelid beginning posterior to the meibomian gland orifices and extending superiorly to the subtarsal fold. This is the region where there is a transition between keratinized and nonkeratinized stratified squamous epithelium and is in direct contact with the ocular surface. As implied by the term, the lid wiper wipes the ocular surface during blinking.

In dry-eye patients, there is boundary lubrication in which the thickness of the tear film between the opposing tissues, particularly the lid wiper and the ocular surface, is inadequate to separate the two surfaces. With inadequate lubrication, there is a concomitant increase in frictional coefficient and an increase in the ocular-surface damage.

Korb and colleagues demonstrated the direct correlation between dry-eye symptoms and the physical finding and severity of lid-wiper epitheliopathy or PLM sign. The UP–PGH Dry Eye Clinic has consistently seen relief of dry-eye symptoms with the disappearance of the PLM sign after instituting topical lubricants. However, we have not done any formal study to document the effect of topical lubricants on the severity grading of PLM sign and how soon these lubricants help resolve the sign.

Demonstrating the effect of these eye drops on PLM sign will aid the clinician in the management of dry-eye syndrome by providing a more objective surrogate measure of symptom resolution. More importantly, it may help the clinician choose the most effective topical lubricant to relieve the patients of dry-eye symptoms as quickly as possible.

As mentioned, the subjectivity of symptoms poses a dilemma in the management of dry-eye patients. Nonetheless, its documentation is crucial since the goal of treatment is patient comfort and improvement in the quality of life. To evaluate patient perception of symptoms, a subjective-grading-of-ocular-discomfort questionnaire was adapted from the Dry Eye Workshop in 2007 based on the most common symptoms documented by Sy and Lim Bon Siong. The questionnaire was translated into Filipino.

This study correlated the PLM sign with dry-eye symptoms among patients with DTS and compared the effect of lubricating eye drops on the PLM sign in terms of its resolution time.

**METHODOLOGY**

Thirty eyes of patients diagnosed with DTS were enrolled in this double-masked, randomized, clinical trial at a hospital-based dry-eye specialty clinic from March 2008 to September 2008. Eligible patients had a primary diagnosis of DTS (either aqueous-tear deficiency, tear-film instability, or both), with PLM sign. They were at least 18 years old, with best-corrected or pinhole visual acuity of at least 20/40 in both eyes. Excluded were patients who had any ocular condition that will mimic dry-eye symptoms, used any form of eye drops within the previous 3 months, had any eyelid or eyelash abnormalities that will mimic the PLM sign (entropion, trichiasis, lid imbrication syndrome, floppy eyelid syndrome), had severe meibomian-gland disease or severe blepharitis, had severe ocular-surface disease (chemical burn, Stevens–Johnson Syndrome), had active ocular allergy or infection, used contact lenses, were pregnant and nursing, had hypersensitivity to any components of the eye drops.

The subjective-grading-of-ocular-discomfort questionnaire was administered by the investigator to the qualified participants after obtaining informed consent. The
questionnaire used a five-point scale (none at all = 0; seldom = 1; sometimes = 2; most of the time = 3; all the time = 4) to grade the following symptoms: discomfort/irritation; dry sensation; burning/stinging sensation; itching; sandiness/foreign-body sensation; tearing or moist sensation; eye strain or fatigue. The sum of the scores was classified into mild (14 and below), moderate (15 to 21), or severe (22 to 28). The symptoms and grading key were translated into Filipino and a standard script for the interviewer as well as visual aid for the key were presented to the subject.

Participants were assigned a study number from 1 to 30, given in ascending order, for documentation. They were then randomly assigned by an independent research assistant based on a predetermined list of random numbers to receive one of the following: PEG 400 propylene glycol (Systane, Alcon Laboratories, Fort Worth, TX, USA), hydroxypropylmethylcellulose (Genteal, Novartis, Annonay, France), or carboxymethylcellulose (Cellufresh, Allergan, Waco, TX, USA). The research assistant was masked as to the type of eye drops assigned to the patients.

Patients were instructed to use their assigned eye drops only, applying 1 drop of the medication at specified hours 4 times a day. Each subject was given a compliance monitoring sheet to mark each time the eye drop was instilled. Subjects were followed up everyday for the first 2 days then every other day thereafter up to a maximum of 2 weeks until the PLM sign disappeared. At every visit, the subjective-grading-of-ocular-discomfort questionnaire was administered and lissamine green staining with measurement and grading of the PLM sign were performed.

The resolution time—the number of days needed for complete disappearance of PLM sign—was recorded. A sterile dye-impregnated strip of lissamine green was moistened with 2 drops of sterile balanced saline solution and agitated for 15 seconds. The dissolved dye was dropped into the inferior fornix of each eye. After letting the patient blink for approximately 5 seconds, the upper eyelid was everted by grasping the eyelashes. The area of the posterior-lid margin was examined under diffused light using the white light of the slitlamp biomicroscope with 10X magnification. The horizontal length of the posterior lid margin, which extends from the upper punctum to the lateral canthus, and its sagittal width, which extends from just proximal to the line of Marx to the subtarsal fold, were examined. Staining of the horizontal length and sagittal width was measured using the slitlamp caliper and was graded adopting the scheme used by Korb and colleagues for fluorescein and rose bengal staining (Table 1). Individual grades for these two categories were averaged to get the final grade.

Grading of PLM sign and classification was based on the final grades obtained: 0.25 to 1.0, grade 1, mild; 1.25 to 2.0, grade 2, moderate; 2.25 to 3.0, grade 3, severe. The eye with the worse (higher grade) PLM sign was assigned as the study eye. For subjects with the same PLM-sign grading in both eyes, the right eye was assigned as the study eye.

For secondary outcome measure, the correlation between ocular-discomfort grading and PLM-sign severity grading before and after treatment was determined. Symptom grading and PLM-sign grading were as described above.

All statistics were computed using Statistical Package for the Social Sciences (SPSS version 10). Assuming a standard deviation of four, a sample size of 15 eyes/group was calculated using a 95% significance level and a 10% risk of a false negative finding.

All numerical continuous data were summarized using descriptive statistics (percentage, measures of central tendency, and frequency distribution). Analysis of variance (ANOVA) was used to test for homogeneity among subjects in terms of age and to compare the resolution time of the PLM sign for the 3 eye drops. Chi-square test was used to test for homogeneity in terms of sex and diagnosis.

Pearson’s correlation coefficient was used to compute for the correlation between subjective grading of ocular discomfort and PLM-sign grading. Descriptive analysis was used to demonstrate the incidence and grading of PLM sign among patients diagnosed with dysfunctional-tear syndrome.

The study conformed with the guidelines set by the Declaration of Helsinki. Informed consent was obtained from all the subjects after thorough explanation of the nature and possible risks and benefits of the study. The hospital Ethics Review Board approved the protocol.

RESULTS

A total of 30 subjects completed the study. There were no dropouts. The baseline characteristics and tests of homogeneity of samples are summarized in Table 2.

Table 1. Grading of the horizontal length and sagittal width of staining of the lid wiper.

<table>
<thead>
<tr>
<th>Horizontal length of staining</th>
<th>Grade</th>
</tr>
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<tbody>
<tr>
<td>&lt;2 mm</td>
<td>0</td>
</tr>
<tr>
<td>2–4 mm</td>
<td>1</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sagittal width of staining</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25% of the width of wiper</td>
<td>0</td>
</tr>
<tr>
<td>25%–&lt;50% of the width of wiper</td>
<td>1</td>
</tr>
<tr>
<td>50%–&lt;75% of the width of wiper</td>
<td>2</td>
</tr>
<tr>
<td>≥75% of the width of wiper</td>
<td>3</td>
</tr>
</tbody>
</table>
The youngest patient was 45 years old and the oldest was 77, with a mean age of 58.2 ± 7.6 years. Females outnumbered males 5 to 1. Twenty-six (87%) had the PLM sign in both eyes, 3 in the left eye only, and 1 in the right eye. Of the 26, 11 had equal grading, 8 had a worse grading in the left eye, and 7 had a worse grading in the right eye. In terms of laterality, 19 (63%) involved the right eye and 11 (37%) the left eye. The patients were not characterized under DTS subtypes since there is currently no universally accepted categorization of DTS.

Comparing between groups, there was no statistically significant difference in terms of age ($p = 0.06$), sex distribution ($p = 0.79$), and diagnosis ($p = 0.30$). The difference in baseline PLM sign between groups ($p = 0.58$) was also not statistically significant.

There was no significant difference ($p = 0.35$) in the mean resolution time (1.1 ± 0.3 days) of the PLM sign for the 3 eye drops (Figure 1). The corresponding PLM resolution times for each of the three eye drops were as follows: Systane: 1.0 ± 0 days; Genteal: 1.1 ± 0.32 days; and Cellufresh: 1.2 ± 0.42 days.

The baseline PLM sign had a positive, moderate correlation with baseline subjective grading of ocular discomfort, with a correlation coefficient of 0.74 (Figure 2). However, there was no correlation between symptom grading and PLM-sign grading after treatment on day 1 with a correlation coefficient of 0.50 (Figure 3).

The baseline ranges of the PLM sign for the different groups were similar.

**DISCUSSION**

The use of lubricants is central in the management of DES. Aside from their lubricating effect, ocular lubricants are also theorized to replace missing tear constituents,
reduce elevated tear osmolarity, reduce or wash out inflammatory agents.

This study mainly evaluated the effect of these eye drops on the PLM sign (Figure 4), which is a newly documented sign associated with dry eyes. The results showed no significant difference among the 3 in terms of the resolution time of the PLM sign.

This study found a positive moderate correlation between the symptoms as perceived by the patients and severity grading of the PLM sign at baseline. However, there was no correlation statistically between the PLM sign and the symptoms after 1 day of treatment. This was probably because all patients but 3 had complete resolution of the PLM sign on day 1. Although there was a corresponding decrease in the grading of symptoms in all subjects, the correlation between the above parameters was poor.

The study was limited to the completion of the investigation defined as the time when the PLM sign has completely resolved. Upon completion of the study, the patients were asked to discontinue the eye drop and were sent back to the UP–PGH Dry Eye Clinic for follow-up. It was not the objective of the study to compare the effects of the eye drops on the symptoms of the patients once the PLM sign had resolved. Moreover, the patients were not classified into different subtypes of DTS. Only the severity of symptoms was correlated with the PLM sign.

In conclusion, Systane, Genteal, and Cellufresh were equally effective in resolving the PLM sign, which was moderately correlated with dry-eye symptoms. A larger study sample taking into consideration the different subtypes of DTS and a longer study period to obtain the prevalence of the PLM sign are recommended for better understanding of the PLM sign in diagnosing and monitoring the treatment of DTS.

References