Tear film lipid layer thickness measurement from Ocular Surface Analyzer as a marker to monitor treatment of meibomian gland dysfunction in a study comparing physiological detergent-free eyelid wipes with conventional therapy: A randomized trial

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Purpose: To compare the efficacy of physiological, non-detergent eyelid wipes with conventional lid hygiene in patients with meibomian gland dysfunction (MGD). Methods: Fifty participants with MGD were recruited and randomized into two groups. Participants in group I used Evolve Pure1 Eyewipes twice a day to clean the eyelid debris along with standard therapy (antibiotic and lubricants) and participants in group II followed lid hygiene with warm compresses along with standard therapy. Symptoms, ocular surface assessment (lipid layer thickness, tear meniscus height, non-invasive tear film breakup time, and meibography), slit-lamp biomicroscopy (eyelash contamination, meibomian gland blockage, meibomian gland secretion, and meibomian gland telangiectasia) and tear film osmolarity were noted at baseline and 90 days after therapy. Results: Significant improvement in symptoms and signs of MGD was observed in both groups after treatment ($P < 0.001$); however, the clinical improvement was better with the use of eyelid wipes. Lipid layer thickness increased significantly in group I ($P = 0.0008$) and group II ($P = 0.0002$), which was maintained even after adjusting for sociodemographic variables such as age, sex, and severity score of symptoms and signs. Conclusion: Lipid layer thickness of the tear film is a sensitive marker in monitoring response to treatment in patients with MGD. The use of physiological detergent-free eyelid wipes is non-inferior to lid hygiene and warm compresses, which remains the mainstay for treatment of MGD; the clinical improvement with eyelid wipes was noted to be better.

Key words: Eyelid wipes, lid hygiene, lipid layer thickness, meibomian gland blockage, meibomian gland dysfunction, ocular surface analyzer

Meibomian gland dysfunction (MGD), as described by the International Tear Film and Ocular Surface Society (TFOS) workshop, is a “chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.”[1] MGD is a leading cause of evaporative dry eye, and its global prevalence has been reported to be 35.8%.[2]

The management of MGD, as recommended by the TFOS subcommittee, includes lid hygiene as the mainstay therapy for MGD, which usually consists of two components, including the application of heat and mechanical massage of the eyelids.[3] Overall, maintenance of eyelid hygiene not only plays a pivotal role in the management of MGD but also contributes to the health of the lacrimal functional unit.[4] Several premixed eyelid wipes are commercially available. Of note, wet eyelid wipes, namely Oculeaf (tea tree oil, glycercine, sodium hyaluronate, and panethanol), Cliradex® (4-terpineol), Blephapad Combo (terpinen-4-ol and hyaluronic acid), and Blephaclean (capryloyl glyicine, iris florentina, and sodium hyaluronate) have been used with proven efficacy in anterior and posterior blepharitis.[5-7] However, there is a lack of robust evidence to support their routine recommendation as has also been documented in a systematic review, apart from the fact that they induce ocular inflammation due to the presence of surfactants and detergents.[8] The eyelid wipes used in the current study (Evolve Pure™ Eyewipes) are physiological, non-detergent, single-use wipes impregnated with sodium chloride, potassium chloride, calcium chloride dehydrate, magnesium chloride hexahydrate, sodium acetate, sodium hydroxide, and purified water, similar to the human tear film. Therefore, the current study was planned to assess the efficacy of these physiological eyelid wipes in patients with MGD and document the change in tear film parameters and
meibomian gland morphology by objective monitoring using the non-invasive ocular surface analyzer (OSA).\[9\]

**Methods**

**Study setting and study participants**

A prospective, randomized double-arm controlled interventional study was undertaken to evaluate the efficacy of physiological eyelid wipes in subjects with MGD. Ethical approval for the study was obtained from the institute’s ethics committee (IEC-377/06.07.2018, RP-5/2018). The study was conducted from March 2019 to March 2020 in compliance with the Declaration of Helsinki, registered at Clinical Trials Registry-India [CTRI/2018/08/015482]. Participants aged 18 years and above, who presented with a clinical diagnosis of MGD, defined as a minimum combined score of 5 for the signs 1) eyelash contamination (flaky material on the eyelash and lid margin comprising desquamated material/debris/glandular secretion), 2) meibomian gland blockage, 3) meibomian gland secretion, and 4) meibomian gland telangiectasia and/or symptoms of 1) dryness, 2) foreign body sensation, 3) burning, 4) redness, 5) crusting, or 6) sticky lids as per MGD symptom questionnaire developed by Schein et al.\[10\] were voluntarily recruited from the ophthalmology outpatient department of a tertiary eye care hospital after obtaining informed consent. Patients with acute ocular infection or inflammation other than MGD, with chronic ocular disease, using topical medications or contact lens, who underwent ocular surgery within the last 6 months, pregnant or lactating females, and/or physically or mentally challenged individuals were excluded.

**Clinical assessment**

A symptom questionnaire was administered to all participants to assess the dry eye symptomatology focusing on key ocular manifestations of MGD, such as a feeling of dryness, foreign body sensation, burning sensation, and feeling of stickiness. These four symptoms were graded on a scale of 0–4 from none to very severe disabling manifestation [Appendix 1]. This was administered by a separate ophthalmologist who did not perform the clinical examination.

The clinical assessment included measurement of ocular surface parameters and slit-lamp biomicroscopy for evaluation of MGD. Ocular surface analysis was conducted by an optometrist by using the ICP Tearscope (SBM Sistemi, Turin, Italy) in the following order: lipid layer thickness (LLT), tear meniscus height (TMH), non-invasive tear film breakup time (NIBUT), and meibography. The least invasive test was performed first to minimize perturbation of tear film physiology for the subsequent tests; tear film osmolarity, slit-lamp examination, and meibomian gland expression were performed sequentially in that order. Analysis of LLT was performed using interference patterns by capturing the video for 5–10 s, allowing for blinking of eyes 3–5 times, then comparing the patient’s lipid layer to the standard image of the lipid layer, and grading was done as per modified Guillon’s classification.\[11\] The lower TMH was assessed using digital imaging under high magnification, captured by the ICP Tearscope, taking a picture with a green cross focused on the pupil and then focusing on the tear meniscus seen along the lower eyelid margin due to internal reflection. The TMH was calculated using an inbuilt software, and three measurements near the center of the lower meniscus were averaged and graded [Appendix 2]. NIBUT was recorded as the time taken following a blink for the grid reflection to first show distortion, and tear break-up time was calculated using an automated inbuilt software. Three measurements were averaged for each eye and graded.\[11\] Meibography was performed by capturing infrared images with the BG-4M noncontact meibography system (SBM Sistemi, Turin, Italy). Images were digitally analyzed using Image software (freely available in the public domain). From the captured image, meibomian gland dropout areas were graded on the five-point meiboscale [Appendix 2].

Slit-lamp examination included assessment of eyelash contamination, lid margin thickening, telangiectasia, foaming, eyelash crusting, the number of blocked meibomian gland orifice, and meibum viscosity and expression graded on a five-point Likert scale [Appendix 1].\[11\] Tear film osmolarity was evaluated for each patient at baseline and at 90-day follow-up visit by using a lab-on-a-chip technique (TearLab®; TearLab Corporation, San Diego, CA). A test card was used to collect and analyze 50 nanoliters of tear sample from the lower tear meniscus near the lateral canthus by capillary action. Quality control was performed before each study day as recommended by the manufacturer. An osmolarity result of ≥308 mOsmol/L was taken as abnormal. To avoid diurnal fluctuation of tear osmolarity, all measurements were taken in the morning between 8.00 and 11.00 AM.\[12,13\]

**Treatment**

Subjects were randomly assigned in 1:1 ratio to one of the two groups of standard therapy for MGD (antibiotics and lubricants) along with eyelid wipes (group I) and those prescribed standard therapy for MGD along with lid hygiene and warm compresses (group II) by an independent clinical research coordinator according to a computer-generated randomization list. Eyelid hygiene measures employed were eyelid scrubs and eyelid massage. Lid hygiene was done by warm compression with a hot wet towel for 10 min followed by mechanical lid massage with fingertips and cleaning of the expressed sebum with cotton buds. The upper eyelid followed by the lower eyelid was first massaged by around 15 firm downward strokes, which were then scrubbed with cotton bud along the lid margin. At the end of the scrub, the ointment was applied along the lid margin at the base of the eyelashes. The randomization sequence was created between 1 and 2 by using the RAND function in Excel 2013 (Microsoft Inc., Redmond, WA) and was stratified with a 1:1 allocation. Thus, the ophthalmologist, who did the clinical examination, was masked to the treatment received by the patient. Standard therapy for MGD included warm compression with mechanical lid massage along with cleaning of the expressed sebum from lid margin and antibiotic eye drop (gatifloxacin 0.3%) installation four times a day and gatifloxacin 0.3% ointment application at night for 2 weeks along with lubricating eyedrop (polyethylene glycol 0.4% and propylene glycol 0.3%) four times a day for 3 months. Participants with severe MGD were prescribed systemic antibiotics (doxycycline 50 mg twice a day for 2 weeks). Lifestyle changes and advice on digital screen use were imparted in certain patients, whenever the same was contributory to MGD. The participants were followed up on days 15, 30, 60, and 90; however, study parameters were noted and analyzed between the baseline and final visit at completion of 3 months.

**Statistical methods**

The study was designed and powered to demonstrate the non-inferiority of the eyelid wipes relative to lid hygiene with respect to the symptoms and signs of MGD. The sample size of 20 subjects (40 eyes) was calculated to test for non-inferiority based on a minimum power of 90%, one-sided type I error of
0.025, non-inferiority limit of 85%, and a true mean difference of 25% (as a percentage of the non-inferiority limit). \[14\]

Data analyses were performed to determine the main effects of intervention, testing occasion, and the interaction effects of group and time. To determine whether the patients in either group experienced changes in their ocular surface analyzer and slit-lamp parameters, a paired t test was used. The primary dependent variables were ocular surface analyzer parameters (NIBUT, LLT, and TMH), and the independent variable was the testing occasion (baseline vs. 90-day follow-up visit). For the comparison of intergroup ocular surface analyzer parameters, a between-subjects ANOVA design (two-way analysis of variance) was performed on the dependent variables (NIBUT, LLT, and TMH), while the independent variable was the intervention in each group (eyelid wipes versus lid hygiene). To detect interaction effects between the groups and testing

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**Table 1: Comparison of baseline clinical and demographic parameters in participants randomized to non-detergent eyelid wipes with standard therapy and conventional lid hygiene along with standard therapy**

| Variable                  | Categories | Eyelid wipes with standard therapy n (%) | Conventional Therapy n (%) | Total patients n (%) | P   |
|---------------------------|------------|------------------------------------------|-----------------------------|----------------------|-----|
| Age (in years)            | 0-39 years | 15 (75)                                  | 8 (47)                      | 23 (62)              | 0.0807 |
|                           | 40+ Years  | 5 (25)                                   | 9 (53)                      | 14 (38)              |     |
| Sex                       | Female     | 6 (30)                                   | 6 (35)                      | 12 (32)              | 0.7317 |
|                           | Male       | 14 (70)                                  | 11 (65)                     | 25 (68)              |     |
| Diabetes Mellitus         | Absent     | 20 (100)                                 | 16 (94)                     | 36 (97)              | 0.4595 |
|                           | Present    | 0 (0)                                    | 1 (6)                       | 1 (3)                |     |
| Coronary Artery Disease   | Absent     | 20 (100)                                 | 15 (88)                     | 35 (95)              | 0.2042 |
|                           | Present    | 0 (0)                                    | 2 (12)                      | 2 (5)                |     |
| Hypertension              | Non-hypertensive | 18 (90)                | 14 (82)                     | 32 (86)              | 0.6443 |
|                           | Hypertensive | 2 (10)                              | 3 (18)                      | 5 (14)               |     |
| Computer Vision Syndrome  | Absent     | 6 (30)                                   | 9 (53)                      | 15 (41)              | 0.1566 |
|                           | Present    | 14 (70)                                  | 8 (47)                      | 22 (59)              |     |
| Total                     |            | 20                                       | 17                          | 37 (100)             |     |

*Column percentages
Figure 2: Representative images of a patient with MGD captured using the ocular surface analyzer at the baseline visit and 90 days after treatment with eyelid wipes and standard therapy. Baseline ocular surface parameters (a) such as non-invasive break-up time (NIBUT), lipid layer thickness (LLT) and type, tear meniscus height (TMH), and meibomian gland loss (MGL) along with post-treatment ocular surface parameters (b) are clearly elucidated. Meibography images of the upper eyelid at baseline in the right (c) and left eye (e) demonstrate 32% and 25% meibomian gland loss (MGL), respectively. Following treatment for MGD, MGL in the right eye (d) and left eye (f) do not show any significant change with treatment.
Table 2: Change in symptoms and signs of meibomian gland dysfunction and ocular surface parameters, in participants randomized to non-detergent eyelid wipes with standard therapy and conventional lid hygiene with standard therapy at baseline and 90-day follow up visit

| Variable                | Eyelid wipes with standard therapy [n=40] | Conventional Therapy [n=34] | P    |
|-------------------------|-----------------------------------------|----------------------------|------|
| **Dry eye symptomatology** |                                         |                            |      |
| Dryness                 | Present 36 (90.0) Absent 4 (10.0)       | Present 26 (76.5) Absent 8 (23.5) | 0.114|
| Baseline                | 8 (20.0)                                  | 4 (11.8)                   | 0.338|
| Day 90                  | 32 (80.0)                                 | 30 (88.2)                  |      |
| *P*                     | <0.001*                                   | <0.001*                    |      |
| **Foreign body sensation** |                                          |                            |      |
| Baseline                | 30 (75.0)                                 | 10 (25.0)                  | 0.138|
| Day 90                  | 28 (70.0)                                 | 6 (17.6)                   | 0.217|
| *P*                     | <0.001*                                   | <0.001*                    |      |
| **Burning**             |                                          |                            |      |
| Baseline                | 30 (75.0)                                 | 10 (25.0)                  | 0.334|
| Day 90                  | 10 (25.0)                                 | 22 (64.7)                  | 0.883|
| *P*                     | <0.001*                                   | <0.001*                    |      |
| **Sticky lids**         |                                          |                            |      |
| Baseline                | 20 (50.0)                                 | 20 (50.0)                  | 0.800|
| Day 90                  | 6 (15.0)                                  | 34 (85.0)                  | 0.350|
| *P*                     | <0.001*                                   | <0.001*                    |      |
| **Slit-lamp parameters** |                                         |                            |      |
| Eyelash contamination   |                                         |                            |      |
| No                      | 2 (5.0)                                   | 10 (25.0)                  | 0.531|
| Slight contamination    | 18 (45.0)                                 | 24 (60.0)                  | 0.080|
| Mild                    | 8 (20.0)                                  | 4 (10.0)                   | 0    |
| Moderate                | 8 (20.0)                                  | 2 (5.0)                    | 0    |
| Severe                  | 4 (10.0)                                  | 0 (0.0)                    | 0    |
| *P*                     | 0.004*                                    | <0.001*                    |      |
| Meibomian gland telangiectasia |                                         |                            |      |
| Grade 0                 | 8 (20.0)                                  | 11 (27.5)                  | 0.653|
| Grade 1                 | 14 (35.0)                                 | 25 (62.5)                  | 0.522|
| Grade 2                 | 16 (40.0)                                 | 4 (10.0)                   | 0.422|
| Grade 3                 | 0 (0.0)                                   | 4 (11.8)                   | 0    |
| Grade 4                 | 2 (5.0)                                   | 0 (0.0)                    | 0    |
| *P*                     | 0.005*                                    | <0.001*                    |      |
| Meibomian gland blockage |                                         |                            |      |
| Grade 0                 | 0 (0.0)                                   | 3 (7.5)                    | 0.852|
| Grade 1                 | 4 (10.0)                                  | 27 (67.5)                  | 0.557|
| Grade 2                 | 20 (50.0)                                 | 8 (20.0)                   | 0.953|
| Grade 3                 | 14 (35.0)                                 | 2 (5.0)                    | 0    |
| Grade 4                 | 2 (5.0)                                   | 0 (0.0)                    | 0    |
| *P*                     | <0.001*                                   | <0.001*                    |      |
| Meibomian gland secretion |                                         |                            |      |
| Grade 0                 | 2 (5.0)                                   | 19 (47.5)                  | 0.745|
| Grade 1                 | 16 (40.0)                                 | 17 (42.5)                  | 0.622|
| Grade 2                 | 16 (40.0)                                 | 4 (10.0)                   | 0.180|
| Grade 3                 | 6 (15.0)                                  | 0 (0.0)                    | 0    |
| Grade 4                 | 0 (0.0)                                   | 3 (8.8)                    | 0    |
| *P*                     | 0.035*                                    | 0.005*                     |      |
| **Ocular Surface Analysis** |                                         |                            |      |
| Meibomian gland loss     |                                         |                            |      |
| Grade 0                 | 2 (5.0)                                   | 2 (5.0)                    | 0    |

Contd...
Table 2: Contd...

| Variable                          | Eyelid wipes with standard therapy [n=40] | Conventional Therapy [n=34] | P     |
|-----------------------------------|-------------------------------------------|----------------------------|-------|
| Grade 1                           | 23 (57.5)                                 | 20 (50.0)                  | 0.9036|
| Grade 2                           | 15 (37.5)                                 | 16 (40.0)                  | 0.8402|
| Grade 3                           | 0                                         | 2 (5.0)                    |       |
| P                                 | 0.5238                                    | 0.6165                     |       |
| Non-invasive break up time (s)    |                                           |                            |       |
| Baseline                          | 7.44 (± 0.263)                            | 7.24 (± 0.276)             | 0.347 |
| Day 90                            | 7.87 (± 0.363)                            | 8.18 (± 0.284)             | 0.944 |
| P                                 | 0.314                                     | 0.020*                     |       |
| Lipid layer thickness (nm)        |                                           |                            |       |
| Baseline                          | 23.12 (± 2.11)                            | 21.32 (± 1.74)             | 0.6875|
| Day 90                            | 33.62 (± 3.19)                            | 37.64 (± 3.99)             | 0.7503|
| P                                 | 0.0006*                                   | 0.0002*                    |       |
| Tear meniscus height (mm)         |                                           |                            |       |
| Baseline                          | 0.17 (± 0.03)                             | 0.57 (± 2.19)              | 0.050 |
| Day 90                            | 0.19 (± 0.05)                             | 0.19 (± 0.043)             | 0.609 |
| P                                 | 0.012*                                    | 0.325                      |       |
| Tear Osmolarity (mOsmol/L)        |                                           |                            |       |
| Baseline                          | 307.93 ± (20.12)                          | 324.27 (± 19.02)           | 0.501 |
| Day 90                            | 311.12 ± (13.02)                          | 315.54 (± 26.80)           | 1.000 |
| P                                 | 0.533                                     | 0.452                      |       |

*Statistically significant difference between groups

Table 3: Multiple regression analysis for predicting change in OSA parameters at 90-day follow-up visit adjusted for baseline parameters

| NIBUT (s)                          | R²  | Adjusted R² | β co-efficient | SE  | t    | P    |
|------------------------------------|-----|-------------|----------------|-----|------|------|
| Intervention                       | 0.1788 | 0.1053     | −0.13          | 0.57 | −0.23 | 0.822 |
| Age                                | −0.017         | 0.02       | −0.77          | 0.91 | 0.366 |
| Sex                                | 0.44          | 0.49       | 0.366          | 0.366 |
| NIBUT at baseline                  | 0.075         | 0.14       | 0.602          | 0.602 |
| Symptom Score                      | −0.48         | 0.24       | 0.052          | 0.052 |
| Sign Score                         | −0.16         | 0.09       | 0.082          | 0.082 |
| Lipid layer thickness (nm)         | 0.2191 | 0.1492     | 2.36           | 5.89 | 0.40  | 0.690 |
| Age                                | 0.259          | 0.23       | 1.31           | 0.263 |
| Gender                             | −1.88         | 5.01       | 0.709          | 0.709 |
| LLT at baseline                    | 0.70          | 0.20       | 0.001*         | 0.001* |
| Symptom Score                      | −0.78         | 2.53       | 0.759          | 0.759 |
| Sign Score                         | 1.03          | 0.93       | 0.275          | 0.275 |
| Tear meniscus height (mm)          | 0.2838 | 0.2197     | −0.02          | 0.01 | −1.80 | 0.077 |
| Age                                | 0.01          | 0.0004     | <0.001*        | 0.001* |
| Gender                             | 0.01          | 0.01       | 0.215          | 0.215 |
| TMH at baseline                    | −0.01         | 0.003      | 0.076          | 0.076 |
| Symptom Score                      | −0.003        | 0.01       | 0.556          | 0.556 |
| Sign Score                         | −0.001        | 0.001      | 0.424          | 0.424 |

*statistically significant difference (<0.05)

occasion, a 2 × 2 mixed-model ANOVA design was used with dependent measures of NIBUT, LLT, and TMH as the main outcomes; the group (eyelid wipes versus lid hygiene) as the between-subjects independent variable; and the time (baseline vs. 90-day follow up visit) as the repeated measures within-subjects independent variable. The data were analyzed using the Stata 14.2 statistical package for Windows by using the intention-to-treat principle. Differences between the groups in the clinical and demographical variables were analyzed using the Chi-squared test. The outcome variables
were normally distributed and analyzed using parametric tests. A stepwise linear regression model was used to assess the differences within and between groups and to determine the predictors of change in the outcome variables. The level of significance was taken as 0.05.

Results

A total of 71 participants with MGD were screened and assessed for eligibility. Out of these, 25 patients who met the eligibility criteria were recruited in each group by using random number tables. These 50 participants with MGD were included in the study [Fig. 1]. A total of 37 patients with MGD completed the follow-up of 90 days. Out of these, 40 eyes of 20 patients (14 men and 6 women; mean age: 33.4 ± 10.53 years) were treated with eyelid wipes along with standard therapy, and 34 eyes of 17 patients (11 men and 6 women; mean age: 42.7 ± 11.25 years) were prescribed standard therapy along with lid hygiene. The two groups had similar demographic and clinical profiles [Table 1]. Moreover, the outcome measures, including the grade of disease, were comparable at baseline between the two groups (P > 0.05) [Table 2].

Dry eye symptoms

There was a significant improvement in all the subjective dry eye symptoms from baseline to the 90-day follow-up visit (P < 0.001) [Table 2]. The symptom of dryness improved in 70.0% of the patients using eyelid wipes and standard therapy (group I) compared to 64.7% of patients using lid hygiene alone with standard therapy (group II). Foreign body sensation ameliorated in 45.0% patients in group I in comparison to 41.2% of patients in group II. Half (50%) of the patients in group I reported relief in burning sensation compared to 41.2% in Group II. At the last follow-up visit, stickiness of eyelids was present in only 15.0% of the patients in group I, and improvement in this symptom was noted in 35% and 29.4% in groups I and II, respectively. Both groups demonstrated marked improvement after 90 days of therapy in all the above symptoms (P < 0.001). However, symptomatic improvement was better in participants using the physiological eyelid wipes.

Slit-lamp parameters

All the slit-lamp parameters showed significant improvement in both groups after 90 days of therapy (P < 0.05). No eyelash contamination was observed at the 90-day follow-up visit in 25.0% of the patients in group I versus 61.8% of the patients in group II, whereas slight contamination was seen in 45.0% versus 64.7% in the aforementioned groups, respectively. None of the patients in either group had discharge in the eyelashes at the 90-day follow-up visit. Statistically significant improvement in meibomian gland telangiectasias was observed in both study groups (P = 0.005 in group I and <0.001 in group II). No signs of telangiectasia were present at the 90-day follow-up visit in 27.5% and 23.5% of patients in groups I and II, respectively. None of the patients in either study group had more than grade 3 telangiectasia, but the majority (62.5% and 70.6% in groups I and II, respectively) had less than one-fourth involvement (grade I telangiectasia) at the 90-day follow-up visit. Meibomian gland blockage demonstrated a statistically significant response with therapy (P = 0.001 in both groups). At the last follow-up visit, most patients (67.5% and 70.6% in groups I and II, respectively) demonstrated less than one-fourth meibomian gland blockage (grade I). The quality of meibomian gland secretions also improved significantly. Clear meibum was expressed in 47.5% and 38.2% of the patients in groups I and II, respectively (grade 0). Thick, white particulate meibum or non-expressibility was observed in neither of the group participants at the last follow-up visit (grades 3 and 4) [Table 2].

Ocular surface parameters

The integrated platform for analysis of the ocular surface helped in recording the change in LLT, TMH, NIBUT, and MGL along with meibography images before and after treatment [Fig. 2].

LLT increased markedly after using eyelid wipes and standard therapy (P = 0.0006), and a similar trend was noted among patients using lid hygiene and standard therapy (P = 0.0002). TMH also improved significantly among eyelid wipes users (P = 0.012), whereas NIBUT showed a favorable response after lid hygiene (P = 0.020). In both groups, meibomian gland loss did not show any appreciable change after 90 days of treatment. When testing the baseline and 90-day intervention effects with the ocular surface analyzer parameters as the dependent variables in a two-way ANOVA for repeated measures, the interaction effect was non-significant, demonstrating that changes in the ocular surface analyzer parameters were the same in the two groups. The multiple linear regression was done to determine the change in ocular surface analyzer parameters at the 90-day follow-up visit, adjusting for the effect of the same parameter at baseline and other independent variables [Table 3]. It indicated that LLT at the 90-day follow-up visit was significantly altered from its baseline values, even after adjusting for the use of eyelid wipes and sociodemographic variables such as age, sex, and symptom or sign score (P < 0.001). On the contrary, NIBUT and TMH at the 90-day follow-up visit were not significantly changed from baseline, after adjusting for these parameters.

Tear film osmolarity showed no significant improvement at the 90-day follow-up visit (311.12 ± 13.02 vs. 315.54 ± 26.80 mOsmol/L in groups I and II, respectively) nor any difference was noted between the groups [Table 2].

Discussion

The primary objective of the current study was to evaluate the efficacy of the eyelid wipes as compared to lid hygiene and warm compresses in the treatment of MGD. Although eyelid wipes are shown to be non-inferior to the mainstay therapy with regard to an efficacy endpoint and both groups demonstrated improvement in both symptoms and signs of MGD with treatment, the clinical improvement with eyelid wipes was noted to be better. To the best of our knowledge, this is the first study on the use of physiological, non-detergent eyelid wipes in MGD patients where objective monitoring was performed using an ocular surface analyzer in patients with MGD.

Remarkable symptomatic relief in dryness, foreign body sensation, burning, and stickiness of lids was observed in both groups, corroborating with the results of a study performed in patients with MGD and anterior blepharitis by using Blephaclean eyelid wipes.5 This study, however, did not have a control arm receiving treatment as per standard of care. Moreover, the use of a non-invasive ocular surface analyzer and meibography makes the current study more comprehensive and holistic. As depicted in previous trials, the ocular surface analyzer is a non-invasive, reproducible method for ocular surface workup, characterized by the standardized recording of meibomian gland function eliminating interobserver bias.15
The symptomatic relief in the study patients corroborated with significant amelioration of eyelid margin health as observed by a decrease in eyelash contamination and meibomian gland blockage with improvement in quality of meibomian gland secretion as has been reported previously.[16] The study participants demonstrated betterment in meibomian gland telangiectasia, which was not noted with the use of eyelid wipes in available published literature.

Both the therapeutic arms in the current study facilitated an increase in the LLT of the patients with MGD, as has been reported by previously published studies.[17,18] On the contrary, other parameters such as TMH and NIBUT did not show an adequate trend of improvement. This result was in contrast to earlier studies.[19,20] In the current study, tear osmolarity demonstrated no significant change in either group as observed in a previous study where automated thermodynamic treatment [Lipiflow®, Johnson & Johnson Inc., New Brunswick, NJ] was compared with standard lid hygiene procedure.[18] Thus, it may be inferred that LLT is a sensitive ocular surface parameter that corroborated the symptoms and signs of MGD and can serve as a useful test in monitoring the amelioration of disease with intervention.

Nonetheless, our study reiterates that lid hygiene with warm compresses combined with standard therapy remains the mainstay for treatment of MGD.[18] Conventional therapy of hot fomentation and massage addresses the pathophysiology of MGD. The melting point of the expressed meibum is raised to 32.2°C–35.3°C, higher than the normal meibum due to the altered composition consisting of desquamated epithelial cells. Thus, raised temperature facilitates the secretion and delivery of meibum to the ocular surface.[21]

Our study has a few limitations. The sample size in each group was small, resulting in an insignificant change in breakup time and tear osmolarity after intervention for MGD. The minimum sample size was taken based on feasibility and resource availability. The follow-up of all patients could not be completed due to the onset of the COVID-19 pandemic, which restricted travel and transport due to the nationwide lockdown in the country. A large-scale study with longer follow-up may be undertaken in the future.

Conclusion

The current study demonstrates that lipid layer thickness (LLT) of the tear film, as determined by the Ocular Surface Analyzer (OSA) is a sensitive parameter to monitor the therapeutic response in patients with MGD. Although lid hygiene and warm compresses along with antibiotics is the mainstay for treatment of MGD, the additive use of physiological detergent-free eyelid wipes can enhance clinical improvement in these patients.

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Conflicts of interest

There are no conflicts of interest.
| Parameters                                                                 | 0     | 1                                      | 2                                      | 3                                      | 4                                      |
|---------------------------------------------------------------------------|-------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Symptomology (discomfort, severity & frequency)                           |       |                                        |                                        |                                        |                                        |
| Dryness                                                                   | None  | Mild and/or episodic;                  | Moderate episodic or                    | Severe frequent                        | Severe and/or                        |
| Foreign body sensation                                                    |       | occurs under environmental stress      | chronic, stress or no stress           | or constant without stress             | disabling and constant                |
| Burning sensation                                                         |       |                                        |                                        |                                        |                                        |
| Lid stickiness                                                            |       |                                        |                                        |                                        |                                        |
| Slit-lamp signs                                                           | Clear | Slight contamination <25% block        | Mild 25%<50% Yellowish liquid <25%     | Moderate 50%<75% Thickened white       | Severe 75% or more                    |
| Eyelash contamination                                                     | None  |                                        | glands                                 | material                               |                                        |
| Meibomian gland blockage                                                  | Clear liquid | Slight contamination <25% block | Mild 25%<50% Opaque and | Thickenened white | Not possible 75% or more |
| Meibomian gland secretion                                                 | None  |                                        | toothpaste-like consistency 25%<50%    | material                               |                                        |
| Meibomian gland telangiectasia                                            | None  |                                        |                                        |                                        |                                        |
### Appendix 2: Severity grading scales of tear osmolarity and ocular surface parameters as assessed by ocular surface analyzer

| Parameter                        | Grading Categories                                                                 |
|----------------------------------|-------------------------------------------------------------------------------------|
| **Tear Osmolarity (mOsmol/L)**   | 295–<308 (hypersecretory MGD)                                                      |
|                                  | ≥ 308-370 (hyposecretory MGD)                                                      |
| **Lipid layer thickness (nm)**   | Grade 0=absence of lipids                                                          |
|                                  | Grade 1=13-30 (open meshwork)                                                      |
|                                  | Grade 2=31-50 (closed meshwork)                                                    |
|                                  | Grade 3=51-80 (wave)                                                               |
|                                  | Grade 4=81-90 (amorphous)                                                          |
|                                  | Grade 5=91-140 (color fringes)                                                     |
| **Tear meniscus height (mm)**    | Grade 0 >0.25 (normal)                                                             |
|                                  | Grade 1 ≤0.25->0.17 (mild DED)                                                     |
|                                  | Grade 2 0.17 to 0.11 (moderate to severe DED)                                       |
| **Noninvasive tear breakup time (s)** | Grade 0=instantaneous                  |
|                                  | Grade 1 = <6                                                                       |
|                                  | Grade 2 = ≥6->12                                                                  |
|                                  | Grade 3 = ≥12->24                                                                 |
| **Meibomian gland loss (%)**     | Grade 0: 0%                                                                        |
|                                  | Grade 1: >0% to ≤25%                                                               |
|                                  | Grade 2: 26%-50%                                                                  |
|                                  | Grade 3: 51%-75%                                                                  |
|                                  | Grade 4: >75%                                                                     |

MGD=Meibomian gland dysfunction; DED=dry eye disease