Effects of Lipiflow Treatment Prior to Cataract Surgery: A Prospective, Randomized, Controlled Study

JONGYEOP PARK, YOUNG-SIK YOO, KYUNGYOON SHIN, GYULE HAN, REIKO ARITA, DONG HUI LIM, AND TAE-YOUNG CHUNG

• PURPOSE: To investigate the effects of preoperative Lipiflow (Johnson & Johnson, Jacksonville, FL, USA) treatment before cataract surgery on meibomian gland dysfunction (MGD) and dry eye induced by surgery.
• DESIGN: Prospective, randomized controlled study.
• METHODS: This study comprised 124 eyes of 124 patients with planned surgery for senile cataract. Participants were randomly allocated into control and Lipiflow groups based on administration of Lipiflow treatment 3 weeks before cataract surgery. For meibomian gland (MG) evaluation, MG atrophy, degree of gland expressibility, and quality of gland secretions were examined at the baseline visit and 1 and 3 months postoperatively. Ocular surface parameters of tear film break-up time, Oxford corneal staining score, and tear film lipid layer thickness were measured at each visit. Ocular Surface Disease Index and Dry Eye Questionnaire were also assessed.
• RESULTS: The control group exhibited a significant decrease in MG expressibility, worsened meibum quality, decreased lipid layer thickness, and worsened corneal staining after cataract surgery. Also, dry eye symptom showed significant worsening. Conversely, the Lipiflow group showed significantly improved MG patency and meibum quality, increased tear film break-up time, and reduced corneal staining, and presented improved subjective outcomes reported on both Ocular Surface Disease Index and Dry Eye Questionnaire. The improvement of each parameter in the Lipiflow group showed a linear correlation with baseline MGD grade. In addition, patients without baseline MGD showed less worsening or improvement of MGD and dry eye induced by surgery, with preoperative Lipiflow treatment.
• CONCLUSIONS: Preoperative Lipiflow treatment conducted before cataract surgery may be a safe and effective intervention for relieving MGD and dry eye induced by surgery. It might be recommended not only for the patients with preoperative MGD but also for those without baseline MGD, to prevent the development of MGD and dry eye induced by ocular surgeries. (Am J Ophthalmol 2021;230: 264–275. © 2021 Elsevier Inc. All rights reserved.)

Dry eye is one of the most frequent complaints after cataract surgery, affecting as many as 55.7% of patients.[1,2] Despite an uneventful and successful surgery performed by a skilled expert, a majority of patients complain of ocular discomfort postoperatively. Patients with postoperative dry eye may experience symptoms such as pain, foreign body sensation, photophobia, visual fatigue, epiphora, and fluctuating or blurry vision.[2,3] Although exacerbation of dry eye after surgery seems to be self-limiting, this may take up to 3-6 months and is unpleasant for both patients and practitioners.[4-6]

Deterioration of the tear film after cataract surgery is multifactorial. Numerous studies have explored the prevalence of meibomian gland dysfunction (MGD) after cataract surgery and have determined that meibomian gland (MG) function may be altered postoperatively.[5-9] Ocular surface inflammation related to the surgery itself, a decreased blink rate resulting from a decrease in corneal sensation, toxicity of topical medications, onset of eyelid dysfunction due to use of an eyelid speculum, and/or coincident development of dry eye syndrome are potential causes.[7] Regardless of the exact mechanism, MGD induced by cataract surgery has been shown to be responsible for postoperative ocular discomfort and dry eye and requires adequate treatment.[10]

Current treatment modalities for MGD include (1) medical treatment such as artificial tears, antibiotics, nonsteroidal anti-inflammatory drugs, and steroid drops; (2) dietary supplements including omega-3 fatty acids; and (3) physical therapy such as eyelid cleansing, manual MG ex-

AJO.com Supplemental Material available at AJO.com.
Accepted for publication April 28, 2021.

From the Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul (J.P., Y.-S.Y., K.S., G.H., D.H.L., T.-Y.C.), Department of Ophthalmology, Dongguk University Gyeongju Hospital, Dongguk University School of Medicine, Gyeongju, Gyeongsangbuk-do (J.P.), Department of Ophthalmology, Uijeongbu St. Mary's Hospital, the Catholic University of Korea, Uijeongbu-si (Y.-S.Y.), Department of Ophthalmology, Seongnam Citizens Medical Center, Seongnam-si, Gyeonggi-do, Republic of Korea (K.S.), Department of Ophthalmology, Itoh Clinic, Saitama, Japan (R.A.), and Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Republic of Korea (D.H.L.)

Inquiries to Tae-Young Chung and Dong Hui Lim Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-Ro, Gangnam-gu, Seoul 06351, Republic of Korea.; e-mail: donghui.lim@samsung.com, tychung@skku.edu

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2021.04.031

pression, application of warm compresses or heated pads or goggles, intense pulse light, and Lipiflow thermal pulsation (Johnson & Johnson, Jacksonville, FL, USA).[11-20] A number of studies have reported the efficacy and safety of Lipiflow treatment in treating MGD and have documented the potential benefit of Lipiflow as a primary treatment option for MGD and dry eye.[21-23]

Effective treatment of MGD and dry eye occurring after cataract surgery remains an area of interest, especially with emergence of novel therapeutic modalities.[3] It is of particular interest to evaluate the role of Lipiflow in the treatment of dry eye and MGD induced by cataract surgery, yet it is not known whether or not prophylactic Lipiflow performed before cataract surgery can alleviate or prevent MGD and dry eye associated with surgery. Herein, we attempted to investigate the effects of preoperative Lipiflow treatment before cataract surgery on alleviating obstructive MGD and dry eye induced by surgery.

MATERIALS AND METHODS

• **PATIENTS:** This study was a prospective randomized controlled study conducted in accordance with the tenets of the Declaration of Helsinki. The prospective study protocol was approved by the Ethical Committee of Samsung Medical Center (IRB no. 2019-03-011), registered as a clinical trial at ClinicalTrials.gov (NCT04457999), and conformed to the CONSORT checklist. Written informed consent was obtained from each participant before enrollment. Patients with cataract were recruited at Samsung Medical Center between April 2019 and December 2019.

The following patients were eligible for inclusion in the present study: (1) those who were diagnosed with senile cataract and deemed eligible for cataract surgery (ie, males and nonpregnant females aged 50-70 years with a clinical diagnosis of cataract), (2) those with a predicted postoperative visual acuity of 20/25 or better by Retinal Acuity Meter (AMA Optics Inc, Miami Beach, Florida, USA), and (3) those who could understand the treatment options and who volunteered to participate in the study. The presence of preoperative MGD or severity of baseline MGD was not necessary for inclusion in this study. Meanwhile, patients were excluded from the study if they had (1) history of ocular trauma or ocular surgery within 6 months, (2) active infectious blepharitis or ocular infection, (3) obvious abnormalities in eyelid margins or severe ocular surface abnormalities other than MGD, (4) other cause of decreased visual acuity other than cataract, or (5) systemic drug use (tetracycline derivatives, antihistamines, isotretinoin).

• **TREATMENT:** The study design included 4 visits: 1 on 3 weeks before the planned cataract surgery (screening and baseline visit), 1 on the day of cataract surgery, and 1 at each 1 and 3 months after surgery (postoperative visits 1 and 2). Patients were enrolled in this study at the screening visit and randomized at a 1:1 ratio to either the Lipiflow group, whose members were treated with Lipiflow thermal pulsation after all preoperative evaluations were completed, or the control group, whose members were managed without Lipiflow treatment. Lipiflow treatment was performed per the method described in detail by Lane and associates[23]; in brief, a topical anesthetic (0.5% proparacaine hydrochloride) was applied before treatment, followed by bilateral application of a 2-part activator. The inner portion of the activator, which covers the conjunctival surface of the upper and lower eyelids, heats to a temperature of approximately 42.5 C. The outer portion of the activator covers the cutaneous surface of the upper and lower lids and is inflated by air pressure. Both eyelids simultaneously receive warming and massaging for a period of 12 minutes.

All patients underwent conventional phacoemulsification and posterior-chamber intraocular lens (IOL) implantation without a femtosecond laser conducted by 2 surgeons (D.H.L., T.-Y.C.). All surgeries were performed using the same technique under topical anesthesia (sutureless cataract surgery through a 2.8-mm clear corneal incision with implantation of a foldable IOL within the capsular bag (Tecnis 1-piece ZCB00; Abbott Medical Optics Inc, Santa Ana, California, USA). No relevant intraoperative complications occurred in any case. The postsurgical drug regimen was the same in all patients and consisted of 0.3% topical gatifloxacin (Gatiflo; Handok, Chungbuk, Korea) and 0.5% topical loteprednol etabonate (Lotepro; Hanlim, Seoul, Korea) 4 times daily for 1 month.

• **OUTCOME MEASUREMENTS:** All participants underwent examination in the same order as follows: tear film lipid layer thickness (LLT) measurement, meibography, tear break-up time (TBUT), Oxford corneal staining score, and MG assessment with slit-lamp examination. After the ocular examinations, each patient was asked to complete the Ocular Surface Disease Index (OSDI) questionnaire and the 5-item Dry Eye Questionnaire (DEQ). All participants were evaluated at the baseline visit and at 1 month and 3 months after cataract surgery.

MG evaluation was performed at each visit, focusing on both anatomical and functional aspects.[24] With LipiView II meibography (Johnson & Johnson), partial or complete loss of MG was scored using the following grades (meiboscore) for each eyelid: grade 0 (no loss of MG), grade 1 (loss of less than one-third of the total area of MG), grade 2 (loss of between one-third and two-thirds of the total area of MG), and grade 3 (loss of more than two-thirds of the total area of MG). Meiboscores for the lower eyelids were summed to obtain a score from 0 to 3 for each eye.[12,25,26]

The MG function was evaluated based on gland expressibility and the characteristics of secretions from gland orifices along the lower eyelid. Under a slit-lamp microscope, the gland orifices were evaluated using a handheld instrument, the Meibomian Gland Evaluator (Johnson & John-

son), which offers a standardized method of applying fixed pressure on each eye to ensure measurement consistency.

The degree of gland expressibility was determined using pressure over the lower lids and was scored according to the number of fluid secretion-expressing glands among the 8 at the center part of the lower eyelid, regardless of qualitative appearance. This was defined as MG yielding liquid secretion (MGYLS) (total score range: 0-8).[12]

The quality of gland secretions from the lower eyelids of each eye was examined and assigned one of the following scores: grade 0, clear; grade 1, cloudy; grade 2, cloudy with granular debris; and grade 3, thick and toothpaste-like. The lower eyelids of each eye were scored separately and defined as MG yielding secretion score (MGYSS): 0 indicated normal and 1 point or more was abnormal, with the highest possible score of 3 points.[17] Meibum quality (MQ) was also assessed for each of 8 glands of the central one-third of the lower eyelid according to a scale of 0 to 3; the scores for the 8 glands were summed to obtain a total score (total score range: 0-24).[13]

The ocular surface parameters of TBUT, Oxford score, and tear film LLT were measured at baseline and each postoperative visit. Corneal staining was evaluated with fluorescein using the Oxford scale ranging from 0 to 5 (0 = no staining, 5 = severe staining). LLT measurements were obtained with the LipiView II interferometer (Johnson & Johnson). The LLT measurements were represented in interferometric color units (ICU), with 1 ICU representing approximately 1 nm. Any values greater than 100 ICU were converted to 100 ICU in the analysis. The OSDI questionnaire was scored from 0 to 100 (100 = most severe disease), and the DEQ questionnaire was scored from 0 to 22 (22 = most severe state).

The primary endpoint with respect to the effect of Lipiflow treatment performed before cataract surgery was the changes in MG function from baseline to postoperative visits after cataract surgery. The secondary endpoint was the changes in ocular surface parameters and dry eye symptom in both groups. Also, the effects of Lipiflow treatment according to preoperative MGD status were investigated. The baseline MG status of the patients was analyzed for classification according to MGD grade as outlined by the International Dry Eye WorkShop report considering eyelid margin status, MG expressibility, and secretion quality.[26] Patients in both groups were assigned an overall preoperative baseline MGD grade of 0 (no MGD), 1 (mild MGD), 2 (moderate MGD), or 3 (severe MGD) based on severity.[26,27] Subgroup analysis that compared the change in MG parameters, ocular surface parameters, and symptom scores from baseline to postoperative visits, according to the baseline MGD status, was performed in both groups.

• **SAMPLE SIZE CALCULATION:** To determine the required sample size, we conducted a power analysis using the data from a previous pilot study that evaluated the change in symptom scores after Lipiflow treatment before cataract surgery in patients with preoperative MGD.[28] On this basis, we calculated the minimum study sample size to be 41 participants per group. However, to ensure adequate reliability, we aimed for a sample size of 62 participants per group.

• **STATISTICAL ANALYSIS:** All categorical variables were summarized by the treatment group with frequency and percentage of participants in each category. Descriptive statistics (mean ± standard deviation) were used to summarize efficacy data, including those of continuous variables. The sex distribution was compared with the χ^2 test. Continuous intergroup variables were analyzed using an independent *t* test, and continuous intragroup variables were tested with a paired *t* test. Categorical intergroup variables were analyzed with the nonparametric Kruskal-Wallis test, whereas intragroup changes in categorical variables were analyzed with the nonparametric Wilcoxon signed-rank test. The correlation between MGD grade and each of the variables under investigation was determined using Pearson's correlation coefficient if the other variable was normally distributed or using Spearman's correlation coefficient if the other variable was not normally distributed. All statistical analyses were conducted using SPSS Statistics version 22.0 for Windows (IBM Corporation, Armonk, New York, USA). *P* values of less than .05 were regarded as statistically significant.

RESULTS

We enrolled 62 patients with cataract for Lipiflow treatment in this study. One patient cancelled the surgery and 1 was lost to follow-up, leaving 60 patients in this group (Figure 1). The mean age of these 60 patients was 64.33 ± 9.06 years (range, 56-69 years), and 34 patients were female. For the control group, we initially evaluated 62 patients; however, 9 cancelled the surgery, and 5 were lost to follow-up, leaving 48 participants in the control group. The mean age of these 48 patients was 65.33 ± 11.57 years (range, 58-68 years), and 26 patients were female. The demographic data and characteristics of the study population are described in Table 1. There were no significant intergroup differences in preoperative and postoperative uncorrected visual acuity and best-corrected visual acuity.

• **CHANGES IN MG PARAMETERS BEFORE AND AFTER CATARACT SURGERY:** The changes in MG parameters in both groups are summarized in Table 2. Meiboscores indicating structural loss of MGs were similar between the control and Lipiflow groups at baseline. No significant difference from baseline was found at either time point in both groups. Also, the intergroup differences were not significant at either 1 or 3 months postoperatively.

The expressibility of MG, scored as MGYLS, was similar in the 2 groups at baseline ($P = .143$). In the control group, gland expressibility decreased from baseline to 5.86

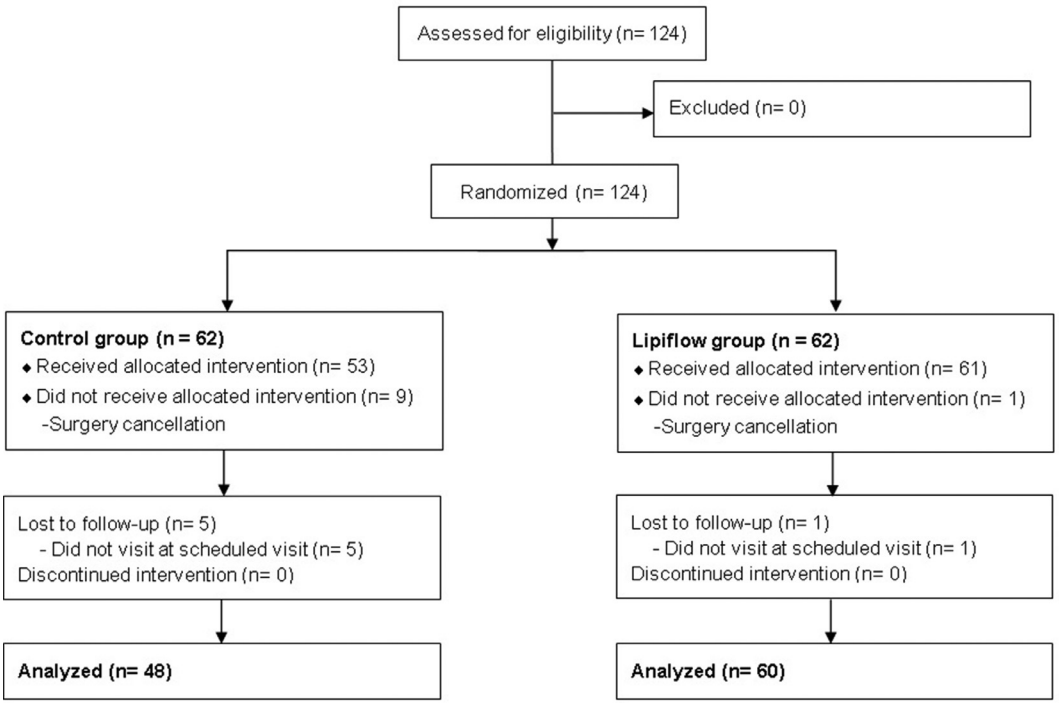

FIGURE 1. CONSORT flow diagram of a randomized controlled study on the effects of Lipiflow treatment before cataract surgery.

TABLE 1. Baseline Characteristics Between the Control and Lipiflow Groups

	Control Group (n = 48)	Lipiflow Group (n = 60)	*P* Value[a]
Age (y)	65.33 ± 11.57	64.33 ± 9.06	.605
Sex (male:female)	22:26	26:34	.736[b]
OD:OS	20:28	32:36	.327
Preoperative UCVA (logMAR)	0.44 ± 0.23	0.38 ± 0.28	.223
Preoperative BCVA (logMAR)	0.13 ± 0.54	0.21 ± 0.30	.101
Interval from screening to surgery (d)	21.27 ± 12.39	20.64 ± 10.80	.704
Postoperative UCVA (3 mo, logMAR)	0.12 ± 0.68	0.13 ± 0.67	.280
Postoperative BCVA (3 mo, logMAR)	0.00 ± 0.54	0.00 ± 0.57	.101

BCVA = best-corrected visual acuity, logMAR = logarithm of minimal angle of resolution, UCVA = uncorrected visual acuity.

[a]Independent *t* test.

[b]χ^2 test.

± 2.65 at 1 month ($P = .043$) and to 5.63 ± 2.59 at 3 months after surgery, a significant difference from baseline ($P = .014$). Conversely, in the Lipiflow group, gland expressibility was significantly improved compared with baseline at both the 1- and 3-month postoperative visits ($P < .001$ and $P = .009$, respectively). Also, differences in MGYLS between the groups were statistically significant at both postoperative visits ($P = .001$ and $P = .001$, respectively) (Figure 2, A).

The MGYSS, indicating the quality of gland secretion, was similar in the groups at baseline ($P = .501$). In the control group, the change in MGYSS from baseline was statistically significant at both follow-up visits ($P < .001$ and $P < .001$, respectively), indicating significantly worsening after surgery. Meanwhile, the change in MGYSS in the Lipiflow group showed significant improvement at both follow-up visits ($P = .005$ and $P = .010$, respectively), suggesting that Lipiflow treatment improves MGYSS. An intergroup comparison indicated that patients in the Lipiflow treatment group had better MGYSS results at both follow-up visits ($P < .001$ and $P < .001$, respectively) (Figure 2, B).

The MQ was similar in the 2 groups at baseline ($P = .160$). In the control group, the MQ statistically worsened at 1 month after surgery ($P = .001$) and further worsened at 3 months after surgery ($P < .001$ vs baseline). Meanwhile, in the Lipiflow group, the MQ was signifi-

TABLE 2. Comparison of Meibomian Gland (MG) Parameters in the Control and Lipiflow Groups Before and After Surgery

	Baseline	1 Month After Surgery	3 Months After Surgery	*P* Value[a]		
				Baseline vs 1 Month	Baseline vs 3 Months	1 Month vs 3 Months
Meiboscore						
Control group	0.87 ± 0.89	0.90 ± 0.92	0.91 ± 0.97	.103	.411	.083
Lipiflow group	0.76 ± 0.77	0.75 ± 0.766	0.65 ± 0.75	.322	.204	.135
P value[b]	.489	.390	.140			
MGYLS						
Control group	6.58 ± 2.07	5.86 ± 2.65	5.63 ± 2.59	**.043**	**.014**	.411
Lipiflow group	6.00 ± 2.09	7.33 ± 1.44	7.05 ± 1.70	**<.001**	**.009**	.312
P value[b]	.143	**.001**	**.001**			
MGYSS						
Control group	0.93 ± 0.80	1.42 ± 0.86	1.71 ± 0.82	**<.001**	**<.001**	**.024**
Lipiflow group	1.04 ± 0.86	0.71 ± 0.75	0.87 ± 0.87	**.005**	**.010**	.280
P value[b]	.501	**<.001**	**<.001**			
MQ						
Control group	7.74 ± 5.08	12.02 ± 6.19	14.27 ± 6.43	**.001**	**<.001**	**.009**
Lipiflow group	9.62 ± 6.65	6.87 ± 4.31	6.50 ± 5.52	**<.001**	**<.001**	.058
P value[b]	.160	**<.001**	**<.001**			

MGYLS = MGs yielding liquid secretion, MGYSS = MGs yielding secretion score, MQ = meibum quality. Bold values denote statistical significance at the p < 0.05 level.

[a]Paired *t* test for continuous variables, and Wilcoxon signed-rank test for categorical variables.

[b]Independent *t* test for continuous variables, and Kruskal-Wallis test for categorical variables.

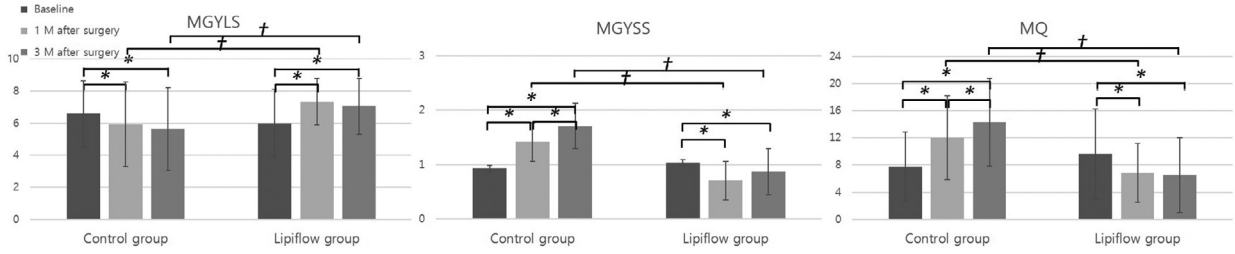

FIGURE 2. Meibomian gland (MG) parameters in the control and Lipiflow groups before and after cataract surgery. Degree of gland expressibility as measured by MGs yielding liquid secretion (MGYLS) (A); and quality of gland secretion as measured both by MGs yielding secretion score (MGYSS) (B) and meibum quality (MQ) (C) at preoperative and postoperative visits in the control group and the Lipiflow group. M = month. *P < .05 (intragroup comparison); †P < .05 (intergroup difference).

cantly improved at both 1 and 3 months after surgery ($P < .001$ and $P < .001$, respectively). An intergroup comparison revealed that patients in the Lipiflow treatment group had better MQ scores than those in the control group at both follow-up visits ($P < .001$ and $P < .001$, respectively) (Figure 2, C).

• **CHANGES IN OCULAR SURFACE PARAMETERS AND DRY EYE SYMPTOMS BEFORE AND AFTER CATARACT SURGERY:** The changes in ocular surface parameters and dry eye symptoms in the 2 groups are summarized in Table 3. At baseline, the TBUT values were similar between the control and Lipiflow treatment groups (3.65 ± 1.49 vs 3.46 ± 1.48 seconds; $P = .505$). After cataract surgery, the mean TBUT values in the control group showed a trend of worsening at 1 month (3.32 ± 1.57 seconds; $P = .546$ vs baseline) and returned to the baseline level at 3 months (3.61 ± 1.56 seconds; $P = .981$ vs baseline). However, in the Lipiflow group, the TBUT increased to 3.93 ± 1.94 seconds at 1 month after surgery ($P = .068$ vs baseline) and 4.37 ± 1.83 seconds at 3 months after surgery ($P = .005$ vs baseline), suggesting that Lipiflow treatment significantly improved the TBUT. Moreover, the difference in this parameter between the 2 study groups was significant at 3 months after surgery ($P = .025$) (Figure 3, A).

At baseline, the Oxford score was similar between the control group and the Lipiflow group (0.68 ± 0.92 vs 0.77 ± 0.90; $P = .625$). In the control group, Oxford staining showed a trend of worsening at 1 month (0.75 ± 0.74; $P = .895$ vs baseline) and then returned to the baseline level at 3 months after surgery (0.62 ± 0.56; $P = .690$ vs baseline). In the Lipiflow group, the Oxford score changed

TABLE 3. Comparison of Ocular Surface Parameters and Dry Eye Symptoms in the Control Group and Lipiflow Group Before and After Surgery

	Baseline	1 Month After Surgery	3 Months After Surgery	*P* Value[a]		
				Baseline vs 1 Month	Baseline vs 3 Months	1 Month vs 3 Months
TBUT						
Control group	3.65 ± 1.49	3.32 ± 1.57	3.61 ± 1.56	.546	.981	.275
Lipiflow group	3.46 ± 1.48	3.93 ± 1.94	4.37 ± 1.83	.068	**.005**	.470
P value[b]	.505	.093	**.025**			
Oxford score						
Control group	0.68 ± 0.92	0.75 ± 0.74	0.62 ± 0.56	.895	.690	.109
Lipiflow group	0.77 ± 0.90	0.44 ± 0.59	0.46 ± 0.56	**.007**	**.009**	.470
P value[b]	.625	**.018**	.131			
LLT						
Control group	90.40 ± 12.90	81.94 ± 11.57	86.21 ± 13.59	**.001**	.122	.100
Lipiflow group	86.76 ± 16.83	88.07 ± 16.42	87.37 ± 21.40	.688	.413	.409
P value[b]	.259	**.041**	.746			
OSDI						
Control group	34.34 ± 20.14	37.60 ± 17.94	29.81 ± 20.82	.251	.222	.059
Lipiflow group	37.92 ± 20.19	33.78 ± 19.40	22.33 ± 16.46	.075	**<.001**	**<.001**
P value[b]	.358	.313	**.037**			
DEQ						
Control group	7.46 ± 4.45	9.93 ± 5.23	9.15 ± 4.87	**.003**	**.047**	.424
Lipiflow group	9.73 ± 5.31	9.90 ± 5.24	8.03 ± 4.60	.831	**.023**	**.007**
P value[b]	**.017**	.977	.209			

DEQ = Dry Eye Questionnaire, LLT = lipid layer thickness, OSDI = Ocular Surface Disease Index, TBUT = tear break-up time. Bold values denote statistical significance at the $p < 0.05$ level.

[a]Paired *t* test for continuous variables, and Wilcoxon signed-rank test for categorical variables.

[b]Independent *t* test for continuous variables, and Kruskal-Wallis test for categorical variables.

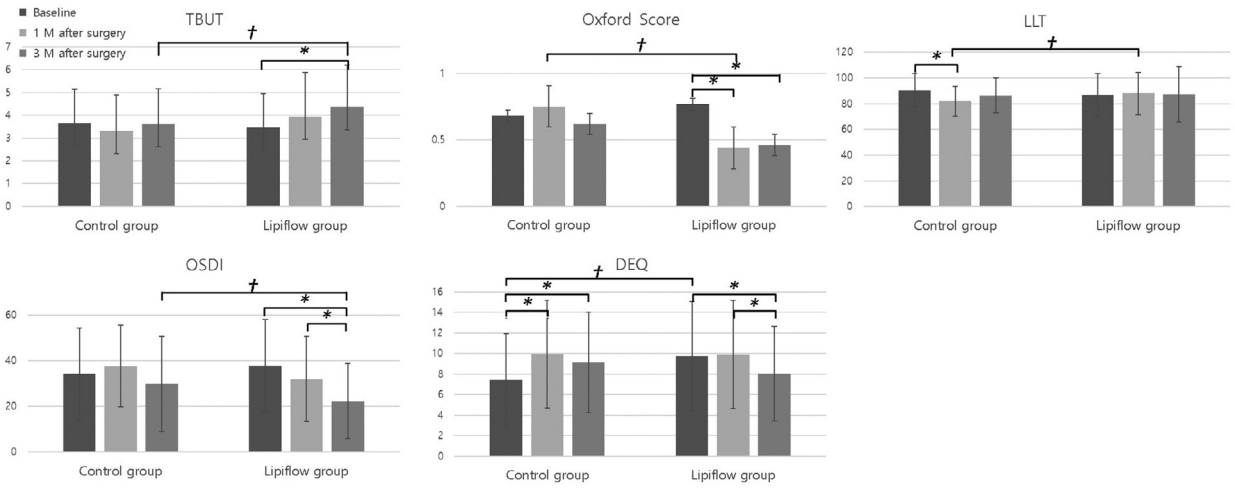

FIGURE 3. Ocular surface parameters and dry eye symptoms in the control group and Lipiflow group before and after cataract surgery. The ocular surface parameters of tear break-up time (TBUT) (A), Oxford corneal staining score (B), and lipid layer thickness (LLT) (C) at pre- and post-treatment in the control group and the Lipiflow group. Symptoms were assessed by Ocular Surface Disease Index (OSDI) (D) and Dry Eye Questionnaire (DEQ) (E) in both groups. M = month. *P < .05 (intragroup comparison); †P < .05 (intergroup difference).

to 0.44 ± 0.59 at 1 month ($P = .007$ vs baseline) and 0.46 ± 0.56 at 3 months after surgery ($P = .009$ vs baseline), which suggested that Lipiflow treatment improved corneal staining score. The difference in Oxford scores between the 2 groups was significant at the 1-month postoperative visit ($P = .018$) (Figure 3, B).

At the screening visit, the LLT value was similar in the 2 groups (90.40 ± 12.90 vs 86.76 ± 16.83 ICU; $P = .259$). In the control group, a significant decrease in LLT was found at 1 month ($P = .001$), whereas it returned to the baseline at 3 months after surgery ($P = .122$ vs baseline). However, in the Lipiflow group, the LLT value did not exhibit a significant change at either postoperative visit ($P = .688$ and $P = .413$). The difference in LLT between the groups was significant at 1 month after surgery ($P = .041$) (Figure 3, C).

The OSDI scores at screening visits were similar between groups (34.34 ± 20.14 vs 37.92 ± 20.19; $P = .358$). In the control group, the OSDI score did not show a significant change from baseline; it was higher at 1 month after surgery than at baseline but decreased at 3 months, and this change was not statistically significant ($P = .251$ vs baseline at 1 month, and $P = .222$ at 3 months). However, in the Lipiflow group, the OSDI score was significantly improved to 33.78 ± 19.40 at 1 month ($P = .075$ vs baseline); subsequently, the OSDI score significantly decreased to 22.33 ± 16.46 at 3 months ($P < .001$ vs baseline) and the change between 1 and 3 months was significant ($P < .001$). The difference in OSDI score between the groups was significant at 3 months after surgery ($P = .037$) (Figure 3, D).

The baseline DEQ score was 7.46 ± 4.45 in the control group and 9.73 ± 5.31 in the Lipiflow group. In the control group, the DEQ score significantly increased to 9.93 ± 5.23 at 1 month ($P = .003$), and then slightly decreased to 9.15 ± 4.87 at 3 months, which remained significantly higher than baseline ($P = .047$ vs baseline). In the Lipiflow group, the DEQ score did not show a significant change from baseline to 1 month (9.90 ± 5.24; $P = .831$) before decreasing to 8.03 ± 4.60 at 3 months ($P = .023$ vs baseline), where the change between 1 and 3 months exhibited a significant difference ($P = .007$). As the baseline DEQ score showed a statistically significant difference between the 2 groups ($P = .017$), the change in DEQ score from baseline was compared between the 2 groups. The change from baseline to 1 month showed a significant difference between the 2 groups (2.47 ± 5.40 in the control group vs 0.16 ± 6.52 in the Lipiflow group; $P = .047$). Also, the change from baseline to 3 months after surgery showed a significant difference between the 2 groups (1.69 ± 5.73 in the control group vs −1.70 ± 6.03 in the Lipiflow group; $P = .003$) (Figure 3, E).

• **SUBGROUP ANALYSIS ACCORDING TO BASELINE MGD GRADE:** In the Lipiflow group, 24 participants were assigned MGD grade 0 (no MGD), 14 participants were assigned grade 1 (mild MGD), 13 participants were assigned grade 2 (moderate MGD), and 9 participants were assigned grade 3 (severe MGD) with respect to baseline MGD severity. The changes of MG parameters, ocular surface parameters, and symptom scores from baseline to 3 months after surgery according to baseline MGD grade are shown in Table 4.

When the correlation between baseline MGD grade and changes in each MG parameter was investigated, an improvement in MG expressibility (MGYLS) in the Lipiflow group was positively correlated with baseline MGD grade ($r = 0.569$; $P < .001$) (Figure 4, A), whereas the change in quality of MG secretion was negatively correlated with baseline MGD ($r = −0.275$; $P = .044$ for MGYSS and $r = −0.570$; $P < .001$ for MQ) (Figure 4, B and C). These results suggest that patients with more severe MGD at baseline experienced greater improvement in expressibility and quality of meibum at 3 months postoperatively when treated preoperatively with Lipiflow compared with those with milder MGD or those without MGD.

Also, linear correlations were found between changes in ocular surface parameters, dry eye symptom scores, and baseline MGD grade. The change in TBUT was correlated significantly with baseline MGD grade ($r = 0.301$; $P = .020$) (Figure 5, A), as was improvement in Oxford score ($r = −0.268$; $P = .044$) (Figure 5, B). Changes in dry eye symptoms (OSDI and DEQ scores) were negatively correlated with baseline MGD ($r = −0.526$; $P < .001$ for OSDI and $r = −0.338$; $P = .007$ for DEQ) (Figure 5, C and D). Those with preoperative MGD experienced significantly greater improvements in TBUT, greater reductions in corneal staining, and greater improvements in dry eye symptoms (both OSDI and DEQ) than non-MGD patients.

In the control group, 22 participants were assigned MGD grade 0 (no MGD), 11 participants were assigned grade 1 (mild MGD), 9 participants were assigned grade 2 (moderate MGD), and 6 participants were assigned grade 3 (severe MGD). Non-MGD patients in the control group (n = 22 patients) and Lipiflow group (n = 24 patients) were compared to investigate the potential effect of Lipiflow treatment in patients without significant MGD before cataract surgery. Table 5 presents the changes in parameters from baseline to 1 month after surgery in non-MGD patients.

The non-MGD patients in the control group showed a worsening of MG expressibility (−0.15 ± 1.15), compared with those in the Lipiflow group, who did not experience any change (0.00 ± 0.68). However, the change in MGYLS did not demonstrate a significant difference between the 2 subgroups ($P = .605$). The non-MGD patients in the control group experienced a worsening of MQ, whereas those in the Lipiflow group experienced improvement. The change as measured by both MGYSS and MQ showed a significant difference between the 2 subgroups ($P = .018$ for MGYSS and $P = .002$ for MQ). The non-MGD participants in the control group showed decreased TBUT and increased corneal staining after cataract surgery, whereas the Lipiflow subgroup showed increased TBUT and decreased staining, with significant differences between the 2 subgroups ($P <$

TABLE 4. Changes of Parameters From Baseline to 3 Months After Surgery According to Each Baseline Meibomian Gland Dysfunction (MGD) Grade in the Lipiflow Group

Parameter	Baseline MGD Grade 0		Baseline MGD Grade 1		Baseline MGD Grade 2		Baseline MGD Grade 3	
	Baseline	3 Months (Changes)	Baseline	3 Months (Changes)	Baseline	3 Months (Changes)	Baseline	3 Months (Changes)
MGYLS	7.96 ± 0.20	6.91 ± 2.29 (−1.04 ± 2.31)	5.51 ± 0.83	7.71 ± 0.73 (2.21 ± 0.80)	3.17 ± 1.53	6.80 ± 1.23 (3.63 ± 2.20)	4.22 ± 1.20	6.63 ± 1.58 (2.11 ± 1.45)
MGYSS	0.92 ± 0.78	0.83 ± 0.83 (−0.09 ± 0.95)	0.73 ± 0.80	0.29 ± 0.61 (−0.44 ± 0.50)	1.00 ± 0.81	0.75 ± 0.75 (−0.25 ± 0.52)	2.22 ± 0.44	1.60 ± 0.73 (−0.67 ± 0.87)
MQ	6.44 ± 5.19	5.74 ± 4.64 (−0.70 ± 4.74)	6.73 ± 5.24	4.07 ± 4.18 (−2.67 ± 4.52)	13.33 ± 3.06	9.40 ± 4.79 (−3.95 ± 2.00)	19.43 ± 3.05	7.67 ± 5.10 (−11.76 ± 4.74)
BUT	2.97 ± 1.15	3.40 ± 1.49 (0.43 ± 1.07)	3.93 ± 1.80	5.59 ± 2.79 (1.66 ± 1.19)	3.80 ± 1.48	4.46 ± 2.91 (0.66 ± 1.28)	3.47 ± 1.70	5.00 ±2.01 (1.53 ± 1.11)
Oxford	0.42 ± 0.65	0.46 ± 0.66 (0.04 ± 0.95)	0.80 ± 0.77	0.36 ± 0.49 (−0.45 ± 0.65)	1.08 ± 0.79	0.50 ± 0.52 (−0.58 ± 0.67)	0.89 ± 0.78	0.44 ± 0.53 (−0.44 ± 1.01)
OSDI	26.39 ± 15.40	22.56 ± 11.07 (−3.83 ± 12.50)	41.43 ± 19.15	20.61 ± 10.56 (−20.82 ± 14.80)	37.97 ± 13.07	24.58 ± 24.80 (−13.39 ± 19.46)	56.58 ± 20.94	18.29 ± 14.02 (−38.29 ± 17.91)
DEQ	7.92 ± 4.28	8.71 ± 3.85 (0.78 ± 3.77)	11.38 ± 5.64	10.06 ± 4.33 (−1.31 ± 4.95)	9.33 ± 4.02	6.64 ± 6.03 (−2.69 ± 7.39)	10.30 ± 6.91	5.78 ± 4.38 (−4.52 ± 6.14)

BUT = Break-Up Time, DEQ = Dry Eye Questionnaire, OSDI = Ocular Surface Disease Index, MGYLS = MGs yielding liquid secretion, MGYSS = MGs yielding secretion score, MQ = meibum quality, TBUT = tear break-up time.

TABLE 5. Changes in Parameters From Baseline to 1 Month After Surgery in Preoperative Non–Meibomian Gland Dysfunction (MGD) Patients in the Control and Lipiflow Groups

	Non-MGD Control Patients (n = 22)	Non-MGD Lipiflow Patients (n = 24)	*P* Value[a]
Change in MGYLS	−0.15 ± 1.15	0.00 ± 0.68	.605
Change in MGYSS	+0.36 ± 0.72	−0.15 ± 0.60	**.018**
Change in MQ	+3.45 ± 4.22	−1.30 ± 3.22	**.002**
Change in TBUT	−0.43 ± 1.76	+1.96 ± 1.98	**<.001**
Change in Oxford score	+0.31 ± 1.17	−0.35 ± 0.87	**.044**
Change in OSDI	+26.08 ± 19.97	+7.94 ± 22.93	**.009**
Change in DEQ	+3.81 ± 5.99	−3.34 ± 6.09	**<.001**

DEQ = Dry Eye Questionnaire, MG = meibomian gland, MGYLS = MGs yielding liquid secretion, MGYSS = MGs yielding secretion score, MQ = meibum quality, OSDI = Ocular Surface Disease Index, TBUT = tear break-up time. Bold values denote statistical significance at the $p < 0.05$ level.

[a]Independent *t* test.

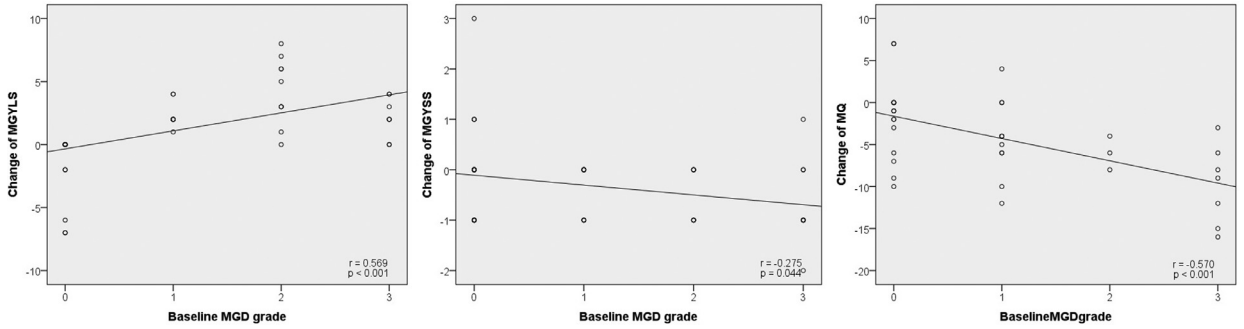

FIGURE 4. Correlations between baseline meibomian gland dysfunction (MGD) grade and changes in meibomian gland (MG) parameters. A. Positive correlation between change in MGs yielding liquid secretion (MGYLS) and baseline MGD grade ($r = 0.569$; $P < .001$). B, C. Negative correlation between change in secretion quality of MG and baseline MGD grade ($r = -0.275$; $P = .044$ for MGYSS and $r = -0.570$; $P < .001$ for MQ). MGYSS = MGs yielding secretion score, MQ = meibum quality.

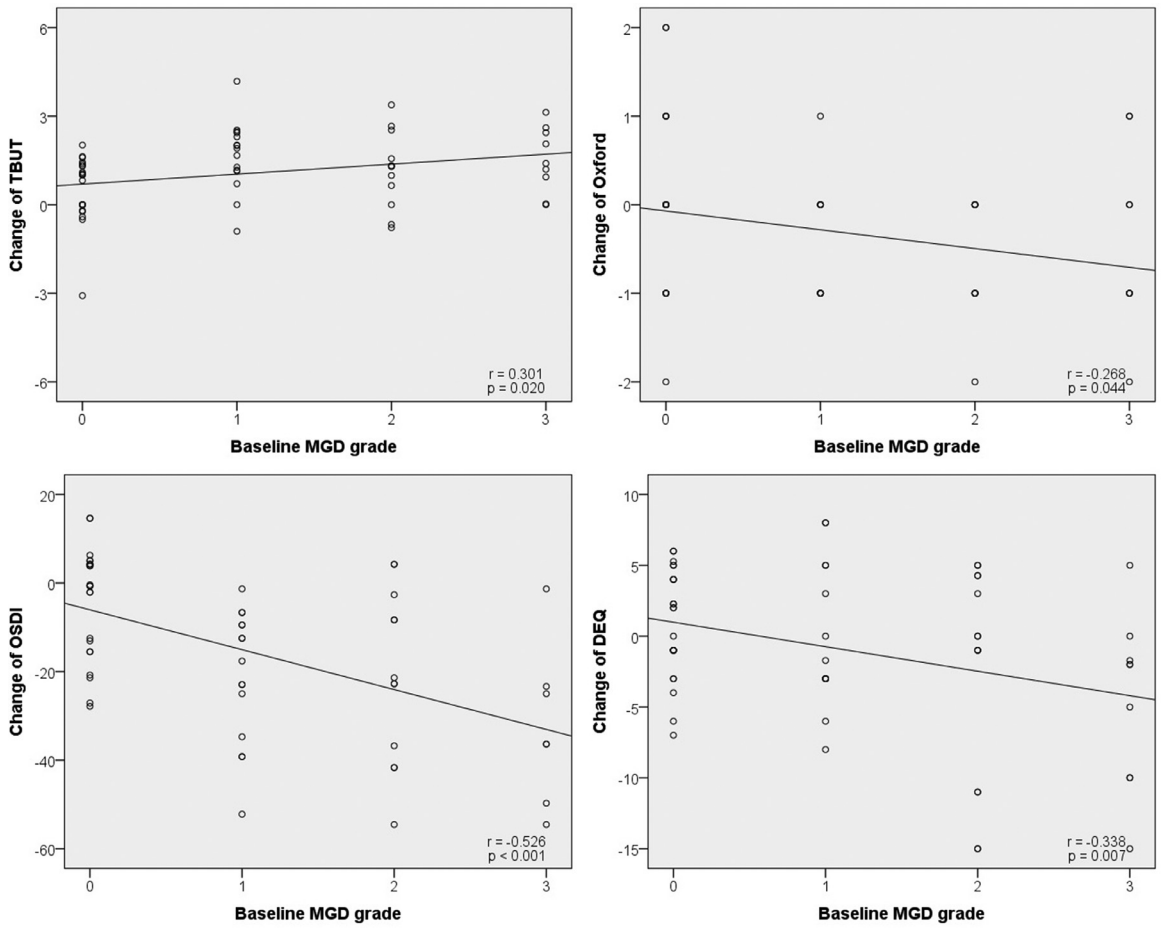

FIGURE 5. Correlation between baseline meibomian gland dysfunction (MGD) grade and changes in ocular surface parameters and dry eye symptoms. A. Positive correlation between change in tear break-up time (TBUT) and baseline MGD grade ($r = 0.301$; $P = .020$). B. Negative correlation between change in Oxford score and baseline MGD grade ($r = -0.268$; $P = .044$). C, D. Negative correlation between change in dry eye symptoms and baseline MGD grade ($r = -0.526$; $P < .001$ for OSDI and $r = -0.338$; $P = .007$ for DEQ). DEQ = Dry Eye Questionnaire, OSDI = Ocular Surface Disease Index.

.001 for TBUT and $P = .044$ for Oxford score). Moreover, the change in dry eye symptoms was significantly different between the 2 subgroups. The subgroup receiving Lipiflow treatment showed less worsening of OSDI score ($P = .009$) and significant improvement in DEQ score ($P < .001$).

DISCUSSION

This prospective randomized clinical trial demonstrates the positive effect of Lipiflow thermal pulsation before cataract surgery in treatment of MGD-related dry eye induced by cataract surgery with respect to both qualitative objective indices and subjective symptoms.

The prevalence of MGD is as high as 70% among Asian individuals. MGD is a chronic diffuse abnormality of the MGs that is characterized by terminal duct obstruction and changes in glandular secretion.[25,29] In this context, the lipid composition of the meibum changes, whereby the melting point of the lipid rises, causing it to become more viscous and stagnated at normal eyelid temperatures.[30] Also, prolonged stagnation of gland secretions inside MGs can lead to dilation of the ductal system and permanent loss of glandular tissue.[7] The altered lipid composition of the tear film increases the rate of tear evaporation and tear osmolarity, leading to inflammation of the corneal surface and damage to the corneal epithelium, triggering ocular symptoms. MGD is the major cause of evaporative dry eye and is also known to contribute to aqueous-deficient dry eye.

A large number of studies have shown that cataract surgery can produce or aggravate MGD, resulting in patients reporting less satisfaction with the surgical results[7,31] and culminating in increased rates of patient complaints even after noncomplicated operations.[31] The exact mechanism by which cataract surgery produces MGD is not well elucidated. However, ocular surface inflammation related to surgery itself, decrease in blink rate resulting

from reduction in corneal sensation, frequent use of topical medication after surgery, and eyelid dysfunction due to use of an eyelid speculum are potential causes.[7] In this study, there was a significant decrease in meibum expressibility, worsening in quality of MG secretions, decreased tear film LLT, and worsening of corneal staining after cataract surgery. Also, dry eye symptoms significantly worsened after surgery. These results agree with those of previous studies suggesting that cataract surgery affects the function of the MGs, causing changes in the tear film and damage to the ocular surface.[5,7-9] The meiboscore reflecting MG dropout showed a trend of worsening but no significant difference before and after surgery, suggesting that cataract surgery did not affect the gland anatomy permanently. These results suggest that the goal of treating MGD in the perioperative period should focus on improving MG function to prevent damage to the ocular surface.

Current treatments for MGD and dry eye after cataract surgery rely on long-term regimens of multidose pharmacological treatments. They include topical antibiotics to lessen the bacterial load, topical steroid or cyclosporine to reduce inflammation, and systemic omega-3 supplementation or oral tetracycline to restore the lipid profile of the meibum.[14-16,19] Despite the several therapeutic options, the cornerstone of MGD treatment continues to be eyelid hygiene, consisting primarily of heat application and subsequent eyelid massage.[20] Song and associates[10] revealed that preoperative treatment of MGD with a warm moist compress and massage with a fingertip was effective in alleviating obstructive MGD and dry eye induced by cataract surgery.[10] They also reported that preoperative treatment with eyelid hygiene was successful than enhanced and intensive postoperative anti-inflammatory pharmacological treatment.

Heat applied to the eyelids tends to reliquefy viscous and stagnated lipids in the gland duct so they can be massaged out of the gland. With this approach, the meibum can be expressed by both the patient and/or practitioners with cotton swabs or fingertip pressure. The positive effects of eyelid warming and massage have been reported in several clinical trials; however, there is no consensus regarding standardized methods or protocols for the treatment.[11,12,20,21] Moreover, eyelid tissue and blood flow impose obstacles to efficiently transferring heat to the inner eyelid surface and MGs when heating the external eyelid surface.[32,33] The Lipiflow system bypasses these obstacles and simultaneously evacuates the gland contents while heating the glands to therapeutic levels of at least 40 C. Recent studies have documented the benefits of Lipiflow as a primary treatment for MGD and dry eye.[11,21-23] Even a single Lipiflow treatment session is reported to be at least as effective as a 3-month regimen of eyelid margin hygiene for MGD-related dry eye.[21]

The current study investigated the effect of Lipiflow treatment performed before cataract surgery. In the present study, eyes treated with Lipiflow before cataract surgery were objectively noted to have significantly improved MG patency and quality of meibum secretion, increased TBUT, and reduction in corneal staining. These data correlate well with the improved subjective outcomes reported via OSDI and DEQ scores, providing support for the validity of preoperative Lipiflow thermal pulsation therapy. The treated eyes showed significant improvements from baseline in both objective and subjective indices at 1 month, with the benefits of a single treatment persisting for up to 3 months after cataract surgery. No unanticipated or serious device-related adverse events during treatment or follow-up were reported. Also, none of the patients reported pain during insertion, treatment, or removal of the device.

Also, the subgroup analysis in the current study revealed that Lipiflow treatment before cataract surgery triggered a better response in patients with preoperative MGD, with a linear relationship according to baseline MGD. Considering that, Lipiflow treatment might act by improving MG patency and secretion quality and could be recommended especially in patients with baseline MGD as a treatment before ocular surgeries. However, the most outstanding finding was that the patients without preoperative MGD can benefit from undergoing Lipiflow treatment before cataract surgery, in terms of MQ, tear film stability, corneal staining, and dry eye symptoms. The change of MG expressibility did not show a significant difference before and after surgery; however, the nonsignificant result might have resulted from the strict definition of grade 0 MGD. The Dry Eye WorkShop report defined non-MGD as all glands expressible with minimal change in secretion quality and no abnormalities in eyelid margin. For that reason, baseline non-MGD patients in the Lipiflow group could not improve more with Lipiflow treatment as they already had perfect expressibility. Except for the MG expressibility, the prophylactic Lipiflow treatment before cataract surgery proved to be effective in preventing MGD and dry eye induced by cataract surgery via improving MQ, tear film stability, corneal staining, and dry eye symptoms. In summary, Lipiflow treatment can be applied before cataract surgeries, not only in patients with preoperative MGD, but also in those without baseline MGD.

Although the result has not been published, a pilot study aimed to explore the effect of Lipiflow treatment before cataract surgery.[28] It showed improvement in mean postoperative dry eye symptoms, as evaluated with Standardized Patient Evaluation of Eye Dryness score, compared with the untreated control group. The results of the current study are consistent with the previous pilot study and bring a more comprehensive understanding of Lipiflow before cataract surgery. In another previous study, Schallhorn and associates[3] applied Lipiflow treatment to patients with recalcitrant dry eye after laser vision correction and reported significant improvements in dry eye symptoms. Also, significant improvements in MG patency, TBUT, and severity of corneal staining were reported. The response to therapy appeared to persist for at least 6 months

after treatment, suggesting a positive impact of Lipiflow in patients after laser vision correction. Although patients who undergo cataract surgery are typically older and have more comorbidities than refractive surgery candidates and often experience more severe symptoms, the results of both studies support the potential of Lipiflow treatment to alleviate the ocular discomfort and MGD induced by ocular surgery.[17,25] Follow-up assessments longer than 3 months might reveal a persisting benefit of Lipiflow treatment also in cataract surgeries.

In this study, the OSDI and DEQ questionnaires were used to evaluate the change of MGD and dry eye before and after cataract surgery. Although in screening and evaluating typical MGD associated dry eye, the Standardized Patient Evaluation of Eye Dryness questionnaire was reported to be a good methodology,[26,34] there has been no clear consensus on which questionnaires should be used to evaluate MGD related to cataract surgery. Both OSDI and DEQ questionnaires are well-structured instruments for the quantification of dry eye symptoms, including the cases of dry eye after ocular surgeries.[6,9,19,35-37] From recent studies for dry eye associated with cataract surgery, moderate positive linear correlation was reported between OSDI and MGD grade.[6,9,10,17,34]

The current study is the first report ever published to offer a prospective evaluation of the role of Lipiflow thermal pulsation therapy for the treatment and prevention of MGD-related dry eye after cataract surgery. Also, this study is an unbiased clinical trial with proper randomization, evaluating each and every parameter for a thorough understanding of preoperative Lipiflow treatment. It demonstrated the quantitative effect of Lipiflow treatment in those with preoperative MGD and the prophylactic effects in those without MGD, being a comprehensive study for the usefulness of preoperative intervention with Lipiflow in cataract surgeries.

This study has some limitations. First, both morphological assessment with meiboscore and functional assessment of MG, such as gland expressibility with MGYLS and the characteristics of secretions from gland orifices with MGYSS and MQ, were conducted only in the lower eyelids. As Lipiflow directly acts on both the upper and lower eyelids, evaluation of both might yield more evident results. Second, although the patients were randomly distributed, baseline DEQ was different between the 2 groups. As such, rather than directly comparing the 2 groups, changes from baseline within each group were compared in this study. Third, the patients could not be masked whether they were included in the Lipiflow or control group, as Lipiflow devices do not offer Sham treatment mode. Future studies that evaluate the role of preoperative Lipiflow treatment in visual quality or outcomes associated with dry eye after cataract surgery might be interesting, especially in the context of multifocal IOL implantation.

In summary, our data indicate that cataract surgery can produce or aggravate MGD and increase dry eye symptoms. Preoperative treatment with Lipiflow before surgery may ensure better outcomes by triggering improvements in ocular surface and MG parameters as well as subjective dry eye symptoms. Lipiflow treatment may be a safe and effective preoperative intervention for alleviating and preventing the MGD and dry eye associated with ocular surgery. It should be recommended before ocular surgeries, not only for patients with preoperative MGD, but also for those without baseline MGD, as it can prevent the development of MGD and dry eye induced by ocular surgeries.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST. Funding/Support: This work was supported by a National Research Foundation of Korea grant funded by the Korean government's Ministry of Education (NRF-2020R1A2C2014139; Seoul, Korea) which was received by T.-Y.C. D.H.L. and T.-Y.C. involved in conception and design; Y.-S.Y., K.S., G.H., D.H.L., and T.-Y.C. conducted the study; J.P., Y.-S.Y., K.S., and G.H. collected, managed, and interpreted the data; J.P., Y.-S.Y., K.S., and R.A. analyzed the data; J.P. wrote the article; and R.A., D.H.L., and T.-Y.C. prepared, reviewed, and approved the manuscript. J.P. and Y.-S.Y. contributed equally to the manuscript as co-first authors. D.H.L. and T.-Y.C. contributed equally to the manuscript as co-corresponding authors. All authors have reviewed the manuscript and approved the final version. Financial Disclosures: None. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Zhao X, Xia S, Chen Y. Comparison of the efficacy between topical diquafosol and artificial tears in the treatment of dry eye following cataract surgery: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2017;96:e8174.
2. Gupta PK, Drinkwater OJ, VanDusen KW, Brissette AR, Starr CE. Prevalence of ocular surface dysfunction in patients presenting for cataract surgery evaluation. *J Cataract Refract Surg*. 2018;44:1090–1096.
3. Schallhorn CS, Schallhorn JM, Hannan S, Schallhorn SC. Effectiveness of an eyelid thermal pulsation procedure to treat recalcitrant dry eye symptoms after laser vision correction. *J Refract Surg*. 2017;33:30–36.
4. Shokoohi-Rad S, Javaheri SZH, Malekabad FZ, Khakshoor H, Daluee MK. Effects of preoperative doses of betamethasone acetate 0.1% on dry eye control after cataract surgery. *Indian J Ophthalmol*. 2020;68:450–454.
5. El Ameen A, Majzoub S, Vandermeer G, Pisella PJ. Influence of cataract surgery on Meibomian gland dysfunction. *J Fr Ophtalmol*. 2018;41:e173–e180.
6. Kim JS, Lee H, Choi S, Kim EK, Seo KY, Kim TI. Assessment of the tear film lipid layer thickness after cataract surgery. *Semin Ophthalmol*. 2018;33:231–236.
7. Han KE, Yoon SC, Ahn JM, et al. Evaluation of dry eye and meibomian gland dysfunction after cataract surgery. *Am J Ophthalmol*. 2014;157:1144–1150 e1.

8. Cochener B, Cassan A, Omiel L. Prevalence of meibomian gland dysfunction at the time of cataract surgery. *J Cataract Refract Surg*. 2018;44:144–148.
9. Jung JW, Han SJ, Nam SM, Kim TI, Kim EK, Seo KY. Meibomian gland dysfunction and tear cytokines after cataract surgery according to preoperative meibomian gland status. *Clin Exp Ophthalmol*. 2016;44:555–562.
10. Song P, Sun Z, Ren S, et al. Preoperative management of MGD alleviates the aggravation of MGD and dry eye induced by cataract surgery: a prospective, randomized clinical trial. *Biomed Res Int*. 2019;2019.
11. Blackie CA, Carlson AN, Korb DR. Treatment for meibomian gland dysfunction and dry eye symptoms with a single-dose vectored thermal pulsation: a review. *Curr Opin Ophthalmol*. 2015;26:306–313.
12. Geerling G, Tauber J, Baudouin C, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci*. 2011;52:2050–2064.
13. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. *Invest Ophthalmol Vis Sci*. 2011;52:1922–1929.
14. Olenik A, Mahillo-Fernandez I, Alejandre-Alba N, et al. Benefits of omega-3 fatty acid dietary supplementation on health-related quality of life in patients with meibomian gland dysfunction. *Clin Ophthalmol*. 2014;8:831–836.
15. Romero JM, Biser SA, Perry HD, et al. Conservative treatment of meibomian gland dysfunction. *Eye Contact Lens*. 2004;30:14–19.
16. Sobolewska B, Doycheva D, Deuter C, Pfeffer I, Schaller M, Zierhut M. Treatment of ocular rosacea with once-daily low–dose doxycycline. *Cornea*. 2014;33:257–260.
17. Ge J, Liu N, Wang X, et al. Evaluation of the efficacy of optimal pulsed technology treatment in patients with cataract and Meibomian gland dysfunction in the perioperative period. *BMC Ophthalmol*. 2020;20:111.
18. Arita R, Fukuoka S, Morishige N. Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction. *Ocul Surf*. 2019;17:104–110.
19. Park J, Yoo YS, Shin E, et al. Effects of the re-esterified triglyceride (rTG) form of omega-3 supplements on dry eye following cataract surgery. *Br J Ophthalmol*. Published Online First: 11 September 2020. In press. doi:10.1136/bjophthalmol-2020-317164.
20. Arita R, Fukuoka S. Non-pharmaceutical treatment options for meibomian gland dysfunction. *Clin Exp Optom*. 2020;103:742–755.
21. Finis D, Hayajneh J, Konig C, Borrelli M, Schrader S, Geerling G. Evaluation of an automated thermodynamic treatment (LipiFlow(R)) system for meibomian gland dysfunction: a prospective, randomized, observer-masked trial. *Ocul Surf*. 2014;12:146–154.
22. Greiner JV. Long-term (12-month) improvement in meibomian gland function and reduced dry eye symptoms with a single thermal pulsation treatment. *Clin Exp Ophthalmol*. 2013;41:524–530.
23. Lane SS, DuBiner HB, Epstein RJ, et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. *Cornea*. 2012;31:396–404.
24. Arita R, Minoura I, Morishige N, et al. Development of Definitive and reliable grading scales for meibomian gland dysfunction. *Am J Ophthalmol*. 2016;169:125–137.
25. Arita R, Fukuoka S, Morishige N. New insights into the morphology and function of meibomian glands. *Exp Eye Res*. 2017;163:64–71.
26. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. *Ocul Surf*. 2017;15:539–574.
27. Suzuki M, Massingale ML, Ye F, et al. Tear osmolarity as a biomarker for dry eye disease severity. *Invest Ophthalmol Vis Sci*. 2010;51:4557–4561.
28. NIH. *Pilot study for treatment of meibomian gland dysfunction (MGD) prior to cataract surgery*. NCT01808560; 2018 Available at https://clinicaltrials.gov/show/NCT1808560. Accessed 01 Mar 2020.
29. Chhadva P, Goldhardt R, Galor A. Meibomian gland disease: the role of gland dysfunction in dry eye disease. *Ophthalmology*. 2017;124(Suppl):S20–S26.
30. McCulley JP, Shine WE. Meibomian secretions in chronic blepharitis. *Adv Exp Med Biol*. 1998;438:319–326.
31. Li XM, Hu L, Hu J, Wang W. Investigation of dry eye disease and analysis of the pathogenic factors in patients after cataract surgery. *Cornea*. 2007;26(1):S16–S20 Suppl.
32. Blackie CA, Solomon JD, Greiner JV, Holmes M, Korb DR. Inner eyelid surface temperature as a function of warm compress methodology. *Optom Vis Sci*. 2008;85:675–683.
33. Murakami DK, Blackie CA, Korb DR. All warm compresses are not equally efficacious. *Optom Vis Sci*. 2015;92:e327–e333.
34. Kim JA, Lee SH. Association between dry eye questionnaires and dry eye sign in meibomian gland dysfunction. *J Korean Ophthalmol Soc*. 2020;61:138–145.
35. Schargus M, Ivanova S, Stute G, Dick HB, Joachim SC. Comparable effects on tear film parameters after femtosecond laser-assisted and conventional cataract surgery. *Int Ophthalmol*. 2020;40:3097–3104.
36. Galor A, Patel S, Small LR, et al. Pregabalin failed to prevent dry eye symptoms after laser-assisted in situ keratomileusis (LASIK) in a randomized pilot study. *J Clin Med*. 2019;8:1355.
37. Recchioni A, Siso-Fuertes I, Hartwig A, et al. Short-term impact of FS-LASIK and SMILE on dry eye metrics and corneal nerve morphology. *Cornea*. 2020;39:851–857.