Opaque Bubble Layer Risk Factors in Femtosecond Laser-assisted LASIK

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ABSTRACT

PURPOSE: To determine the characteristics and risk factors for occurrence of opaque bubble layer (OBL) during femtosecond laser-assisted flap creation for LASIK.

METHODS: One hundred ninety-eight eyes of 102 consecutive patients who underwent LASIK flap creation performed with the Alcon WaveLight FS200 laser (Alcon Laboratories, Inc., Fort Worth, TX) were retrospectively analyzed in a cohort study. Preoperative manifest refraction, corneal keratometry, central corneal thickness, white-to-white corneal diameter, corneal hysteresis, corneal resistance factor, and programmed flaps parameters were collected. Digital images automatically recorded after flap creation were analyzed to measure OBL areas. Correlation tests were performed between preoperative corneal parameters and OBL areas.

RESULTS: The incidence rate of OBL was 48% (103 eyes). The mean OBL area as a percentage of the corneal flap area in the OBL group was 4.25% ± 7.16% (range: 0% to 32.9%). The central corneal thickness, corneal resistance factor, and corneal hysteresis were significantly positively correlated with the OBL area (r = 0.242, P = .001; r = 0.254, P = .028; and r = 0.351, P < .0001, respectively). Corneal hysteresis and OBL area were positively correlated, independently of the central corneal thickness and other confounder factors with standardized coefficient (r = 0.353 ± 0.227, P = .002).

CONCLUSIONS: This study confirms the already known OBL risk factors with a larger cohort and suggests for the first time that an elevated corneal hysteresis is an independent predictive risk for OBL occurrence.

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LASIK flap creation is the most used femtosecond laser application in refractive surgery. Compared to the microkeratome, the femtosecond laser technique has equivalent visual and refractive outcomes.[1-4] However, this technology increases predictability,[5] accuracy, and precision[6] of LASIK flap creation. Also, it allows for flap customization (thickness, diameter, side-cut angle) and is better suited for thin corneas, high spherical ametropia, and high astigmatisms with a fast learning curve.[7] Despite the improved safety gained by using femtosecond laser in flap creation, specific complications exist including the occurrence of opaque bubble layer (OBL).

Femtosecond pulses are focused in the corneal tissue where it causes covalent bonds to rupture between the atomic nucleus and electrons (ionization). Plasma expansion in the tissue creates a cavitation bubble causing a separation between stromal lamellae. OBL is the accumulation of gas bubbles temporarily detained in the intrastromal interface, creating transient opacity. The mechanism of OBL is not clearly understood. However, it is suggested that the gas bubbles infiltrate the stroma because they cannot escape and due to corneal compression with a high level of vacuum created by applanation. Histopathology of OBL has not been described because of the transient nature of the phenomenon. In vivo structural characteristics with ultra-high-resolution optical coherence tomography has allowed a more detailed structural analysis without providing further explanation of the mechanism.[8]

Although OBL formation is rarely dangerous, it represents a frequent and sometimes inconvenient complication. The purpose of this study was to determine the incidence

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TABLE 1

Femtosecond Laser Flap Creation Settings of the Alcon WaveLight FS200

Setting	Measurement
Flap	
Diameter (range)	7.70 to 9.50 mm
Thickness (range)	120.00 to 135.00 μm
Canal	
Length (range)	0.30 to 1.20 mm
Width	1.70 mm
Bed cut	
Spot separations	8.0 μm
Line separations	8.0 μm
Pulse energy (range)	0.79 to 0.85 μJ
Side cut	
Spot separations	5.0 μm
Line separations	3.0 μm
Angle	70°
Pulse energy (range)	0.79 to 0.85 μJ
Hinge	
Position	90°
Length	3.8 mm
Angle	50°
Width	0.4 mm

The Alcon Wavelight FS200 is manufactured by Alcon Laboratories, Inc., Fort Worth, TX.

and risk factors of OBL occurrence using the Alcon WaveLight FS200 laser (Alcon Laboratories, Inc., Fort Worth, TX) for current femtosecond laser-assisted LASIK procedures.

PATIENTS AND METHODS

Patients and Femtosecond Laser Settings

The retrospective study included 102 successive patients (198 eyes) who had femtosecond laser-assisted LASIK surgery for myopia, astigmatism, or hyperopia. Interventions were performed by two surgeons (DG and AS) using the same operating methods from January to December 2013. All procedures were performed with the WaveLight FS200 laser. The study protocol was approved by the local research ethics committee.

Preoperative data analyzed were manifest refraction (sphere, cylinder, and spherical equivalent). The corneal keratometry, central corneal thickness (CCT), and white-to-white corneal diameter were measured with the ORBSCAN II Corneal Topographer (Bausch & Lomb, Orbtek, Inc., Salt Lake City, UT). The corneal biomechanical parameters, corneal hysteresis (CH), and corneal resistance factor (CRF) were measured with the Ocular Response Analyzer (Reichert Ophthalmic Instruments, Buffalo, NY).

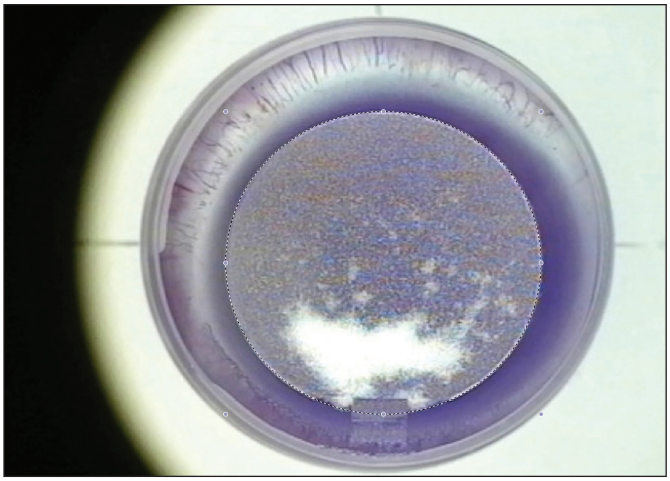

Figure 1. Screenshot of delimitation and extraction using Preview software (Apple, Inc., Cupertino, CA).

For femtosecond laser flap creation, the only set parameters were flap diameter, flap thickness, and canal length. Canal width and flap bed cut, side cut, and hinge were WaveLight FS200 laser default settings and the same for all procedures (**Table 1**). Patients with missing or incomplete data were excluded from the study.

Standardized OBL Measurement Procedure

The OBL measurement procedure was highly reproducible to ensure the best repeatability of OBL area quantification.

Digital images automatically recorded and stored in the WaveLight FS200 storage system during the flap creation procedure were collected. Different software were used to analyze the images and evaluate the OBL areas. To obtain a reproducible method of measurement, each step was standardized.

Step 1: Image extracting and editing (Preview software; Apple, Inc., Cupertino, CA).

1. Laser Alcon WaveLight FS200 flap creation: treatment parameters and procedure screenshot.
2. Screenshot image extraction.
3. Flap side-cut delimitation using the circular selection tool (**Figure 1**).

Step 2: Image processing and analysis (ImageJ software; National Institutes of Health, Bethesda, MA).

1. Image color conversion to grayscale (8-bit) (**Figure A1**, available in the online version of this article).

TABLE 2

Preoperative Corneal Parameters Analyzed

Parameter	Minimum	Maximum	Mean	SD
CCT (μm)	492.00	632.00	570.32	28.39
K1 (D)	40.30	47.20	44.27	1.37
K2 (D)	40.00	46.80	43.20	1.42
Sphere (D)	-11.50	5.50	-3.53	3.48
Cylinder (D)	-5.00	0.00	-0.92	0.93
SE (D)	-12.12	4.62	-3.99	3.45
CRF	6.70	15.00	11.28	1.60
CH	6.70	14.80	11.84	1.39
WW (mm)	10.70	13.10	11.84	0.39

SD = standard deviation; CCT = central corneal thickness; K1 = flat keratometry; K2 = steep keratometry; D = diopters; SE = spherical equivalent; CRF = corneal resistance factor; CH = corneal hysteresis; WW = white-to-white distance

2. Standardized contrast adjusting. The optimal adjustment was previously subjectively defined (**Figure A2**).
3. Image binarization (**Figure A3**).
4. The calculation tool allowed defining the percentage of black area in the flap area (**Figure A4**). The flap area was defined by the WaveLight FS200 settings because several studies showed an excellent accuracy and precision of flap size.[6,9] Then, knowing the flap area in mm^2 and the OBL percentage of the flap, OBL areas were calculated using a simple rule of three.

Statistical Analysis

All statistical analyses were performed with XLSTAT software (Addinsoft, Paris, France). Data were expressed as the mean ± standard deviation. The Mann–Whitney test was used for preoperative comparisons, and logistic regression was used for the subsidiary analysis. The Pearson correlation was used to express the relationship between the size of the OBL and the measured data. A *P* value less than .05 was considered statistically significant.

RESULTS

In our study of 198 eyes, 101 were right eyes and 97 were left eyes. Of the 102 patients, 62.7% (64 patients) were female. The mean age was 34.20 ± 9.83 years (range: 20 to 69 years).

The incidence rate of OBL was 48% (95 eyes). The mean OBL area in the OBL group was 8.86% ± 8.09% (range: 0% to 32.90%) of the flap area. The preoperative corneal parameters are shown in **Table 2**.

TABLE 3

Comparison of the Main Parameters Between the Two Groups

Parameter	No OBL (n = 103)	OBL (n = 95)	*P*
OBL area (%)	0	8.86 ± 8.09	–
Age	35.33 ± 11.19	32.80 ± 7.81	.527
Corneal parameters			
CCT (μm)	563.87 ± 28.75	577.32 ± 26.40	.001
K1 (D)	44.20 ± 1.46	44.34 ± 1.26	.577
K2 (D)	43.17 ± 1.51	43.24 ± 1.31	.739
Sphere (D)	-3.18 ± 3.46	-3.91 ± 3.48	.088
Cylinder (D)	-0.88 ± 0.83	-0.97 ± 1.02	.945
SE (D)	-3.62 ± 3.52	-4.40 ± 3.34	.092
CRF	11.07 ± 1.64	11.50 ± 1.52	.028
CH	10.99 ± 1.28	11.85 ± 1.37	< .0001
WW (mm)	11.89 ± 0.42	11.78 ± 0.36	.093
Flap parameters			
Flap area (mm^2)	82.22 ± 4.54	82.11 ± 4.37	.761
Flap thickness (mm)	121.84 ± 4.08	122.00 ± 4.02	.702
Canal width (mm)	1.70 ± 0.00	1.70 ± 0.00	1.00
Canal length (mm)	0.80 ± 0.19	0.77 ± 0.18	.183

OBL = opaque bubble layer; CCT = central corneal thickness; K1 = flat keratometry; K2 = steep keratometry; D = diopters; SE = spherical equivalent; CRF = corneal resistance factor; CH = corneal hysteresis; WW = white-to-white distance

For the preoperative corneal biomechanical parameters, the mean CRF and CH were 11.28 ± 1.60 mm Hg (range: 6.70 to 15.00 mm Hg) and 11.40 ± 1.39 mm Hg (range: 6.70 to 14.80 mm Hg), respectively.

The mean flap diameter, flap thickness, and canal were 9.06 ± 0.32 mm (range: 7.80 to 9.50 mm), 121.92 ± 4.04 µm (range: 120 to 135 µm), and 0.78 ± 0.18 mm (range: 0.30 to 1.20 mm), respectively. The mean flap area was 82.17 ± 4.45 mm^2 (range: 69.60 to 90.25 mm^2).

The CCT, CRF, and CH were statistically different between the no OBL and the OBL group. There was no significant difference between the two groups for flap creation settings (**Table 3**).

Pearson correlation tests were performed between preoperative corneal parameters and the OBL area. The CCT, CRF, and CH were positively correlated with the OBL area ($r = 0.242$, $P < .001$; $r = 0.254$, $P < .001$; and $r = 0.351$, $P < .001$, respectively). Thicker corneas and higher corneal biomechanical values have a significantly higher risk of developing OBL. None of the flap parameters were correlated with a lower or higher risk of OBL.

A linear regression analysis was performed and showed a positive correlation between CH and OBL

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TABLE 4

Standardized Correlation Coefficients of Corneal and Flap Parameters With the OBL Area

Variable	Standardized Coefficients	Standard Error	*t*	*P*	Lower 95% CI	Upper 95% CI
Corneal parameters						
CCT	0.175	0.084	2.094	.038	0.010	0.340
K1	-0.066	0.243	-0.273	.785	-0.546	0.413
K2	0.009	0.253	0.038	.970	-0.490	0.509
Sphere	0.061	0.098	0.622	.535	-0.133	0.255
Cylinder	-0.069	0.126	-0.547	.585	-0.317	0.179
Spherical equivalent	-0.020	0.070	-0.291	.771	-0.158	0.117
CRF	-0.081	0.115	-0.705	.482	-0.309	0.146
CH	0.353	0.115	3.069	.002	0.126	0.580
WW	0.030	0.082	0.364	.716	-0.131	0.191
Flap parameters						
Flap diameter	0.052	0.092	0.563	.574	-0.130	0.233
Flap area	0.011	0.100	0.114	.910	-0.186	0.208
Flap thickness	-0.130	0.094	-1.383	.168	-0.314	0.055
Canal length	-0.019	0.073	-0.254	.800	-0.163	0.126

95% CI = 95% confidence interval; CCT = central corneal thickness; K1 = flat keratometry; K2 = steep keratometry; CRF = corneal resistance factor; CH = corneal hysteresis; WW = white-to-white distance

area independent of the CCT and other confounder factors with standardized coefficient ($r = 0.353 \pm 0.227$, $P = .002$) (**Table 4**).

DISCUSSION

In our study, the occurrence of OBL was frequent with an incidence of 48.0%. Excessive OBL may interfere with eye tracker pupil recognition. It also causes difficulties in flap lifting and intraoperative pachymetry measurements. These problems can result in longer interventions and possibly induce an undercorrection during the photoablation procedure due to a reduced fluence.

In our experience, we have not encountered serious problems; however, after flap creation complicated with OBL we found subjectively that flaps were more difficult to lift.[10] Our study is concordant with the literature, because no serious complications have been reported after OBL occurrence.[10,11]

Femtosecond lasers use near infrared (wavelength of 1,053 nm) with a femtosecond pulse duration (range: 10 to 15 seconds) producing photodisruption. Multiple pulses of the laser, with a pulse frequency of 200 Hz with the Alcon WaveLight FS200, generate an ionization resulting in formation of microscopic gas bubbles next to each other, dissipating and expanding into corneal tissue. This cutting process causes a separation between stromal lamellae with minimal collateral tissue damage, creating the LASIK flap.[12]

Previous studies have described two different types of OBLs.[11,12,13] "Soft," "diffuse," or "delayed" OBLs have a more transparent appearance and occur later, after completion of the laser dissection in a particular area. "Hard," "advancing," or "early" OBLs appear earlier and have a denser appearance.[6]

The preoperative and intraoperative characteristics comparison of groups with hard and diffuse OBL showed no statistically significant difference.[12] However, it is sometimes difficult to determine whether it is diffuse or hard OBL. In our study, we did not differentiate between the two types of OBLs.

Our results confirm the correlations between CCT and OBL shown in previous studies[12,14] with a larger population of 198 eyes: thicker corneas were associated with more frequent and larger OBL.

In the statistical methods, we decided to use fellow eyes so that our study can be compared to those already published in the literature, despite possible changes in relationships.

To our knowledge, this is the first time in the literature that corneal biomechanical parameters are correlated with the occurrence of OBL. Incidence and importance of OBL have been positively correlated with high CH and high CRF. Furthermore, a linear correlation between CH and the occurrence and importance of OBL was identified independently of the CCT and other confounder factors. However, these correlations are low, constituting the main limitation of this study.

We know that the CH value is proportional to the degree of the corneal viscosity and inversely proportional to its degree of elasticity. Thus, we believe that the lower corneal elasticity and higher viscosity might increase the OBL occurrence due to the lower capacity for reversible deformation of the cornea with a greater gas bubble infiltration between stromal lamellae.

Gas bubbles have been described in other locations, and may escape in corneal sub-epithelial space, subconjunctiva, or anterior chamber.[15-17] The WaveLight FS200 femtosecond laser can also create a gas bubble evacuation canal to minimize OBL. However, this canal may be associated with blood extending from the canal into the flap interface and may require a flap lift.[18]

Based on our study, the occurrence of OBL with the Alcon WaveLight FS200 laser is frequent (42%) and usually innocuous. Thicker corneas and higher corneal biomechanical parameters are associated with an increased risk of OBL.

In the future, it could be interesting to compare refractive and visual outcomes (halos, glare, and higher-order aberrations) between laser flap creation complicated with OBL and those without OBL.

AUTHOR CONTRIBUTIONS

Study concept and design (AS, DG); data collection (RC, AS, DG); analysis and interpretation of data (RC, AS, EG, AG-D, DG); writing the manuscript (RC); critical revision of the manuscript (AS, EG, AG-D, DG); statistical expertise (AS)

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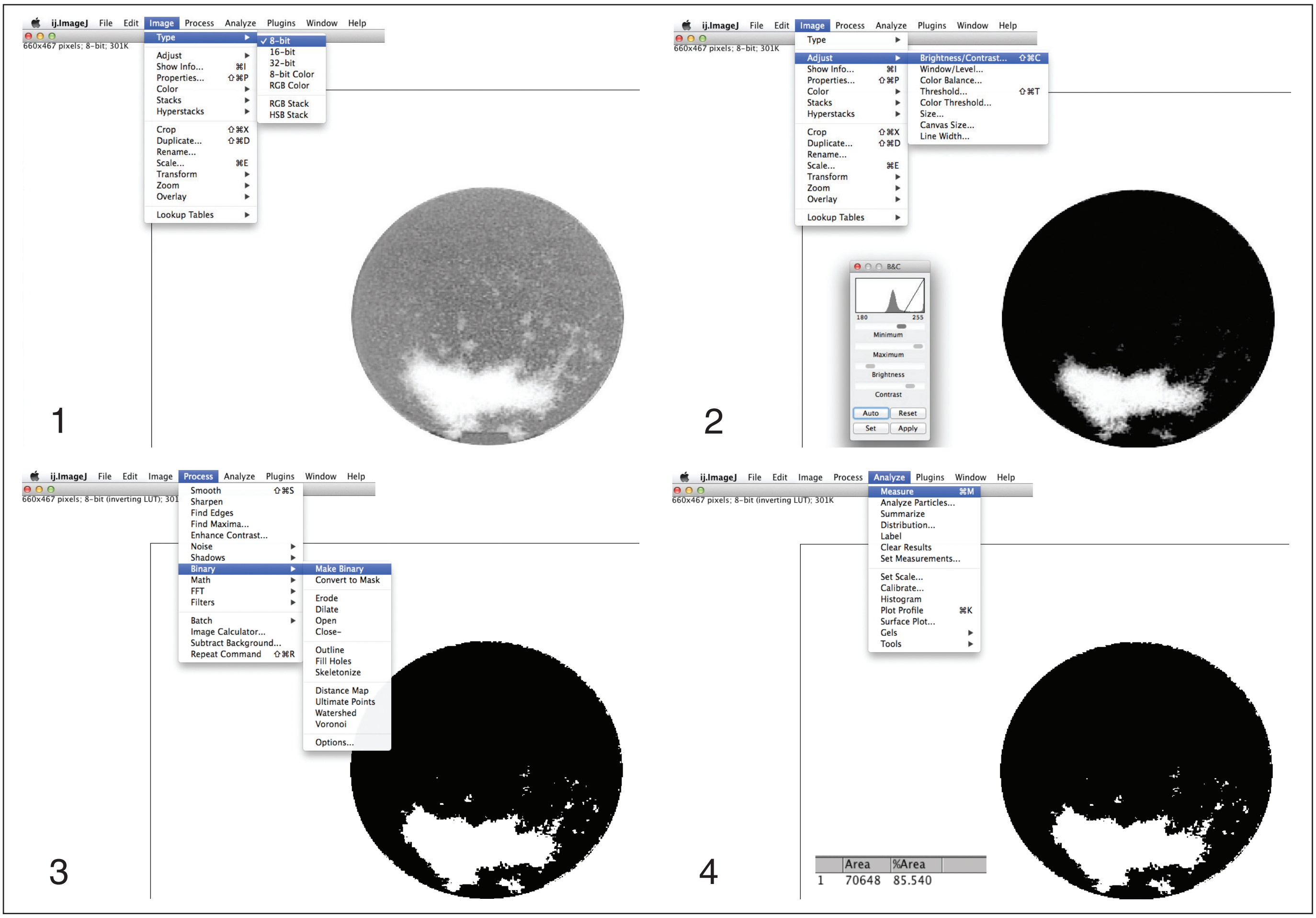

Figure A. Steps of image processing and analysis using ImageJ software (National Institutes of Health, Bethesda, MD) after flap image extraction. (1) Conversion in 8-bit (grayscale). (2) Standardized contrast adjusting. (3) Binarization (black and white). (4) Measure of black area percentage.