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Effect of corneal flap thickness on opaque bubble layer formation in Visumax FS-LASIK using GEE analysis

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A R T I C L E I N F O

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A B S T R A C T

Introduction: This study aimed to investigate two types of corneal flap thickness on opaque bubble layer (OBL) formation in Visumax femtosecond laser-assisted stromal for situ keratomileusis (FS-LASIK).

Methods: This retrospective study analyzed 203 eyes of 103 patients (32 men and 71 women) who underwent Visumax FS-LASIK between January 2020 and June 2020, and according to corneal flap thickness, they were divided into the 100-μm group (64 eyes) and the 110-μm group (139 eyes). Anterior-segment examination revealed no abnormal findings. Preoperatively, intraocular pressure (IOP), central corneal thickness (CCT), residual stromal thickness (RST), spherical power, cylindrical power, flat keratometry (K1), steep keratometry (K2), and biomechanical parameters including deformation amplitude (DA) ratio, Integrated Radius, stiffness parameter at first applanation (SP-A1), and Ambrosio relational thickness to the horizontal profile (ARTh) were evaluated. Primary outcomes were the incidence of OBL formation in the two groups compared by the Chi-square test and the correlation between the incidence of OBL and the above preoperative data by Spearman's Rho test. Secondary outcomes were the comparisons corrected by the generalized estimating equation (GEE) model.

Results: The incidence of OBL formation in the 100-μm group was 59.4 %, which was higher than that in the 110-μm group (23.0 %) with a significant difference ($\chi^2 = 25.635$, $P < 0.001$). The thinner corneal flap thickness ($r = -0.355$, $P < 0.001$) and higher spherical power ($r = -0.142$, $P < 0.05$) correlated with OBL formation. Higher K1 ($r = 0.217$, $P < 0.01$) and K2 ($r = 0.198$, $P < 0.01$) also correlated with OBL formation. The results of the GEE correction analysis showed higher rates of OBL formation in the 100-μm group (odds ratio [OR] = 4.704, 95 % CI 1.681–13.161, $P < 0.01$).

Conclusions: OBL was more likely to occur with the 100-μm corneal flap than with the 110-μm corneal flap in Visumax FS-LASIK. The risk of OBL formation in the 100-μm group was 4.704 times higher than that in the 110-μm group.

1. Introduction

Femtosecond laser-assisted stromal in situ keratomileusis (FS-LASIK) has been a popular and effective method of correcting myopic astigmatism, and flap creation is one of the most important steps of this surgery [1,2]. Compared with microkeratomes, flap creation

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with femtosecond laser showed good predictability, accuracy, and safety [3]. However, it could cause complications such as opaque bubble layer (OBL), which was an opaque region formed by the accumulation of gas bubbles during femtosecond flap creation. The reported incidence of OBL formation ranges from 5.0 % to 56.4 % [4–6]. Several studies have shown that OBL formation did not appear to affect postoperative visual acuity [4–6]; however, the OBL may influence the surgical procedure. OBL made the flap adhere more tightly; thus, it may cause flap tears or iatrogenic buttonholes during the attempted lifting of the flap [2,7]. Moreover, OBL could interfere with the tracker or iris registration of the excimer laser [1,2].

Some studies [4–6] have indicated that OBL formation was related to corneal thickness, corneal curvature, and hard docking technique. To the best of our knowledge, there was a lack of studies that objectively analyzed the effect of corneal flap thickness on the OBL. Thus, this study aimed to compare the effects of two types of corneal flap thickness on intraoperative OBL formation.

2. Methods

2.1. Subjects

This retrospective study was conducted from January 2020 to June 2020 at Dongguan Aier Eye Hospital. This study recruited a total of 103 patients diagnosed with refractive error (203 eyes) who underwent Visumax FS-LASIK surgery for the correction of myopic astigmatism. Data of all 203 eyes were recorded and analyzed.

All eyes were divided into two groups according to the corneal flap thickness. The version of Visumax default used and the manufacturer-recommended flap thickness is 110 μm. In addition, thinner flaps may have a higher risk of tearing [8]. Combined with clinical practice, the 100- and 110-μm flap thicknesses are the two most commonly used flap settings in our department. Therefore, 64 eyes of 32 patients were classified into the 100-μm group and 139 eyes of 71 patients into the 110-μm group.

Anterior-segment examination revealed no abnormal findings. Preoperatively, the intraocular pressure (IOP), central corneal thickness (CCT), residual stromal thickness (RST), spherical power, cylindrical power, flat keratometry (K1), steep keratometry (K2), and biomechanical parameters including the deformation amplitude (DA) ratio, Integrated Radius, stiffness parameter at first applanation (SP-A1), and Ambrosio relational thickness to the horizontal profile (ARTh) were evaluated. The abovementioned biomechanical parameters were measured by corneal visualization using Scheimpflug technology (Corvis ST, OCULUS). The IOP was measured three times, and the average was selected. Other data were collected through Pentacam and Corvis ST. Quality specification (QS) was used to assess image quality. When the QS were not OK, then the examination was performed at least twice. The accuracy of the final certificate images and data was verified by at least two experienced ophthalmologists.

The study was approved by the ethics committee of Dongguan Aier Eye Hospital and adhered to the tenets of the Declaration of Helsinki. All patients provided signed informed consent before the operation. All patients underwent COVID-19 evaluation, and COVID-19 protocols were followed.

2.2. Surgical technique

The LASIK flap was created using a 500-kHz femtosecond laser system (VisuMax 3.0, Carl Zeiss Meditec, Germany), and the following procedure was performed using the WaveLight EX500 Excimer Laser System (Alcon Surgical, USA). Details of the surgical parameters are described in Table 1. All FS-LASIK surgeries were performed by the same experienced surgeon. OBL occurred when cavitation gas bubbles produced by the femtosecond laser gathered in the anterior stroma. The OBL was confirmed and recorded independently by two observers.

2.3. Statistical analysis

IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Continuous variables were expressed as mean ± standard deviation. Normality analysis was performed using the Kolmogorov–Smirnov test. Primary outcomes were the incidence of OBL formation in two groups compared by the Chi-square test and the correlation between the incidence of OBL and preoperative parameters by Spearman's Rho test. Secondary outcomes were the comparisons corrected by the generalized estimating equation (GEE) model. A *P*-value <0.05 was considered statistically significant.

Table 1
Surgical parameters.

Flap data	
Thickness (μm)	100 or 110
Diameter (mm)	8.1
Side cut angle (°)	90
Hinge position (°)	90
Hinge angle (°)	50
Hinge width (mm)	3.53
Energy	30
Track distance (μm)	4.5
Spot distance (μm)	4.5

3. Results

3.1. Patient characteristics

All surgeries were performed successfully, and 203 eyes of 103 patients (32 men and 71 women) were analyzed. The mean age of the patients included was 28.2 ± 6.4 years. Preoperatively, the mean central corneal thickness was 528.7 ± 26.6 μm, the mean spherical power was −5.17 ± 1.52 D, and the mean cylindrical power was −0.52 ± 0.41 D. Table 2 shows the demographic data and preoperative eye characteristics of the 100-μm and 110-μm groups.

3.2. Primary outcome

In total, 70 of 203 eyes (34.5 %) developed OBL intraoperatively. In the 100-μm group, 38 of 64 eyes (59.4 %) developed OBL, and in the 110-μm group, 32 of 139 eyes (23.0 %) developed OBL ($\chi^2 = 25.635$, $P < 0.001$) (Fig. 1). Table 3 shows the correlation coefficients between preoperative parameters and OBL formation. The thinner corneal flap thickness ($r = -0.355$, $P < 0.001$) and higher spherical power ($r = -0.142$, $P < 0.05$) correlated with OBL formation. Higher flat keratometry ($r = 0.217$, $P < 0.01$) and steep keratometry ($r = 0.198$, $P < 0.01$) also correlated with OBL formation. IOP, CCT, RST, cylindrical power, DA ratio, Integrated Radius, SP-A1, and ARTh were not correlated with OBL formation ($P > 0.05$).

3.3. Secondary outcomes

Furthermore, GEE models were performed to analyze the independent effect of corneal flap thickness on OBL formation. After adjustment for other factors including spherical power, CCT, RST, K1, and K2, the incidence of OBL was statistically different between the 100-μm and 110-μm groups (Table 4). The risk of OBL in the 100-μm group was 4.704 times higher than that in the 110-μm group (OR = 4.704, 95 % CI 1.681–13.161, $P < 0.01$).

4. Discussion

The application of femtosecond laser in flap creation greatly improves the safety and predictability of LASIK; however, complications may occur. The corneal stromal plane was separated by ionization and photodisruption of the femtosecond laser, and the OBL formed was a unique complication of femtosecond laser [2,9]. OBL may disturb complete flap creation and affect subsequent flap lifting and excimer laser eye tracking. Thus, OBL should clear naturally or by spatula to help with pupillary tracking [2,8]. Therefore, reducing OBL formation during surgery is necessary.

Some studies have reported the risk factors for and incidence of OBL. Jung [4] reported that OBL occurred in 5 % of 827 myopic eyes with Visumax femtosecond laser. They concluded that a steeper cornea may be a risk factor for OBL formation because a steeper cornea may be subjected to more pressure when it touched the patient interface. The comparison of the corneal curvature between groups showed that the mean Flat K and Steep K in the OBL group were greater than those in the OBL-free group ($P < 0.001$) [4]. According to the regression analysis, the effect of the mean flat K was reconfirmed ($P < 0.003$) [4]. In the present study, although higher corneal curvature (K1 and K2) weakly correlated with OBL formation, the correlation was not statistically different according to the GEE analysis.

This study revealed that thinner corneal flaps correlated with OBL formation, and the independent effect on OBL formation was reconfirmed by GEE models, which indicated that OBL occurred more frequently with 100-μm corneal flap than with 110-μm corneal flap. Similarly, in a previous study [10], the incidence of OBL in the 120-μm group was 8 %, which was lower than 19 % in the 80-μm

Table 2
The demographic data and preoperative characteristics.

Baseline Characteristics	100-μm Group (Flap 100 μm)	110-μm Group (Flap 110 μm)
Eyes	64	139
Age, y	27.7 ± 6.4	28.4 ± 6.5
Sex, (male/female)	9/23	24/47
Corneal parameters		
Spherical power, D	−6.17 ± 1.4	−4.71 ± 1.3
Cylindrical power, D	−0.48 ± 0.3	−0.54 ± 0.4
Flat keratometry, D	42.8 ± 1.2	43.1 ± 1.2
Steep keratometry, D	43.8 ± 1.2	43.7 ± 2.8
CCT, μm	516.5 ± 23.2	534.3 ± 26.3
RST, μm	414.4 ± 22.4	422.9 ± 25.7
SP-A1	102.0 ± 15.9	109.1 ± 14.9
Integrated Radius	8.4 ± 1.0	8.0 ± 0.9
ARTh	504.7 ± 99.6	514.3 ± 91.1
DARatio	4.4 ± 0.4	4.2 ± 0.4
IOP	13.3 ± 3.4	14.0 ± 2.7

D diopters, *CCT* central corneal thickness, *RST* residual stromal thickness, *IOP* intraocular pressure.

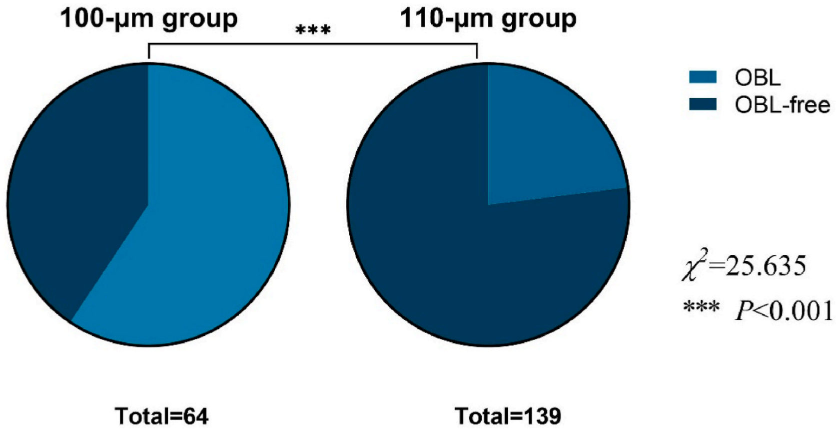

Fig. 1. The Comparison of the incidence rate of OBL in 100-μm group and 110-μm group.

Table 3
Correlation coefficients between preoperative parameters and OBL formation.

Parameters	*r* Value	*P* Value
Age	0.10	0.156
Spherical power	−0.142	**0.044**
Cylindrical power	−0.016	0.819
Flat keratometry	0.217	**0.002**
Steep keratometry	0.198	**0.005**
CCT	−0.094	0.181
RST	−0.023	0.749
SP-A1	−0.082	0.246
Integrated Radius	0.09	0.203
ARTh	0.004	0.955
DARatio	0.089	0.204
Flap thickness	−0.355	**0.000**
IOP	−0.004	0.960

CCT central corneal thickness, *RST* residual stromal thickness, *IOP* intraocular pressure.

Table 4
Parameters estimation result of GEE analysis in 100-μm and 110-μm group.

Parameters	Exp(*β*)	95 % CI	Waldχ^2 Value	*P* Value
100-μm flap	4.704	1.681 to 13.161	8.701	**0.003**
110-μm flap				
Spherical power	1.048	0.779 to 1.410	0.095	0.758
RST	1.051	0.990 to 1.116	2.661	0.103
CCT	0.957	0.903 to 1.015	2.109	0.146
Flat keratometry	1.282	0.785 to 2.094	0.985	0.321
Steep keratometry	1.348	0.830 to 2.190	1.456	0.228

Gee generalized estimating equation; *95 % CI* 95 % confidence interval.

flap group with Visumax femtosecond laser. Another study [11] showed that the 80-μm flap group was associated with a higher OBL occurrence than the 80-μm flap group ($P = 0.0424$, OR = 0.481). Denser anterior corneal stroma may be more resistant, and this higher resistance may interfere with the dispersion of cavitation bubbles into the surrounding tissue [10]. Thinner flaps were located where the corneal stroma is denser, and their higher resistance may lead to more frequent OBL formation, which may explain the higher incidence of OBL in the 100-μm corneal flap group.

Li et al. [12] suggested that the risk of OBL significantly decreased with increasing myopia (diopters) in small incision lenticule extraction (SMILE) surgery (OR = 0.44; 95 % CI 0.30–0.64; $P < 0.0001$). In this study, higher spherical power ($r = -0.142$, $P < 0.05$) correlated with OBL formation; however, it was corrected by GEE analysis, showing no association between spherical power and OBL formation. This could be attributed to the higher spherical power accompanied by the thinner corneal flap in our clinical practice, resulting in the increasing possibility of OBL formation.

Moreover, some studies have indicated that corneal thickness was a risk factor for OBL formation in FS-LASIK [4–6]. This agreed with the findings of previous studies on SMILE. Son et al. [13] and Ma et al. [14] demonstrated that thicker corneas could increase OBL formation in SMILE. Thicker corneas could create more resistance and provide greater rigidity, which could limit the clearance of cavitation bubbles, finally increasing OBL formation [6]. Corneal thickness positively correlated with the corneal resistance factor and corneal hysteresis [15].

The stiffness parameter (SP), which represents the ability of the cornea to resist elastic deformation, was closely related to OBL formation [9]. When the cornea is more rigid, the ability to resist elastic deformation is stronger. Although the bubble spreads, it cannot spread along the path of least resistance, forming OBL [9]. On the contrary, with low corneal stiffness, the ability to resist elastic deformation is weak. The bubbles formed by the femtosecond laser have less resistance to diffusion to the surrounding area; thus, OBL is not easily formed [9].

Furthermore, the corneal resistance factor, corneal hysteresis, and central corneal thickness significantly positively correlated with OBL formation [16]. However, no significant association was found between central corneal thickness, corneal biomechanics parameters (including DA ratio, Integrated Radius, SP-A1, and ARTh) and OBL formation. Thus, further observations with larger sample sizes and longer follow-ups are needed. In addition, a study suggested that the decrease in postoperative optical density correlated with the delayed visual recovery observed after SMILE [17], whereas OBL may influence the early corneal density. The correlation between these two could be further explored in subsequent studies.

This study determined the influence of thin corneal flap thickness on OBL formation in FS-LASIK and could provide evidence for better preoperative flap design to reduce OBL formation, with clinical significance. However, some limitations remain. The span of flap thickness was small; thus, more groups and spans are needed in later studies. Given the retrospective design, a prospective confirmatory study is necessary to confirm the findings.

5. Conclusions

This study reveals that OBL was more likely to occur with a 100-μm corneal flap than with a 110-μm corneal flap in Visumax FS-LASIK, which could contribute to an optimal surgical design for surgeons.

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Data availability statement

Data will be made available on request.

Ethics statement

Approval for this study has been obtained from the ethics committee at the Dongguan Aier Eye Hospital (number: 2021KYPJ001).

Consent for publication

Not Applicable.

CRediT authorship contribution statement

Na Zhou: Conceptualization, Formal analysis, Project administration, Validation, Writing – original draft, Writing – review & editing. **Xiaobei Chen:** Conceptualization, Methodology, Validation, Visualization. **Na Yin:** Investigation, Project administration, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not Applicable.

List of abbreviations

OBL opaque bubble layer
FS-LASIK femtosecond laser-assisted stromal in situ keratomileusis
IOP intraocular pressure
CCT central corneal thickness

RST residual stromal thickness
K1 flat keratometry
K2 steep keratometry
DA ratio deformation amplitude ratio
SP-A1 stiffness parameter at first applanation
ARTh Ambrosio relational thickness to the horizontal profile
GEE generalized estimating equation
OR Odds Ratio
D diopters
95 % CI 95 % confidence interval

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