Efficacy of 0.015% intracameral epinephrine for significant miosis induced by photodisruption during femtosecond laser-assisted cataract surgery

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Abstract
Despite the various advantages of femtosecond laser-assisted cataract surgery (FLACS), pupillary constriction during laser photodisruption is considered one of the most unfavorable events. This study aimed to investigate the efficacy of intracameral 0.015% epinephrine injection for miosis after laser pretreatment during FLACS.

A total of 82 patients who underwent FLACS for age-related cataracts were investigated in this retrospective study. The epinephrine group included patients who received intracameral epinephrine injection for miosis after femtosecond laser pretreatment, while the no-epinephrine group included the patients who underwent FLACS without intracameral epinephrine due to minimal miosis. Quantitative pupil area measurements were performed through the analysis of captured images extracted from surgical videos of both femtosecond laser pretreatment and phacoemulsification.

Laser photodisruption induced miosis in both groups, although the degree of miosis was greater in the epinephrine group (4.65 ± 0.87 mm) than in the no-epinephrine group (6.30 ± 0.65 mm; P < .001). The intracameral epinephrine injection significantly increased the pupil diameter from 4.65 ± 0.87 to 5.49 ± 0.76 mm (21.61 ± 22.68%; P < .001) and the pupil area from 70.28 ± 24.46 to 96.49 ± 25.24 mm² (52.89 ± 63.54%; P < .001). After additional viscomydriasis, there was no difference between groups in pupil diameter (epinephrine vs no-epinephrine group: 6.10 ± 0.77 vs 6.39 ± 0.65 mm; P = .073).

A single intracameral injection of 0.015% epinephrine provided immediate and appropriate redilation of pupil in patients with significant miosis after femtosecond laser photodisruption. Intracameral epinephrine is a simple and practical option for pupil redilation in case of miosis during FLACS.

Abbreviations: FLACS = femtosecond laser-assisted cataract surgery, IOL = intraocular lens, NSAID = nonsteroidal anti-inflammatory drug.

Keywords: cataract surgery, femtosecond laser-assisted, intracameral epinephrine, miosis

1. Introduction
Since the introduction of femtosecond laser technology for cataract surgery procedures in 2009,[1] the efficacy and safety of femtosecond laser-assisted cataract surgery (FLACS) in comparison with those of manual cataract surgery have been demonstrated. Precise and predictable capsulotomy,[2-4] accurate and stable corneal incisions,[5,6] and low erroneous astigmatic keratotomies have been demonstrated.[3,4] In addition, the effective phacoemulsification time can be significantly decreased by laser fragmentation during FLACS.[9,10]

Despite the various advantages of FLACS, pupillary constriction induced by prostaglandin release during laser photodisruption is considered one of the most unfavorable events.[11,12] Early studies on the complications of FLACS have reported that the incidence of intraoperative miosis due to femtosecond laser pretreatment is approximately 9.5% to 32%,[13-15] and we reported that the pupil area can be decreased by nearly 30% after femtosecond laser photodisruption.[16] Schultz et al.[17-19] suggested that laser capsulotomy is associated with prostaglandin release and hypothesized that lower pulse energy and reduced incision depth during capsulotomy could prevent miosis because shockwaves delivered to the ciliary body might induce prostaglandin release. Recent trials have reported the efficacy of pretreatment with nonsteroidal anti-inflammatory drug (NSAID) eye drops for the prevention of miosis after femtosecond laser procedures. In these studies, NSAID pretreatment effectively minimized the elevation of prostaglandin E₂ concentrations in the aqueous humor. However, we observed that significant miosis still occurred at a constant rate after this pretreatment, and that the pupil area decreased after the laser procedure even if the degree of miosis was lowered.[20-23]
There are 2 solutions for miosis occurring after the laser procedure despite pretreatment with NSAID eye drops. One is mechanical redilation with iris retractors or expansion rings, which is an easily applicable and effective solution. However, pupillary constriction interferes with observation of the laser capsulotomy margin, and capsulotomy using a mechanical device results in more easy tearing compared with continuous curvilinear manual capsulotomy. In addition, the use of a mechanical device can increase surgical costs. Therefore, redilation using mydriatics or intracameral injection of adrenergic receptor agonists such as epinephrine or phenylephrine would be a more efficient, cost-effective, and easily applicable strategy compared with mechanical dilation in patients undergoing FLACS. However, the actual efficacy of intracameral mydriatics for the redilation and maintenance of mydriasis in pupillary effects on both the pupil diameter and area.

In the present study, we investigated the efficacy of a single intracameral injection of 0.015% epinephrine for pupil redilation in patients with significant miosis induced by femtosecond laser pretreatment during FLACS and quantitatively analyzed its effects on both the pupil diameter and area.

2. Methods

This retrospective study enrolled patients who underwent FLACS from December 2013 to September 2015 at Seoul St. Mary’s Hospital, Seoul, South Korea. Institutional Review Board (IRB) approval was obtained (IRB no. KC14RISI0570), and the study was performed in accordance with the tenets of the Declaration of Helsinki. The patients were divided into 2 groups. The epinephrine group included patients who received a single bolus intracameral injection of 0.015% epinephrine for significant pupillary constriction to cover the capsulotomy margin at the initiation of phacoemulsification, while the no epinephrine group included patients with minimal miosis after femtosecond laser pretreatment who did not require epinephrine.

Patients with a history of intraocular surgery or a significant previous history of ocular trauma, those with pseudoxfolliation syndrome, those using glaucoma medications, and those with preoperative zonular weakness or poor pupil dilation (measured pupil diameter < 5.5mm) were excluded. Patients who had consumed systemic or topical steroids or NSAIDs within the previous 2 weeks or a systemic α1A-adrenoceptor antagonist such as tamsulosin were also excluded. All patients with available data pertaining to age, sex, the laterality of surgery, suction duration, and laser treatment duration were included.

2.1. Pupil dilation regimen

All patients in both groups received a mydriatic fixed-combination eye drop containing sympathomimetics and parasympatholytics (0.5% tropicamide and 0.5% phenylephrine; Mydrin-P, Santen Pharmaceutical Co., Ltd., Osaka, Japan) for preoperative mydriasis 3 or 4 times in the hour before femtosecond laser pretreatment. In case of insufficient pupil dilation (< 5.5mm), a dilating eye drop was administered once or twice. Preoperative NSAIDs were not used in the present study.

2.2. Intracameral epinephrine injection

Preservative-free (bisulfite-free) epinephrine is not available in South Korea. Therefore, preservative (bisulfite)-containing epinephrine was used. To minimize bisulfite toxicity in the corneal endothelium, 0.3 mL of bisulfite-containing (preservative-containing) 1:1000 (0.1%) epinephrine (DAIHAN Pharm., Seoul, South Korea) was diluted in 1.7 mL of balanced salt solution (BSS, Alcon Laboratories Inc., Fort Worth, TX) to achieve a final concentration of 0.015%. In the epinephrine group, approximately 0.1 mL of diluted epinephrine was injected into the anterior chamber.

2.3. Parameters of femtosecond laser pretreatment

Following confirmation of sufficient pupillary dilatation (≥ 5.5 mm), femtosecond laser pretreatment using the Catalys Precision Laser System (Johnson & Johnson Vision Care Inc., Jacksonville, FL) was performed for all patients. All laser procedures and cataract surgeries were performed under topical anesthesia. The capsulotomy size ranged from 4.9 to 5.8 mm, and the pulse energy was set at 4.0 μJ with a depth of 600 μm. Lens fragmentation was performed quadrant-wise with an 8/10 (anterior/posterior)-μJ pulse energy. The arcuate incision was created with an energy of 5 μJ. The primary and secondary laser incisions were created with a pulse energy of 6 μJ. Spot spacing (horizontal/vertical) of capsulotomy, lens fragmentation, and arcuate, primary, and sideport incision were 5/10, 10/40, 5/10, 4/8, and 3/5 μm, respectively. Width/length of primary and sideport incision were 2.3/1.1 and 1.1/1.1 mm, respectively. Following completion of the entire laser emission procedure, each patient was transferred to a day-surgery operation room. The phacoemulsification procedure was performed using the Infiniti Vision System (Alcon Laboratories, Fort Worth, TX) with the conventional technique. All femtosecond laser pretreatments and phacoemulsifications were performed by the same experienced surgeon (C-KJ).

2.4. Pupil area measurement

Measurements of the pupil area before femtosecond laser pretreatment and after each individual procedure of phacoemulsification were obtained using a previously described method.[16] Captured images derived from surgical video files of the femtosecond laser and phacoemulsification procedures were used. The pupil area during phacoemulsification was calculated before and after intracameral injection of 0.015% epinephrine, after injection of the ocular viscoelastic device, at the initiation and termination of phacoemulsification, at the removal of the lens cortex, and at the insertion of the intraocular lens (IOL). Both the pupil and capsulotomy areas for analysis of the actual pupil area were measured using ImageJ software (National Institutes of Health, Bethesda, MD).[56] To overcome the error of pupil area measurement according to magnification, we recalculated pupil area and diameter in video capture images at every time the surgeon adjusted the magnification during phacoemulsification. The pupil area was calculated using the following proportional equation:

\[
\text{Pupil area (mm}^2\text{)} = \frac{\text{Measured pupil area}}{\text{Measured capsulotomy area}} \times \pi \left( \frac{\text{Diameter}}{\text{Target}} \right)^2
\]

2.5. Statistical analyses

A paired t test was used to evaluate the efficacy of the single intracameral epinephrine injection for pupil redilation in the
epinephrine group. An independent $t$ test was used to compare the pupil areas before and after femtosecond laser pretreatment and after each phacoemulsification procedure. A chi-squared test was used to compare parameters such as sex and laterality of surgery. A $P$-value of $<.05$ was considered statistically significant, and all statistical analyses were performed using SPSS Statistics for Windows Version 12.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 82 eyes of 82 patients, including 34 in the epinephrine group and 48 in the no epinephrine group, was included. The mean patient ages were 60.74±13.03 and 64.08±11.41 years in the epinephrine and no epinephrine groups, respectively, with no significant difference between groups ($P=.221$). Surgery was performed on the right side in 16 and 30 patients and the left side in 18 and 18 patients in the epinephrine and no epinephrine groups, respectively. The sex distribution (male/female) was 12/22 in the epinephrine group and 17/31 in the no epinephrine group. There were no significant differences in the laterality of surgery and sex distribution between the 2 groups ($P=.165$ and .991, respectively). The suction and laser treatment durations were 273.75±50.39 and 261.41±64.07 seconds, respectively, in the epinephrine group and 62.93±20.11 and 69.96±20.63 seconds, respectively, in the no epinephrine group, with no significant differences between groups ($P=.345$ and .139, respectively). The patient characteristics are shown in Table 1.

3.2. Efficacy of the single intracameral injection of 0.015% epinephrine

The mean pupil diameter significantly increased from 4.65±0.87 to 5.49±0.76 mm (21.61%) after the intracameral epinephrine injection ($P<.001$), while the mean pupil area significantly increased from 70.28±24.46 to 96.49±25.24 mm$^2$ (52.89%; $P<.001$; Table 2).

3.3. Comparison of pupil diameters from femtosecond laser pretreatment to IOL implantation

The mean pupil diameters before laser pretreatment were not different between groups. Laser photodisruption induced miosis in both groups (epinephrine group: 7.13±0.75–4.65±0.87 mm, $P<.001$; no epinephrine group: 7.14±0.61–6.30±0.65 mm, $P<.001$). After laser pretreatment, the mean pupil diameter in the epinephrine group was significantly smaller than that in the no epinephrine group (6.30±0.63 vs 4.65±0.87 mm; $P<.001$). After intracameral epinephrine injection, the mean pupil diameter in the epinephrine group increased to 5.49±0.76 mm. There was no significant difference between groups in the pupil diameter after additional viscomydriasis using oculair viscoelastic devices (epinephrine vs no epinephrine group: 6.10±0.77 vs 6.39±0.65, $P=.073$). The mean pupil diameter was additionally increased at the initiation of phacoemulsification by fluid infusion through the hand piece tubing to the anterior chamber, with the no epinephrine group exhibiting a slightly wider pupil (epinephrine group: 6.26±0.99 mm, no epinephrine group: 6.74±0.88 mm; $P=.023$). However, during phacoemulsification, the pupil diameter in the epinephrine and no epinephrine groups decreased to 6.01±0.93 and 6.18±0.94 mm, respectively ($P=.418$). At the end of phacoemulsification, there was no difference between the 2 groups ($P=.418$), and at the initiation of lens cortex removal and IOL implantation, the no epinephrine group exhibited wider pupils compared with the epinephrine group (cortex removal: $P=.018$, IOL implantation: $P=.006$). Although significant miosis occurred during femtosecond laser pretreatment, intracameral epinephrine induced redilation and maintained a pupil diameter of over 5.17 mm, which indicated the mean laser capsulotomy diameter (Fig. 1).

3.4. Comparisons of specular microscopy findings before and after FLACS

For evaluation of the toxicity of 0.015% intracameral epinephrine on corneal endothelial cells, we evaluated differences in cell density, the coefficient of variation, and hexagonality between the 2 groups using a specular microscope (Noncon ROBO-CA SP-8800, Konan Medical Inc., Tokyo, Japan). There were no significant differences between groups in the preoperative and 1-month postoperative endothelial cell density, coefficient of variation, and hexagonality (Table 3).

4. Discussion

Maintenance of adequate mydriasis is one of the most essential conditions necessary to perform cataract surgery without intraoperative complications and improve surgical outcomes. In the present study, we sought to confirm the efficacy of a single intracameral injection of 0.015% epinephrine for the maintenance of mydriasis during phacoemulsification and quantitatively determine its effects on pupillary constriction.

Relatively large-scale studies including early cases of FLACS have been reported, and FLACS surgeons are aware
of the occurrence of intraoperative miosis due to laser photodisruption. Therefore, to decrease the incidence of miosis during this procedure, modified dilating regimens or additional instillation of dilating agents until intracocular lens implantation was similar in the epinephrine and no epinephrine groups. Nevertheless, intraoperative miosis still occurs. In the present study, we attempted to introduce and investigate the efficacy of a single intracameral epinephrine injection for the management of miosis caused by laser pretreatment, despite previously suggested preoperative modifications. To achieve our aim, we included patients with early FLACS who did not receive pretreatment with NSAID eye drops. Our findings suggested that miosis occurs at a greater rate and to a greater degree than usual, and we were able to evaluate the effects of intracameral epinephrine.

Miosis occurred after femtosecond laser pretreatment in all our patients, as reported previously. Compared with the mean pupil diameter of 6.30 ± 0.65 mm in the no epinephrine group, that in the epinephrine group decreased to 4.65 ± 0.87 mm and was significantly smaller than the established femtosecond laser capsulotomy diameter of 5.17 mm. However, immediately after intracameral epinephrine injection, pupil diameter increased to an average of 5.49 ± 0.76 mm, an increase of 21.6%. The average pupil area increased from 70.28 ± 24.46 to 96.49 ± 25.24 mm², indicating that >50% of the surgical field was secured. With additional injection of ocular viscoelastic devices (viscomydriasis), the pupil diameter was further increased, with no statistically significant difference between the 2 groups. These results suggest that the intracameral epinephrine injection was very effective for redilation in patients with significant intraoperative miosis immediately after laser pretreatment.

Following redilation of miotic pupils with a single intracameral epinephrine injection, maintenance of adequate mydriasis would be another concern with regard to appropriate phacoemulsification of the lens nucleus or cortex cleavage. In the present study, pupil diameters were calculated sequentially after each procedure. Although the mean pupil diameter in the epinephrine group was significantly smaller than that in the no epinephrine group after each procedure during FLACS, a mean diameter of
approximately 6.0 mm was maintained after the single epinephrine injection. Because the mean planned laser capsulotomy diameter is 5.17 mm, a 6.0-mm pupil diameter is adequate for cataract surgery procedures such as phacoemulsification, cortex removal, and IOL implantation.

Intracamerale epinephrine injection, particularly in patients with intraoperative miosis, has been associated with endothelial toxicity due to preservatives and bisulfite-containing epinephrine. However, bisulfite-free or preservative-free epinephrine is unavailable in South Korea and other countries. Fortunately, direct intracameral injection of a 1:4 dilutions of bisulfite-containing epinephrine is not toxic to the corneal endothelium. In the present study, we administered a single bolus intracameral injection of 0.3 mL epinephrine diluted with 1.7 mL of balanced salt solution (＞5-fold dilution, 0.015% epinephrine hydrochloride). In addition, we evaluated the findings of specular microscopy to identify the effects of our regimen and found no significant difference in cell density, the coefficient of variation, and hexagonality between the 2 groups after 1 month.

One limitation of this study is that epinephrine was used to resolve the complication of intraoperative miosis, which is a surgical complication of FLACS. Therefore, it was not possible to conduct a prospective controlled study because the incidence was low. Therefore, the results of this study provide limited information on the efficacy of intracameral injection of 0.015% epinephrine for intraoperative miosis. Follow up studies such as prospective, multicenter study will be needed as the incidence of intraoperative miosis is low.

In conclusion, this study demonstrated the effectiveness of a single intracameral injection of 0.015% epinephrine for significant miosis due to femtosecond laser photodisruption during FLACS. The single injection could maintain the pupil diameter during the entire phacoemulsification procedure. Our findings suggest that this technique is practical and safe for the successful and uneventful completion of phacoemulsification in patients with significant miosis during FLACS.

Author contributions
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