Eye (2020) 34:2300–2306
https://doi.org/10.1038/s41433-020-0812-5

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ARTICLE

Comparison of the effects of 1/10,000 and 1/100,000 concentrations of intracameral epinephrine on corneal endothelium and macular thickness after uncomplicated phacoemulsification

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Received: 25 February 2019 / Revised: 9 October 2019 / Accepted: 21 October 2019 / Published online: 3 March 2020

Abstract

Purpose To evaluate the changes in the corneal endothelial cell parameters and macular thickness after intraocular application of epinephrine $\frac{1}{10,000}$ and epinephrine$\frac{1}{100,000}$.

Methods In this study, 210 eyes from 210 patients with age-related cataracts who underwent uncomplicated surgery were included. For all patients, specular microscopy of the corneal endothelium and macular OCT were performed before surgery and 3 months after the surgery. Patients were divided randomly into three groups: without drug (control group), epinephrine $\frac{1}{10,000}$, and epinephrine$\frac{1}{100,000}$. Three months after the surgery, specular microscopy of the cornea and macular OCT measurements were performed. Measurements were compared between the three groups. Postoperative measurements were also compared with those measurements obtained before surgery.

Results All the three groups showed a statistically significant decrease in the endothelial cell density after surgery; the reduction in endothelial cell density in the epinephrine $\frac{1}{10,000}$ group was significantly more than those of the other two groups (P value < 0.001). Hexagonality of endothelial cells was significantly reduced in the three groups after the surgery, the epinephrine $\frac{1}{10,000}$ group had more reduction compared with both other groups (P values < 0.001). All the three groups showed a statistically significant increase in the macular thickness after the surgery (P values < 0.001). The mean increase in the macular thickness in the epinephrine $\frac{1}{10,000}$ group was significantly more than those of the other two groups (P values < 0.05).

Conclusion Toxicity of the drug to many endothelial cell parameters and macula was reduced with decreasing concentration of epinephrine to $\frac{1}{100,000}$.

Introduction

Adequate mydriasis is necessary for most intraocular surgeries especially for cataract operation. Topical administration of cycloplegics (anticholinergics) and sympathomimetic mydriatic agents such as tropicamide, cyclopentolate, and phenylephrine is generally used to achieve mydriasis preoperatively. Although these agents provide adequate mydriasis in many patients, in some patients the mydriasis is inadequate and in some others pupillary constriction may occur during cataract surgery due to insufficient adrenergic stimulation of the pupil dilators or inadvertent manipulation of the iris [1, 2]. Pupillary constriction during cataract surgery is a major risk factor for intraoperative complications, including posterior capsule rupture, vitreous loss, posterior dislocation of the lens materials, iris damage, zonulysis, and incomplete cortex removal [3]. Therefore, maintenance of mydriasis during the procedure is of paramount importance. Several methods such as mechanical mydriasis using iris retractors [4], pharmacological pupillary dilation using topical nonsteroidal anti-inflammatory drugs [5–7], or epinephrine

Supplementary information The online version of this article (https://doi.org/10.1038/s41433-020-0812-5) contains supplementary material, which is available to authorized users.

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[8, 9], are suggested to achieve and maintain intraoperative mydriasis. Intracameral mydriatics have also been evaluated for maintaining mydriasis during phacoemulsification cataract surgery [1, 10]. Because of several complications associated with mechanical dilatation of the pupil, pharmacological pupillary dilation with epinephrine is commonly used for achieving or maintaining mydriasis during surgery. It is used either as a single bolus dose or in the irrigating solution. An important issue in application of intraocular medications is concerns regarding their safety. Endothelial toxicity is a major concern when intracameral administration of drugs is performed. Few studies have evaluated the effects of epinephrine on the corneal endothelium. Some of these studies have shown endothelial toxicity associated with perioperative usage of epinephrine [11–13]. However, in other studies epinephrine had no toxic effects on the endothelium [14, 15].

Epinephrine use is known as a risk factor for macular oedema; concept of epinephrine-induced macular oedema has been demonstrated statistically since more than three decades ago and has been supported by other studies thereafter [16–18]. Finding a safe dose of epinephrine is a research goal.

The purpose of the present study was to evaluate the changes in the corneal endothelial cell parameters and macular thickness after intraocular application of epinephrine $\frac{1}{10,000}$ and epinephrine $\frac{1}{100,000}$ in patients who underwent uneventful phacoemulsification cataract surgery.

Materials and methods

Study design and participants

In this prospective interventional study, we randomly enroled 218 eligible patients with age-related cataracts, all of whom were scheduled for unilateral phacoemulsification and intraocular lens (IOL) implantation. Randomization and assignment were performed using research randomizer software (version 4.0; Urbaniak, G. C. & Plous, S.; 2011). Sample size was calculated before inclusion of the first patient. With 90% power, and at alpha level of 0.05, 42 patient calculated as the minimum requirement for each group. However, we included more than 70 in each arm. The eyes with history or objective sign of trauma, previous intraocular surgery, uveitis, glaucoma, corneal opacity, corneal endothelial dystrophies, pseudoexfoliation syndrome, iris atrophy, macular problems, or any ocular disorder other than cataract were excluded. Patients with any systemic disorders such as diabetes, thyroid disease, rheumatologic disease, and so on were also excluded. In addition, patients with any intraoperative complications including posterior capsular rupture, inadvertent iris manipulation, and patients with extended phacoemulsification times were excluded. (Two hundred and eighteen patients were enroled that after exclusion of patients with intraoperative complications 210 patients were remained.) The study was conducted according to the tenets of the Declaration of Helsinki, and the study protocol was approved by the ethics committee at Shiraz University of Medical Sciences. Written Informed consent was obtained from each patient. Once they had signed the informed consent, they were randomly assigned to the three study groups.

Participants were unaware of the group in which they were assigned. The surgeon was blinded to the concentration of epinephrine used in every patient. The technicians who assessed study outcomes (specular microscopy and macular OCT parameters) were also blinded to the concentration of the medication. All the cases underwent a complete ocular examination including Snellen VA, applanation tonometry, slit-lamp exam, and dilated fundus examination. Lens Opacities Classification System III protocol was used preoperatively for grading of nuclear and cortical cataracts to rule out preoperative differences between the two groups. The mean surgery time (min), mean US time, mean US power (%), mean total US energy, and mean irrigation volume (mL) were measured during the surgery for all patients.

Surgical procedure

Before the surgery, tropicamide 1.0% was used to achieve mydriasis in all patients. All operations were performed by the same surgeon (S. B) and a similar phacoemulsification machine was used for all operations. A similar technique was used for all operations: Using general or local anaesthesia, after preparation with povidone iodine 10%, a 3.0 mm temporal clear cornea incision was created. Then, the control group did not receive epinephrine; the epinephrine groups received either an injection of 0.2 mL preservative-free epinephrine (1:10,000) or 0.2 mL preservative-free epinephrine (1:100,000). In all the three groups, the same visoelastic (HPMC, Ocucoat, Bausch & Lomb) was injected into the anterior chamber. Then, a continuous curvilinear capsulorhexis was created and phacoemulsification performed using a stop-and-chop technique. The cortex was aspirated in irrigation/aspiration mode. Sodium hyaluronate 1% (Healon) was injected into the capsular bag and a foldable acrylic IOL implanted in the bag. Viscoelastic was irrigated from the anterior chamber and stromal hydration was used to close the corneal incisions. Topical chloramphenicol and prednisolone acetate eye drops were given six times daily for the first week. Then, chloramphenicol eye drop was continued four times daily for 3 weeks and the prednisolone acetate was slowly tapered over 4 weeks postoperatively and then discontinued. Postoperative

Table 1 The demographic characteristics of the patients and the time and energy of phacoemulsification in the three groups.

	Group 1	Group 2	Group 3
Age: mean(±SD)	63.6429 (6.884)	64.5571 (9.227)	63.7714 (9.735)
Sex: male(%) percent	61.4	55.7	61.4
Phacoemulsification time: mean (±SD)	47.22 (23.38)	41.0900 (19.260)	48.72 (18.690)
Phacoemulsification energy: mean (± SD)	29.2800 (10.397)	29.6871 (11.972)	26.4086 (11.170)

Group 1: control group, Group 2: epinephrine $\frac{1}{10,000}$ group, Group 3: epinephrine $\frac{1}{100,000}$ group.

examinations included BSCVA, slit-lamp biomicroscopy, IOP measurement, and indirect ophthalmoscopy.

Study outcome measures

Corneal endothelial density: Central corneal endothelial photographs were taken with the Topcon SP-3000P specular microscope (Topcon Europe BV, Capelle a / d Ijssel, the Netherlands) preoperatively and at 3 months postoperatively. The corneal endothelial morphology was calculated from a central cluster of 50 cells from each photograph. Three photographs were taken, and the measurements recorded and averaged. The hexagonality quantifying the percentage of endothelial cells with the ideal hexagonal cell shape was also calculated and recorded. The coefficient of variation in cell size (CV) was also calculated. A comparison between pre- and postoperative values was performed.

Macular thickness: OCT measurements were performed preoperatively and at 1 and 3 months post operation. Macular thickness measurements were performed using Optical coherence tomography (Spectralis OCT, Heidelberg Engineering, SN:TR-KT-1457, Germany).

The central 1.0 mm retinal thickness measurements were taken from the fast macular thickness maps, which were calculated from the six low-resolution diagonal scans. The six radial diagonal scans were used to quantitatively evaluate the macula. Before the inclusion, all patients in the study had normal macular morphology and thickness.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software version 21 (SPSS Inc., Chicago, IL). Independent-samples *T*-test was used to compare the outcomes between the control and epinephrine groups. Intragroup changes in the outcome measures were assessed by the repeated-measures ANOVA test. A P value < 0.05 was considered as statistically significant.

Results

After exclusion of eight patients with intraoperative complications such as posterior capsular rupture, inadvertent iris manipulation, and patients with extended phacoemulsification times, 210 eyes of 210 patients were included in the study. The demographic chara cteristics of the patients and also the time and energy of phacoemulsification are summarized in Table 1.

Table 2 Baseline endothelial cell density measurements and the endothelial cell density measurements after surgery in the three groups.

Endothelial cell density	Group 1	Group 2	Group 3
Pre operation	2110.700	2169.757	2180.771
Post operation	1921.742	1589.228	1859.157

Group 1: control group, Group 2: epinephrine $\frac{1}{10,000}$ group, Group 3: epinephrine $\frac{1}{100,000}$ group.

There were no statistically significant differences in age and sex among the three study groups ($P > 0.05$). There was also no significant difference among the three groups regarding the time and energy of phacoemulsification. ($P > 0.05$). Baseline endothelial cell density measurements and the endothelial cell density measurements after surgery in the three groups are summarized in Table 2.

There was no significant difference among the mean endothelial cell densities of the three groups at baseline. All the groups showed a statistically significant decrease in the endothelial cell density after the surgery (P values < 0.001). When the group results were compared, the postoperative endothelial cell density in the epinephrine $\frac{1}{10,000}$ group was significantly less than the other two groups (P values $<$ 0.001). Mean postoperative value of the epinephrine $\frac{1}{100,000}$ group was not significantly different from that of control group (0.689). Difference between the baseline and postoperative endothelial cell density (postoperative endothelial cell density minus baseline endothelial cell density: mean reduction in the endothelial cell density) was also compared among the groups. When the groups' results were compared, the mean reduction in the endothelial cell density in the epinephrine $\frac{1}{10,000}$ group was significantly more than the control group and the epinephrine $\frac{1}{100,000}$ group (P values $<$ 0.001). In addition, the mean reduction in the endothelial cell density in the epinephrine $\frac{1}{100,000}$ group was significantly more than the control group (P value $= 0.033$). The mean percentage of the endothelial cell hexagonality at baseline and post operation in the three groups are summarized in Table 3.

Table 3 Baseline endothelial cell CV measurements and the endothelial cell CV measurements obtained after surgery in the three groups.

	Group 1	Group 2	Group 3
Preop CV: mean (SD)	34.6429 (9.253)	33.6571 (7.081)	35.1000 (9.354)
Postop CV: mean (SD)	35.2429 (10.004)	35.0571 (6.786)	36.0857 (8.586)

Group 1: control group, Group 2: epinephrine $\frac{1}{10,000}$ group, Group 3: epinephrine $\frac{1}{100,000}$ group.

Table 4 Measurements of baseline and postoperative percent of hexagonality of endothelial cell obtained in the three groups.

	Group 1	Group 2	Group 3
Preop hexagonality: mean (SD)	53.7571 (17.073)	54.8143 (16.162)	55.6714 (16.161)
Postop hexagonality: mean (SD)	50.8857 (15.206)	40.4429 (16.556)	50.4714 (14.646)

Group 1: control group, Group 2: epinephrine $\frac{1}{10,000}$ group, Group 3: epinephrine $\frac{1}{100,000}$ group.

Table 5 Summarizes the baseline macular thickness measurements and the macular thickness measurements obtained after the surgery in the three groups.

	Group 1	Group 2	Group 3
Preop macula thickness	258.6714 (17.971)	251.3429 (31.570)	257.5429 (22.840)
Postop macula thickness	268.7714 (20.880)	273.0000 (31.703)	266.0286 (31.632)

Group 1: control group, Group 2: epinephrine $\frac{1}{10,000}$ group, Group 3: epinephrine $\frac{1}{100,000}$ group.

There was no significant difference among the mean endothelial cell hexagonality measurements of the three groups preoperatively. Compared with preoperative values, hexagonality of the endothelial cells was significantly reduced in the three groups after the surgery (P values < 0.001). The mean percentage of the endothelial cell hexagonality in the epinephrine $\frac{1}{10,000}$ group was significantly less than the other two groups (P value < 0.001). However, the percentage of the endothelial cell hexagonality in the epinephrine $\frac{1}{100,000}$ group was not significantly different from the control group (P value = 0.98). When the difference between hexagonality before and after the surgery (mean reduction in endothelial cell hexagonality) was compared among the groups, the epinephrine $\frac{1}{10,000}$ group showed more reduction compared with the other two groups, but there was no statistically significant difference between the control and epinephrine $\frac{1}{100,000}$ groups (P value = 0.524). The CV of the endothelial cells was also compared among the three groups. The baseline and postoperative mean CV of the endothelial cells in the three groups are summarized in Table 4.

There was no significant difference between the CV of the three groups at baseline. Mean reduction of CV (difference between baseline and postoperative endothelial cell CV) was also compared among the groups. There was no significant difference among the groups regarding the mean reduction of the endothelial cell C (P values > 0.05). Table 5 summarizes the baseline macular thickness measurements and the macular thickness measurements obtained after the surgery in the three groups.

There was no significant difference among the mean macular thickness of the three groups at baseline (P values > 0.05). All the three groups showed a statistically significant increase in the macular thickness after the surgery (P values < 0.001). However, there was no significant difference among the groups regarding the mean postoperative macular thickness values (P > 0.05). When the group results were compared, the increase in the macular thickness (difference between baseline and postoperative macular thickness) in the epinephrine $\frac{1}{10,000}$ group was significantly more than the other two groups (P value = 0.016 when control group compared with epinephrine $\frac{1}{10,000}$ group, and P value = 0.005 when epinephrine $\frac{1}{100,000}$ group was compared with $\frac{1}{10,000}$ group), but there was no statistically significant difference between the epinephrine $\frac{1}{100,000}$ and control groups (P value = 0.92). Baseline pupil size measurements and the pupil size measurements after application of epinephrine $\frac{1}{10,000}$ and $\frac{1}{100,000}$ are summarized in Supplementary Table 6.

There was no significant difference between the mean pupil sizes of the two epinephrine groups at baseline. Both epinephrine groups showed a statistically significant increase in the pupil size after epinephrine injection (P values < 0.001). When the groups' results were compared, the mean increase in the pupil size in the epinephrine $\frac{1}{10,000}$ group was significantly more than the epinephrine $\frac{1}{100,000}$ group (P value < 0.001). Postinjection size of the pupil was also significantly more in the epinephrine $\frac{1}{10,000}$ group (P value < 0.001).

Discussion

Pharmacological pupillary dilation with epinephrine is commonly used for achieving or maintaining mydriasis during intraocular surgeries. Although several studies have

evaluated the efficacy of different concentrations of this drug, the optimum concentration remains unknown. In the study on 55 patients during extracapsular cataract surgery, the pupillary responses to various doses of intraocular epinephrine have been studied and the authors concluded that an extremely dilute concentration of epinephrine (i.e., 1:96,000 or less) may be effective in maintaining mydriasis during cataract surgery [19]. Liou et al. have also studied the pupillary response to various concentrations of intracameral epinephrine during cataract surgery. The authors demonstrated that there was no significant difference between the mean mydriatic responses to the epinephrine concentrations they used in their study; they stated that an extremely dilute concentration of epinephrine (i.e., 1:400,000) may be as effective as 1:25,000 concentration in maintaining mydriasis [9].

Intraocular irrigation with adrenaline 1:1,000,000 has also been used for maintaining mydriasis during cataract surgery; it has been demonstrated to be safe and effective [8, 20]. In the present study, we assessed the effects of intraocular application of epinephrine $\frac{1}{10,000}$, the concentration that is usually used as the bolus dose for mydriasis compared with epinephrine$\frac{1}{100,000}$. Although pupillary dilation was significantly more in the $\frac{1}{10,000}$ group than the $\frac{1}{100,000}$ epinephrine group, the difference of 0.8 mm of the pupil size (8.06 mm versus 8.84 mm) is not clinically significant for cataract surgery. According to our results, intraocular use of epinephrine had toxic effects on the endothelial cells. All the three groups showed a significant decrease in the endothelial cell density after the surgery, the reduction in endothelial cell density in the epinephrine $\frac{1}{10,000}$ group was significantly more than the control and epinephrine $\frac{1}{100,000}$ groups. In addition, the mean reduction in the endothelial cell density in the epinephrine $\frac{1}{100,000}$ group was significantly more than the control group. The percentage of hexagonality of the endothelial cells was also significantly reduced in the three groups, postoperatively. Mean reduction in the endothelial cell hexagonality in the epinephrine $\frac{1}{10,000}$ group was more compared with the other two groups, but there was no significant difference between the control and epinephrine $\frac{1}{100,000}$ groups.

There is uncertainty regarding the toxic effects of epinephrine on the corneal endothelial cells in the literature. Toxic endothelial cell destruction syndrome following IOL repositioning using intracameral epinephrine has been reported. The authors have attributed the presentation to the prolonged, direct exposure of the corneal endothelium to relatively high concentrations of intracameral epinephrine. They recommended that intracameral epinephrine should not be used for intraoperative mydriasis in procedures in which minimal irrigating solution is used [13].

Commercial epinephrine 1:1000 with its preservative sodium bisulfite damaged the corneal endothelial function and ultrastructure in rabbit and monkey's eyes. The authors stated that sodium bisulfite is the source of damage. No endothelial damage was observed with solutions diluted fivefold [12, 13].

In another experimental study, the toxic effects of diluted concentrations of epinephrine on the corneal endothelial cells have been assessed. Various concentrations of epinephrine were injected into the anterior chamber of rabbits and in vivo and in vitro morphological changes of the corneal endothelium and changes of thickness were assessed. Their results indicated that intracameral injection of epinephrine in rabbits had no toxic effect on the corneal endothelial cells [15]. In a retrospective study, toxic effects of injection of 1:100,000 dilution epinephrine with sodium bisulfite preservative on the corneal endothelium in 36 patients with age-related cataracts were compared with 34 patients who underwent surgery without any intracameral adrenaline use. Comparisons of postoperative specular microscopy measurements showed no statistically significant differences in comparison of the cell density, cell sizes, and cell shapes between the adrenalin and control groups. Interestingly, the postoperative mean endothelial cell density was not significantly less than the preoperative measurements in the epinephrine and control groups [14]. However, in our study on 210 patients that underwent uncomplicated phacoemulsification, mean endothelial cell densities and percentage of hexagonality of endothelial cells were significantly reduced in three groups post operation. Therefore, as our results indicated, intracameral epinephrine has toxic effects on the corneal endothelium, and with decreasing the concentration of epinephrine to $\frac{1}{100,000}$, the toxic effects of the drug to many endothelial cell parameters reduced.

According to our results, in both epinephrine and control groups a significant increase in the macular thickness occurred after the surgery. However, there was no significant difference among the groups regarding the mean postoperative macular thickness values. This result is in line with those of the previous study by Bozkurt et al. that demonstrated an increase in the retinal thickness postoperatively in both epinephrine 1:5000 and control groups [21]. As their results indicated, no significant differences were present between the two groups in the mean retinal thickness throughout the follow-up examinations [21]. This is similar to our results. However, when the difference between baseline and postoperative macular thickness was assessed in our study, the mean increase in the macular thickness in the epinephrine $\frac{1}{10,000}$ group was significantly more than the epinephrine $\frac{1}{100,000}$ and control groups, but the mean increase in the macular thickness in the epinephrine $\frac{1}{100,000}$ and control groups was not different. Epinephrine maculopathy presents with transient blurred vision decreased visual acuity, flame-shaped haemorrhages, and cystoid macular oedema is a well-known, reversible side

effect of topical epinephrine in aphakic eyes. Epinephrine-induced macular oedema has been supported by several studies since it was demonstrated statistically since more than three decades ago [16–18]. The onset of symptoms may range from a few days to several months after treatment with topical epinephrine. Optical coherence tomography, as a noncontact and noninvasive method, is extensively used clinically for a cross-sectional assessment of the macula. The very low spatial resolution has made it appropriate for detection of even subclinical changes and for the quantitative measurement of retinal thickness. In our study, retinal thickness was determined in the foveal centre (1.0 mm) by a fast macular thickness map. It might have been better to evaluate a larger macular area to determine the effect of epinephrine on the entire fovea.

An increase in the macular thickness after uneventful cataract surgery in the control group, as shown in our study, is supported by previous studies [16, 17, 21]. It has been shown that cataract surgery results in clinical and subclinical macular thickness changes [16, 17]. Although most of these changes resolve spontaneously, they have visual consequences that are proportional to the macular elevation [17].

Using retinal thickness analyser, Cohen et al. showed a decrease in macular thickness in early postoperative weeks. However, they discussed that this was an artefact of imaging the retina through a hazy media [22]. Perente et al. used OCT preoperatively and after uneventful phacoemulsification, they detected significant changes in the mean central foveal thickness, foveal thinnest retinal thickness, and mean perifoveal retinal thickness [23].

We used 3 month postoperation measurements to evaluate the relatively late changes in the macular thickness. In line with the mentioned studies, our results in the control group indicated changes in the retinal thickness after the uneventful surgery. However, further studies with a longer follow-up are recommended to evaluate the significance of this finding in long term. According to our results, when $\frac{1}{100,000}$ concentration of epinephrine was used instead of $\frac{1}{10,000}$ concentration, the postoperative increase in the macular thickness was reduced. In fact, the effect of $\frac{1}{100,000}$ concentration of epinephrine on macular thickness was similar to that of the control group. Therefore, we recommend using this concentration for achievement of mydriasis to decrease the possible adverse effects of epinephrine on the macula.

In conclusion, intraocular epinephrine had toxic effects on the endothelial cells. Toxicity of the drug to many endothelial cell parameters was reduced with decreasing concentration of epinephrine to $\frac{1}{100,000}$. Using $\frac{1}{100,000}$ instead of $\frac{1}{10,000}$ concentration of epinephrine reduced the increase in the macular thickness postoperatively.

Summary

What was known before

- Some of previous studies have shown endothelial and macular toxicity associated with perioperative usage of epinephrine. However, in other studies epinephrine had no toxic effects on the endothelium. This subject remains controversial.

What this study adds

- In this study we evaluated the changes in the corneal endothelial cell parameters and macular thickness after intraocular application of epinephrine 1/10,000 and epinephrine 1/100,000. The results showed that toxicity of the drug to many endothelial cell parameters and macula was reduced with decreasing concentration of epinephrine to 1/100,000.

Acknowledgements The present article was extracted from the thesis written by RR which was under the supervision of SB and was financially supported by Shiraz University of Medical Sciences grants No. 91-01-01-4863.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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