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The Effect of Cumulative Dissipated Energy on Changes in Intraocular Pressure Following Uncomplicated Cataract Surgery by Phacoemulsification

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Abstract

Purpose—To investigate the association between ultrasound energy, expressed as cumulative dissipated energy, and changes in intraocular pressure following uncomplicated cataract surgery by phacoemulsification.

Methods—In this prospective study, nonglaucomatous subjects underwent cataract surgery by phacoemulsification. Intraocular pressure was compared by clustered linear regression at four separate time points: preoperative, 1 day, 1 month, and 3 months after cataract surgery. Changes in intraocular pressure were evaluated as a function of cumulative dissipated energy using univariate and multivariate clustered linear regression models, which adjusted for sex, ethnicity, age, axial length, spherical equivalent, mean preoperative Shaffer gonioscopy grade of all four quadrants, cataract grade, preoperative intraocular pressure, central corneal thickness, and use of both eyes in the same subject.

Results—One hundred and sixty one eyes (89 Asian, 49 Caucasian, 12 African, and 11 Hispanic) from 116 nonglaucomatous subjects were analyzed. The 161 eyes included 81 right and 80 left eyes. The 89 Asian eyes included 46 Chinese, 35 Filipino, and 8 Vietnamese. Preoperative intraocular pressure was 14.9±3.2 mmHg. Postoperative intraocular pressure significantly increased to 16.0±4.9 mmHg at 1 day (P=0.037) and decreased to 12.4±3.1 and 12.3±3.0 mmHg at 1 and 3 months, respectively (both P<0.0001). Intraocular pressure changes at 1 day, 1 month, and 3 months did not demonstrate significant associations with cumulative dissipated energy measurements in either univariate or multivariate clustered linear regression analyses (all P>0.05).

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Conclusions—The amount of ultrasound energy delivered to the eye during phacoemulsification, expressed as cumulative dissipated energy, was not associated with postoperative changes in intraocular pressure.

Keywords

phacoemulsification; cataract surgery; ultrasound energy; cumulative dissipated energy; intraocular pressure

Introduction

Phacoemulsification cataract surgery has been shown by numerous studies to significantly reduce intraocular pressure (IOP)[-]. IOP is a function of aqueous humor secretion rate, episcleral venous pressure, and outflow facility at the anterior chamber (AC) angle. Although the mechanism of action responsible for postoperative IOP reduction remains under debate[,], many studies lend support to the theory of improved aqueous access to the trabecular meshwork (TM) as one of the mechanisms of IOP reduction. The following changes in AC parameters after cataract removal have been demonstrated: increased AC depth[-], increased AC volume[,], and increased AC angle width[-].

In patients with primary angle closure glaucoma (PACG), a crowded AC is associated with impaired aqueous humor outflow through the drainage angle of the eye, which can lead to IOP elevation. An inverse relationship exists between IOP and the width of the drainage angle, in which higher IOP tends to correlate with narrow angles or angle closure.[,] Since cataract surgery by phacoemulsification improves many of the anatomical factors that contribute to space narrowing between the peripheral iris and the TM, a reduction in IOP should reasonably be expected postoperatively. Indeed, patients with narrow angles and PACG experience significant reduction in IOP following cataract extraction.[-]

Improved access of aqueous humor to the TM likely explains IOP reduction in patients with PACG. However, studies have also shown IOP reduction in patients with primary open angle glaucoma (POAG) following cataract surgery by phacoemulsification.[,] By definition, AC anatomical features that directly impede aqueous humor drainage in PACG are absent in POAG.[-] Instead, elevated IOP in POAG stems from increased resistance to aqueous humor outflow that originates from compromised trabecular and uveoscleral outflow facilities. Therefore, IOP reductions following cataract surgery by phacoemulsification may be only partially mediated by anatomic changes in the AC. Wang N *et al.* proposed that modulation of TM function might be another mechanism responsible for IOP reduction. They demonstrated that the propagation of ultrasound energy in TM cell cultures from tissues isolated from human cadaveric eyes induced interleukin-1 alpha (IL-1α) release. IL-1α, an inflammatory cytokine, exerts IOP-lowering effects in vitro by inducing the expression of matrix metalloproteinases, which in turn increases extracellular matrix turnover and improves aqueous humor outflow facility.

Cumulative dissipated energy (CDE) measures the amount of ultrasound energy delivered to the eye during phacoemulsification cataract surgery. The purpose of this study is to investigate the association between ultrasound energy, expressed as CDE, and IOP reduction following uncomplicated cataract surgery by phacoemulsification in nonglaucomatous subjects.

Methods

Study Population

Approval for this prospective study was obtained from the University of California, San Francisco (UCSF) Committee on Human Research. The study was carried out in accordance with the tenets of the Declaration of Helsinki. Study subjects were consecutively recruited from the UCSF general ophthalmology and glaucoma clinics between March 2009 and May 2012. All enrolled subjects provided written informed consent. The subjects' self-description of ethnicity determined their classification into one of the following ethnic study groups: Asian, Caucasian, African, and Hispanic. The Asian study group included individuals of self-reported Chinese, Filipino, and Vietnamese ancestries. The Caucasian study group included only European-derived whites.

Inclusion criteria for subject enrollment included: (1) adult patients (age > 18 years) with a visually significant age-related cataract in at least one eye; (2) patients consenting to cataract surgery by phacoemulsification with foldable lens implantation; (3) patients willing to undergo routine ophthalmic examination preoperatively, and at 1 day, 1 month, and 3 months following the operation; and (4) patients with confirmed normal perimetry and normal appearing optic discs. Exclusion criteria for enrollment included the following: (1) eyes with trauma- or steroid-related cataract; (2) eyes with prior penetrating ocular surgery; (3) complications related to cataract removal such as posterior capsular rupture and vitreous loss; (4) non-adherence to the follow-up regimen; (5) eyes with corneal abnormalities such as edema, abrasion or dystrophy, pterygium, and other degenerative changes; (6) eyes with IOP > 21 mmHg; and (7) eyes with primary or secondary glaucoma, peripheral anterior synechiae, or topical glaucoma therapy. A visually significant cataract was defined as the following: best corrected visual acuity was worse than 20/30, the patient complained of significant blurring or glare in that eye, and the stage of the cataract matched the level of vision and symptomatology, as judged by a single board-certified ophthalmologist. The International Society of Geographic and Epidemiologic Ophthalmology scheme provided the basis for diagnosis of glaucoma: a glaucomatous optic nerve appearance (vertical cup:disc ratio > 0.6) and a corresponding reliable visual field defect. A glaucomatous visual field defect was considered to be present when the hemifield test was graded outside normal limits (with a probability of less than 5% based upon comparison with age-matched controls in the pattern deviation plot) and showed a cluster of three or more non–edge contiguous points that did not cross the horizontal meridian. Visual fields were defined as reliable if they fulfilled the following criteria: fixation losses < 33%, false positives < 20%, and false negatives < 20%.

Preoperative and Postoperative Evaluation

Prior to cataract surgery, all enrolled subjects received a routine ophthalmic examination that included visual acuity testing, visual field testing using the 24-2 Swedish Interactive Threshold Algorithm (SITA) standard strategy with the Humphrey Visual Field Analyzer

(Model 750i; Carl Zeiss Meditec, Inc., Dublin, CA, USA), manual refraction, gonioscopy with a Zeiss-style 4-mirror lens (Model OPDSG; Ocular Instruments, Inc., Bellevue, WA, USA), IOP measurement by Goldmann applanation tonometry (Model AT900; Haag-Streit AG, Koeniz, Switzerland), slit lamp examination (Model BM900; Haag-Streit AG, Koeniz, Switzerland), central corneal thickness measurement (CCT) by ultrasound pachymetry (Model DGH-550 Pachette 2; DGH Technology Inc., Exton, PA, USA), and axial length measurement by optical biometry (Model Lenstar LS 900; Haag-Streit AG, Koeniz, Switzerland).

The various types of cataract were classified by a 1-4 severity grading system. For nuclear cataracts, the range was from grade 1 for mild nuclear opalescence and color to grade 4 for brown nuclear opacification. Cortical cataracts ranged from a quarter or less of total lens area for grade 1 to more than three quarters of total lens area for grade 4. Posterior subcapsular cataracts were judged on both degree of central opacification and extent of spread of the opacity, with grade 1 as mild and grade 4 as severe.

A single trained ophthalmologist (SCL) performed gonioscopy at ×16 magnification with slit-lamp microscopy in a darkroom setting. The Shaffer gonioscopic classification determined the AC angle grading in all four quadrants: an angle between the iris and the TM surface of 35° to 45° was classified as grade 4, between 20° and 35° was classified as grade 3, between 10° to 20° was classified as grade 2, and less than 10° was classified as grade 1 if not closed. Grade 0 was assigned if angle structures were not observed.

To improve accuracy in IOP measurements, the same ophthalmologist (SCL) measured IOP twice for each patient with a designated technician reading the value on the dial during a scheduled time period between 1:00PM and 3:00PM. From the two IOP measurements, an average was derived for statistical analysis. If the two IOP values differed by more than 2 mmHg, then a third measurement was performed and the median value was used. This procedure was used for both preoperative and postoperative examinations.

Postoperative follow-up for visual acuity and IOP measurements occurred at 1 day, 1 month, and 3 months after cataract surgery. CDE, which measures the total amount of ultrasound energy expended at the incision, was obtained from the automatically calculated value displayed on the monitor of the phacoemulsification machine after each case.

Surgical Technique

Phacoemulsification settings and irrigation-aspiration parameters were standardized for every case and are summarized in Table 1. The phacoemulsification machine used was the same in all cases (Model Infiniti; Alcon Laboratories, Inc., Fort Worth, TX, USA). The same surgeon (SCL) performed all operations utilizing conventional surgical techniques. In brief, operative eyes received a sub-Tenon's injection of anesthesia in the infero-nasal quadrant consisting of 3cc of a 50/50 mixture of 0.5% bupivicaine and 4% lidocaine with Vitrase® (Bausch & Lomb Inc., Rochester, NY, USA). A paracentesis was created using a Supersharp blade, and viscoelastic was injected into the AC. A scratch incision was created with a guarded diamond blade, and a 3 mm wide × 2 mm long clear corneal incision was performed temporally with a diamond keratome blade. After the incision, a continuous curvilinear capsulorrhexis measuring approximately 5.5 mm in diameter was started with a cystotome and carried to completion with Utrata forceps. After hydrodissection and hydrodelineation, a stop-and-chop technique was employed to remove the nucleus. The epinucleus was then removed using the phacoemulsification handpiece, followed by cortex removal using the irrigation-aspiration handpiece. The capsular bag was then filled with PROVISC® (Alcon Laboratories, Inc., Fort Worth, TX, USA). Using a cartridge system, a single-piece foldable acrylic posterior chamber intraocular lens (Model SA60AT; Alcon Laboratories, Inc., Fort Worth, TX, USA) was delivered into the capsular bag. At the end of the operation, the surgeon always confirmed that the intraocular lens was implanted in the capsular bag. Viscoelastic was removed from the anterior and posterior chambers. Balanced salt solution was used to re-inflate the AC, and corneal incisions were checked for leakage. The patient then received a subconjunctival injection of ceftazidime and cefazolin in the infero-temporal quadrant.

Main Outcome Variables and Statistical Analysis

All statistical analyses were conducted with the Julia scientific computing language (version 0.3 for Macintosh, http://www.julialang.org) and two-sided P values less than 0.05 were considered to indicate statistical significance. Mean and standard deviations were calculated for the following variables using data from both eyes: age, axial length, spherical equivalent, preoperative Shaffer gonioscopy grades of all four quadrants, cataract grade, CCT, CDE, and IOP. The spherical equivalent was derived from the refractive error using the following formula: sphere power plus half of the cylinder power. We tested the hypothesis of no change in IOP from preoperative to postoperative measurements at 1 day, 1 month, and 3 months after cataract extraction using clustered linear regression because of possible dependence between the two eyes of a given patient. Changes in IOP achieved at 1 day, 1 month, and 3 months after cataract surgery by phacoemulsification were evaluated as a function of CDE using univariate and multivariate clustered linear regression models to determine the association between ultrasound energy and postoperative IOP reduction. The multivariate clustered linear regression model adjusted for sex, ethnicity, age, axial length, spherical equivalent, mean preoperative Shaffer gonioscopy grade of all four quadrants, cataract grade, preoperative IOP, CCT, and use of both eyes in the same subject. Changes in IOP were calculated as the preoperative mean IOP subtracted from the postoperative mean IOP. Sex, ethnicity, age, axial length, spherical equivalent, AC angle grade, cataract grade, and CCT were controlled in the statistical model due to their potential confounding effects.

Results

A total of 129 consecutively enrolled patients received cataract surgery by phacoemulsification. Among them, 13 patients were excluded due to surgical complications or loss to follow-up. One hundred and sixteen patients were available, among whom 161 eyes (89 Asian, 49 Caucasian, 12 African, and 11 Hispanic) were included in the analysis. The 161 eyes included 81 right and 80 left eyes. The 89 Asian eyes included 46 Chinese, 35 Filipino, and 8 Vietnamese.

Table 1 summarizes the standardized phacoemulsification settings and irrigation-aspiration parameters used for every case. Table 2 provides the clinical characteristics of the study subjects. Table 3 contains CDE and the results of IOP comparisons at four different time points: preoperative, 1 day, 1 month, and 3 months after cataract surgery. Prior to cataract surgery, average IOP was 14.9 ± 3.2 mmHg. Postoperative IOP significantly increased to 16.0 ± 4.9 mmHg at 1 day ($P = 0.037$) and decreased to 12.4 ± 3.1 and 12.3 ± 3.0 mmHg at 1 and 3 months, respectively (both $P < 0.0001$). Postoperative IOP reductions achieved at 1 month were sustained up to the 3 months time point. Changes in IOP at 1 day, 1 month, and 3 months did not demonstrate significant associations with CDE measurements in either univariate and multivariate clustered linear regression models, which adjusted for sex, ethnicity, age, axial length, spherical equivalent, mean preoperative Shaffer gonioscopy grade of all four quadrants, preoperative IOP, cataract grade, CCT, and use of both eyes in the same subject (all $P>0.05$). Assuming a standard deviation of 2.7 mmHg for IOP, a sample size of 50 individuals per group (contributing one eye each) would provide approximately 80% power to detect a difference of 1.5 mmHg between two groups, and this was used to guide the sampling frame. All available subjects between March 2009 and May 2012 were enrolled. In practice, both eyes were used in this analysis, providing somewhat more power than the conservative sample size plan suggested.

Discussion

In the present study, postoperative IOP significantly increased from preoperative values at 1 day after cataract surgery by phacoemulsification. This finding is consistent with a previous study examining transient IOP elevation within the first 24-hours postoperative period in nonglaucomatous patients. Phacoemulsification can temporarily cause IOP spike due to obstruction of the trabecular meshwork by lenticular debris and viscoelastic material, intraocular inflammation, prostaglandin release, or type of surgical wound utilized., Our investigation of the relationship between the amount of ultrasound energy delivered to the eye during phacoemulsification cataract surgery, expressed as CDE, and postoperative changes in IOP at 1 day did not yield statistical significance. This result suggests that ultrasound energy consumption may not be a risk factor associated with the immediate transitory rise in IOP.

Postoperative IOP significantly decreased from preoperative values at 1 and 3 months following cataract surgery by phacoemulsification. This result confirms prior reports of long-term IOP reduction after cataract surgery.- Although the reasons behind IOP reduction following cataract surgery are not fully understood, two current theories implicate postoperative improvements in TM function and aqueous humor access to the TM. Support for the former speculation emerged from observations that IL-1α, an inflammatory cytokine, decreased IOP in perfused eyes of rats, rabbits, and pigs, as well as in human anterior segment tissue culture. IL-1α promotes IOP reduction by inducing synthesis of matrix metalloproteinases, which in turn enhance the degradation of extracellular matrix and increase outflow facility. Wang *et al.* demonstrated that IL-1α can be induced by phacoemulsification ultrasound energy. However, currently no clinical study has implicated IL-1α release from exposure to ultrasound energy during phacoemulsification cataract surgery as one of the mechanisms behind IOP reduction.

The results of our univariate and multivariate clustered linear regression analyses, which adjusted for potential confounders, suggest no relationship between the amount of ultrasound energy delivered to the eye during phacoemulsification cataract surgery, expressed as CDE, and long-term postoperative IOP reduction. There are at least two interpretations of this outcome. The first interpretation concerns the findings of the Wang *et al*. study. Whereas their finding regarding the effect of ultrasound on the expression of IL-1α was derived from in vitro experiments on TM cell culture models, our study assessed the effect of ultrasound on IOP (and indirectly, on TM cells) in vivo. Studies conducted in an in vitro setting are not always reproducible in vivo. Furthermore, although expression of IL-1α has been shown to produce molecular changes associated with IOP reduction, Wang *et al*.'s study did not directly measure IOP in their experiment and consequently cannot demonstrate a cause-effect relationship between these molecular changes and a decrease in IOP. Finally, several studies have reported elevated levels of transforming growth factor beta (TGF-β), an IL-1α antagonist, in the aqueous humor of a large percentage of POAG patients.[-] TGF-β has been shown to partially abolish the IOP reduction elicited by IL-1α. Our study population is comprised only of nonglaucomatous patients and therefore is appropriate for studying the effect of phacoemulsification ultrasound treatment on IOP reduction, without the complicating issue of glaucoma medication usage.

The second interpretation of our results is that while ultrasound energy delivered to the eye during phacoemulsification may be associated with long-term IOP-lowering effects, CDE may not be the appropriate parameter for measuring ultrasound energy delivery. CDE quantifies the total amount of ultrasound energy emitted by the phacoemulsification probe, which does not necessarily represent the amount of ultrasound energy directly delivered to the TM. During cataract surgery, the phacoemulsification probe may be directed towards either the center of the AC (away from the angle) or the periphery of the AC (proximal to the angle), thereby varying the amount of ultrasound energy received by the TM. Studies have also shown that removal of dense cataracts requires higher CDE during phacoemulsification.[,] During phacoemulsification of dense cataracts, a large proportion of the ultrasound energy utilized is allocated for removal of the cataractous lens and therefore the increased ultrasound energy expenditure may not translate to more energy distributed to the TM. Our statistical model controlled for the density of the cataracts in the analysis;however, the relationship between the amount of ultrasound energy delivered to the eye during phacoemulsification, expressed as CDE, and long-term postoperative IOP reduction remained insignificant.

The main limitation of the present study lies in our cataract classification. The Lens Opacities Classification System III was not utilized in this study. Instead a different but commonly used method of cataract grading in the clinical setting was employed.

In summary, this study demonstrated that cataract surgery by phacoemulsification caused transient IOP elevation, but provided long-term IOP reduction. The amount of ultrasound energy delivered to the eye during phacoemulsification, expressed as CDE, was not associated with postoperative changes in IOP. Further studies on a larger population are warranted to confirm our findings.

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Table 1

Standardized Parameters for Each Step of Phacoemulsification and Irrigation/Aspiration

	Sculpt	Chop	Quad	Epi	Cortex	Polish
Phacoemulsification						
Bottle Height (cm)	95	95	95	95	-	-
Phaco Power (%)	60	30[a]	40[a]	10	-	-
Vacuum (mm Hg)	70	400	330	230	-	-
Aspiration flow rate (cc/min)	25	33	33	30	-	-
Torsional Amplitude (%)	0	60[b]	60[b]	25	-	-
Irrigation/Aspiration						
Bottle Height (cm)	-	-	-	-	78	78
Vacuum (mm Hg)	-	-	-	-	500	20
Aspiration flow rate (cc/min)	-	-	-	-	35	10

[a]35 ms bursts;

[b]70 ms bursts; Quad = Quadrant removal; Epi = Epinucleus removal; Cortex = Cortex removal; Polish = Polishing the capsule.

Table 2
Clinical Characteristics of the Study Population

Number of Patients	116
Number of Eyes	161
Number of Right eye: Left eye	81:80
Sex (male:female)	56:105
Ethnicity	
Asian	89
Caucasian	49
African	12
Hispanic	11
Age (years)	74.8 ± 8.4[a]
Axial Length (mm)	24.0 ± 1.5[a]
Spherical Equivalent (diopter)	0.60 ± 10.9[a]
Preoperative Shaffer Gonioscopy Grade of All Four Quadrants[b]	2.59 ± 0.96[a]
Cataract Grade	2.14 ± 0.55[a]
Central Corneal Thickness (μm)	543.6 ± 41.2[a]

[a]Data are expressed as mean value ± standard deviation.

[b]Evaluation of the anterior chamber angle was based on the Shaffer gonioscopic grading classification: an angle between the iris and the trabecular meshwork surface of 35° to 45° was classified as grade 4, between 20° and 35° was classified as grade 3, between 10° to 20° was classified as grade 2, and less than 10° was classified as grade 1. Grade 0 was assigned if angle structures were not observed.

Table 3

Analysis of the Association Between Cumulative Dissipated Energy (CDE) and Change in Intraocular Pressure (IOP)

CDE (%-seconds)	14.5 ± 15.2
Pre-operative IOP measurements (mmHg)[b]	14.9 ± 3.2
One day post-operative IOP measurements (mmHg)[b]	16.0 ± 4.9
Changes in IOP from pre-operative measurements (mmHg)[b]	0.8 ± 4.5
P value of IOP change by clustered linear regression	0.037
Association between CDE and changes in IOP at 1 day	
P value of univariate clustered linear regression model	0.721
P value of multivariate clustered linear regression model[c]	0.532
One month post-operative IOP measurements (mmHg)[b]	12.4 ± 3.1
Changes in IOP from pre-operative measurements (mmHg)[b]	-2.5 ± 2.9
P value of IOP change by clustered linear regression	<0.0001
Association between CDE and changes in IOP at 1 month	
P value of univariate clustered linear regression model	0.551
P value of multivariate clustered linear regression model[c]	0.824
Three months post-operative IOP measurements (mmHg)[b]	12.3 ± 3.0
Changes in IOP from pre-operative measurements (mmHg)[b]	-2.6 ± 2.6
P value of IOP change by clustered linear regression	<0.0001
Association between CDE and changes in IOP at 3 months	
P value of univariate clustered linear regression model	0.449
P value of multivariate clustered linear regression model[c]	0.807

[a]Data are expressed as mean value ± standard deviation.

[b]IOP = intraocular pressure by Goldmann applanation tonometry.

[c]Multivariate clustered linear regression models adjusted for sex, ethnicity, age, axial length, spherical equivalent, mean preoperative Shaffer gonioscopy grade of all four quadrants, cataract grade, central corneal thickness, preoperative IOP, and use of both eyes in the same subject.