THE EFFECTS OF PHACOEMULSIFICATION AND INTRAOCULAR LENS IMPLANTATION ON ANATOMICAL AND FUNCTIONAL PARAMETERS IN PATIENTS WITH PRIMARY ANGLE CLOSURE: A PROSPECTIVE STUDY. (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

By Carlo Enrico Traverso, MD and Carlo Alberto Cutolo, MD

ABSTRACT

Purpose: To investigate the clinical, anatomical, and patient-reported outcomes of phacoemulsification (PE) with intraocular lens implantation performed to treat primary angle closure (PAC) and primary angle-closure glaucoma (PACG).

Methods: Patients were evaluated at baseline and at 6 months after PE. The examination included visual acuity, intraocular pressure (IOP), visual field, optic nerve head, endothelial cell count (ECC), aqueous depth, and ocular biometric parameters. Patient-reported visual function and health status were assessed. Coprimary outcome measures were IOP changes, angle widening, and patient-reported visual function; secondary outcome measures were visual acuity changes, use of IOP-lowering medications, and complications. Univariate and multivariate analyses were performed to determine the predictors of IOP change.

Results: Thirty-nine cases were identified, and postoperative data were analyzed for 59 eyes, 39 with PACG and 20 with PAC. Globally, PE resulted in a mean reduction in IOP of -6.33 mm Hg (95% CI, -8.64 to -4.01, $P<.001$). Aqueous depth and angle measurements improved ($P<.01$), whereas ECC significantly decreased ($P<.001$). Both corrected and uncorrected visual acuity improved ($P<.01$). The EQ visual analog scale did not change ($P=.16$), but VFQ-25 improved ($P<.01$). The IOP-lowering effect of PE was greater in the PACG compared to the PAC group ($P=.04$). In both groups, preoperative IOP was the most significant predictor of IOP change ($P<.01$). No sight-threatening complications were recorded.

Conclusions: Our data support the usefulness of PE in lowering the IOP in patients with PAC and PACG. Although PE resulted in several anatomical and patient-reported visual improvements, we observe that a marked decrease in ECC should be carefully weighed before surgery.

Trans Am Ophthalmol Soc 2017;115:T7[1-12].

INTRODUCTION

The purpose of this thesis is to prospectively evaluate the outcomes of patients with primary angle closure (PAC) and primary angle-closure glaucoma (PACG) undergoing phacoemulsification (PE) and intraocular lens (IOL) implantation as a treatment for angle closure. Our work addresses a topic that is relevant for clinical practice. Because of increased life expectancy and demographic expansion, the number of glaucoma cases worldwide is estimated to increase to 76 million by 2020, of which 23 million will be due to PAC.[1]

Lens extraction, both clear and cataractous, with IOL implantation to treat PAC has progressively gained popularity for about 12 years and quite extensively over the last 8 years, according to published reports of good results on series of patients with a variety of primary angle closure types and definitions.[2-29] One recently published prospective randomized trial, commonly known as the Eagle trial,[30,31] challenged the established initial treatment modalities for PAC and PACG, ie, laser iridotomy and medication with eye drops to reduce intraocular pressure (IOP). The Eagle trial compared laser peripheral iridotomy vs PE in patients with angle closure and no lens opacities; the results showed a small but significant advantage of the latter for IOP control, quality of life, and cost. The endothelial cell damage observed after PE in PAC and PACG is well known.[33-41] Lens extraction has been recommended, on an individual basis, for the management of angle closure, also by guidelines.[32]

Last but not least, the technological advances in surgical techniques allow for safe PE surgery in eyes with glaucoma. Today "clear lens exchange," that is, PE and IOL implantation in the absence of any cataract, is perceived as safe enough to be offered as a refractive procedure to presbyopic patients with high myopia and high hyperopia; the eyes with high hyperopia are often characterized by shallow anterior chamber, shorter axial length as in PAC, and the potential for more surgical complications.[42-44] Phacoemulsification with IOL implantation has been slowly and increasingly adopted in our institution in selected patients with angle closure, progressively becoming routine.

Our hypothesis is that PE with implantation of an IOL can substantially improve the IOP control in patients with angle closure, with improvements in the quality of life, without disproportionate risks for the patients. Our research was aimed at studying the functional, anatomical, and quality-of-life consequences, as well as the safety, of such an approach. We are not aware of any report where IOP, quality of life, visual acuity, endothelial cells, and angle features were evaluated prospectively in one sample of patients with PAC treated with PE and IOL implantation while investigating possible correlations with anterior segment optical coherence tomography (AS-OCT) and biometric parameters.

METHODS

This is a prospective, uncontrolled, interventional cohort study involving 59 cases, 39 eyes with PACG and 20 eyes with PAC; patients were recruited consecutively at the Clinica Oculistica, Ospedale Policlinico San Martino, University of Genoa, Italy. PAC was defined by the presence of iridotrabecular contact combined with either elevated IOP or peripheral anterior synechiae, or both.

From the Clinica Oculistica, Department of Neuroscience, Ophthalmology, Genetics, Rehabilitation, Maternal and Infantile Sciences (Di.N.O.G.M.I), University of Genova, Italy (Prof. Traverso, Dr. Cutolo), and U.O.C. Clinica Oculistica, Ospedale Policlinico San Martino, Genova, Italy (Prof. Traverso). Corresponding Author: Carlo Enrico Traverso, MD Email: mc8620@mclink.it

The term *glaucoma* was added if unquestionable glaucomatous optic neuropathy was present (ie, PACG). Inclusion criteria were the presence of PAC and patients' willingness to undergo the supplementary examinations and follow-up visits. Eyes with any form of secondary glaucoma and any other eye disease besides glaucomatous optic neuropathy were excluded. Low preoperative corneal endothelial cell count (ECC) (<1000 cells/mm^2) was also considered an exclusion criterion. The principal investigator judged whether any such patient was clinically appropriate to undergo PE surgery to treat angle closure. Informed consent was obtained from all patients after they received a thorough explanation of the surgery and its risk. All procedures followed the tenets of the Declaration of Helsinki.

In addition to a full ophthalmological examination and history taking, this study included visual field static automated white-on-white threshold perimetry, gonioscopy with a 4-mirror Forbes-type lens for dynamic angle assessment, endothelial cell evaluation by noncontact specular microscopy (Konan specular microscope; Konan Medical Inc), AS-OCT for pachymetry and for the evaluation of the anterior chamber angle (RTVue; Optovue, Inc), and optical biometry by Lenstar LS 900 (Haag-Streit AG) (Table 1). The Schwalbe line angle opening distance (SL-AOD) and Schwalbe line trabecular iris space area (SL-TISA) were used as parameters for AS-OCT angle.[33,34] The SL-AOD was defined as the distance from SL at the termination of the Descemet membrane to the anterior iris surface, perpendicular to the corneal endothelial surface. The SL-TISA was defined as an area bounded anteriorly by the SL-AOD; posteriorly by a line drawn along the trabecular meshwork at 500 μm from the SL, perpendicular to the plane of the inner sclera wall to the opposing iris; superiorly by the inner corneoscleral wall; and inferiorly by the iris surface (Figure 1).

TABLE 1. SUMMARY OF EXAMINATIONS PERFORMED AT BASELINE AND DURING THE SIX-MONTH FOLLOW-UP

PROCEDURE	ELIGIBILITY VISIT	1 DAY AND 1 WEEK	1 MONTH	6 MONTHS
History (diseases, conditions, drugs)	✓	✓	✓	✓
EQ-5D	✓		✓	✓
NEI-VFQ-25	✓			✓
Visual acuity (UCVA, BCVA)	✓	✓	✓	✓
Slit lamp and funduscopy	✓	✓	✓	✓
Visual field	✓			✓
Anterior chamber angle evaluation*	✓		✓	✓
Pachymetry*	✓			✓
Endothelial cell count†	✓		✓	✓
Keratometry‡	✓			✓
Aqueous depth‡§	✓		✓	✓
Axial length, lens thickness‡	✓			
IOP	✓	✓	✓	✓
Gonioscopy	✓		✓	✓

BCVA, best-corrected visual acuity; EQ-5D, European Quality of Life-5 Dimensions questionnaire; IOP, intraocular pressure; NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; UCVA, uncorrected visual acuity.
*Anterior-segment OCT.
†Noncontact specular microscopy.
‡Optical biometry LENSTAR 900.
§Intended as central depth from corneal endothelium to lens, excluding corneal thickness.

Intraocular pressure was taken as the average of two readings by Goldmann tonometry. If the two readings differed by more than 2 mm Hg, then a third reading was performed and the median reading served as the IOP measurement.[35]

Health status score was assessed with the Italian version of the European Quality of Life-5 Dimensions questionnaire (EQ-5D) value set.[35] The EQ-5D-3L version consists of two pages. The first page contains the descriptive system (dimensions and levels) The five dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. We elected not to use the set of questions in the first page, since no official translation in Italian is yet available. The second page contains the EQ visual analogue scale (EQ VAS). The EQ VAS records the respondents' self-rated health on a vertical visual analogue scale, where the end points are labelled "Best imaginable health state" and "Worst imaginable health state." This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

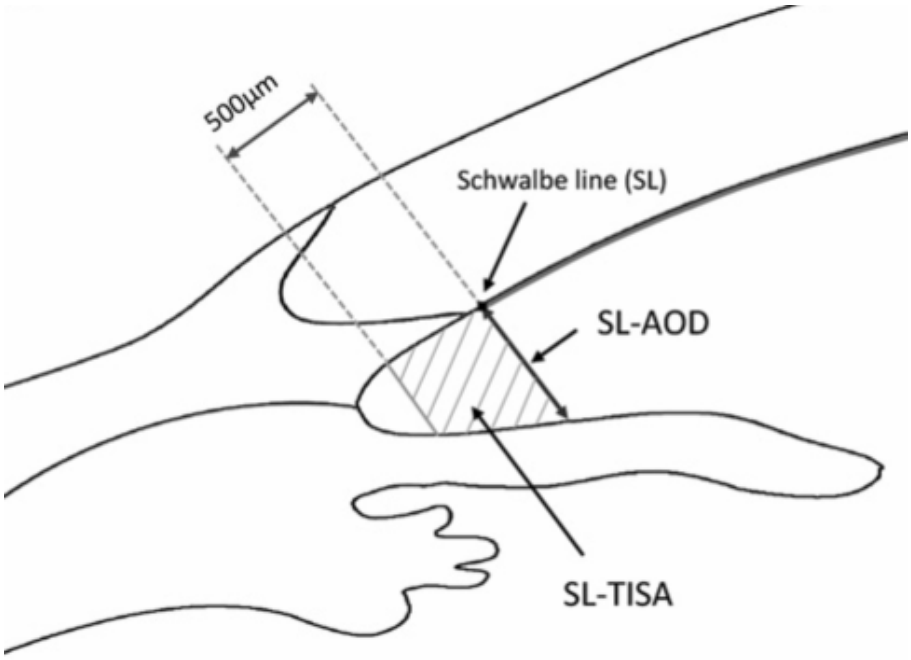

FIGURE 1

Quantitative parameters of anterior segment optical coherence tomography (AS-OCT). The Schwalbe line angle opening distance (SL-AOD) is the distance from the SL at the termination of the Descemet membrane to the anterior iris surface, perpendicular to the corneal endothelial surface. The SL-trabecular iris space area (SL-TISA) is bounded anteriorly by the SL-AOD; posteriorly by a line drawn along the trabecular meshwork at 500 µm from the SL perpendicular to the plane of the inner sclera wall to the opposing iris; superiorly by the inner corneoscleral wall; and inferiorly by the iris surface. Modified from Cheung et al.[34]

Vision-related quality of life was measured by the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25).[36] This questionnaire consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 also includes an appendix of additional items from the 51-item version that researchers can use to expand the scales up to 39 total items. In our study, the term *VFQ-25* is used to refer to the base set of items. The VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format. The VFQ-25 generates the following vision-targeted subscales: global vision rating (1), difficulty with near vision activities (3), difficulty with distance vision activities (3), limitations in social functioning due to vision (2), role limitations due to vision (2), dependency on others due to vision (3), mental health symptoms due to vision (4), driving difficulties (3), limitations with peripheral (1) and color vision (1), and ocular pain (2). Additionally, the VFQ-25 contains the single-item general health rating question, which has been shown to be a robust predictor of future health and mortality in population-based studies.

Coprimary outcome measures were IOP changes, angle widening, and patient-reported visual function; secondary outcome measures were visual acuity changes, use of IOP-lowering medications, ECC changes and complications. For all patients, final postoperative data were collected after 6 months from PE.

Institutional review board approval for prospective data collection was obtained.

STATISTICAL ANALYSIS

All data were evaluated with an intent-to-treat analysis. Five of 59 cases did not continue the study; data were included for the complications but were excluded for the analysis of results, performed on 54 eyes (37 PACG and 17 PAC).

Preoperative data were obtained at the eligibility visit, and postoperative data are referred to at the 6-month follow-up. The 1-month follow-up data were almost identical, and it was elected not to analyze them separately nor to report them.

In descriptive statistics, variables conforming to normal distribution were summarized as mean (SD). For preoperative and postoperative comparisons, the paired Student *t* test was used for parametric data and the Wilcoxon paired signed rank test was used for nonparametric data. Our primary outcome measure was the IOP change.

Within each group, univariate and multivariate linear regression models were built using IOP reduction percentage as the dependent variable and biometry parameters, AS-OCT parameters, preoperative IOP, and other demographic and ocular characteristic variables as the independent variables. Multiple scatter plots were built to show the effect of the PE on IOP, aqueous depth (AD), VFQ, and ECC in both groups. All statistical analyses were performed with MedCalc version 16.8.4 (MedCalc Software). The α level (type I error) was set at .05 for all comparisons.

SURGICAL TECHNIQUE

All patients were prepared with 0.5 mg/kg mannitol IV 18%, dosed at 180 mg/mL. Sedation was applied according to the judgment of the anesthesiologist. In most cases midazolam IV, 2 to 5 mg, was used, with continuous blood pressure and heart rate monitoring.

Patients were instructed to continue all IOP-lowering medications excluding miotics, and to take additional netilmycin sulfate, 3 mg/mL, and indomethacin, 5 mg/mL, three times a day for 2 days prior to surgery. Topical anesthetics were used in all cases, with oxybuprocaine hydrochloride eye drops, 4 mg/mL, administered 5 to 8 times in the 20 minutes preceding the operation. Mydriasis was pursued with instillation of tropicamide, 5 mg/mL, and phenylephrine, 100 mg/mL, 3 to 5 times in the 45 minutes preceding surgery. The eyelids and periocular skin were prepped with a povidone-iodide solution, 50 mg/mL, and then a sterile adhesive drape was positioned and a wire speculum placed to open the eyelids. The same povidone-iodine solution was instilled on the cornea and on the conjunctiva and rinsed with balanced salt solution after 2 minutes.

Two clear corneal paracenteses were made, one inferotemporally and one superonasally at the limbus, for the purpose of slowly decompressing the globe each time the IOP was not below 20 mm Hg, at the start of the surgery after the speculum was in place and, during surgery, for lens manipulation and bimanual irrigation/aspiration. Cohesive viscoelastic chondroitin sulfate 4% (Viscoat; Alcon) was injected to deepen the anterior chamber and protect the corneal endothelium. Lysis of posterior synechiae and pupil stretching were obtained mechanically when deemed useful; iris hooks were used to maintain an enlarged pupil where indicated.

After capsulorhexis and hydrodissection, PE was performed via a temporal clear cornea incision; the surgeon, seated at the 12-o'clock position, used the right or left hand to hold the ultrasonic handpiece for right or left eyes, respectively. The Whitestar Signature Pro PE system (Abbott Medical Optics Inc) was used in all cases. Foldable and injectable IOLs were implanted into the capsular bag. A complete evacuation of viscoelastic agent was attempted in every case at the end of surgery. Immediately after surgery, one dose of acetazolamide, 500 mg orally, was given as prophylaxis against IOP spikes. Eye drops consisting of a combination of dexamethasone sodium sulfate, 1 mg/mL, with netilmicin sulfate, 3 mg/mL, and levofloxacine, 3 mg/mL, were prescribed four times a day and tapered during the following 3 weeks. Intraocular pressure was first assessed within 8 hours from surgery and, where appropriate, gentle anterior chamber decompression via the inferotemporal paracentesis was performed electively at the slit lamp, with patients under topical anesthesia and instillation of povidone iodine, 50 mg/mL. Additional oral acetazolamide, 250 mg every 12 hours, was used as needed for the first 36 hours. The preceding procedure has been for many years the routine postoperative practice at our institution for any patient with glaucoma who is undergoing PE.

Glaucoma eye drops were gradually tapered if the mean IOP at two consecutive visits was less than 21 mm Hg.

RESULTS

The coprimary outcome measures were IOP changes, angle widening, and vision-targeted functioning; secondary outcome measures were visual acuity changes, use of IOP-lowering medications, and complications.

Patient demographics and baseline characteristics are summarized in Table 2. More women than men were present in the PAC group. There were no significant differences between PAC and PACG patients except for IOP-lowering topical (*P*=.0003) and oral medications (13% vs 30%), IOP (*P*=.0008), lens thickness (*P*=.021), AD (*P*=.0268), central corneal thickness (*P*=.0204), and ECC (*P*=.0244).

TABLE 2. PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF 54 PATIENTS

VARIABLE	PAC GROUP (n=17)	PACG GROUP (n=37)	*P* VALUE
Demographics			
Women, No. (%)	9 (53%)	13 (35%)	
Age, yr mean (SD)	73.1 (8.5)	70.7 (11.7)	.44
Ocular characteristics and previous treatments			
Study eye was right eye, No. (%)	6 (35%)	13 (35%)	
Glaucoma topical medication mean (SD)	0.53 (1.4)	1.97 (1,2)	.0003
Glaucoma oral medication (acetazolamide), No. (%)	2 (11.8**%)**	10 (27.0%)	
IOP, mm Hg	15.50 (4.85)	22.29 (8.83)	.0008
Clear lens, No. (%)	5 (29%)	11 (30%)	

TABLE 2. CONTINUED

VARIABLE	PAC GROUP (n=17)	PACG GROUP (n=37)	*P* VALUE
Previous laser surgery, No. (%)			
Iridotomy	7 (41%)	14 (38%)	
Iridoplasty	2 (12%)	0	
Glaucoma severity, No. (%)			
Mild MD ≤6		10 (27%)	
Moderate MD >6, <12		20 (54%)	
Advanced MD ≥12		7 (19%)	
BCVA, ETDRS letters	74 (13)	68 (15)	.233
Refractive error, diopters	+ 1.6 (3.6)	+ 0.04 (2.1)	.417
Lens thickness, mm	4.71 (0.36)	4.97 (0.37)	.0210
Aqueous depth,* mm	2.17 (0.27)	1.99 (0.27)	.0268
Central corneal thickness, µm	560 (31)	543 (33)	.0204
ECC, cells/mm^2	2094 (445)	2436 (392)	.0244
Axial length, mm	21.79 (1.10)	22.24 (0.82)	.17
EQ-5D score (SD)	75.4 (10.3)	72.0 (15.3)	.49
NEI-VFQ-25 score (SD)	83.4 (11.0)	82.2 (12.9)	.81
SL-AOD (µm)	165 (138)	159 (130)	.20
SL-TISA (mm^2)	0.056 (0.04)	0.059 (0.05)	.99

BCVA, best-corrected visual acuity; ECC, endothelial cell count; EQ-5D, European Quality of Life-5 Dimensions questionnaire; IOP, intraocular pressure; MD, mean deviation; NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; PAC, primary angle closure; PACG, primary angle-closure glaucoma; SL-AOD, Schwalbe line angle-opening distance; SL-TISA, Schwalbe line trabecular iris space area;
*Intended as the distance between the central corneal endothelium and the anterior surface on the lens.

Table 3 summarizes the changes observed in the whole sample (N=54) from preoperative to postoperative assessment. All are mean values with SD; 95% confidence intervals and *P* values are also shown. For IOP, topical medications, AD, SL-AOD, SL-TISA, UCVA, BCVA, endothelial cells density, and NEI-VFQ-25, the observed changes were significant, with the highest *P* value at .0011.

The percentage IOP-lowering effect was larger in PACG than in PAC (Table 4). Both quantitative parameters assessed with anterior segment OCT (SL-AOD and SL-TISA) were increased as an effect of lens surgery; the former more than doubled and the latter tripled. Changes in refractive error, central corneal thickness (CCT), and self-reported general health value scale were not significant.

TABLE 3. PREOPERATIVE AND POSTOPERATIVE VALUES FOR 54 PATIENTS

VARIABLE	PREOPERATIVE		POSTOPERATIVE		PAIRED DIFFERENCES			
	MEAN	SD	MEAN	SD	MEAN	SD	95% CI	*P*
IOP, mm Hg	20.67	9.12	14.33	2.84	-6.33	8.49	-8.64 to -4.01	<.0001
Glaucoma topical medication, number	1.38	1.40	0.74	1.23	-0.64	1.10	-0.94 to -0.34	<.0001
Aqueous depth,* mm	2.06	0.30	3.53	0.39	1.46	0.53	1.28 to 1.63	<.0001
SL-AOD, µm	174.33	143.09	520.86	254.50	346.53	211.97	267.38 to 425.68	<.0001
SL-TISA, mm^2	0.084	0.13	0.18	0.09	0.10	0.17	0.03 to 0.16	.0033
Refractive error, diopters	0.50	2.67	-0.16	0.45	-0.66	2.77	-1.56 to 0.23	.1403
UCVA, ETDRS letters	47.67	22.60	71.47	10.97	23.80	24.41	15.99 to 31.60	<.0001
BCVA, ETDRS letters	69.30	14.68	77.52	7.90	8.22	14.70	3.52 to 12.92	.0011
ECC, cells/mm^2	2254.87	409.13	1959.12	536.34	-295.74	405.38	-406.38 to -185.09	<.0001
CCT, µm	546.29	34.29	547.72	36.30	1.42	12.57	-2.00 to 4.85	.4086

TABLE 3. CONTINUED

VARIABLE	PREOPERATIVE		POSTOPERATIVE		PAIRED DIFFERENCES			
	MEAN	SD	MEAN	SD	MEAN	SD	95% CI	*P*
NEI-VFQ-25 score	83.08	12.12	89.20	8.83	6.11	7.73	4.00 to 8.22	<.0001
EQ-5D (VAS) score	72.27	17.30	69.40	20.04	-2.87	14.72	-6.88 to 1.14	.1579

*Intended as the distance between the central corneal endothelium and the anterior surface on the lens.
BCVA, best-corrected visual acuity; CCT, central corneal thickness; ECC, endothelial cell count; EQ-5D, European Quality of Life-5 Dimensions questionnaire; IOP, intraocular pressure; NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; SL-AOD, Schwalbe line angle opening distance; SL-TISA, Schwalbe line trabecular iris space area; UCVA, uncorrected visual acuity; VAS, visual analogue scale.

TABLE 4. COMPARISON OF CHANGES AFTER PHACOEMULSIFICATION IN PAC AND PACG GROUPS

VARIABLE	PAC MEAN (SD)	PACG MEAN (SD)	*P* VALUE
AD* change, mm	+ 1.22 (0.59)	+1.58 (0.49)	.058
ECC change, cells/mm^2	-145 (302)	-334 (426)	.181
IOP change, mm Hg	- 3.1 (4.8)	- 8.45 (8.03)	.044

AD, aqueous depth; ECC, endothelial cell count; IOP, intraocular pressure; PAC, primary angle closure; PACG, primary angle-closure glaucoma.
*Intended as the distance between the central corneal endothelium and the anterior surface on the lens.

We have built scatter plots to show the effect of the PE on IOP, AD, VFQ, and ECC in both groups of PAC and PACG. Figures 2 through 7 represent those scatter plots, where the effect of PE and IOL implantation is visually highlighted for each of the above parameters, separating PAC and PACG cases. Univariate and multivariate analysis was performed using the percentage IOP change at 6 months as dependent variable vs candidate predictors of the observed IOP changes: preoperative IOP, age, AD, and lens thickness (LT). Results are shown in Table 5. For PAC, univariate analysis was significant for preoperative IOP (*P*=.006) only; multivariate analysis did not show any significant correlation. For PACG, univariate analysis was significant for preoperative IOP, age, AD, and LT; multivariate analysis was significant for AD (*P*=.031) as well as for LT (*P*=.003). When directly comparing PAC and PACG cases for the effect of PE on AD, ECC, and IOP changes, only IOP change was significant (*P*=.044). There was no relationship between AD and percentage ECC loss (*P*=.97) and between percentage ECC loss and preoperative ECC (*P* =18). No correlation was found between direct angle measurements and percentage IOP lowering.

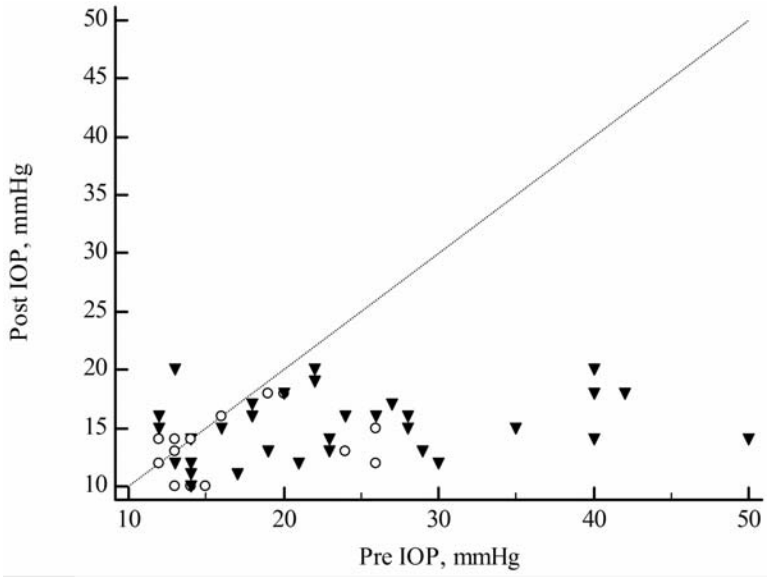

FIGURE 2
Scatter plot showing preoperative vs postoperative intraocular pressure (IOP). Circles represent primary angle closure; triangles represent primary angle closure glaucoma. Cases plotted under the line of equity had a 6-month postoperative IOP lower than the preoperative IOP.

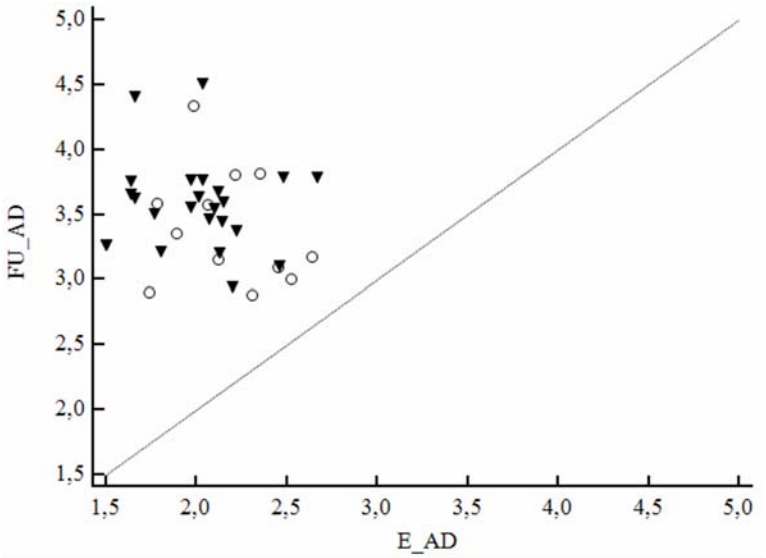

FIGURE 3

Scatter plot showing preoperative vs postoperative aqueous depth (AD). Circles represent primary angle closure; triangles represent primary angle closure glaucoma. E_AD is the distance between the central corneal endothelium and the anterior surface on the lens at eligibility visit; FU_AD is 6 months after the surgery. Cases plotted above the line of equity had a postoperative AD at 6 months greater than the preoperative AD.

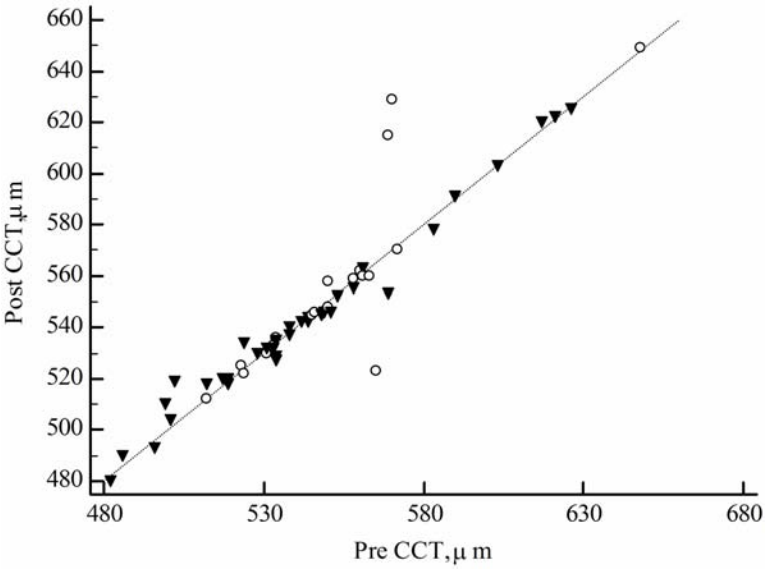

FIGURE 4

Scatter plot showing preoperative vs postoperative central corneal thickness (CCT). Circles represent primary angle closure; triangles represent primary angle closure glaucoma. Cases on the equity line showed an unchanged CCT between the preoperative visit and the 6-month postoperative visit.

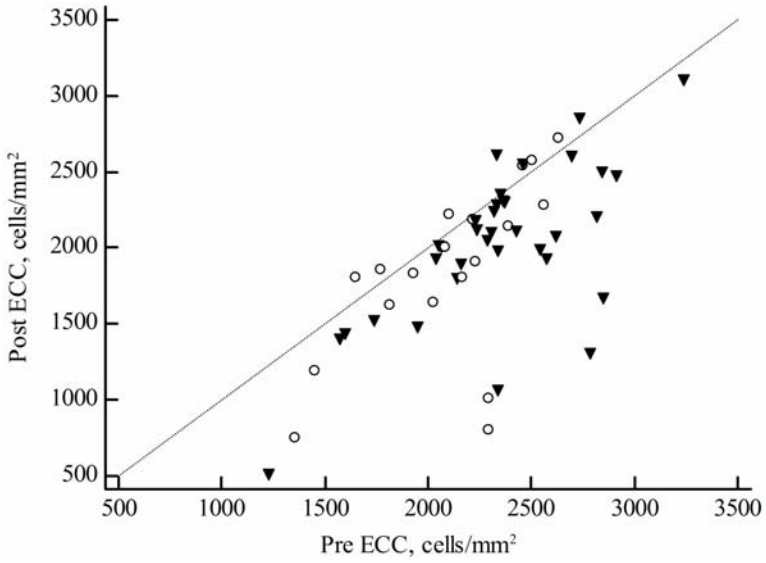

FIGURE 5

Scatter plot showing preoperative vs postoperative corneal endothelial cell count (ECC). Circles represent primary angle closure; triangles represent primary angle closure glaucoma. ECC is measured as cells per square millimeter. Cases plotted under the line of equity showed a reduction of ECC at 6 months after the surgery.

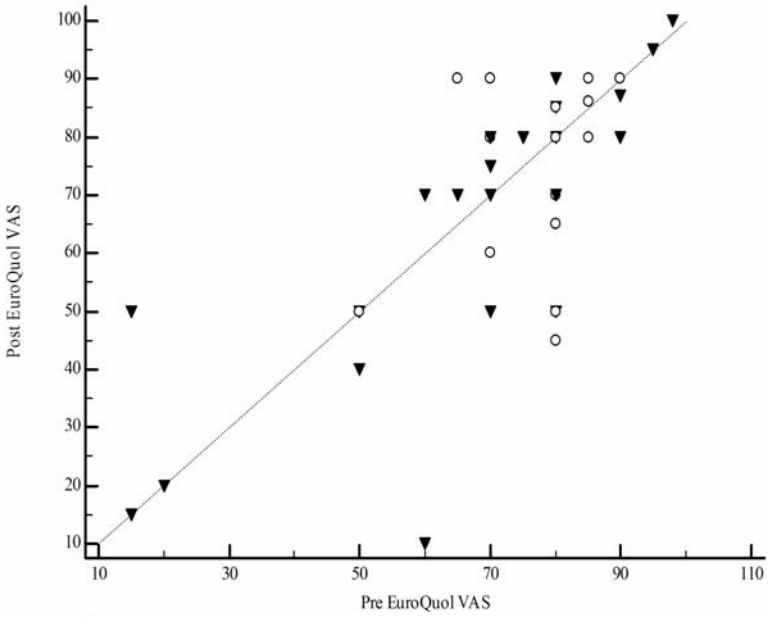

FIGURE 6
Scatter plot showing preoperative vs postoperative value set from the European Quality of Life visual analogue scale (EuroQual VAS). Circles represent primary angle closure; triangles represent primary angle closure glaucoma.

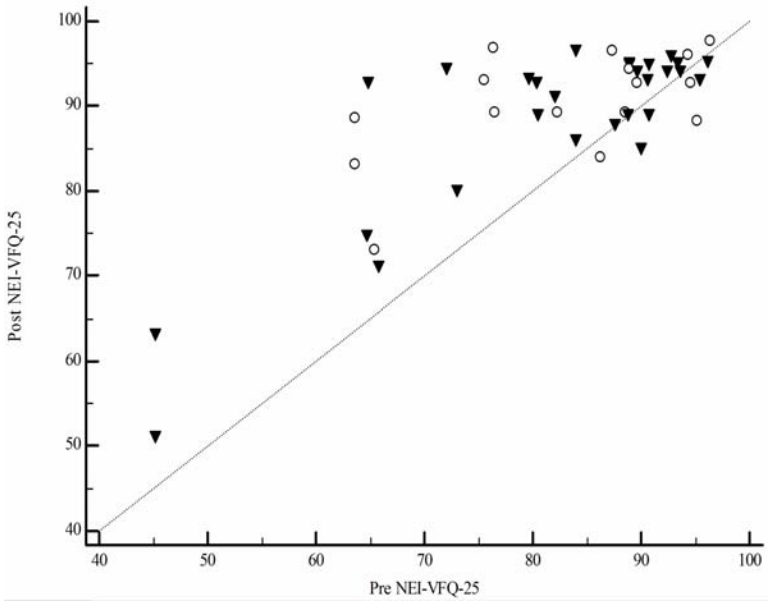

FIGURE 7
Scatter plot showing preoperative vs postoperative scores of the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25). Circles represent primary angle closure; triangles represent primary angle closure glaucoma.

TABLE 5. ASSOCIATION OF VARIOUS PREDICTORS OF IOP CHANGE AMONG PAC AND PACG GROUPS (INDEPENDENT VARIABLE: PERCENTAGE IOP REDUCTION AT 6 MONTHS)

PARAMETER	PAC				PACG			
	UNIVARIATE		MULTIVARIATE		UNIVARIATE		MULTIVARIATE	
	B (SE)	*P* VALUE	B (SE)	*P* VALUE	B (SE)	*P* VALUE	B (SE)	*P* VALUE
Preop IOP	3.38 (0.97)	.006			2.38 (0.34)	<.0001		
Age	0.93 (0.80)	.28			-1.12 (0.38)	.009		
AD	3.80 (23.9)	.88	-33.34 (16.27)	.291	51.21 (13.91)	.001	21.16 (8.63)	.031
LT	-15.57 (19.81)	.45	-81.29 (31.26)	.234	50.60 (7.76)	<.0001	-27.58 (7.25)	.003

AD, aqueous depth; B, regression coefficient; IOP, intraocular pressure; LT, lens thickness; PAC, primary angle closure; PACG, primary angle-closure glaucoma. For all parameters, multivariate models adjust for the effects of preoperative IOP, age, central corneal thickness, and axial length.

Intraoperative complications included two cases of capsular tear (3.4%). Both were managed without the need for vitrectomy, and foldable IOLs were implanted in the sulcus. Postoperatively, one patient developed posterior aqueous misdirection. This was initially managed with YAG laser iridotomy, capsulotomy, and anterior vitreolysis but required surgical anterior vitrectomy through the iridectomy for anterior chamber deepening and IOP control. There was no visual acuity loss, and IOP control was successfully maintained.

DISCUSSION

In our study, the coprimary outcome measures were IOP changes, angle widening, and patient-reported visual function; secondary outcome measures were visual acuity changes, use of IOP-lowering medications, ECC, and complications.

CHANGES IN INTRAOCULAR PRESSURE

The effect on IOP observed was large and uniform, with very few outliers (Table 3, Table 5, and Figure 2). The mean decrease was significantly larger in PACG than in PAC (Table 4), reflecting the higher preoperative IOP level of the former (Table 3), in agreement with other reports.[22-24] The favorable effect of lens extraction on IOP and on complications compared to filtration surgery in uncontrolled PACG was highlighted already with extracapsular cataract extraction by the early work of Greve and coworkers[2,3] and confirmed shortly afterwards.[4]

Our data confirm those of previous studies on lens extraction in angle-closure glaucoma, where a correlation between the IOP-lowering effect of PE and the severity of angle closure, the preoperative IOP level, and the presence of glaucomatous optic nerve changes[22-24] were directly related to the final IOP-lowering effect.

CHANGES IN ANGLE WIDTH AND ANTERIOR CHAMBER DEPTH

In our patients, the angle width was greatly increased by PE both in PAC and in PACG. Angle widening measured linearly with the SL-AOD doubled, whereas the angle area measured with the SL-TISA tripled (Figure 3, Tables 2 and 3). Such changes are in parallel with the increased central anterior chamber depth. Those findings are in agreement with recently published data on PACG patients undergoing PE.[45,46] Tham and coworkers[16,17,47] observed a widening of the angle after PE, but it was not systematically assessed or quantified.

CHANGES IN PATIENT-REPORTED VISUAL FUNCTION AND HEALTH STATUS

We measured vision problems on vision-targeted functioning and health-related quality of life using the NEI-VFQ-25. This questionnaire has 11 subscales and one general health rating question, from which a composite score is generated. The health status was measured with the EQ-5D questionnaire, which assesses five dimensions of health (mobility, self-care, usual activity, pain or discomfort, and anxiety or depression) at three levels (no problems, some problems, extreme problems). The majority of our patients had some degree of ametropia (Tables 2 and 3). As a consequence, their uncorrected vision for both far and near is expected to improve greatly after properly planned PE and IOL implantation, irrelevant of the other parameters evaluated. Although the observed refractive changes were not statistically significant, in our patients the mean refractive error shifted from low hyperopia to low myopia; also, the SD decreased significantly after PE, with many more patients nearing emmetropia after surgery.

We speculate that the effect on function-oriented questionnaires has to be interpreted as if the patients were undergoing elective refractive surgery, which was definitely not the primary aim, but is an outcome that may skew the results. For example, almost anywhere in the developed world, if a 60-year-old patient with +3 D hyperopia with or without angle closure asks his or her ophthalmologist to eliminate the need for glasses for distance vision, the patient will be offered a clear lens PE with IOL. In the age range of the patients recruited for this study, nuclear sclerosis and other lens changes are present even when the visual acuity is 20/25 to 20/20; such changes may cause decreased contrast and a sharp improvement in pale colors after PE for angle closure. We speculate that this "refractive surgery" effect had a sizeable influence on the patient-reported visual function outcomes.

EFFECTS ON ENDOTHELIAL CELLS AND CENTRAL CORNEAL THICKNESS

The decrease of corneal endothelial cell density was significant in both groups. Although no case of corneal decompensation was observed, Figure 5 clearly shows that in some individuals the loss of endothelial cell density was severe. As shown in Figure 4, the corneal thickness remained substantially unchanged. The corneal endothelial damage observed after PE, and specifically so in angle closure, is well known.[37-40] In PACG, PE resulted in a 19% decrease in corneal endothelial cells[34]; cataract extraction by PE was also observed to cause continued progressive endothelial cell losses,[40,41] and older age is associated with lower ECCs.[42] Several reports showed increased endothelial cell loss after PE performed in eyes with shallower anterior chamber and short axial length, both features associated with angle closure. Interestingly, the reports from Azuara-Blanco and coworkers[30,31] did not assess the effects on the corneal endothelium after PE for PAC or PACG.

CHANGES IN VISUAL ACUITY

We observed a significant change in UCVA and BCVA (Table 3). This was an expected result with UCVA, because the target refraction used in the IOL formula was emmetropia, whereas many patients were ametropic at the baseline visit. The mean BCVA for the whole sample of the enrolled patients improved too, even though more than half of the cases had a clear lens. As noted above, age-related changes of the lens can affect the quality of vision even when the measured visual acuity is within the normal limits.

PAC and PACG are different conditions, since patients who were developing glaucoma had an IOP elevation for a period

sufficient to cause optic nerve head damage. This is evident by the IOP levels of PACG at recruitment in our study. In some patients, at such a high level of IOP, damage of the optic nerve/VF would not occur slowly. In the Eagle trial, the investigators highlight that their results are applicable only to patients with PAC and IOP above 30 mm Hg, which are not the majority of patients, or to PACG without too advanced damage[30,31]; results were evaluated as a whole for both groups.[31] In the Eagle trial, postoperative gonioscopy data are not reported and were admittedly largely missing for the postoperative assessment; corneal endothelial cells were not evaluated.[29]

COMPLICATIONS AND FURTHER SURGERY

Very few complications were observed. Intraoperative complications were well within the expected rates for this type of eye. Postoperatively one case of posterior aqueous misdirection was treated with the sequence of YAG laser iridotomy, capsulotomy, and vitreolysis and required further core vitrectomy; no untoward effects on visual acuity or IOP were recorded. None of the patients underwent further glaucoma surgery to control the IOP; comments on this finding are prohibited by the short follow-up time of our study, which was not planned to measure long-term outcomes.

Phacoemulsification in angle closure can be technically challenging. Complications were modest and did not affect the final outcome. In our study, the surgical procedures for all cases were performed by one senior surgeon with extensive experience in complex cataract extraction and glaucoma subspecialty training. The results shown in this study with the herein reported safety margin may not be applicable in other settings.

In conclusion, our data support the usefulness of PE in lowering the IOP in patients with PAC and PACG, if performed by an experienced ophthalmologist with adequate preparation and careful surgical technique. Intraoperative complications were not frequent. General health-related self-reported evaluation was not influenced by the procedure, whereas vision-related interviews improved significantly. We speculate that the latter finding is likely due to the improvement in uncorrected visual acuity. The most worrisome concern is the severe decrease of endothelial cell density, which could lead to corneal decompensation in case of further worsening.

Our study has some drawbacks and limitations, and results should be interpreted with caution. All surgeries were performed by one surgeon, thus reducing variations in surgical technique; however, this may not reflect accurately the outcomes and complications obtainable by surgeons not specifically accustomed to treating angle-closure patients. The sample size is not large, the follow-up is limited, and there is no control group. No conclusions can be drawn on the progression of glaucoma nor on the progression of corneal endothelial damage. The results in our series are encouraging, showing favorable effects on IOP, angle width, self-reported visual function, the need for IOP-lowering medications, and visual acuity; however, further research is warranted. This work confirms our hypothesis that PE with IOL implantation is a useful procedure for patients affected by primary angle closure with or without glaucoma and highlights the potential for harmful side effects on the corneal endothelium.

ACKNOWLEDGMENTS

Funding Support: Funded in part by an educational grant from Fondazione Ines Malerba. Dr Traverso and Dr Cutolo are full-time employees of the University of Genova.
Financial Disclosures: None.
Author Contributions: Conception and design (C.E.T.); conduct of the study (C.E.T., C.A.C.); collection, management, analysis, and interpretation of the data (C.E.T., C.A.C); preparation of the manuscript (C.A.C., C.E.T.); review of the manuscript (C.E.T.); final approval of thesis (C:E:T).
Other Acknowledgments: Sebastiano Ziola and Carlo Catti, both sixth-year medical students, helped with the collection and organization of data.

REFERENCES

1. Tham Y-C, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040. *Ophthalmology* 2014;121:2081-2090.
2. Greve EL. Primary angle closure glaucoma: Extracapsular cataract extraction or filtering procedure? Int Ophthalmol 1988;12:157-162.
3. Gunning FP, Greve EL. Lens extraction for uncontrolled angle-closure glaucoma: long-term follow-up. *J Cataract Refract Surg* 1998;24:1347-1356.
4. Wishart PK, Atkinson PL. Extracapsular cataract extraction and posterior chamber lens implantation in patients with primary chronic angle-closure glaucoma: effect on intraocular pressure control. *Eye* 1989;3:706-712.
5. Teekhasaenee C, Ritch R. Combined phacoemulsification and goniosynechialysis for uncontrolled chronic angle-closure glaucoma after acute angle-closure glaucoma. *Ophthalmology* 1999;106:669-675.
6. Roberts TV, Francis IC, Lertusumitkul S, et al. Primary phacoemulsification for uncontrolled angle-closure glaucoma. *J Cataract Refract Surg* 2000;26:1012-1016.
7. Jacobi PC, Dietlein TS, Lüke C, Engels B, Krieglstein GK. Primary phacoemulsification and intraocular lens implantation for acute angle-closure glaucoma. *Ophthalmology* 2002;109:1597-1603.
8. Ming Zhi Z, Lim ASM, Yin Wong T. A pilot study of lens extraction in the management of acute primary angle-closure glaucoma. *Am J Ophthalmol* 2003;135:534-536.

9. Harasymowycz PJ, Papamatheakis DG, Ahmed I, et al. Phacoemulsification and goniosynechialysis in the management of unresponsive primary angle closure. *J Glaucoma* 2005;14:186-189.
10. Nonaka A, Kondo T, Kikuchi M, et al. Cataract surgery for residual angle closure after peripheral laser iridotomy. *Ophthalmology* 2005;112:974-979.
11. Imaizumi M, Takaki Y, Yamashita H. Phacoemulsification and intraocular lens implantation for acute angle closure not treated or previously treated by laser iridotomy. *J Cataract Refract Surg* 2006;32:85-90.
12. Nolan W. Lens extraction in primary angle closure. *Br J Ophthalmol* 2006;90:1-2.
13. Lai JSM, Tham CCY, Chan JCH. The clinical outcomes of cataract extraction by phacoemulsification in eyes with primary angle-closure glaucoma (PACG) and co-existing cataract: a prospective case series. *J Glaucoma* 2006;15:47-52.
14. Pachimkul P, Intajak Y. Effect of lens extraction on primary angle closure in a Thai population. *J Med Assoc Thai* 2008;91:303-308.
15. Lam DSC, Leung DYL, Tham CCY, et al. Randomized trial of early phacoemulsification versus peripheral iridotomy to prevent intraocular pressure rise after acute primary angle closure. *Ophthalmology* 2008;115:1134-1140.
16. Tham CCY, Kwong YYY, Leung DYL, et al. Phacoemulsification versus combined phacotrabeculectomy in medically controlled chronic angle closure glaucoma with cataract. *Ophthalmology* 2008;115:2167-2173.e2.
17. Tham CCY, Kwong YYY, Leung DYL, et al. Phacoemulsification versus combined phacotrabeculectomy in medically uncontrolled chronic angle closure glaucoma with cataracts. *Ophthalmology* 2009;116:725-731, e1-3.
18. Zhuo Y-H, Wang M, Li Y, et al. Phacoemulsification treatment of subjects with acute primary angle closure and chronic primary angle-closure glaucoma. *J Glaucoma* 2009;18:646-651.
19. Tham CCY, Kwong YYY, Leung DYL, et al. Phacoemulsification vs phacotrabeculectomy in chronic angle-closure glaucoma with cataract: complications [corrected]. *Arch Ophthalmol* 2010;128:303-311.
20. Su W-W, Chen PY-F, Hsiao C-H, Chen HS-L. Primary phacoemulsification and intraocular lens implantation for acute primary angle-closure. *PloS One* 2011;6:e20056.
21. Husain R, Gazzard G, Aung T, et al. Initial management of acute primary angle closure: a randomized trial comparing phacoemulsification with laser peripheral iridotomy. *Ophthalmology* 2012;119:2274-2281.
22. Shams PN, Foster PJ. Clinical outcomes after lens extraction for visually significant cataract in eyes with primary angle closure. *J Glaucoma* 2012;21:545-550.
23. Tham CCY, Kwong YYY, Baig N, et al. Phacoemulsification versus trabeculectomy in medically uncontrolled chronic angle-closure glaucoma without cataract. *Ophthalmology* 2013;120:62-67.
24. Kameda T, Inoue T, Inatani M, et al. Long-term efficacy of goniosynechialysis combined with phacoemulsification for primary angle closure. *Graefes Arch Clin Exp Ophthalmol* 2013;251:825-830.
25. White AJR, Orros JMA, Healey PR. Outcomes of combined lens extraction and goniosynechialysis in angle closure. *Clin Exp Ophthalmol* 2013;41:746-752.
26. Rao A. Clear lens extraction in plateau iris with bilateral acute angle closure in young. *J Glaucoma* 2013;22:e31-32.
27. Dada T, Rathi A, Angmo D, et al. Clinical outcomes of clear lens extraction in eyes with primary angle closure. *J Cataract Refract Surg* 2015;41:1470-1477.
28. Moghimi S, Hashemian H, Chen R, et al. Early phacoemulsification in patients with acute primary angle closure. *J Curr Ophthalmol* 2015;27:70-75.
29. Traverso CE. Clear-lens extraction as a treatment for primary angle closure. *Lancet* 2016;388:1352-1354.
30. Azuara-Blanco A, Burr JM, Cochran C, et al. The effectiveness of early lens extraction with intraocular lens implantation for the treatment of primary angle-closure glaucoma (EAGLE): study protocol for a randomized controlled trial. *Trials* 2011;12:133.
31. Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. *Lancet* 2016;388:1389-1397.
32. European Glaucoma Society. Terminology and guidelines for glaucoma. Anders Heijl, Carlo E. Traverso, editors. Chapter 2: Classification and terminology. Flowchart VII page 113*Br J Ophthalmol* 2017;101:73-127.
33. Qin B, Francis BA, Li Y, et al. Anterior chamber angle measurements using Schwalbe's line with high resolution Fourier-domain optical coherence tomography. *J Glaucoma* 2013;22:684-688.
34. Cheung CY, Zheng C, Ho C-L, et al. Novel anterior-chamber angle measurements by high-definition optical coherence tomography using the Schwalbe line as the landmark. *Br J Ophthalmol* 2011;95:955-959.
35. Gordon MO, Kass MA, for the Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol* 1999;117(5):573-583.
36. Rossi GCM, Milano G, Tinelli C. The Italian version of the 25-item National Eye Institute Visual Function Questionnaire: translation, validity, and reliability. *J Glaucoma* 2003;12:213-220.
37. Park HL, Lee NY, Park CK, Kim MS. Long-term changes in endothelial cell counts after early phacoemulsification versus laser peripheral iridotomy using sequential argon:YAG laser technique in acute primary angle closure. *Graefes Arch Clin Exp Ophthalmol* 2012;250:1673-1680.
38. Ko Y-C, Liu CJ, Lau L-I, et al. Factors related to corneal endothelial damage after phacoemulsification in eyes with occludable angles. *J Cataract Refract Surg* 2008;34:46-51.

39. Ko Y-C, Liu CJ-L, Chou JC, Hsu W-M. Effects of phacoemulsification and intraocular lens implantation on the corneal endothelium in primary angle-closure glaucoma. *J Med Ultrasound* 2004;12:33-37.
40. Liesegang TJ. The response of the corneal endothelium to intraocular surgery. *Refract Corneal Surg* 1991;7:81-86.
41. Bourne WM, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. *Ophthalmology* 1994;101:1014-1022.
42. Galgauskas S, Norvydaite D, Krasauskaite D, Stech S, Asoklis RS. Age-related changes in corneal thickness and endothelial characteristics. *Clin Interv Aging* 2013;8:1445-1450.
43. Küchle M, Viestenz A, Martus P, et al. Anterior chamber depth and complications during cataract surgery in eyes with pseudoexfoliation syndrome. *Am J Ophthalmol* 2000;129:281-285.
44. Cho YK, Chang HS, Kim MS. Risk factors for endothelial cell loss after phacoemulsification: comparison in different anterior chamber depth groups. *Korean J Ophthalmol* 2010;24:10-15.
45. Kim M, Park KH, Kim T-W, Kim DM. Anterior chamber configuration changes after cataract surgery in eyes with glaucoma. *Korean J Ophthalmol* 2012;26:97-103.
46. Shao T, Hong J, Xu J, et al. Anterior chamber angle assessment by anterior-segment optical coherence tomography after phacoemulsification with or without goniosynechialysis in patients with primary angle closure glaucoma. *J Glaucoma* 2015;24:647-655.
47. Tham CCY, Kwong YYY, Baig N, Leung DY, Li FC, Lam DS. Author reply. *Ophthalmology* 2013;120:e71-72.