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GLAUCOMA

Safety and efficacy of multiple cyclocoagulation of ciliary bodies by high-intensity focused ultrasound in patients with glaucoma

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Abstract
Purpose To evaluate long-term efficacy and safety of repeated ultrasonic circular cyclocoagulation (UCCC) in patients with uncontrolled glaucoma.
Methods Forty eyes of 40 patients affected by primary or secondary uncontrolled glaucoma under maximal tolerated medical therapy were enrolled in this prospective non-comparative case series study. A complete ophthalmic examination was performed before and after each month for 1 year. The UCCC treatment was repeated at 4 months if the intraocular pressure (IOP) was > 21 mmHg without major complications. Complete success was defined as a final IOP > 5 mmHg and ≤ 21 mmHg without hypotensive medication adjunction and no major or vision-threatening complications.
Results The mean preoperative IOP was 32.5 ± 9.9 mmHg. Four months after the first UCCC treatment the overall IOP reduction was 27.8%. Twenty-two of the treated eyes did not achieve the complete success and a second treatment was performed in 20 of these eyes. Four months after the second UCCC procedure, the IOP reduction was 20.3% from preoperative values and 34.7% from baseline. Twelve of the retreated eyes needed a third treatment. Four months after the third UCCC treatment, the overall IOP reduction was 34% and 52.6% from baseline. No major complications occurred during or after any of the procedures. At 12 months, complete success was achieved in 85% (34/40) of treated eyes, with a maximum of three procedures and a significant medication reduction.
Conclusions Multiple UCCC treatments are safe, and additional treatments increase the overall procedure efficacy.

Keywords Glaucoma · Cyclocoagulation · High-intensity focused ultrasound · Ciliary body · Glaucoma procedure · Non invasive therapy

Introduction

Glaucoma is considered one of the leading causes of blindness. Traditional management of glaucoma starts with medical treatment and, if necessary, proceeds to incisional surgery. Noninvasive glaucoma procedures (NIGPs) are a valid alternative in glaucoma management, as they try to fill the gap between the shortcomings of glaucoma surgeries and antiglaucoma medications. NIGPs do not require penetration into the eye and should not be confused with minimally-invasive glaucoma surgeries (MIGS), which refers to a small-incision conjunctiva-sparing surgery [1].

Different types of energy sources and methods, destroying the ciliary processes, have been investigated, resulting in coagulative necrosis of the ciliary body following heating or freezing, including diode laser, cryotherapy, and microwave heating. Many of these procedures have been abandoned because of serious and vision-impairing complications as a result of non-selective tissue treatment and an unpredictable dose–effect relationship [2]. Moreover, diode laser energy, which is currently the standard for transcleral cyclophotocoagulation, is mainly absorbed by pigmented tissues and this can produce damage to iris and choroid [3].

Therapeutic ultrasound in the treatment of glaucoma was introduced for the first time in the 1980s by Coleman et al.

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[4–6]; the following development of a new circular cyclocoagulation device which uses miniaturized transducers to produce high-intensity focused ultrasound (HIFU), also defined ultrasonic circular cyclocoagulation (UCCC), has renewed interest on this technique [7].

UCCC has recently been described by Abdelrahman [1] as a NIGP because, compared to diode laser cyclocoagulation, it permits a selective and controlled thermic effect on the target organ with limited damage to adjacent structures. In fact, histological animal studies have demonstrated that UCCC is only focalized on the distal part of the ciliary body and the effect is independent from the degree of tissue pigmentation [8].

Furthermore, a fluid-filled space created between sclera and ciliary body and between sclera and adjacent choroid has been demonstrated in treated eyes, indicating an uveoscleral pathway outflow [9, 10].

First clinical trials in humans showed that this device allowed a significant and predictable intraocular pressure (IOP) reduction from 26% to 36% at 12 months [11, 12]. Further studies confirmed a significant IOP reduction and good local tolerance after one UCCC treatment [13].

In this study, we aimed to evaluate success rate, long-term effectiveness and safety of multiple UCCC, up to three times, in patients who showed lack of efficacy or incomplete success with only one treatment.

Methods

We performed this prospective non-comparative interventional study in agreement with the tenets of the Declaration of Helsinki and in conformity with standards of ISO 14155 (Clinical Investigation of Medical Device for Human Subjects). This study was designed and conducted according to the World Glaucoma Association Guidelines [14] on the design and reporting of glaucoma surgical trials. All patients provided both verbal and written consent.

Inclusion criteria were men or women of 18 years old or older with primary or secondary glaucoma with a baseline IOP > 21 mmHg under maximal tolerated medical therapy.

Exclusion criteria were: pregnancy, concomitant systemic medications that could affect IOP, history of ocular tumor, ocular infection, and ocular surgical/laser procedure in the last 6 months.

Hypotensive medical therapy was maintained during the follow-up.

HIFU procedure

For all treatments reported in this study we used the currently available second-generation EyeOP1 probes. The first generation probe has been previously described in detail [9]. The second generation probe has the following features: six active piezoelectric transducers with a cylinder shape of 10.2 mm radius, 5.5 mm width, and 7 mm length, with an active area surface of approximately 25 mm^2 (width 4 mm x length 6.3 mm). The focal volume of each transducer has an elliptic cylinder shape with an axial length of 3.2 mm (major section of the ellipse), a transverse focal width of 0.2 mm (minor section of the ellipse), and lateral focal width of 3.1 mm (length of the elliptical cylinder). Differently from the first generation, in second-generation probes the following parameters are standard and not editable: 21 MHz operating frequency; six activated sectors; 2–3 W acoustic power; 8 s of the HIFU delivery time for each sector.

Three different probe sizes (11, 12, or 13 mm ring diameters) are available and have been selected for each eye using preoperative biometric data based on AS-OCT image (Visante AS-OCT mod 1000, Carl Zeiss Meditec Inc., Dublin, CA, USA).

All HIFU procedures were performed by one ophthalmic surgeon (ADG), and all patients were treated under Sub-Tenon anesthesia.

The surgical procedure using second-generation probes is substantially the same as previously described for first-generation probes [8, 9]. Briefly, the device is formed of two parts: a polymer-made cone, placed in direct contact with the ocular surface, manually centered and held in place by a mild suction system and a ring, containing six active piezoelectric elements, which is inserted in the coupling cone and filled with saline solution. The ring is connected by a cable to a control module that allows the sequential activation of each transducers for 8 s.

Postoperative treatments included a combination of dexamethasone and tobramycin (Tobradex, Alcon Laboratories, Inc., Fort Worth, TX, USA) given 3 times daily for 15 days. Preoperative hypotensive medications were maintained during the follow-up if IOP was > 15 mmHg, otherwise they were gradually reduced if IOP < 15 mmHg.

Outcome assessment

We evaluated all patients before treatment and at 1, 4, 10 days and each month till 1 year after the last treatment.

The preoperative ocular examination included: best-corrected visual acuity (BCVA), ocular surface and anterior segment slit-lamp examination, Goldmann applanation tonometry, complete fundus examination, ultrasound corneal pachymetry, gonioscopy, AS-OCT (Visante AS-OCT mod 1000, Carl Zeiss Meditec Inc., Dublin, CA, USA), RNFL OCT analyses (3D OCT-1 Maestro, Topcon Corporation, Tokyo, Japan) and Humphrey visual field test (24–2 SITA Standard, Carl Zeiss Meditec Inc., Dublin, CA).

Each follow-up ocular examination included: BCVA, ocular surface and anterior segment slit-lamp examination,

Goldmann applanation tonometry, and complete fundus examination.

At 4 months we evaluated the success rate, and we decided to retreat patient if IOP was > 21 mmHg with no adverse major complications related to HIFU procedure.

The diameter and the position of the probe for each retreated patient were unchanged in the second and third treatment.

Statistical analysis

The primary efficacy outcome was based on IOP reduction at 4 and 12 months from each treatment defining the complete success as final IOP higher than 5 and less than or equal to 21 mmHg without adding hypotensive medications and without major or vision-threatening complications.

We considered as secondary end-points hypotensive medication reduction and as safety profile any minor and major intra and postoperative complications.

We expressed results of descriptive analysis as means and standard deviation, median and range for quantitative variables, and as counts and percentages for categorical variables.

Student's *t*-test was used to compare means and percentages and statistical significance was set at $p < 0.01$.

We performed statistical analysis through SPSS software (IBM SPSS Statistics for Windows, version 22.0. IBM Corp., Armonk, NY, USA).

Results

Forty eyes of 40 patients with medically uncontrolled primary and secondary glaucoma under maximal tolerated medical therapy were enrolled to undergo UCCC treatment.

Demographic data and ocular characteristics are reported in Table 1.

The mean preoperative IOP was 32.5 ± 9.9 mmHg. Four months after the first treatment the IOP reduction was 27.8% (Fig. 1).

Eighteen (45%) of 40 treated eyes achieved the complete success with a mean IOP reduction of 44.3% at 4 months and of 45.7% at 12 months (Fig. 2).

There was not a statistically significant difference in the efficacy between the group with previous glaucoma surgery (17/40 eyes 26.12% mean IOP reduction; mean preoperative IOP 32.4 ± 7.6 and mean postoperative IOP 23.92 ± 6.9 mmHg) and those without previous glaucoma surgery (23/40 eyes 27.8% mean IOP reduction; mean preoperative IOP 31.9 ± 10.9 and mean postoperative IOP 23 ± 9.8 mmHg).

In 22 (55%) of the 40 treated eyes we observed a IOP decrease in the first month and a gradual IOP increase in the following 3 months (Fig. 2). These patients did not achieve the target IOP at 4 months even though there was a mean IOP reduction of 18.4%; therefore a second UCCC treatment was performed.

One patient refused a second treatment even though the IOP was more than 21 mmHg, and one patient underwent trabeculectomy surgery.

Four months after the second UCCC procedure, the mean IOP reduction was 20.3% from preoperative values (Fig. 3).

Table 1 Baseline patient demographics and characteristics ($n = 40$)

Patient characteristics	Number (%)
Sex, *n* (%)	
Male	20 (50%)
Female	20 (50%)
Age (years)	
Mean ± SD	71.8 ± 13.6
Range	29–94
Median	73
Ethnicity, *n* (%)	
Caucasian	37 (92.5%)
African	1 (2.5%)
Asian	2 (5%)
Type of glaucoma, *n* (%)	
Primary open angle	14 (35%)
Chronic close angle	3 (7.5%)
Exfoliative	8 (20%)
Neovascular	12 (30%)
Uveitic	3 (7.5%)
Previous surgery, *n* (%)	
Filtering surgery	17 (42.5%)
Phacoemulsiphication and IOL implant	25 (62.5%)
Preoperative glaucoma medications, *n* (%)	
Prostaglandins	25 (62.5%)
Beta-blockers	30 (75%)
Alpha-adrenergic agonists	21 (52.5%)
Carbonic anhydrase inhibitors	24 (60%)
Parasympathomimetics	2 (5%)

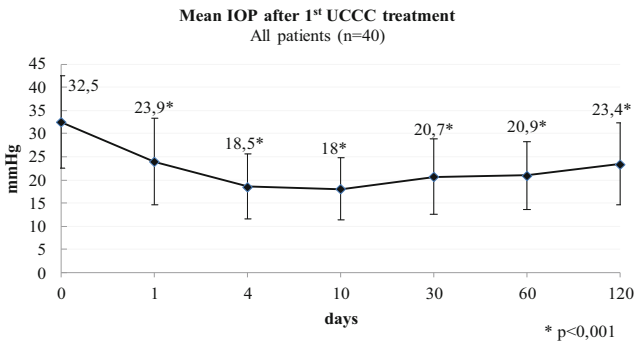

Fig. 1 Mean IOP (mmHg) in 40 eyes of 40 patients after the 1st UCCC. *Error bars* represent standard deviation. Postoperative IOP values were significantly lower than preoperative values across all timepoints. (2-tailed, paired *t*-test, $p < 0.001$)

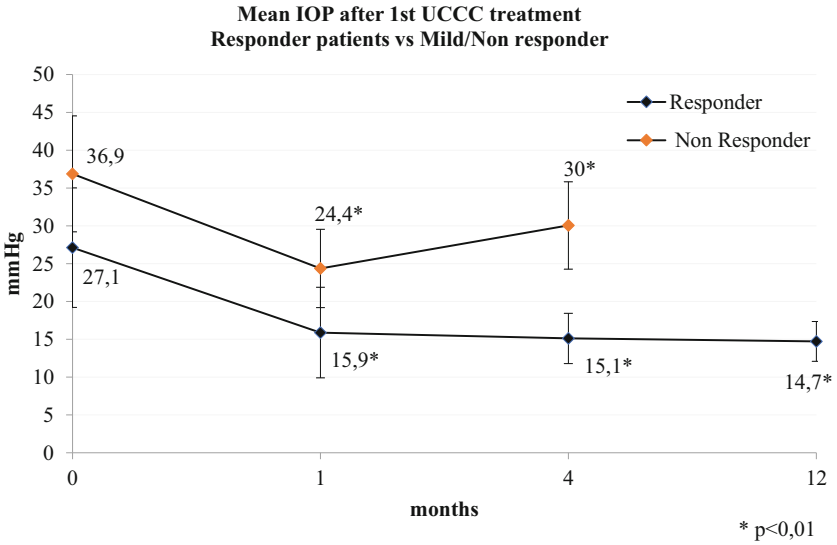

Fig. 2 Mean IOP (mmHg) after the 1st UCCC in responder patients ($n = 18$) and in mild/non responder patients ($n = 22$). *Error bars* represent standard deviation. Postoperative IOP values were significantly lower than preoperative values across all timepoints (2-tailed, paired *t*-test, $p < 0.01$)

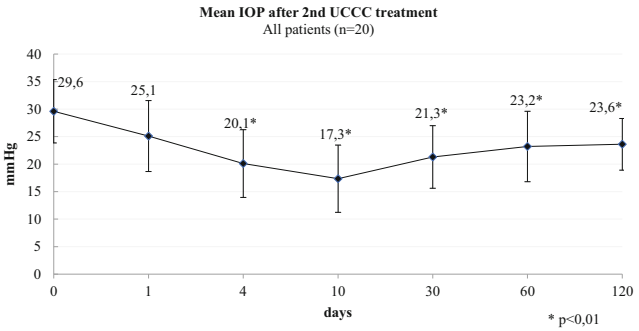

Fig. 3 Mean IOP (mmHg) after the 2nd UCCC in 20 patients who did not achieved the target IOP 4 months after the 1st UCCC. *Error bars* represent standard deviation. Postoperative IOP values were significantly lower than preoperative values across all timepoints, except in the first postoperative day (2-tailed, paired *t*-test, $p < 0.01$)

In this group of 20 eyes, the baseline IOP was 36.15 ± 8.7 mmHg, and we obtained a mean IOP reduction of 18.1% after one and of 34.7% after two treatments when compared to the baseline IOP values.

Four months after the second UCCC, eight (40%) of 20 eyes achieved the target IOP with a mean IOP reduction of 33.1% at 4 months and of 32.4% at 12 months (Fig. 4).

Twelve (60%) of the 20 retreated eyes did not achieve the target IOP even though a mean IOP reduction of 14% at 4 months. Also in these mild/non-responder patients we observed a IOP decrease in the first month and a gradual IOP increase in the following 3 months (Fig. 4), therefore we decided to perform a third UCCC treatment.

Four months after the third UCCC procedure, the mean IOP reduction was 34% and 36.5% after 12 months (Fig. 5).

In this group, at 4 months of follow-up, we obtained 16.5%, 32.7%, and 52.6% of mean IOP reduction after the first, the second, and the third treatments respectively when compared to the baseline IOP values (Fig. 6).

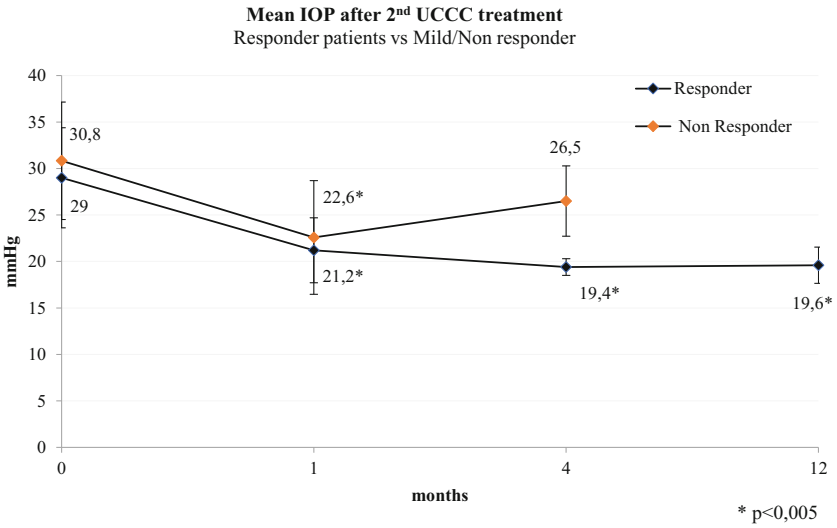

Fig. 4 Mean IOP (mmHg) after 2nd UCCC in responder patients ($n = 8$) and in mild/non responder patients ($n = 12$). *Error bars* represent standard deviation in mean IOP. Postoperative IOP values were significantly lower than preoperative values across all timepoints in responder patients. In mild/non-responder patients at 4 months, postoperative IOP values were not significantly lower than preoperative (2-tailed, paired *t*-test, $p < 0.005$)

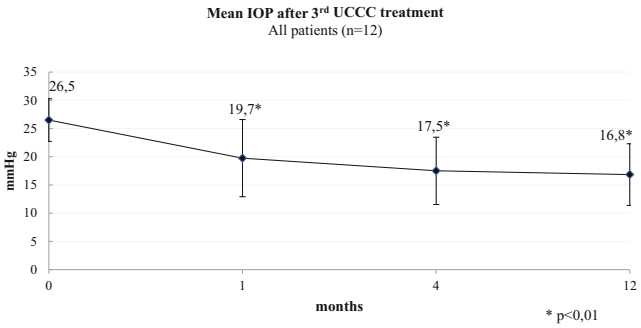

Fig. 5 Mean IOP (mmHg) after the 3rd UCCC in 12 patients who did not achieved the target IOP 4 months after the 2nd UCCC. *Error bars* represent standard deviation. Postoperative IOP values were significantly lower than preoperative values across all timepoints (2-tailed, paired *t*-test, $p < 0.01$)

Complete success was obtained in eight (66.7%) out of 12 three-times treated patients.

At 12 months, complete success was achieved in 85% (34/40) of treated eyes with a maximum of three procedures.

Before the treatment the mean number of hypotensive therapy classes was 3.6 ± 0.7 (range 2–5). After 12 months from the last successful UCCC treatment, we observed a statistically significant decrease in the mean number of hypotensive therapy classes (2.4 ± 1.3; range 0–4; $p < 0.01$).

Mean visual acuity remained statistically unchanged, and no major complications occurred during and after any of the procedures (Table 2).

In 25% of patients we observed a scleral thinning corresponding to the treated sectors (Fig. 7).

Table 2 Intra-operative and post-operative ocular complications after UCCC procedures

Ocular complications	Number (%)
Intraoperative	
Pain	30/40 (75%)
Sub-conjunctival hemorrhage	15/40 (37.5%)
Postoperative	
Conjunctival hyperemia	40/40 (100%)
Superficial punctate keratitis	18/40 (45%)
Sub-conjunctival hemorrhage	12/40 (30%)
Scleral thinning	10/40 (25%)
Loss of visual acuity (> 2 lines)	2/40 (5%)
Corneal ulcer	2/40 (5%)
Corneal edema	0/40 (0%)
Choroidal detachment	0/40 (0%)
Phtisis	0/40 (0%)
Anterior chamber reaction	0/40 (0%)

Discussion

Many mechanisms have been advanced to explain IOP reduction after UCCC treatments. Previous histological study [8] demonstrated that the main mechanism was the decrease of AH production due to a localized and circumferentially distributed coagulation necrosis of the ciliary body. Further studies [9, 10] reported also a scleral architecture rearrangement with a fiber delamination that allows a AH drainage into the suprachoroidal and transcleral space. Several of these studies also reported a percentage of non-responder patients with a poor or absent IOP reduction after one treatment. One explanation suggested was the insufficient amount of ciliary body tissue coagulated, and some patients with an insufficient response were retreated, rotating the probe with the intention of targeting different areas to increase the ciliary body coagulation amount [6, 13].

In our clinical results, in mild/non-responder patients we observed a maximum IOP reduction spike during the first month and a loss of efficacy during the following 3 postoperative months, suggesting a possible reactivation of the ciliary body.

It was possible to indirectly confirm this hypothesis by previous histological findings on a series of enucleated eyes,

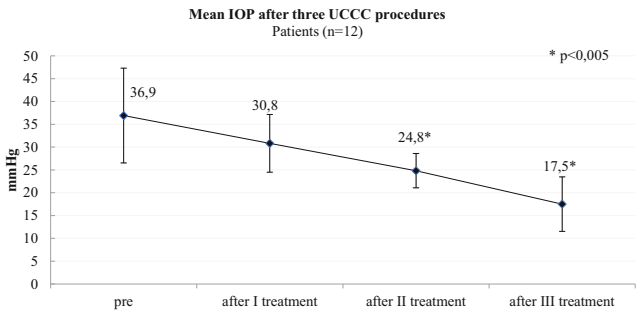

Fig. 6 Mean IOP (mmHg) 4 months after each UCCC treatment in patients achieved IOP target with three UCCC procedures. *Error bars* represent standard deviation. Postoperative IOP values were significantly lower than preoperative values across all timepoints (2-tailed, paired *t*-test, $p < 0.005$)

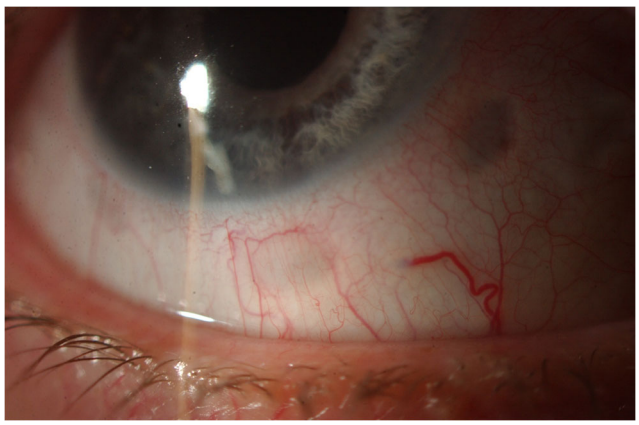

Fig. 7 Postoperative clinical images of a patient underwent UCCC procedure with scleral thinning (grey areas at 5–6-7 o'clock) without any sign of inflammation

which demonstrated that the epithelium can regenerate after diode laser cyclophotocoagulation, resulting in restoration of AH secretion [3].

On the basis of this evidence and observations, we decided to perform retreatments without rotating the probe, with the intention of targeting the same areas to contrast a possible reactivation, even if partial, of the ciliary body. Mastropasqua R. et al. instead postulated that the presence or the absence of a AH suprachoroidal drainage seems to play a critical role in the final success [10].

In our study, we did not analyze suprachoroidal space drainage, but the presence or the absence of scleral signs does not seem to be correlated to the efficacy.

The scleral thinning observed after UCCCs may pose concerns for later filtering surgery, but at this moment there are no studies that focus on this point. Only one patient of our group underwent trabeculectomy surgery after one UCCC treatment, and in this case we try to performe a scleral flap distant from thinning areas. In this case, after the surgery, there were no tissue complications or abnormal reactions.

No major vision-threatening complications occurred during any of the procedures. In two cases we reported a two-line visual loss; one was due to cataract evolution and the other to glaucoma disease progression. We also reported two corneal ulcers, rapidly solved with only medical treatment, probably caused by a worsening of a preexisting corneal surface disease, frequently observed in patients with long-term topical multitherapy (Table 2).

Considering the total success rate we can affirm that 45% (18/40) of the initial group of patients needed only one UCCC, 50% (20/40) needed two UCCCs, and 30% (12/40) three UCCC treatments to achieve the target IOP. At the end of the follow-up (12 months from the last treatment), 85% (34/40) obtained complete success with also a significant reduction of hypotensive medications.

In conclusion, even though this study has some limitations (small case size, non-comparative, inclusion of different glaucoma subtypes), multiple UCCC treatments seems to increase the overall procedure efficacy. Specifically the total IOP reduction percentage compared to the preoperative values was 27.8%, 20.3%, and 34% 4 months after 1st, 2nd, and 3rd UCCC respectively.

Furthermore if we consider only the group that underwent to three UCCCs and compare to the baseline IOP values, the total efficacy was 16.5%, 32.7%, and 52.6% 4 months after 1st, 2nd, and 3rd UCCC respectively. These data demonstrated a possible step-by-step success achievement in most refractory glaucomatous eyes.

Although our data need to be confirmed by further study with a longer follow-up and a larger sample size, the UCCC procedures, even multiple, seems to have a safer profile than other previous available cyclodestructive procedures.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvements in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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