

Ultrasound Cyclo-Plasty in Patients with Glaucoma: 1-Year Results from a Multicentre Prospective Study

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Keywords

Glaucoma · Ultrasound cyclo-plasty · High-intensity focused ultrasound · Intraocular pressure · Ciliary body

Abstract

Purpose: The aim of this study was to evaluate the safety and efficacy of ultrasound cyclo-plasty (UCP) for reducing intraocular pressure (IOP) in patients with glaucoma. **Methods:** This is a multicentre prospective study conducted in 3 Italian glaucoma centres. UCP was performed by EyeOP1, which delivers ultrasound beams using 6 piezoelectric transducers activated for 4/6 s (first generation) or 8 s (second generation). Primary outcomes were the mean IOP reduction and the rates of success after 1 year. Secondary outcomes were the mean IOP reduction at each follow-up, and the reduction of the number of hypotensive medications. **Results:** In total, 49 eyes from 47 patients were treated. One year postoperatively, the mean IOP had decreased from 27.7 ± 9.2 to 19.8 ± 6.9 mm Hg ($p < 0.001$), and the mean number of hypotensive drops and tablets had decreased from 3.2 and 0.5 to 2.3 and 0.2, respectively ($p < 0.05$). Postoperative IOP reduction was significantly related to preoperative IOP ($r^2 = 0.5034$; $p < 0.0001$). Second-generation probes determined a signifi-

cantly higher IOP reduction ($p < 0.05$). Qualified success was achieved in 25 eyes (51.1%) and complete success in 21 (42.9%), while failure was recorded in 12 (24.5%). **Conclusions:** UCP is safe and effective for reducing IOP. The procedure determines a greater IOP reduction in patients with higher preoperative IOP. Second-generation probes improve outcomes without detrimental effects on safety.

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Introduction

Glaucoma is the most frequent cause of visual impairment worldwide, leading to progressive visual field damage, and eventually blindness [1]. Elevated intraocular pressure (IOP) is still considered the most important and the only modifiable risk factor to halt or slow the progression of visual field loss [2]. IOP can be lowered by reducing the inflow and/or increasing the outflow of aqueous humour. Traditionally, the reduction of aqueous humour

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secretion can be achieved by partially destroying the ciliary body with different physical methods, including lasers and cryotherapy [3–5]. However, the use of cyclodestructive techniques is currently mainly limited to eyes with refractory glaucoma with poor or null visual acuity, due to the lack of selectivity for the targeted ciliary body, the unpredictable dose-effect relationship, and the high rate of complications [2, 5, 6]. In recent years, a novel device employing high-intensity focused ultrasound for the coagulation of the ciliary body (ultrasound cyclo-plasty; UCP) has been introduced, with the aim of achieving selective coagulation of the ciliary body while sparing the adjacent structures [7–11]. Here, we report the 1-year results of UCP procedures performed in 3 Italian glaucoma centres.

Materials and Methods

Study Design

This multicentre prospective interventional clinical study was conducted between January 2014 and January 2016 in 3 Italian glaucoma centres: S. Orsola-Malpighi University Hospital (Bologna), University Eye Clinic (Genoa), and Scientific Institute Capitanio Hospital (Milan). All participants provided both verbal and written informed consent before any study procedure. The study was approved by the local institutional review boards and was carried out in accordance with the principles of the Declaration of Helsinki. Inclusion criteria were age older than 18 years, a diagnosis of glaucoma with an uncontrolled baseline IOP (≥ 21 mm Hg) while on maximum medical therapy or intolerance to glaucoma medications despite well-controlled IOP. Exclusion criteria were pregnancy, a diagnosis of normal-tension glaucoma, a laser or surgical procedure within the last 6 months, ocular infections and uveitis in the prior 3 months.

HIFU Device and Surgical Procedure

The device (EyeOP1, Eye Tech Care, Rillieux-la-Pape, France) was previously described in detail by us [12]. Briefly, the treatment probe contains 6 piezoelectric transducers, which produce and deliver the ultrasound energy beams. The probe is supplied in 3 different sizes (11-, 12- and, 13-mm ring diameters) in order to best adapt to the eye. The treatment acts on 6 circular sectors of the ciliary body, with a 20-s interval between each shot. Two generations of probes have been commercialized since the device's introduction: the first one allowed the surgeon to choose between 4 or 6 s of treatment time duration according to the preoperative conditions; the second one offers a unique exposure time of 8 s, treating up to an average 45% of the entire ciliary body circumference. All of the procedures were performed under peribulbar anaesthesia by the same surgeon in each centre (E.C.C. in Bologna; C.E.T. in Genoa; F.B. in Milan).

Visits and Therapy

The baseline evaluation included best-corrected visual acuity (BCVA), slit lamp biomicroscopy, gonioscopy, fundus examination, IOP measurement, optical biometry (Lenstar LS 900; Haag-

Streit, Köniz, Switzerland), and a 30-2 pattern automated visual field test (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA, USA). Postoperatively, patients received tobramycin and dexamethasone combination eye drops (Tobradex; Alcon Inc., Fort Worth, TX, USA) 4 times daily for 2 weeks. Hypotensive medications were interrupted after surgery, and then prescribed again only if postoperative IOP was ≥ 21 mm Hg at any follow-up visits. Slit lamp biomicroscopy, BCVA, fundus examinations, and IOP measurements were performed postoperatively at 1, 7, and 14 days, 1, 3, 6, and 9 months, and 1 year. The visual field test was performed 6 and 12 months after the treatment.

IOP measurements were carried out approximately at the same time of the day by 2 experienced examiners at each centre (G.G. and S.S. in Bologna, A.V. and P.C. in Genoa, L.E.U. and L.C. in Milan) using a calibrated Goldmann applanation tonometer. Three consecutive IOP measurements were recorded, and the average value was calculated and used for the analysis. Data from BCVA were converted to logMAR equivalents of Snellen acuity. We used extrapolated values of 2.6, 2.7, 2.8, and 2.9 logMAR to represent the vision of counting fingers, hand motion, light perception, and no light perception, respectively [13].

Main Outcomes

Primary outcomes were the mean IOP reduction at the last follow-up visit, and the rates of qualified or complete success and failure. Qualified success was defined as an IOP reduction $\geq 20\%$ and >5 mm Hg without adjunctive hypotensive medication, while complete success was as above plus IOP <21 mm Hg. Cases with an increase in the number of postoperative daily hypotensive medications (regardless of the IOP value) and the need for additional subsequent surgery during the study period were considered as failures. Secondary outcomes were the mean IOP reduction at each follow-up visit, the mean number of daily hypotensive medications, and the complication rates.

Statistical Analysis

Data analysis was performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA). The homogeneity of variances was assessed by the Levene test. Variables following a normal distribution were presented as the mean \pm SD. Paired *t* tests were used to compare pre- and postoperative IOP values, while the Wilcoxon test was used to compare the changes of the number of hypotensive medications before and after surgery. One-way ANOVA tests were conducted to assess the differences of IOP reductions among glaucoma types and surgical settings. Linear regression analysis between preoperative IOP and IOP reduction at the final follow-up visit was conducted. Survival curves of eyes treated with first- and second-generation probes were calculated according to the Kaplan-Meier analysis and compared with the log-rank test. Statistical significance was set at $p < 0.05$.

Results

Forty-nine eyes of 47 patients were enrolled in the study. The characteristics of patients, eyes, and treatment are summarized in Table 1. Before surgery, the mean IOP (\pm SD) was 27.7 ± 9.2 mm Hg, the mean number of daily

Table 1. Characteristics of patients and treatments

Patients/eyes, <i>n</i>	47/49
Age \pm SD, years	73.8 \pm 14.3 (33–98)
Male/female, <i>n</i>	24/23
Glaucoma type	
OAG	24 (49.0)
XFG	9 (18.4)
ACG	11 (22.5)
NVG	5 (10.2)
Lens status	
Phakic	16 (32.7)
Pseudophakic	30 (61.2)
Aphakic	3 (6.1)
Previous glaucoma treatments	
Laser trabeculoplasty	13 (26.5)
Trabeculectomy	12 (24.5)
Diode laser cyclophotocoagulation	0 (0)
Probe generation	
First generation	35 (71.4)
Second generation	14 (28.6)
BCVA, logMAR	
Before surgery	1.65 \pm 1.14
Last follow-up	1.66 \pm 1.14
Visual field \pm SD, dB	
Before surgery	-17.8 \pm 10.3
Last follow-up	-19.1 \pm 9.0

Values are presented as *n* (%) or mean \pm SD (range). ACG, angle closure glaucoma; BCVA, best-corrected visual acuity; OAG, open angle glaucoma; NVG, neovascular glaucoma; XFG, exfoliative glaucoma.

hypotensive drops was 3.2 ± 1.1 , and the mean number of daily acetazolamide tablets was 0.5 ± 0.5 . One day after the treatment, the mean IOP was significantly reduced compared to the preoperative value (17.9 ± 6.3 mm Hg; $p < 0.0001$). This significant reduction was steadily maintained during the follow-up, when the mean IOP value was 19.8 ± 6.9 mm Hg ($p < 0.0001$). Additionally, a significant decrease of daily hypotensive drops and acetazolamide tablets was found 1 year after treatment ($p < 0.05$). In particular, the percentage of patients using acetazolamide tablets decreased 1 year after the procedure from 53.1 to 16.7%. Figure 1 shows the trend of the IOP value for each visit, expressed as both the mean value and percentage of reduction, along with the mean number of daily hypotensive medications.

Linear regression analysis showed that postoperative IOP reduction after 1 year was significantly related to preoperative IOP ($r^2 = 0.5034$; $p < 0.0001$; Fig. 2). One year postoperatively, patients treated with second-generation

probes showed a significantly higher percentage of IOP reduction compared to those treated with first-generation probes ($p < 0.05$; Fig. 3). Conversely, the mean IOP reduction at the last follow-up visit did not statistically differ according to both types of glaucoma and lens status (always $p > 0.05$). However, the highest IOP reduction on average was found in eyes with angle closure glaucoma (-13.3 mm Hg from baseline to 1-year follow-up; 41% of reduction), followed by open angle glaucoma (-7.3 mm Hg; 28.5%), neovascular glaucoma (-7.1 mm Hg; 20.5%), and exfoliative glaucoma (-4.3 mm Hg; 18.3%).

No patients experienced vision loss ≥ 1 line at 1 year, and postoperative final visual acuity and visual field mean deviation did not significantly differ from preoperative values (always $p > 0.05$). Qualified success was achieved in 25 eyes (51.1% of the total) with a mean IOP reduction of 40.8% compared to baseline, while complete success was achieved in 21 eyes (42.9%) with a mean IOP reduction of 41.3% (Fig. 4). Conversely, treatment failure was registered in 12 eyes (24.5%). Of these, 9 eyes were treated with the first-generation probe, and the remaining 3 with the second-generation probe. Among overall failures, 7 eyes exited the study before the last follow-up and required additional surgery after an average interval of 3 months (trabeculectomy in 6 eyes and implantation of the Ahmed valve in 1 eye), while the remaining 5 patients had to increase the number of daily hypotensive medications at the final follow-up visit. Seven failures were classified as early (within 6 months from the procedure), while the remaining 5 were late.

No major intra- or postoperative complications occurred; minor complications included conjunctival hyperaemia (71.4% of the total), conjunctival chemosis (42.9%), superficial punctate keratitis (38.8%), subconjunctival haemorrhage (24.5%), transient anterior chamber uveal reaction (18.4%), and focal areas of scleral thinning (8.2%). Fluctuation of visual acuity within 2 lines was experienced during the first postoperative month by 7 patients (14.3%); 8 patients (4%) presented semi-mydriasis that reversed after a median time interval of 3.5 weeks.

Discussion

Despite the recent advances in screening, diagnosis, and treatment, glaucoma still represents the most frequent cause of visual impairment and irreversible blindness. Recently, the micropulse diode laser [14] and UCP [8] have been introduced among others as novel techniques to partially destroy the ciliary body, with a more

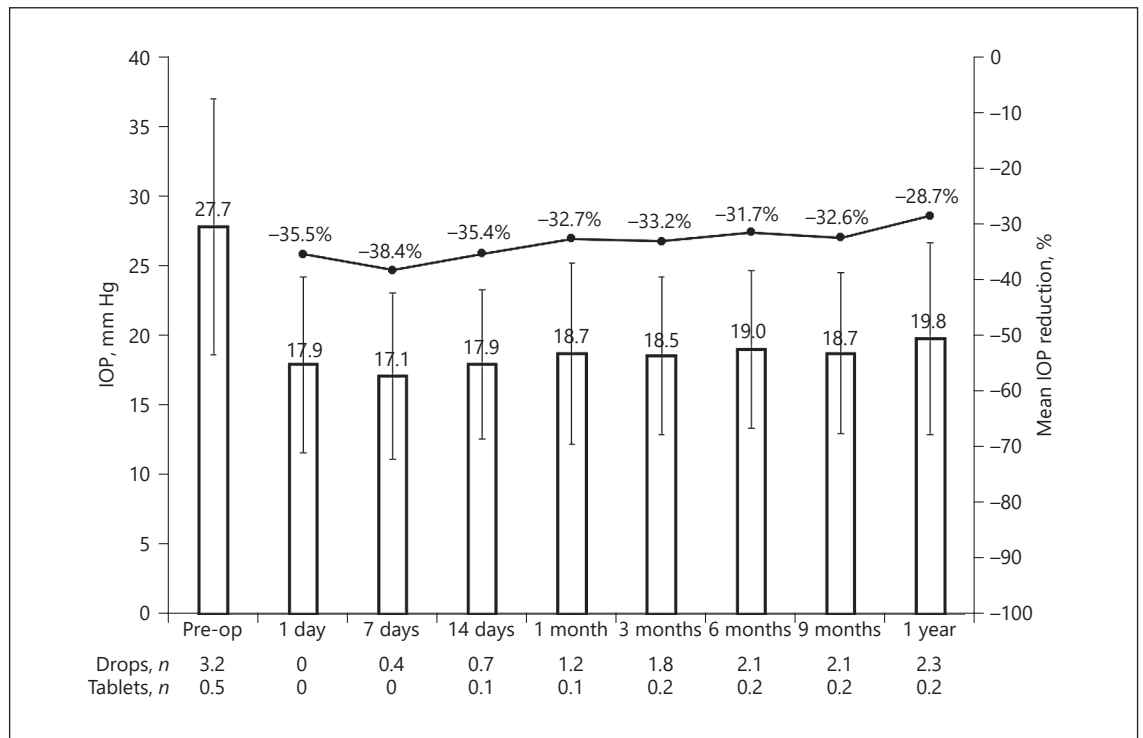


Fig. 1. Preoperative and postoperative IOP at each follow-up visit, expressed as both the mean value (bar graph) and percentage of reduction (line graph), with the corresponding number of daily hypotensive drops and acetazolamide tablets used.

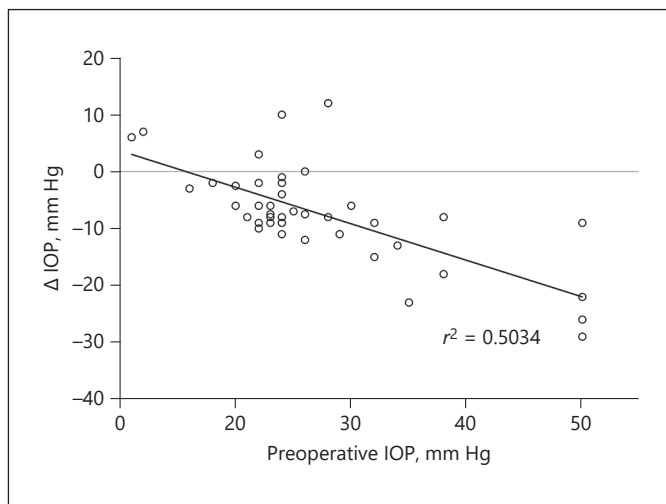


Fig. 2. Linear regression analysis between preoperative IOP and postoperative IOP variation 1 year after the procedure.

predictable and controlled IOP reduction as compared to traditional cyclodestructive procedures. Recent studies showed that UCP also induces the stimulation of the suprachoroidal and transscleral portions of the uveoscleral outflow pathway, thus allowing another additional hypotensive effect [7, 9, 15]. The technique is simpler, faster, safer, and less invasive than traditional cyclodestructive procedures [3–5], with comparable results in terms of IOP reduction. Recent technical improvements made the second-generation UCP probes more surgeon friendly, thanks to the use of the same setting throughout the entire procedure.

In the present study, UCP allowed an IOP reduction of approximately 30% throughout the entire 1-year follow-up period, in agreement with previous works, which reported a mean IOP reduction ranging from 26 to 38% [8, 16–20]. The treatment also allowed at the same time the reduction of the daily number of hypotensive medications. Qualified and complete successes of the procedure were achieved in about half of the eyes. These percentages are slightly lower compared to those reported in the other studies. However, it should be noted that several param-

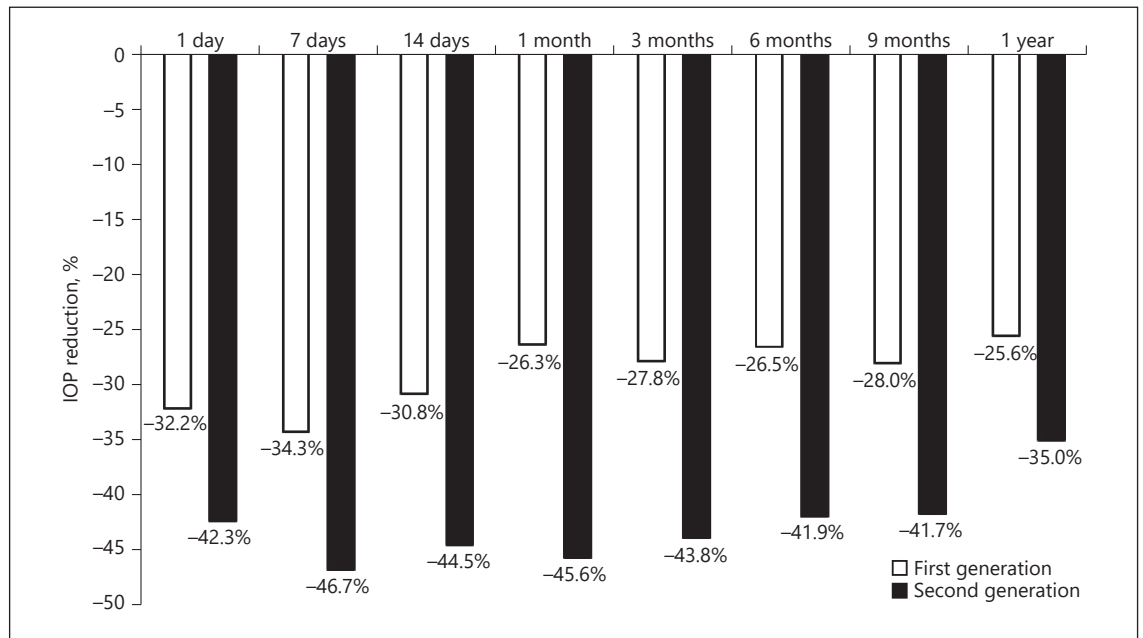


Fig. 3. Percentage of postoperative IOP reduction at each follow-up visit according to the generation of the probe used.

eters, including the criteria of success and failure, the generation of the probe, the unchanged or interrupted use of postoperative hypotensive medications, and the study populations were not homogeneous among all the studies, thus making it difficult to draw an effective comparison.

Interestingly, we found a significant linear relation between preoperative IOP and its decrease after surgery, as UCP treatment determined a greater IOP reduction in patients with higher preoperative values. This finding is demonstrated here for the first time, and could have crucial implications for daily clinical practice. In fact, UCP could be more effective in patients with highly elevated IOP, one of the most challenging glaucoma populations; on the other hand, it could likely determine a smaller IOP reduction in patients with lower baseline IOP values, thus reducing or eliminating the risk of postoperative hypotony, the most serious complication of the traditional cyclodestructive procedures [3, 5, 6].

We also found a significantly higher IOP reduction in the group of eyes treated with second-generation probes, the only now available on the market. This finding has not been investigated before by previous studies, which analysed only patients treated with first-generation probes.

Approximately a quarter of the patients did not respond to the treatment, with no/minimal IOP reduction,

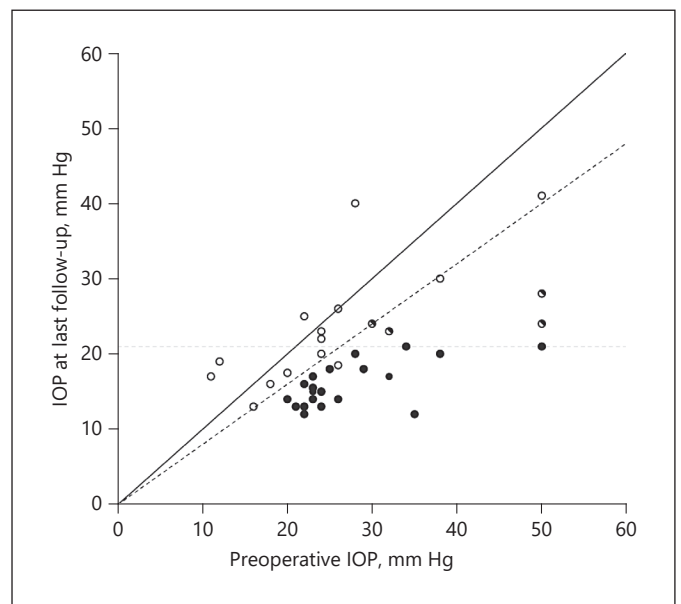


Fig. 4. Scattergram showing IOP values before and 1 year after the procedure. All dots below the diagonal line represent eyes with IOP reduction. All dots below the dashed oblique line represent eyes with IOP reduction $\geq 20\%$. Full black dots represent eyes with complete success; half black/white dots represent eyes with qualified success.

and nearly half of them required subsequent surgery to better control IOP. A hypothetical model could be proposed to explain the causes of the failures according to the timeframe of their onset: early failures may reflect an insufficient amount of ciliary body tissue coagulated during the procedure [19], while late failures may reflect the possible re-epithelialization of the ciliary processes with the progressive recovery of their function [21, 22], or the gradual narrowing of the stimulated uveoscleral outflow pathway [7, 9, 15].

The non-comparative design of the study is its main limitation; however, it should be highlighted that UCP likely represents a step forward compared to traditional cyclodestructive techniques, with the possibility of treating even patients naïve to previous surgery and with full visual acuity. Other additional limitations include the inhomogeneous patient characteristics which reflect a real-

world glaucoma population, and the use of success criteria different from the World Glaucoma Association criteria [23] in order to conduct a more reliable comparison with the existing literature [18–20].

In conclusion, the present study showed that UCP is a fast, easy, safe, and effective non-incisional technique for reducing IOP in glaucoma patients, with the need for minimal instrumentation and learning curve of the surgeons. The procedure determines a greater IOP reduction in patients with higher preoperative IOP values. Second-generation probes appear to improve efficacy outcomes without any detrimental effect on safety.

Disclosure Statement

The authors declare no conflicts of interest and no financial disclosures.

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