Video Article

Ultrasound Cyclo Plasty in Eyes with Glaucoma

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Abstract

Glaucoma is a chronic disease caused by the progressive degeneration of the optical nerve fibers, resulting in decreased visual field that can lead to severe visual impairment, and eventually blindness. This manuscript describes a simple, surgeon-friendly, non-incisional technique, named Ultrasound Cyclo Plasty (UCP), for reducing intraocular pressure (IOP) in glaucoma patients. The technique determines a selective coagulation necrosis of the ciliary body; in addition, the stimulation of supra-choroidal and trans-scleral portions of the uveo-scleral outflow pathway has been recently proposed. UCP shows several technical improvements in ultrasound technology compared to previous techniques, providing more precise focusing on the target zone. The procedure is performed in the operating room under peribulbar anesthesia. Briefly, the coupling cone is put in contact with the eye and the ring probe, that contains six piezoelectric transducers which produce the ultrasound beams, is inserted inside it. Their proper centering over the ocular surface represents a crucial step for the correct targeting of the ciliary body. Sterile balanced salt solution is used to fill the empty spaces to ensure ultrasound acoustic propagation. Surgical treatment consists in the sequential automatic activation of each of the six transducers, for a total duration of less than 3 min. The patient leaves the hospital 1 h after the procedure with the treated eye patched. In the present study, 10 patients with open-angle glaucoma were followed-up during at least 12 months after the procedure. IOP was reduced at each interval compared to pre-operative, as well as the number of hypotensive medications. Twenty percent of patients did not respond to the treatment, and needed subsequent surgery to better control IOP. Treatment tolerability was good, with no cases of hypotony or phthisis. The UCP procedure is simpler, faster, safer, and less invasive than traditional cyclodestructive procedures with similar results in reducing IOP.

Video Link

The video component of this article can be found at https://www.jove.com/video/56192/

Introduction

Glaucoma represents one of the major causes of blindness worldwide, affecting about 100 million people[1]. It is an optical neuropathy generated by the progressive degeneration of the nerve fibers that converge on the optic nerve, resulting functionally in a decrease of the visual field that can progress to visual disability and eventually blindness without adequate treatment[2].

Elevated IOP is still considered the main risk factor for glaucoma onset and progression, and currently the only treatable parameter to reduce the visual field loss[3]. IOP reduction can be achieved by both reducing the production of aqueous humor and/or increasing its outflow through trabecular meshwork by the use of topical or systemic drugs, laser, or surgery[3,4]. Many physical processes have been already introduced to induce the coagulation necrosis of the ciliary body following heating or freezing[5,6,7,8,9,10,11,12]. However, the lack of selectivity for the target tissue and the unpredictable dose-effect relationship in reducing IOP limit their use only to eyes with glaucoma resistant to conventional medical and surgical therapies[4].

Over the last years, a new device, named UCP, that employs high-intensity focused ultrasound (HIFU) has been developed, with the purpose of overcoming the limitations of traditional cyclodestructive techniques by achieving a more selective coagulation of the ciliary body and avoiding possible damages to the adjacent ocular structures[13,14,15,16,17,18,19,20,21]. In addition, the stimulation of supra-choroidal and trans-scleral portions of the uveo-scleral outflow pathway has been recently proposed as a possible adjunctive mechanism of the procedure in reducing IOP[22]. To date, seven major clinical studies have been conducted using the UCP device in different types and severity grades of glaucoma, demonstrating the effectiveness and the safety of this non-incisional procedure[14,15,19,20,21,22,23,24].

The aim of this study is to describe the above-mentioned procedure in detail, in order to spread the knowledge of its introduction to the scientific medical community, and to provide useful tips and tricks to surgeons who would like to approach this novel field.

Protocol

All participants provided both verbal and written informed consent before any study procedure. The protocol of the study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for human research of S.Orsola-Malpighi Teaching Hospital.

1. Preoperative Procedures and Ophthalmological Evaluation

1. Test distance and near Best Corrected Visual Acuity (BCVA).
2. Evaluate the anterior segment of the eye using a slit lamp biomicroscope.
3. Examine the anterior chamber angle using a slit lamp gonioscopy lens after having instilled topical anesthetic eye drops.
4. Evaluate the fundus by slit lamp indirect ophthalmoscopy with the use of a non-contact fundus lens. Pay particular attention to the optic disc head.
5. **Measure the IOP using Goldmann applanation tonometry.**
    1. Instill topical anesthetic eye drops to obtain corneal anesthesia.
    2. Color the tear film using 2% fluorescein (ophthalmic strips).
    NOTE: It is crucial to color the tear film with the proper amount of fluorescein. High amounts produce too thick fluorescein rings with overestimated IOP measures, while low amounts produce too thin rings with underestimated IOP readings.
    3. Mount the tonometer on the guide plate over the slit lamp axis.
    4. Set the blue cobalt filter light and the light beam as wide and bright as possible with the slit diaphragm fully open.
    5. Properly direct the blue light beam on the tonometer head putting the slit beam at 60° on the same patient's side of the eye under examination, in order to avoid the contact of the slit lamp with the patient's face and the covering of the light beam by the patient's nose.
    6. Ask the patient to lean the head on the slit lamp headrest, open both eyes wide, look straight ahead, and keep perfectly still.
    7. Move the tonometer using the slit lamp joystick until the biprism head is gently in contact with the center of the corneal surface: two regular hemi-circles of fluorescein tear meniscus are visualized through each prism when looking through the slit lamp eyepieces.
    8. Turn clockwise the calibrated knob on the side of the tonometer to bring near the visualized fluorescein hemi-circles until their inner borders just touch each other, forming a horizontal "S" shape: the number indicated in the calibrated knob represents the IOP measure.
    NOTE: Be sure to properly disinfect, rinse with sterile water, and wipe the tonometer head before any measurement.

6. **Measure the ocular anatomical parameters by means of a non-contact optical biometer.**
    1. Ask the patient to lean the head on the headrest, open both eyes wide, look straight ahead, and keep perfectly still.
    2. Move the optical biometer using its joystick to properly focus on the center of the corneal surface: an arrow and a green circle on the display help the clinician to find the correct position.
    3. Click the button on the joystick to start the measurement: a green line appears on the display and starts to move forming a circle. Keep the position as still as possible during this time.
    4. Perform at least 5 measurements per eye to reduce possible errors and increase reliability. The instrument automatically calculates the average value.

7. Use the nomogram tool (**Figure 1**) to calculate the appropriate size of the treatment probe among the 3 possible options (11, 12, or 13 mm of ring diameters).
NOTE: Two ocular anatomical parameters are needed: the white-to-white (WTW, distance equal to the corneal horizontal diameter) and the axial length (AL, distance from corneal apex to fovea).
8. Prescribe to the patient pilocarpine eye drops 3 times per day starting from 3 days before surgery to ensure the proper intraoperative miosis, allowing a more precise targeting of the ciliary body by the ultrasound beams delivered by the probe.

2. Pre-surgical Procedures

1. Place the patient in a supine position on the surgical bed.
2. **Administer local anesthesia by performing one peribulbar infiltration with 10 mL of local anesthetics (mepivacaine plus ropivacaine) 30 min before the surgery.**
    1. Perform the injection inferotemporally at the junction of outer one third and inner two third of the lower orbital rim or superonasally beneath the superior orbital notch using a 27-gauge needle.

3. Preparation of the Treatment Device

1. Enter data about the surgeon and patient using the control unit touch screen, and then select the eye to treat.
NOTE: First generation probes also can choose between 4 s or 6 s of ultrasound exposure time, while the second-generation probes (the only ones now available on the market) allow only 8 s of exposure time.
2. Open the sterile single-use device pack containing the coupling cone and the treatment probe and connect their cables to the control unit.

4. UCP Procedure

1. Disinfect accurately the palpebral and periorbital skin with 10% povidone-iodine 3 times. Wipe the disinfected skin with clean sterile gauzes.

2. Put a sterile surgical drape over the face of the patient with a central hole centered over the eye under treatment in order to properly expose it.
3. Place the patient's head lying slightly backwards in order to put the ocular surface horizontally allowing a comfortable placement of the cone of the device (**Figure 2**).
4. Open the patient's eye without using the speculum.
5. Put the coupling cone over the ocular surface, with tubing on the temporal side, and gently move to correctly position and center it, forming a uniform white scleral ring surrounding the limbus (**Figure 3**). Use a surgical clamp to reposition the cone, if needed.
   NOTE: A minimal uniform ring of 2 mm of white sclera should be visible between the limbus and the cone inner boarder. This ring should be as regular as possible all along the 360° of the eye to ensure the optimal centering of the probe and consequently the correct targeting of the ciliary body (**Figure 3**).
6. Push the aspiration button on the foot switch to start a low-level suction from the peripheral ring of the coupling cone until the vertical bar on the screen becomes green. This allows the maintenance of the coupling cone in direct contact to the patient's eye throughout the entire procedure (**Figure 4A**).
7. Insert the treatment probe inside the coupling cone, with the cable in nasal position.
   NOTE: A "click" sound confirms the proper anchorage of the probe to the cone (**Figure 4B**).
8. Fill the empty space delimited by the eye, the cone, and the probe with sterile balanced salt solution (BSS) at room temperature at the beginning and during the entire procedure to allow good propagation of the therapeutic ultrasounds (**Figure 4C**). Refill at the appropriate level in case of BSS leakage.
9. Ask the patient to hold the position and keep perfectly still the head.
10. Push the start button on the foot switch to start the treatment and hold the pressure during all the procedure (the passage between each treatment sector is completely automatic without the need to release pressure of the foot switch).
11. **Maintain firmly in the optimal position the probe and the coupling cone during the entire procedure. Avoid moving, rotating, or pushing the probe in order to permit the best centering of therapeutic ultrasounds beams during the treatment (Figure 4D).**
    NOTE: During the treatment, each of the six transducers are sequentially activated for 4, 6, or 8 s (depending on the generation of the probe), with 20 s of interval before each activation, starting from the superior sectors and moving clockwise. The control unit shows the sequential activation of the six transducers. Surgical treatment lasts 124 s, 136 s, or 148 s.
    1. Release the pressure on the foot switch to stop the procedure. In case of interruption of the treatment during the interval between the activation of two consecutive sectors, the treatment can continue without losing any sector; on the contrary, in case of interruption of the treatment during the activation of a sector, the treatment in the sector in question is not completed.
12. At the end of the procedure, deactivate the suction system by pressing the aspiration button on the foot switch and slowly tilt the cone until BSS is removed through the tube.

5. Post-surgical Procedures

1. Instill antibiotic plus steroid eye drops in the treated eye immediately after the procedure, and patch the treated eye for 24 h.
   NOTE: The patients can leave the hospital 1 h after the procedure.
2. Remove the eye patch the day after the procedure, examine the treated eye, and measure the IOP.
3. Prescribe to the patient antibiotic plus steroid eye drops 4 times per day for 1 month.
4. Examine the treated eye and measure the IOP at 1, 7, and 14 days, 1, 3, 6, and 9 months, and 1 year after the procedure.

Representative Results

Ten eyes of 10 patients (6 men and 4 women, mean age 64.9 ± 13.7 years, range 39–80 years) affected by open-angle glaucoma were treated with UCP device according to the technique described above. Treatment exposure time was 4 s for 2 patients, 6 s for 4 patients, and 8 s for 4 patients. Before surgery, the mean IOP was 24.8 ± 9.6 mmHg (mean ± standard deviation), while the mean number of daily hypotensive drops was 3.9 ± 1.0 and the mean number of daily acetazolamide tablets was 0.6 ± 0.5. Additionally, the mean visual acuity was 0.48 logMAR ± 0.6, and the mean visual field mean deviation was -12.65 ± 12.1 dB.

Eight patients completed the 1-year follow-up study period, while two patients underwent incisional surgery for a better IOP control, respectively 3 and 6 months after the UCP procedure. Mean IOP value decreased compared to pre-operative value at each post-operative visit. In particular, **Figure 5** shows the reduction of IOP values, hypotensive eye drops, and oral acetazolamide tablets numbers over time, expressed as both mean value (± standard deviation) and percentage of reduction. At 1 year, the mean IOP was reduced compared to pre-operative values (16.9 ± 2.8 mmHg) as well as the mean number of post-operative hypotensive eye drops (1.9 ± 1.5). No patient needed to use longer oral acetazolamide tablets at the last follow-up visit. Mean post-operative visual acuity remained approximately stable throughout the 1-year follow-up (mean 0.52 ± 0.64 logMAR) as well as the visual field mean deviation (mean -13.34 ± 11.8 dB).

No major complications occurred neither during nor after surgery, except for a case of fixed and dilated pupil with accommodation deficit, which spontaneously resolved 3 months after UCP procedure.

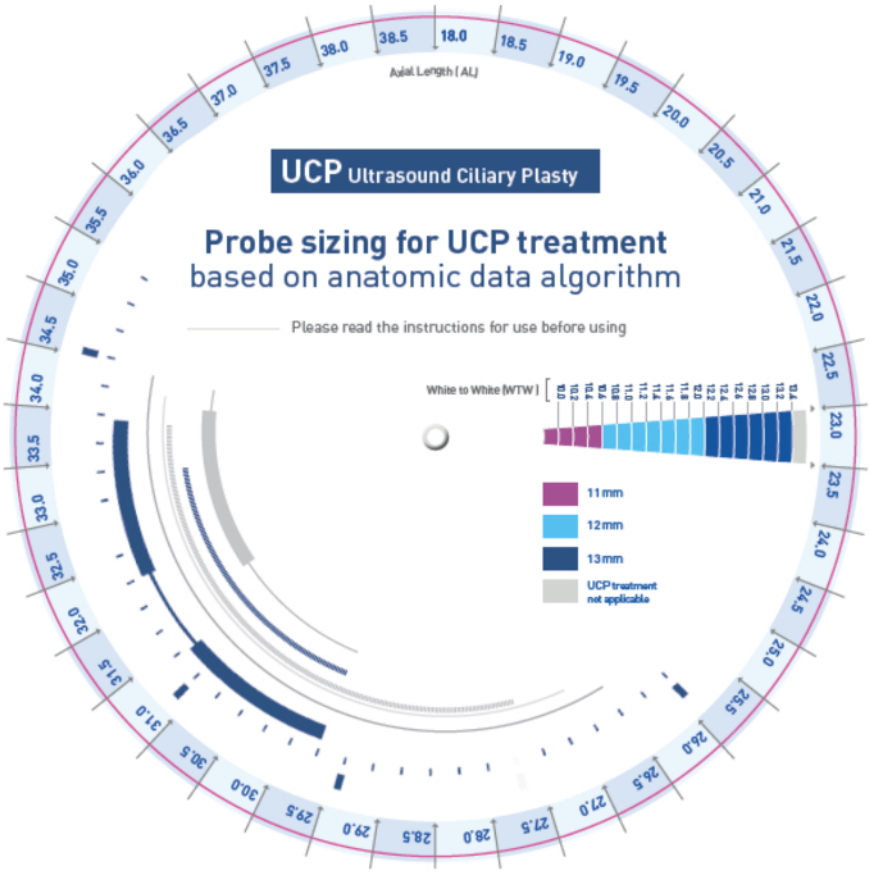


Figure 1: The nomogram tool. The nomogram tool that permits calculation of the appropriate probe size (11, 12, or 13 mm of diameter) for the patient, based on two parameters calculated by optical biometry: white-to-white (WTW, distance equal to the corneal horizontal diameter) and axial length (AL, distance from corneal apex to fovea). Please click here to view a larger version of this figure.

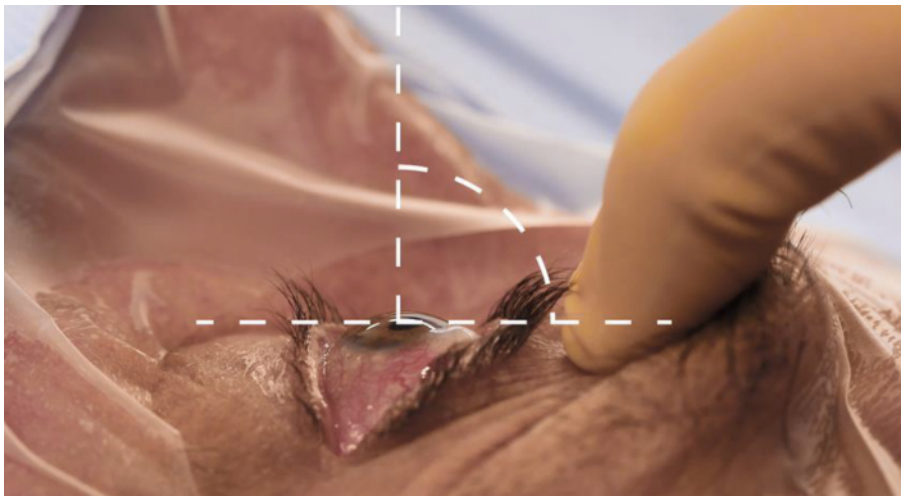


Figure 2: Head and eye positions. Correct head and eye position in order to ensure the proper and comfortable placement of the coupling cone. Please click here to view a larger version of this figure.

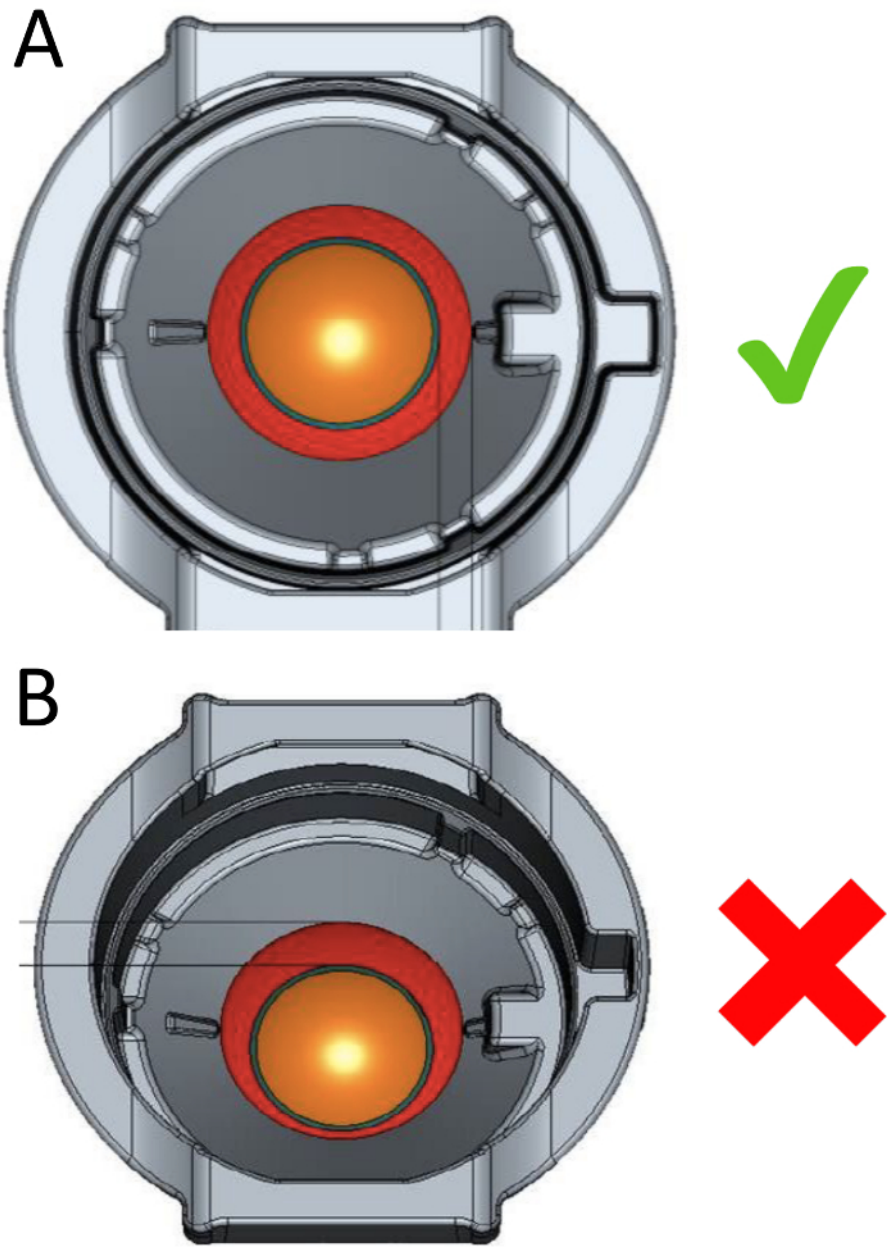


Figure 3: Correct and wrong placement of the coupling cone. (**A**) Correct position of the coupling cone with a regular and uniform scleral ring (red ring) between limbus and cone along all 360°. In this way, the probe correctly targets the ciliary body when inserted in the coupling cone. (**B**) Wrong placement of the coupling cone with a non-uniform scleral ring surrounding the limbus circumference. Please click here to view a larger version of this figure.

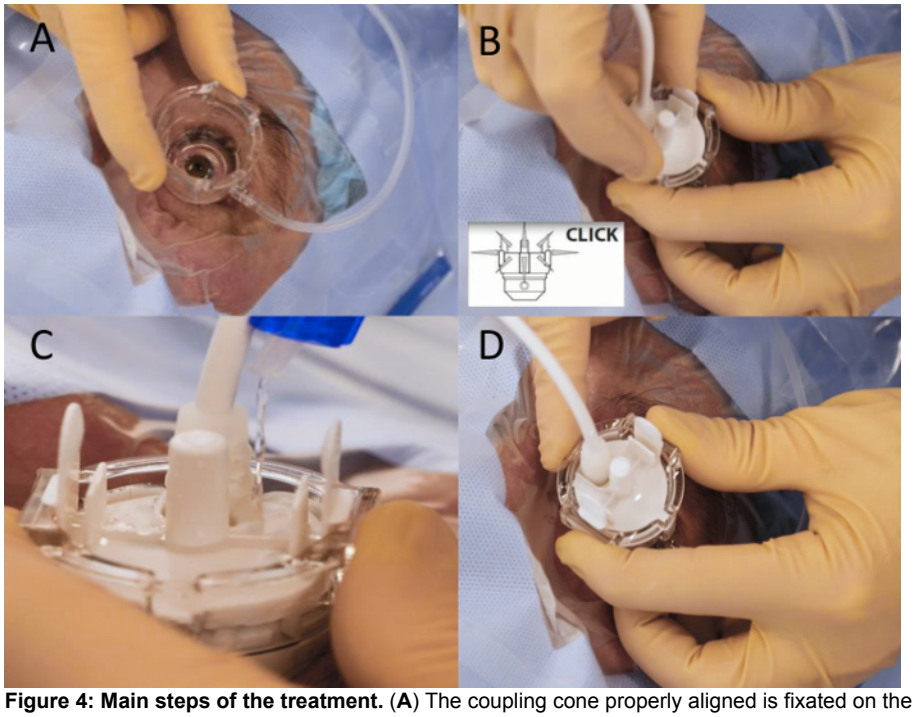
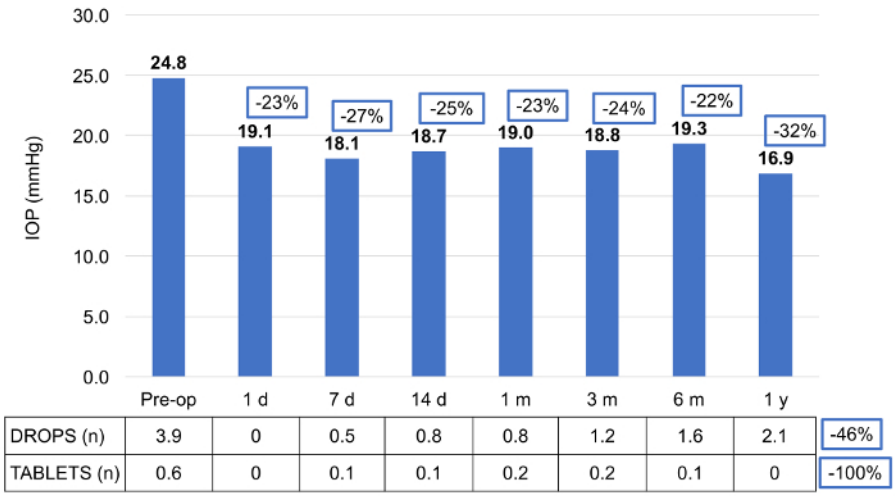


Figure 4: Main steps of the treatment. (**A**) The coupling cone properly aligned is fixated on the patient's eye by the suction ring using a low-level vacuum system; (**B**) the treatment probe is inserted inside the coupling cone, with cable in nasal position. A "click" sound confirms the proper anchorage of the probe to the cone; (**C**) the cavity created among the eye, the cone, and the probe is filled with sterile balanced salt solution at room temperature at the beginning and during the entire procedure to allow good propagation of the therapeutic ultrasounds; (**D**) the probe and the coupling cone must be maintained firmly by clinician's two hands in the optimal position during the entire procedure. Please click here to view a larger version of this figure.



DROPS (n)	3.9	0	0.5	0.8	0.8	1.2	1.6	2.1	-46%
TABLETS (n)	0.6	0	0.1	0.1	0.2	0.2	0.1	0	-100%

Figure 5: Representative image of IOP values during the entire study. Pre-operative and post-operative intraocular pressure values (± standard deviation) at each follow-up visit expressed both as mean value and as percentage of reduction from baseline. At the bottom, the number of hypotensive eye drops, acetazolamide tablets, and the percentage of their reduction at 1 year are shown (d = day; m=month; y = years). Please click here to view a larger version of this figure.

Discussion

Glaucoma is a chronic progressive disease affecting the optic nerve for which new effective treatments are needed to improve long-term prognosis. The reduction of IOP is still considered the only effective therapy to prevent or delay visual field loss, in eyes both with and without elevated IOP[3].

UCP is a new non-incisional cyclodestructive procedure that can lower IOP, acting in two different ways: it reduces the aqueous humor inflow determining the selective necrosis of the secretory epithelium of the ciliary body, and it increases the aqueous humor uveo-scleral outflow stimulating the trans-scleral and supra-choroidal pathways[13,16,22]. The technique is fast, easy, safe, and surgeon-friendly, resulting less invasive and similarly effective in terms of IOP reduction, compared to both earlier HIFU[25,26,27] and traditional cyclodestructive procedures[28,29]. Several

technical improvements have been made in UCP technology compared to the previous techniques, providing more precise focusing on the target zone. In particular, the probe is placed in direct contact with the eye, and the treatment is conducted using the same setting throughout the entire procedure, thus minimizing the risk for surgeon's errors. In addition, the higher operating frequency (21 MHz) compared to previous systems (5 MHz) allows centering the target zone while sparing the adjacent tissue[19].

The UCP device is composed by a sterile, single-use treatment pack, which comprises a polymer-made coupling cone and a treatment probe. The coupling cone and the probe are connected by cables to a portable control unit (36 cm length x 32 cm width x 26 cm height) that permits setting of the treatment parameters, and controls the procedure by means of a touch screen. The probe is a ring of 30 mm diameter and 15 mm height and contains six piezoelectric transducers, which produce and deliver the ultrasound beams. Each transducer is approximately a cylinder segment of 7.0 mm length, 4.5 mm width, and 10.2 mm radius, for a total surface area of about 35 mm^2. Their focal active volumes are similar to elliptic cylinders with axial length of 1.2 mm, transverse width of 0.4 mm, and lateral width (length of the cylinders) of 3.5 mm. Three different probe sizes (11, 12, and 13 mm of ring diameters) are available to best adapt the device to the eye's size and shape. Depending on the diameter, the six piezoelectric elements are centered on 11 mm, 12 mm, or 13 mm diameter circle over the circumference of the eye and the ultrasound beams are focused 2 mm below the sclera corresponding to the spatial position of the ciliary body, resulting in a highly precise and focused tissue targeting.

The six transducers deliver ultrasound operating at a frequency of 21 MHz with an acoustic power of 2 W, determining the rapid increase of the local temperature of the ciliary body up to 90 °C (avoiding tissue boiling) and allowing treatment of up to 30% of the ciliary body.

Data on the effectiveness and the safety of the procedure appear here similar to those reported in the literature. In particular, 10 patients with open-angle glaucoma were followed-up during at least 12 months after the procedure. IOP was reduced at each interval compared to pre-operative values, as well as the number of hypotensive topical and systemic medications. Twenty percent of patients did not reach the target IOP, with no or minimal reduction, requiring further incisional surgery to better control IOP. Several hypotheses have been previously postulated by Aptel *et al.* to explain the failure in the latter cases, including the insufficient amount or suboptimal centering of ciliary body coagulation, mainly caused by an involuntary movement of the device or an excessive pressure exerted on the probe during the procedure, with consequent deformation of the sclera and the ciliary body[24]. Treatment safety and tolerability were good, in agreement with previous studies[19,21,23,24], with no cases of hypotony or phthisis over the long-term, representing the most serious adverse events of the traditional cyclodestructive methods. Furthermore, no patient experienced pain during or after the procedure. However, an optimal peribulbar block is mandatory to make this procedure comfortable.

One concern with overall cyclodestructive procedures is long-term maintenance of IOP reduction[9,12]. This pilot study has a limited follow-up duration of at least 12 months, and a multicenter study evaluating the long-term efficacy of this procedure in a larger group of patients is currently ongoing. Indeed, the procedure is conducted according to a standardized, minimally operator-dependent technique, and appears particularly suitable for multicenter clinical trials. Another major limitation of this pilot study is represented by the characteristics of the treated patients, which are not homogeneous reflecting a real-world glaucoma population. Furthermore, the non-comparative design is another additional limit of the study.

However, a few basic rules must be followed to properly perform the procedure. In particular, the surgeon must center the cone and maintain the probe firmly in the optimal position during the entire procedure, and avoid moving, rotating, or pushing in order to best center therapeutic ultrasounds on the target site. In addition, the surgeon must fill the cavity among the eye, the cone, and the probe with BSS at the beginning and during the entire procedure in order to allow good propagation of the therapeutic ultrasounds. Another unsolved issue is that the UCP device is not perfectly "customized" to each treated eye, but is available in three different sizes that better fit to the shape and size of the eye. This aspect could theoretically impair the effectiveness of the procedure due to an imperfect centering of the ultrasound on the targeted ciliary body, especially in patients with high myopia or shallow chamber, two anatomic features frequently associated with glaucoma.

In summary, the present study showed that UCP using HIFU is a simple, safe, and effective non-incisional technique for reducing intraocular pressure in open-angle glaucoma patients.

Disclosures

The authors have nothing to disclose.

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