• Clinical Research •

Efficacy and safety of high-dose ultrasound cyclo-plasty procedure in refractory glaucoma

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Abstract

● **AIM:** To evaluate the efficacy and safety of high-dose ultrasound cyclo-plasty (UCP) for the treatment of refractory glaucoma in Chinese patients.

● **METHODS:** In this 6-month retrospective study, 37 eyes of 37 patients suffering from severe glaucoma with uncontrolled intraocular pressure (IOP) of ≥21 mm Hg underwent 8-s ultrasonic cyclocoagulation with ten active piezoelectric elements. A complete ophthalmic examination was performed before and at 1d, 1, 3, 6mo after UCP. Therapeutic success was defined as IOP reduction from baseline ≥20% and IOP ≥5 mm Hg without adding new glaucoma medication compare to baseline at the 6-month follow-up visit. In addition to mean IOP at each follow-up visit, medications used and complications were also detected and compared to baseline.

● **RESULTS:** After UCP procedure, the mean IOP was significantly reduced (P<0.01) from the preoperative 44.1±11.9 mm Hg to postoperative 26.7±11.8 mm Hg at 3mo, and 30.4±14.5 mm Hg at 6mo. The overall mean IOP reductions achieved at 3 and 6mo were 39% and 31% compared to baseline IOP. Sixty-one percent of patients responded well to UCP treatment with a mean IOP reduction of 48% at 3mo and 42% at 6mo. Ocular pain in most of patients were alleviated. No serious intraoperative or postoperative complications occurred.

● **CONCLUSION:** High-dose UCP treatment is an effective and safe procedure to reduce IOP in Chinese patients with severe glaucoma.

● **KEYWORDS:** ultrasound cyclo-plasty; cyclodestruction; intraocular pressure reduction; glaucoma

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INTRODUCTION

As the second leading cause of blindness, glaucoma is a neurodegenerative disorder characterized by the progressive loss of retinal ganglion cell[1]. Glaucoma can remain a long and asymptomatic initial phase until it becomes severe, when irreversible visual loss has occurred[2]. Glaucoma prevalence has a positive association with older age[3]. Therefore, the large number of glaucoma patients with the dramatic increase of public health burden can be predicted, as China gradually enters an aging society in the coming decades[4-5]. The intraocular pressure (IOP) remains a proven and modifiable risk factor which could directly affect the development and progression of glaucoma[6].

All treatments for glaucoma aim to reduce IOP by decreasing aqueous humor (AH) production or facilitating its drainage. When pharmacologic treatment is insufficient to stabilize the disease, surgical treatment must be considered[7]. Many physical methods for destroying ciliary processes have been proposed to coagulate the ciliary body following heating (laser, microwave) or freezing (cryotherapy) leading to IOP reduction[8]. Most current cyclodestructive methods are non-selective for the target tissue resulting in damage to adjacent structures, and their dose-effect relationships are usually unpredictable[9]. To overcome the limitations of cyclodestruction, ultrasound cyclocoagulation using high-intensity focused ultrasound (HIFU) technology has arisen as a potentially safer, more selective and precise approach to destroy the ciliary body tissue while sparing the adjacent ocular structures[10]. Recently, a new device using miniaturized transducers produced HIFU cyclocoagulation of the ciliary body was developed, which called ultrasound cyclo-plasty (UCP) treatment[11]. Several clinical trials have confirmed that UCP procedure could achieve a significant and predictable IOP reduction with an acceptable safety profile[9].

So far, most studies on UCP treatment have used single UCP procedure with six transducers, which chose different activation time of treatment to evaluate the effect of different

therapeutic doses on its efficacy and safety. Additionally, two studies focused on the efficacy and safety of multiple UCP procedures[12-13], which assessed their therapeutic effects of a second and possibly third procedures in patients who do not respond well to a single UCP treatment. Standard UCP usually refers to single UCP procedure with 6 sectors, which the therapeutic dose is defined by the circumference of treated ciliary body. High-dose UCP means increasing the circumference of treated ciliary body by using 10 sectors. Therefore, it is feasible to increase the therapeutic dose of UCP by means of increasing the number of sectors activated to improve the therapeutic effect. Our present study aims to evaluate the efficacy and safety of high-dose single UCP procedure (10 sectors activated) for the treatment of refractory glaucoma in Chinese patients.

SUBJECTS AND METHODS

Ethical Approval This non-comparative, single-center study was conducted and reported according to the World Glaucoma Association guidelines on the design and reporting of glaucoma surgical trials and adhered to the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of the Second Hospital of Anhui Medical University (SL-LC2019007). All enrolled patients provided both verbal and written informed consent. This study was conducted from May 2018 to July 2019 and the data were analyzed retrospectively.

Patient Enrolment Inclusion criteria were as follows: age ≥18 and <90y; baseline IOP≥21 mm Hg despite the medical therapy; refractory glaucoma, defined as glaucoma that is difficult to control IOP with drugs and has poor prognosis after conventional surgery, or glaucoma with previous failure of filtering surgery, juvenile glaucoma, aphakic glaucoma, glaucoma with a long history of medication, neovascular glaucoma and some other secondary glaucoma; ability and willingness to return for scheduled visits. Exclusion criteria were as follows: mental impairment conflicting with informed consent or follow-up; concomitant systemic medications that could affect IOP; retinal detachment or ocular tumor; ocular infection; pregnancy; serious systemic disease.

Ultrasound Cyclo-Plasty Procedure The ultrasound device (EyeOP1, Eye Tech Care, France) equipped with six piezoelectric transducers was used in the study. The EyeOP1 activated successively the 6 sectors first, then 4 sectors were activated again after rotating the probe (4 sectors plus 6 sectors equals 10 sectors). Before the UCP treatment, baseline evaluations were collected including the best-corrected visual acuity (BCVA), slit-lamp biomicroscopy with gonioscopy and mydriatic fundus examination, non contact tonometer, ultrasound pachymetry and ultrasound biomicroscopy (UBM). The standard UCP procedure was performed as previously described[14]. The optimal and individualized size of ultrasound probe (11, 12, and 13 mm) was preoperatively determined by the measurements of UBM. The parameters of the control module were set as follows: operating frequency (21 MHz), acoustic power (2.45 W), ultrasound exposure time per sector (8s), sequential sector activation interval (20s). After routine surgical disinfection and retrobulbar anesthesia with the mixture of lidocaine and ropivacaine, the probe was filled with saline solution and manually centered on the eye, avoiding the 3 o'clock and the 9 o'clock positions to prevent direct damage to the long posterior ciliary blood vessels, then UCP procedure can be started by continuous pressing of the foot pedal.

Follow-up Postoperative follow-up contains corresponding baseline examination data, which were collected at 1, 7d, 1, 3, and 6mo after the UCP procedure. At each visit, photographs of the anterior segment were taken for comparison. All IOP measurements were taken at the same time of day as the preoperative IOPs. One ophthalmologist was in charge of the eye examination and data recording.

Outcome Evaluation In terms of efficacy, the therapeutic success rate and the mean IOP reduction after UCP procedure were evaluated at each follow-up visits. Therapeutic success was defined as IOP reduction from baseline ≥20% and IOP≥5 mm Hg without adding new glaucoma medication compared to baseline. Oppositely, the definition of failure is IOP reduction from baseline <20% or the decrease of IOP<5 mm Hg, or if another procedure such as glaucoma filtering surgery or cyclodestructive treatment using laser or freezingwas performed. The change of glaucoma medication use was also recorded and compared to baseline as an auxiliary evaluation index. In terms of safety, the occurrence of postoperative complications was assessed, including ocular pain, bleeding, edema, visual acuity decrease, scleral thinning, hypotony, choroidal detachment, and retinal detachment.

Statistical Analysis Student's *t*-test and analysis of variance were used to compare means, and Chi-squared tests were used for the analysis of dichotomous variables. Statistical significance was set at $P<0.05$. Statistical software (SPSS version 17.0, USA) was used for data analysis.

RESULTS

Demographics As shown in Table 1, demographic data are summarized. Thirty-seven patients were enrolled and treated with high-dose UCP procedure between May 2018 and July 2019. Only one eye underwent UCP procedure for each patient. Types of glaucoma in our study could be divided into primary open angle glaucoma (2/37), primary angle-closure glaucoma (3/37), neovascular glaucoma (20/37) and secondary glaucoma (12/37). As for the preoperative visual acuity, 17 patients presented no light perception, while the remaining 20 patients presented finger count or light perception. In addition, 35 patients have ocular pain symptoms.

Table 1 Patient demographics mean±SD

Parameters	*n*=37
Age, y (range)	60.8±13.4 (30-83)
Gender (M/F)	20/17
Lens status (P/PP/A)	27/10/0
Glaucoma type, *n* (%)	
POAG	2 (5.4)
ACG	3 (8.1)
NVG	20 (54.1)
SG	12 (32.4)
Previous ocular surgery, *n* (%)	
Trabeculectomy	10 (27)
Valve	2 (5.4)
Stent	1 (2.7)
Baseline IOP (mm Hg)	44.1±11.9
Preop. hypotensive medications (range)	2.8±0.4 (2-3)
Baseline vision acuity	
NLP	17
≥LP	20
Preop. ocular pain	35

P/PP/A: Phakic/pseudophakic/aphakic; POAG: Primary open angle glaucoma; ACG: Angle-closure glaucoma; NVG: Neovascular glaucoma; SG: Secondary glaucoma; IOP: Intraocular pressure; NLP: No light perception; LP: Light perception; SD: Standard deviation.

Efficacy The mean and relative IOP reductions from baseline to each follow-up in the overall population are shown in Table 2. At 1d after high-dose UCP procedure, the mean IOP significantly decreased from 44.1±11.9 mm Hg to 30.3±11.0 mm Hg (P<0.01). At 1 and 3mo after UCP, the mean IOP further reduced to 26.8±12.4 mm Hg and 26.7±11.8 mm Hg, respectively. Even at 6mo post UCP, the IOP reduction can be maintained at 31%. The IOP reduction was obtained with a decrease in glaucoma medication. The mean number of hypotensive medications significantly decreased from 2.8 before UCP to 2.1 at the 6-month follow-up visit (P<0.05). UCP therapeutic success rates of the 3-month and 6-month visit were achieved respectively in 22 of 32 eyes (69%) and in 19 of 31 eyes (61%), with other 31% and 39% eyes did not respond. The IOP reductions for the responsive patients are shown in Table 3, respectively 48% and 42% at 3mo and at 6mo, accompanied by a significant decrease in the number of medication use. Moreover, the number of patients with preoperative ocular pain reduced from 30 to 14 at the 6-month follow-up visit. In order to reduce IOP, we did other treatments on non-responsive patients whose situation were described in Table 3, including increasing drugs and reoperation.

Safety The high-dose UCP procedure was moderately tolerated in all patients. No major complication, such as corneal burn, cataract formation or retinal detachment, occurred during any therapeutic procedures. As shown in Table 4, most of the complications occurred before UCP operation. On the contrary, many patients' previous symptoms, such as hyperemia, ocular pain and corneal edema, were completely relieved at the 6-month follow-up visit. Most of intraoperative and postoperative complications were transient and disappeared on subsequent follow-up visit. Almost all patients have conjunctival hyperemia and scleral marks, which is substantially higher than the rate reported in previous studies[9]. A total of 30 of 37 patients reported tolerable ocular pain during the procedure. A total of 8 of 37 patients have transient corneal edema. But after 6mo, most of the above minor complications resolved. The transient hypotony occurred in one patient immediately after the procedure and disappeared at day 7 follow-up visit. One patient presented with mydriasis that lasted till the end of the follow-up. For patients with insufficient response to UCP, one of them required valve implant surgery and one required eye removal.

DISCUSSION

Currently, UCP procedure using HIFU technology has been shown to offer a new good efficacy and safety profile for glaucoma treatment. Our study investigated the efficacy and safety of high-dose UCP procedure on Chinese patients with refractory glaucoma during the 6-month follow-up period. In according to all the published studies, UCP achieved significant IOP reduction rate at the 6-month follow-up visit, ranging from 20.1% to 40.8%[9]. Our results showed that mean IOP was significantly reduced from 44.1±11.9 mm Hg in baseline to 30.4±14.5 mm Hg at 6mo in all of the patients, corresponding to a mean IOP reduction of 31% [range 20.1% to 40.8%] and to a therapeutic success of 61% (19/31 subjects). We also observed that not all patients responded to the UCP treatment, 10 out of 32 (31%) resulted as non-responders at 3mo and 12 out of 31 (39%) at 6mo.

Therapeutic ultrasonic coagulation was firstly used for cyclodestruction since the 1980s[10,15], which was proved to be an effective method of IOP reduction. With the development of a new HIFU system using miniaturized transducers (EyeOP1, Eye Tech Care, France)[11,16-17], the interest in ultrasound cyclodestructive procedures was recently revived. The new UCP procedure uses a therapeutic circular-shaped probe with 6 cylindrical piezoceramic transducers, which allow the treatment of up to 41% of the ciliary body circumference (6 sectors)[18]. The rotation of the probe into the cone allows the treatment of up to 55% of the circumference (8 sectors)[14]. A short-term retrospective study by Hu *et al*[14] investigated the comparison of IOP reduction between 6-sectors and 8-sectors

Table 2 Baseline and postoperative mean IOP and hypotensive glaucoma medications in all patients

Patients	No. of patients	Mean IOP (mm Hg)	Relative IOP reduction (%)	Glaucoma medications (*n*)	Success rate (%)
Baseline	37	44.1±11.9		2.8	
Day 1	37	30.3±11.0[b]	29	2.7	70
Month 1	33	26.8±12.4[b]	39	2.3	64
Month 3	32[a]	26.7±11.8[b]	39	2.2	69
Month 6	31[c]	30.4±14.5[b]	31	2.1	61

IOP: Intraocular pressure; [a]Five visits not done; [b]$P<0.01$ *vs* baseline; [c]Six visits not done.

Table 3 Baseline and postoperative mean IOP and hypotensive glaucoma medications in responsive and non-responsive patients

Catalogue	Responsive patients					Non-responsive patients			
	No. of patients	Mean IOP (mm Hg)	Relative IOP reduction (%)	Glaucoma medications	Success rate (%)	No. of patients	Mean IOP (mm Hg)	Relative IOP reduction (%)	Glaucoma medications (*n*)
Baseline	22	43.3±11.2		2.8		10	43.3±11.2		2.8
Month 3	22	22.3±8.6[a]	48	1.8	69	10	37.4±12.3	18	3
Baseline	19	43.2±11.9		2.3		12	44±13.3		2.9
Month 6	19	25.1±10.5[a]	42	1.7	61	12	40.4±17	10	2.6

IOP: Intraocular pressure; [a]$P<0.01$ *vs* baseline.

Table 4 Preoperative, intraoperative, and postoperative complications *n* (%)

Complications	Preop.	Intraoperative	6-month follow-up
Scleral marks	0	37 (100)	15 (43)
Hyperemia	36 (97)	36 (97)	15 (43)
Ocular pain	35 (95)	30 (81)	14 (40)
Corneal edema	10 (27)	8 (22)	1 (3)
Mydriasis	0	1 (3)	1 (3)
Hypotony	0	1 (3)	0
Choroid detachment	0	1 (3)	1 (3)

UCP therapy. As expected, there was much more extent of IOP reduction in the 8 sectors group at the early stage. However, no statistical difference of the IOP reduction and success rate was found between the two groups at 3-month follow-up visit[14]. Therefore, for patients with inadequate response or extremely high IOP, high-dose UCP therapy by means of increasing the number of sectors activated should be taken into consideration to improve the therapeutic effect. A recent animal study compared the effects of different UCP doses including 6, 8, and 10 sectors, which found that the greater the number of treated sites, the greater the lowering effect on IOP[19]. In our study, the baseline mean IOP was up to 44.1±11.9 mm Hg, which was the highest in current clinical studies[9]. At month-3 and month-6 follow-up visit, the postoperative efficacy was relatively stable and similar to the early efficacy.

In general, reducing AH production by coagulation of the ciliary body epithelium was the main mechanism of UCP procedure. In an animal study[20], a vascular corrosion cast and a sustained fluid space between the sclera, ciliary body, and choroid, which confirmed that increased aqueous humor outflow *via* the uveoscleral pathway plays a role in the mechanism of the UCP procedure. In further human study[21], UBM examinations showed the formation of suprachoroidal fluid spaces, which correlated with IOP reduction. In our study, although the high-dose UCP therapy has been expected to be more effective, nearly a quarter of patients did not respond to the treatment. If the UCP procedures were all standardized, there were different explanations depending on when the failure occurred. Early failure cases were mainly due to the lack of initial treatment dose, which resulted in less thermal coagulation of ciliary body tissue[22]. Late failure cases may due to the possible reactivation of the ciliary body[23-24] or the gradual narrowing of uveoscleral outflow[21]. In the case of our failure, the author believes that there are two reasons: one is that the baseline IOP is too high to select an adequate initial measurement; the other is that in some patients, especially the younger ones, the function of ciliary body epithelial cells is easy to regenerate. Therefore, for patients with inadequate response, repeated treatment could be recommended. In the clinical treatment, we used other treatment on non-responders to reduce IOP, including increasing drugs, implanting valve and re-treatment of UCP. Unfortunately, two eyes of two patients (one later after the end of the study follow-up) had to be enucleated because of severe ocular pain and subsequent expensive treatment costs.

According to current published studies, UCP procedure is described to be safe with few complications. No serious complications such as severe hypotony, phthisis, macular

edema or retinal detachment were observed during the follow-up period. Most transient or minor complications resolved with one month. Although recent cases of UCP complications, such as transient choroidal detachment[25], intraocular inflammation[26], and pupil ovalization[27], have been reported, UCP procedure has been proven to achieve a notable reduced rate of serious complications when compared to previous cyclodestructive procedures[28]. The most severe complication we encountered was transient choroidal detachment, while it recovered in a few days. It may be caused by sharp decrease of IOP after UCP procedure[25]. Therefore, the UCP procedure has been proven to be effective and safe in previous studies, and it remains important for every physician to be aware of some transient complications that may induce visual acuity. Ocular pain and corneal edema induced by high IOP existed prior to UCP treatment. On the contrary, many patients' previous symptoms such as ocular pain and corneal edema were relieved by the IOP reduction after UCP treatment.

The main limitation of our study is the non-comparative design. In order to clarify the necessity of using high-dose UCP with 10 sectors activated, other groups using conventional doses including 6-sectors and 8-sectors should also be established. The sample size of patients can be appropriately increased in future research, so that the response of different types of glaucoma to high-dose UCP can be compared. In addition, with the continuous development and innovation of HIFU technology, the cyclodiode technique is also evolving, especially the micro pulse mode. If conditions permit, a comparative study of cyclodestructive procedures using these new technologies should be established to provide the optimal therapeutic strategy for glaucoma patients.

In conclusion, high-dose UCP treatment using HIFU delivered by a circular miniaturized device is an effective and well-tolerated procedure to reduce IOP in Chinese patients with refractory glaucoma.

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