NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of high-intensity focused ultrasound for glaucoma

Glaucoma is usually caused by an increase in the pressure of the fluid that fills the inside of the eye. This damages the nerve that connects the eye to the brain (optic nerve) and can gradually lead to permanent loss of sight.

In this procedure, a device uses high-intensity focused ultrasound to destroy a small amount of the tissue that produces the fluid. The aim is to reduce the amount of fluid released into the eyeball, to reduce the eye pressure. Reduced eye pressure may slow or stop further damage to vision.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2019 and updated in July 2019.

Procedure name

- High-intensity focused ultrasound for glaucoma.

Specialist societies

- Royal College of Ophthalmologists (RCOphth)
- UK and Éire Glaucoma Society (UKEGS).

Description of the procedure

Indications and current treatment

Glaucoma is usually a chronic condition associated with elevated intraocular pressure. The most common type of glaucoma in the UK is primary open-angle glaucoma, also known as chronic open-angle glaucoma. It leads to progressive damage to the optic nerve. Early stages are usually asymptomatic but as the condition progresses it causes visual impairment and, if untreated, blindness.

NICE's guideline on glaucoma describes its diagnosis and management. Treatment is usually eye drops containing drugs that either reduce the production of aqueous humor (fluid) or increase its drainage. Surgical procedures such as trabeculectomy, drainage tubes, deep sclerectomy, viscocanalostomy or laser trabeculoplasty may also be used.

What the procedure involves

This procedure uses high intensity focused ultrasound (HIFU) to partially destroy the ciliary body to reduce the production of aqueous humor and thereby decrease the intraocular pressure (IOP).

The procedure can be done using local or general anaesthesia, or topical anaesthesia. One device available for this procedure consists of a compact operator console and a disposable probe (which includes a coupling cone and a therapy probe that generates the ultrasound beams). The coupling cone is placed directly on the centre of the patient's cornea and held in place by a low vacuum suction ring. A ring shaped therapy probe (connected to the console) that generates ultrasound beams is inserted into the cone. The space between the eye, cone and the probe is filled with saline solution to ensure dissemination of ultrasound energy. By pressing the foot switch, miniature transducers in the ring-shaped probe are sequentially activated to deliver HIFU beams directly into the ciliary body. These beams pass through the scleral tissue without disruption of ocular tissue to reach the ciliary body. The ultrasound heats and inactivates tissue within the ciliary body to decrease the production of aqueous humor.

Efficacy summary

Intraocular pressure

In a meta-analysis of 251 patients (7 studies), the mean IOP reduction 6 months after the HIFU procedure was 29% for the first generation device and 35% for the second generation device; 31% for refractory glaucoma and 33% for non-refractory glaucoma.[1] In a case series of 61 patients with end-stage refractory glaucoma, the mean reduction in IOP was 23% at 3-month follow-up (from 41.1 mmHg at baseline to 31.6 mmHg at 3 months).[3] In a case series of 30 patients with refractory glaucoma, the mean reduction in IOP was 33% at 6-month follow-up (from 30.1 mmHg at baseline to 20.2 mmHg at 6 months, $p<0.0001$).[4] In a case series of 47 patients with glaucoma, the mean reduction in IOP was 32% at 6-month follow-up and 29% at 1 year (from 27.7 mmHg at baseline to 19.8 mmHg at 1 year, $p<0.0001$).[5] In a case series of 40 patients, the mean IOP reduced from 32.5 mmHg at baseline to 23.4 mmHg at 120 days after HIFU ($p<0.001$). The mean IOP reduction for patients with complete success after 1 procedure was 46% at 1 year. In 20 patients who had a second HIFU procedure, the IOP reduced from 29.6 mmHg before the procedure to 23.6 mmHg at 120 days follow-up ($p<0.01$). In 12 patients who had a third procedure, the mean IOP reduced from 26.5 mmHg to 16.8 mmHg at 12-month follow-up ($p<0.01$).[6] In a case series of 62 patients, the mean IOP reduction was 44%, 48% and 42% at 3, 6 and 12 months respectively ($p<0.0005$ for all).[9]

In a non-randomised comparative study of 86 patients, the absolute reduction in IOP at 1 month was 3.3±7 mmHg for patients who had HIFU and 16.1±13 for those who had cyclodiode treatment ($p<0.0001$).[8]

Success rate

In the meta-analysis of 251 patients, the success rate at 6-month follow-up (defined as IOP reduction of at least 20% compared with baseline with no medication added) was 54% for the first generation device and 64% for the second generation device.[1] In the case series of 61 patients with end-stage refractory glaucoma, the success rate was 50% (26/52) at 3-month follow-up.[3] In the case series of 30 patients with refractory glaucoma, the complete success rate (defined as an IOP reduction of more than 20% and more than 5 mmHg, and IOP 21 mmHg or less, without adjunctive hypotensive medication) was 47% (14/30) at 6-month follow-up.[4] In the case series of 47 patients with glaucoma, the complete success rate was 43% (21/49) of eyes at 6-month follow-up.[5] In the case series of 40 patients, the complete success rate after 1 procedure was 45% (18/40). After a maximum of 3 procedures, the complete success rate was 85% (34/40) at 12-month follow-up.[6] In the case series of 62 patients, the qualified success rate (defined as IOP >5 mmHg and reduction by ≥30% from baseline values with or without medication) was 90%, 95% and 77% at 3, 6 and 12 months respectively ($p<0.0005$ for all).[9]

In the non-randomised comparative study of 86 patients, the treatment success rate at last follow-up was 25% for patients who had HIFU (median follow-up 6 months) and 52% for those who had cyclodiode treatment (median follow-up 3 months, $p=0.01$).[8]

Failure rate

In a case series of 73 patients, the failure rate (IOP was not reduced by 20%, IOP reduction was 5 mmHg or less on 2 consecutive follow-up visits, and additional intervention was necessary) at 6-month follow-up was 20% (5/25) for patients who had 8 seconds HIFU exposure time and 23% (10/43) for patients who had 10 seconds HIFU exposure time. At 12 months, the failure rates were 21% (4/19) and 22% (9/41) respectively.[2] In the case series of 30 patients with refractory glaucoma, the failure rate (defined as increase in the number of hypotensive medications after the procedure, regardless of the IOP, or if the patient needed filtering surgery) was 7% (2/30) at 6-month follow-up.[4] In the case series of 47 patients with glaucoma, the failure rate (defined as an increase in the number of postoperative daily hypotensive medications or the need for subsequent surgery during the study period) was 25% (12/49) of eyes at 6-month follow-up.[5]

Pain

In the case series of 61 patients with end-stage refractory glaucoma, the mean pain score reduced from 1.0 at baseline to 0.1 at 3-month follow-up and the proportion of patients reporting local pain reduced from 23% (14/61) to 2% (1/52).[3]

Reduction in medication use

In the case series of 47 patients, the mean number of daily hypotensive drops reduced from 3.2 at baseline to 2.3 at 1 year follow-up and the mean number of acetazolamide tablets reduced from 0.5 to 0.2 ($p<0.05$ for both). The proportion of patients using acetazolamide tablets decreased at 1 year after the procedure from 53% to 17%.[5] In the case series of 40 patients, the mean number of hypotensive therapy classes reduced from 3.6 at baseline to 2.4 at 12 month follow-up ($p<0.01$).[6] In the case series of 62 patients, the mean number of topical anti-glaucoma medications decreased from 3.2±0.4 before treatment to 2.1±1.02 at 12 months ($p<0.0005$).[9]

Need for additional surgery

In the case series of 30 patients, 1 patient needed a trabeculectomy 3 months after the HIFU procedure.[4] In the case series of 47 patients, 7 patients needed additional surgery after an average interval of 3 months (6 trabeculectomy and 1 implantation of Ahmed valve)[5]. In the case series of 52 patients, 23% (12/52) of patients needed retreatment; 9 patients had trabeculectomy, 2 had diode laser cyclodestruction, and 1 had Ahmed valve surgery. These treatments were done between 6 and 12 months after the HIFU procedure.[7]

Safety summary

Intraoperative complications

Intraoperative corneal pain was reported in 2% (4/251) of patients and subconjunctival haemorrhage was reported in 6% (14/251) of patients in a meta-analysis of 251 patients.[1] Intraoperative pain and subconjunctival haemorrhage were each reported in 21% (13/61) of patients in a case series of 61 patients.[3] Subconjunctival haemorrhage was reported in 10% (3/30) of patients in a case series of 30 patients.[4] Intraoperative pain was reported in 75% (30/40) of patients and subconjunctival haemorrhage in 38% (15/40) of patients in a case series of 40 patients.[6]

Postoperative complications

Loss of visual acuity

Loss of visual acuity (>2 Snellen lines) was reported in 2% (6/251) of patients in the meta-analysis of 251 patients.[1] Loss of more than 2 lines of visual acuity was reported in 2 patients in the case series of 40 patients: 1 was caused by cataract evolution and 1 was caused by glaucoma disease progression.[6] Fluctuation of visual acuity within 2 lines during the first postoperative month was reported in 14% of patients (actual numbers not reported) in a case series of 47 patients.[5]

Loss of more than 2 lines of visual acuity (Snellen chart) was reported in 17% (12/70) of patients who had HIFU and 31% (9/29) of patients who had cyclodiode treatment (p=0.176) in a non-randomised comparative study of 86 patients.[8]

Transient macular oedema

Transient macular oedema was reported in 2% (4/251) of patients in the meta-analysis of 251 patients. This was treated with steroids (not further described) and resolved within a few months without a further decline in visual acuity.[1] Macular oedema was reported in 5% (3/62) of patients in a case series of 62 patients.[9]

Corneal abrasion or epithelial defect

Corneal abrasion or epithelial defect was reported in 2% (4/251) of patients in the meta-analysis of 251 patients. The corneal abrasions 'healed several weeks after treatment'.[1]

Corneal ulcer

Corneal ulcer was reported in 1 patient in the meta-analysis of 251 patients.[1] It was reported in 5% (2/40) of patients in the case series of 40 patients (treated with medication, not further described).[6]

Hypotony

Early hypotony (<10 mmHg) was reported in 2% (4/251) of patients in the meta-analysis of 251 patients. Early transient hypotony (<6 mmHg) was reported in 1 patient and early transient hypotony with choroidal detachment was reported in 1% (3/251) of patients in the same review. The hypotony resolved within 1 month in all patients after steroid treatment (not further described).[1] Hypotony was reported in 3% (2/61) of patients in the case series of 61 patients.[3] Hypotony (phthisis bulbi) was reported in no patients who had HIFU and 14% (4/29) of patients who had cyclodiode treatment (p=0.006).[8]

Retinal detachment

Retinal detachment was reported in 1 patient in the case series of 61 patients. The causality was not confirmed because of dense cataract and no ultrasound scan of the fundus before treatment.[3]

Induced astigmatism

Induced astigmatism was reported in 1% (3/251) of patients in the meta-analysis of 251 patients. This improved over 3 to 6 months after the procedure.[1] Astigmatism (>1 dioptre) was reported in 1 patient in the case series of 61 patients.[3]

Conjunctival hyperaemia

Conjunctival hyperaemia (<7 days) was reported in 69% (173/251) of patients in the meta-analysis of 251 patients.[1] Conjunctival hyperaemia was reported in 25% (15/61) of patients in the case series of 61 patients.[3] It was reported in all patients in a case series of 40 patients.[6]

Superficial punctate keratitis

Superficial punctate keratitis was reported in 24% (61/251) of patients in the meta-analysis of 251 patients.[1] Superficial punctate keratitis was reported in 7% (4/61), 13% (4/30) and 45% (18/40) of patients in the case series of 61, 30 and 40 patients respectively.[3,4,6] Punctate keratitis was reported in 10% (6/62) of patients in the case series of 62 patients.[9]

Anterior chamber inflammation

Anterior chamber inflammatory reaction (>7 days) was reported in 21% (53/251) of patients in the meta-analysis of 251 patients.[1] Anterior chamber inflammatory reaction was reported in 36% (22/61) of patients in the case series of 61 patients.[3] Transient anterior chamber inflammatory reaction was reported in 20% (6/30) and 18% (actual numbers not reported) of patients in the case series of 30 and 47 patients respectively.[4,5] Anterior chamber reaction was reported in all patients in the case series of 62 patients.[9]

Ocular pain

Transient ocular pain was reported in 8% (20/251) of patients in the meta-analysis of 251 patients.[1]

Corneal oedema

Corneal oedema was reported in 8% (20/251) of patients in the meta-analysis of 251 patients.[1] It was reported in 3% (2/61) of patients in the case series of 61 patients.[3]

Chemosis

Chemosis was reported in 3% (7/251) of patients in the meta-analysis of 251 patients.[1] Chemosis was reported in 23% (14/61) of patients in the case series of 61 patients.[3] Chemosis was reported in 43% of patients in a case series of 47 patients.[5]

Goniosynechiae

Goniosynechiae was reported in 1 patient in the meta-analysis of 251 patients.[1]

Posterior synechiae

Irido-crystalline lens synechiae was reported in 1 patient in the meta-analysis of 251 patients.[1]

Mydriasis

Mydriasis was reported in 1 patient in the meta-analysis of 251 patients.[1] Semi-mydriasis was reported in 4% of patients in the case series of 47 patients; it reversed after a median time interval of 3.5 weeks.[5] Mydriasis was reported in 3% (2/62) of patients in the case series of 62 patients.[9]

Pupil irregularities

Minor pupil irregularities were reported in 3% (7/251) of patients in the meta-analysis of 251 patients.[1]

Scleral thinning

Scleral thinning was reported in 20% (12/61) and 25% (10/40) of patients in the case series of 61 and 40 patients respectively.[3,6] Focal areas of scleral thing were reported in 8% of patients in the case series of 47 patients.[5]

Scleral marks

Scleral marks were reported in 10% (26/251) of patients in the meta-analysis of 251 patients.[1]

Foreign body sensation

Foreign body sensation was reported in 8% (5/61) of patients in the case series of 61 patients.[3]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: refractive change (including induced astigmatism), persistent inflammation after the procedure, fixed mid-dilated pupil, unusual macular oedema, intraoperative pain, and failure to fit the device onto the eye. They did not describe any additional theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to high-intensity focused ultrasound for glaucoma. The following databases were searched, covering the period from their start to 17 May 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with glaucoma.
Intervention/test	High-intensity focused ultrasound.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 580 patients from 1 meta-analysis, 1 non-randomised comparative study and 7 case series (2 of which were also included in the meta-analysis).[1–9]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for glaucoma

Study 1 Denis P (2016)

Details

Study type	**Meta-analysis**
Country	Not reported for individual studies
Recruitment period	Not reported
Study population and number	**n=251** (7 studies) Patients with refractory or non-refractory glaucoma
Age and sex	Mean 63 years; 64% male
Patient selection criteria	Patients with refractory or non-refractory glaucoma with IOP >21 mmHg.
Technique	High-intensity focused ultrasound device consisted of a probe with 6 active piezoceramic transducers and a positioning cone. A second generation device was used in 2 studies. This differed from the first generation in having a broader active transducer area (4 mm instead of 2.5 mm) and more precise temperature calibration of each single transducer. Other enhancements included optimised suction and centring on the eye globe, improved coupling of ultrasound by removal of air bubbles in the liquid, optimised ergonomics and improved clip to attach the probe into the cone.
Follow-up	**Up to 12 months**
Conflict of interest/source of funding	Publication of the article was supported by Eye Tech Care. Medical writing assistance was funded by Eye Tech Care. The author has been a consultant to Alcon, Alimera, Allergan, Eye Tech Care, Istar and Thea.

Analysis

Follow-up issues: Follow-up in the individual studies ranged from 6 to 12 months. Losses to follow-up are not addressed in the review.

Study design issues: The review provides no details of the search strategy or methods used for identifying studies for inclusion. There is no discussion on the quality of the included studies. There are no details of the statistical methods used and no assessment of heterogeneity. Of the 7 studies included in the review, 6 were described as prospective multicentre trials and 1 was a prospective single centre trial.

Study population issues: Four studies included only patients with refractory glaucoma (at least 1 attempt at filtering surgery), 2 included only patients with non-refractory glaucoma and 1 study included both. Of the 251 patients, 53% had refractory glaucoma. Most patients (84%) had primary open-angle glaucoma.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **251**

Mean intraocular pressure (IOP) reduction at 6 months

- First generation device=29%
- Second generation device=35%
- Refractory glaucoma=31%
- Non-refractory glaucoma=33%

Success rate at 6 months (defined as IOP reduction of at least 20% compared with baseline with no medication added)

- First generation device=54%
- Second generation device=64%

Safety

Safety results for first and second generation devices

	First generation		Second generation		Total	
	n	%	n	%	n	%
Patients	141		110		251	
Intraoperative						
Corneal pain	4	3	0	0	4	2
Corneal burn	0	0	0	0	0	0
Subconjunctival haemorrhage	6	4	8	7	14	6
Postoperative						
Conjunctival hyperaemia (<7 days)	86	61	87	79	173	69
Superficial punctate keratitis	44	31	17	15	61	24
Anterior chamber reaction (>7 days)	41	29	12	11	53	21
Transient ocular pain	13	9	7	6	20	8
Corneal oedema*	16	11	4	4	20	8
Corneal ulcer	1	1	0	0	1	<1
Corneal abrasion/epithelial defect	1	1	3	3	4	2
Chemosis	7	5	0	0	7	3
Transient macular oedema	3	2	1	1	4	2
Astigmatism	1	1	2	2	3	1
Goniosynechiae	1	1	0	0	1	<1
Scleral marks	4	3	22	20	26	10
Irido-crystalline synechiae	1	1	0	0	1	<1
Early hypotony (<10 mmHg)	4	3	0	0	4	2
Early transient hypotony (<6 mmHg)	0	0	1	1	1	<1
Early transient hypotony with choroidal detachment	2	1	1	1	3	1
Mydriasis	0	0	1	1	1	<1
Minor pupil irregularities	0	0	7	6	7	3
Loss of visual acuity (>2 lines)	6	4	0	0	6	2
Phthisis bulbi	0	0	0	0	0	0
Cataract induced	0	0	0	0	0	0
Hypotony (<6 mmHg) (not further described)	0	0	0	0	0	0

* Patients with high IOP before treatment and pre-existing compromised fragile cornea

Conjunctival hyperaemia was frequently pre-existing from long-term treatment with medication. Scleral marks (brownish spots at the ultrasound entry point) were more common in Indian eyes than in Caucasian eyes, which may be attributed to the more

darkly pigmented sclera. In some patients the marks faded over time, whereas in others they got darker.

Serious complications

Complication	n
Loss of visual acuity (>2 Snellen lines)	6
Transient macular oedema	4
Corneal abrasion – epithelial defect resulting from mechanical effect due to placement of cone	4
Hypotony with choroidal detachment	3
Induced astigmatism	3

The transient macular oedema was treated with steroids (not further described) and resolved within a few months without a further decline in visual acuity.

The corneal abrasions 'healed several weeks after treatment'.

The hypotony resolved within 1 month in all patients after steroid treatment (not further described).

The induced astigmatism improved over 3 to 6 months.

Abbreviations used: IOP, intraocular pressure

Study 2 Deb-Joarder N (2018)

Details

Study type	**Case series (ETC-IND-02)**
Country	India
Recruitment period	Not reported
Study population and number	**n=73 (73 eyes)** Patients with open-angle glaucoma
Age and sex	Mean 62 years; 74% (54/73) male
Patient selection criteria	Inclusion criteria: primary open-angle glaucoma, pseudoexfoliative or pigmentary glaucoma with or without previous trabeculectomy; average baseline IOP between 21 and 45 mmHg, not adequately controlled with glaucoma medication; age between 18 and 90 years; no intraocular surgery or laser treatment during the 90 days before the procedure. Exclusion criteria: angle-closure glaucoma or narrow anatomical anterior chamber; normal tension glaucoma, secondary glaucoma and aphakia; history of cyclo-destructive procedure or glaucoma drainage device implantation; any ocular or retrobulbar tumour or ocular infection within past 2 weeks; ocular disease other than glaucoma that may affect assessment of visual acuity or IOP.
Technique	Device: EyeOP1 (Eye Tech Care, France); second generation probe. Patients were divided into 2 groups. Group 1 (n=28) had 8 seconds of exposure time for each transducer and group 2 (n=45) had 10 seconds. The treatment parameters were as follows: frequency=21 MHz, sectors activated=6, acoustic power=2.45w, time between shots=20 seconds. All patients were treated under peribulbar anaesthesia. Preoperative hypotensive medications were maintained unchanged after the procedure unless a favourable IOP response made their withdrawal necessary.
Follow-up	**12 months**
Conflict of interest/source of funding	The trial was funded by Eye Tech Care, France.

Analysis

Follow-up issues: Patients were followed up at day 1, 7 and month 1, 2, 3, 6 and 12. In group 1, 89% (25/28) of patients were followed up at 6 months and 68% (19/28) at 12 months; 4 patients were lost to follow-up and 4 withdrew. In group 2, 96% (43/45) of patients were followed up at 6 months and 89% (40/45) at 12 months; 2 patients were lost to follow-up and 1 withdrew.

Study design issues: Prospective, single-centre case series. The primary endpoint was IOP reduction at 6 and 12 months. Treatment response was defined as 'IOP reduction from baseline more than 20% and final IOP more than 5 mmHg without supplemental hypotensive medications and without reintervention (complete success)', whereas qualified success was defined as achieving the same with supplemental hypotensive medications. Failure was considered where IOP was not reduced by 20%, IOP was 5 mmHg or less on 2 consecutive follow-up visits, and additional intervention was necessary.

Study population issues: 89% (65/73) of patients had primary open-angle glaucoma. The remaining patients had pigmentary (n=1) or pseudoexfoliative (n=7) glaucoma. Of 72 patients, 69 (95%) did not have a previous trabeculectomy. The preoperative mean IOP was 23.5 mmHg.

Other issues: A conference abstract reporting results from this study was included in the meta-analysis by Denis P (2016).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **73**

Intraocular pressure (IOP) at baseline and during follow-up – all patients

Follow-up	Mean±SD IOP mmHg (n); mean glaucoma medications	Relative IOP reduction (%)	Response rate (%)	p value
Baseline	23.5±3.9 (73); 0.7	-	-	-
Day 1	14.2±5.1 (73); 0.7	39.6	82	<0.001
Day 7	12.4±4.4 (73); 0.7	47.1	93	<0.001
Month 1	14.5±5.0 (73); 0.6	37.6	85	<0.001
Month 2	15.6±4.0 (71); 0.7	33.1	76	<0.001
Month 3	15.5±3.8 (72); 0.8	33.7	81	<0.001
Month 6	15.8±3.5 (68); 0.9	32.3	78	<0.001
Month 12	15.7±5.4 (59); 1.0	32.6	78	<0.001

Intraocular pressure (IOP) at baseline and during follow-up – group 1 (8 seconds exposure time)

Follow-up	Mean±SD IOP mmHg (n); mean glaucoma medications)	Relative IOP reduction (%)	Response rate (%)	p value
Baseline	23.3±2.4 (28); 0.5	-	-	-
Day 1	15.3±5.4 (28); 0.5	34.6	75	<0.001
Day 7	13.2±4.3 (28); 0.5	43.4	89	<0.001
Month 1	15.9±5.0 (28); 0.5	31.3	75	<0.001
Month 2	16.8±4.3 (27); 0.7	26.6	67	<0.001
Month 3	16.1±3.5 (27); 0.9	30.5	70	<0.001
Month 6	15.4±3.5 (25); 1.0	34.0	80	<0.001
Month 12	14.3±3.8 (19); 1.2	37.4	79	<0.001

Intraocular pressure (IOP) at baseline and during follow-up – group 2 (10 seconds exposure time)

Follow-up	Mean±SD IOP mmHg (n); mean glaucoma medications	Relative IOP reduction (%)	Response rate (%)	p value
Baseline	23.7±3.4 (45); 0.8	-	-	-
Day 1	13.4±4.7 (45); 0.8	42.7	87	<0.001
Day 7	11.9±4.4 (45); 0.8	49.4	96	<0.001
Month 1	13.7±5.0 (45); 0.7	41.5	91	<0.001
Month 2	14.8±3.6 (44); 0.7	37.1	82	<0.001
Month 3	15.1±3.9 (45); 0.7	35.6	87	<0.001
Month 6	16.1±3.5 (43); 0.8	31.3	77	<0.001
Month 12	16.4±5.9 (40); 1.0	30.4	78	<0.001

Safety

Intraoperative and postoperative complications, n (%)

Ocular complication	All	Group 1	Group 2	p
Intraoperative				
Subconjunctival haemorrhage	4 (7)	2 (7)	2 (4)	0.6349
Postoperative				
Hyperaemia	68 (93)	26 (93)	43 (93)	0.6349
Anterior chamber reaction (<7 days)	67 (92)	25 (89)	42 (92)	0.6691
Ocular pain (<1 day)	36 (49)	21 (75)	15 (33)	0.0007
Scleral marks	22 (30)	6 (21)	16 (35)	0.2945
Minor pupil peak	10 (14)	5 (18)	5 (11)	0.4923
Superficial punctate keratitis	4 (7)	4 (14)	-	-
Transient hypotony	3 (5)	1 (4)	2 (4)	1
Corneal epithelial defect or oedema	3 (5)	2 (7)	1 (2)	0.5543
Astigmatism (>1 dioptre)	2 (4)	-	2 (4)	-
Transient hypotony with choroidal detachment	1 (1)	1 (4)	-	-
Transient macular oedema	1 (1)	1 (4)	-	-
Mild mydriasis	1 (1)	-	1 (2)	-
Phthisis	-	-	-	-
Induced cataract	-	-	-	-

Of the 3 patients with postoperative hypotony, 1 patient, who had choroidal detachment, was treated with systemic steroids and choroidal drainage and the other 2 had conservative management.

One patient had branch retinal vein occlusion with macular oedema and was treated with an anti-VEGF injection and argon laser photocoagulation.

Complete success at 6 month follow-up: • Group 1 (8-second exposure)=56% (14/25) • Group 2 (10-second exposure)=65% (28/43) **Complete success at 12 month follow-up**: • Group 1=42% (8/19) • Group 2=51% (21/41) **Qualified success at 6 month follow-up**: • Group 1=24% (6/25) • Group 2=12% (5/43) **Qualified success at 12 month follow-up**: • Group 1=37% (7/19) • Group 2=27% (11/41) **Failure rate at 6 month follow-up**: • Group 1=20% (5/25) • Group 2=23% (10/43) **Failure rate at 12 month follow-up**: • Group 1=21% (4/19) • Group 2=22% (9/41)	Visual acuity loss of 2 or more lines=8% (6/73) (Caused by progression of pre-existing cataract in 2 patients, persistent superficial punctate keratitis in 2 patients, persistent uveitis in 1 patient and worsening of end-stage glaucoma in 1 patient.)
Abbreviations used: IOP, intraocular pressure; sd, standard deviation	

Study 3 Hu D (2018)

Details

Study type	**Case series**
Country	China
Recruitment period	2016 to 2017
Study population and number	**n=61 (61 eyes)** Patients with end-stage refractory glaucoma
Age and sex	Mean 57 years (range 22 to 86); 56% (34/61) male
Patient selection criteria	Inclusion criteria: end-stage glaucoma, according to the Glaucoma Severity Staging (GSS) system; IOP≥21 mmHg despite the use of glaucoma medications; age older than 18 years and younger than 90 years. Exclusion criteria: previous cyclophotocoagulation or other cyclodestructive surgery; the presence of a glaucoma drainage device; ocular infection; other diseases that can affect intraocular pressure; pregnancy or serious systemic disease.
Technique	Device: EyeOP1 (Eye Tech Care, France). 8 seconds (2 W) of ultrasound exposure time per sector were applied, with a 20 second interval between exposures. The entire procedure lasted 2 minutes and 28 seconds. There were 2 treatment modes used during the study. The first 43 patients had a 6-sector activated modality and the last 18 patients were treated with 8 sectors.
Follow-up	**3 months**
Conflict of interest/source of funding	No conflicts of interest. The study was supported by the National Natural Science Foundation of China.

Analysis

Follow-up issues: Follow-up was completed by 85% (52/61) of patients.

Study design issues: Retrospective single-centre case series with consecutive recruitment. Success was defined as 'IOP reduced by 20% or more but still 5 mmHg or higher (despite the presence of ocular hypotensive agents)'. The 2 treatment modes (6 and 9 sectors) were compared and outcomes were also stratified by glaucoma type.

Study population issues: 16% (10/61) of patients had primary open angle glaucoma, 30% (18/61) had primary angle-closure glaucoma, 48% (29/61) had neovascular glaucoma and 7% (4/61) had traumatic glaucoma. Of the 61 patients, 55 (90%) presented with no light perception, while the other 6 patients ranged from finger counting to light perception; 21% (13/61) of patients had previous glaucoma surgery (including 12 who had trabeculectomy). The mean (±SD) IOP at baseline was 41.1±10.7 mmHg.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **61**

IOP trend for all patients

Follow-up	Mean IOP±SD (mmHg)	Percentage reduction in IOP
Baseline	41.1±10.7	-
1 day	29.1±10.1	29.2%
7 days	23.4±11.4	43.2%
1 month	26.8±12.4	34.8%
3 months	31.6±14.6	23.1%

Success rate at 3 months

- All patients=50.0% (26/52)
- 6-sector group=48.6% (17/35)
- 8-sector group=52.9% (9/17), p=0.768 between 6-sector and 8-sector groups
- Primary open angle glaucoma (POAG)=55.6% (5/9)
- Primary angle closure glaucoma (PACG)=80.0% (12/15)
- Neovascular glaucoma (NVG)=29.2% (7/24)
- Traumatic glaucoma=50.0% (2/4), p=0.013 between glaucoma subgroups

IOP levels in 6-sector group of patients

Follow-up	n	Mean IOP±SD (mmHg)	p	IOP range	IOP reduction (%)	Mean no. of medications±SD	p
Baseline	43	40.1±10.2	-	22 to 59	-	2.6±1.1	-
1 day	41	30.9±10.1	<0.001	11 to 55	22.2	2.6±1.1	1.00
7 days	43	25.4±11.1	<0.001	8 to 48	36.6	2.6±1.1	1.00
1 month	42	28.3±12.9	<0.001	8 to 58	29.4	2.6±1.2	0.59
3 months	34	31.7±12.6	<0.001	2 to 55	22.0	2.4±1.2	0.34

IOP levels in 8-sector group of patients

Follow-up	n	Mean IOP±SD (mmHg)	p	IOP range	IOP reduction (%)	Mean no. of medications±SD	p
Baseline	18	43.6±11.6	-	26 to 64	-	2.7±0.7	-
1 day	18	25.0±9.2	<0.001	5 to 36	42.0	2.7±0.7	1.00
7 days	18	18.5±10.7	<0.001	4 to 37	57.7	2.7±0.7	1.00
1 month	17	23.0±10.2	<0.001	9 to 40	50.2	2.6±0.7	0.32
3 months	17	31.6±18.4	0.019	3 to 79	28.5	2.3±1.1	0.04

IOP levels by type of glaucoma

Subgroup	n	Mean baseline IOP±SD (mmHg)	Mean IOP reduction at 3 months±SD (mmHg)	Percentage IOP reduction
POAG	9	37.8±9.2	6.7±8.2	17.7
PACG	15	44.0±11.9	15.9±13.7	36.1
NVG	24	41.8±11.1	7.8±17.1	18.6
Traumatic	4	39.3±14.2	8.5±15.2	21.6

Mean pain scores

Follow-up	Mean pain score	Number of patients reporting local pain
Baseline	1.0	23.0% (14/61)
Day 1	1.3	34.4% (21/61)
Day 7	0.6	19.7% (12/61)
1 month	0.2	6.6% (4/61)
3 months	0.1	1.9% (1/52)

Safety

Intraoperative and postoperative complications

Complication	6-sector (n=43)	8-sector (n=18)	Total (n=61)
Anterior chamber reaction	13	9	22 (36.1%)
Conjunctival hyperaemia	10	5	15 (24.6%)
Keratic precipitates	9	6	15 (24.6%)
Chemosis	8	6	14 (23.0%)
Intraoperative pain	10	3	13 (21.3%)
Subconjunctival haemorrhage	6	7	13 (21.3%)
Scleral thinning	7	5	12 (19.7%)
Foreign body sensation	4	1	5 (8.2%)
Superficial punctate keratitis	3	1	4 (6.6%)
Corneal oedema	1	1	2 (3.3%)
Hypotony	1	1	2 (3.3%)
Astigmatism (>1 dioptre)	1	0	1 (1.6%)
Retinal detachment (causality not confirmed because of dense cataract and no ultrasound scan of the fundus before treatment)	1	0	1 (1.6%)

Abbreviations used: IOP, intraocular pressure; NVG, neovascular glaucoma; PACG, primary angle closure glaucoma; POAG, primary open angle glaucoma; sd, standard deviation

Study 4 Giannaccare G (2017)

Details

Study type	**Case series**
Country	Italy (2 centres)
Recruitment period	2014 to 2015
Study population and number	**n=30 (30 eyes)** Patients with refractory glaucoma
Age and sex	Mean 73 years; 53% (16/30) male
Patient selection criteria	Inclusion criteria: age older than 18 years and diagnosis of advanced glaucoma with uncontrolled baseline IOP 21 mmHg or above, refractory to maximum medical topical and systemic treatment. Exclusion criteria: pregnancy, normal-tension glaucoma, laser trabeculoplasty or incisional glaucoma surgery within the previous 6 months, ocular infection in the previous 3 months.
Technique	Device: EyeOP1 HIFU device (Eye Tech Care, France). Treatment consisted of the sequential activation of each transducer for 4, 6 or 8 seconds exposure time. The other surgical parameters were as follows: frequency=21 MHz, number of sectors activated=6, acoustic power=2.45 W, time between each shot=20 seconds. The procedure itself lasted between 124 to 148 seconds. Topical and systemic hypotensive medications were stopped after the procedure and only started again if postoperative IOP was higher than 21 mmHg at any of the follow-up visits.
Follow-up	**180 days**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No patients were lost to follow-up. One patient exited the study 3 months after the procedure and had a trabeculectomy.

Study design issues: Prospective, multicentre case series. Patients were randomly allocated to the 4, 6 or 8 second exposure time group by using computer-generated random numbers. The main outcomes were the mean reduction in IOP at the last follow-up in the overall population and by exposure time group, and the rates of complete success, qualified success and failure. Qualified success was defined as ‘a reduction in IOP≥20% and ≥5 mmHg without adjunctive hypotensive medication’. Complete success was defined as ‘an IOP reduction >20% and >5 mmHg, and IOP≤21 mmHg, without adjunctive hypotensive medication’. Failure was considered if the number of hypotensive medications was increased after the procedure, regardless of the IOP, or if the patient needed filtering surgery.

Study population issues: 53% (16/30) of patients had open-angle glaucoma, 33% (10/30) had angle-closure glaucoma and 13% (4/30) had neovascular glaucoma. The mean preoperative IOP was 30.1±10.5 mmHg. 20% (6/30) of patients had previous selective laser trabeculoplasty and 13% (4/30) had previous incisional surgery for glaucoma. Preoperative mean visual acuity was 1.46±0.85 logMAR.

Other issues: There may be some patient overlap with Giannaccare G et al, 2018 (study 5).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30**

Baseline and postoperative IOP, with the corresponding number of hypotensive drops and acetazolamide tablets used, mean values

Follow-up	IOP (mmHg)	Percentage drop in IOP	Number of drops	Number of tablets
Baseline	30.1	-	2.7	0.8
Day 1	18.4*	39%	0	0
Day 7	18.4	39%	0.2	0
Day 14	18.6	38%	0.5	0.1
Day 30	19.5	35%	0.9	0.1
Day 90	19.5	35%	1.4	0.2
Day 180	20.2*	33%	2.0^	0.3*

*p<0.0001 compared with baseline

^p=0.005 compared with baseline

The reduction in IOP was not statistically different among the 3 types of glaucoma.

There was no statistically significant difference in visual acuity or visual field mean deviation on day 180 compared with baseline.

Qualified success=23.3% (7/30)

Complete success=46.7% (14/30)

Failure=6.7% (2/30) (1 patient had to increase the number of hypotensive medications after the procedure and the other needed a trabeculectomy 3 months after the procedure.)

Mean (±SD) reduction in IOP (mmHg) by exposure time group

- Group 1 (4 seconds)=−3.7±6.5 (n=9)
- Group 2 (6 seconds)=−8.8±6.6 (n=9)
- Group 3 (8 seconds)=−16.2±8.3 (n=12)

p=0.02 for group 3 versus group 2 and p<0.001 for group 3 versus group 1

Correlation between ultrasound exposure time and IOP reduction (p=0.03)

IOP reduction	Group 1 n=9	Group 2 n=9	Group 3 n=12
<20%	6 (66.7%)	1 (11.1%)	1 (9.1%)
20 to 29%	0 (0%)	4 (44.5%)	0 (0%)
30 to 39%	1 (11.1%)	2 (22.2%)	3 (27.3%)
≥40%	2 (22.2%)	2 (22.2%)	7 (63.6%)

Safety

One patient had a fixed and dilated pupil with concomitant accommodation deficit, which spontaneously resolved within 3 months.

Complications diagnosed during first postoperative visit (day 1)

- Transient anterior chamber inflammatory reaction=20% (6/30)
- Superficial punctate keratitis=13.3% (4/30)
- Subconjunctival haemorrhage=10% (3/30)

All these complications resolved without the need for additional treatment and were not detected during subsequent visits.

Abbreviations used: IOP, intraocular pressure

Study 5 Giannaccare G (2018)

Details

Study type	**Case series**
Country	Italy (3 centres)
Recruitment period	2014 to 2016
Study population and number	**n=47 (49 eyes)** Patients with glaucoma
Age and sex	Mean 74 years (range 33 to 98); 51% (24/47) male
Patient selection criteria	Inclusion criteria: age older than 18 years, a diagnosis of glaucoma with an uncontrolled baseline IOP ≥21 mmHg while on maximum medical therapy or intolerance to glaucoma medications despite well-controlled IOP. Exclusion criteria: pregnancy, diagnosis of normal-tension glaucoma, a laser or surgical procedure within the last 6 months, ocular infections and uveitis in the previous 3 months.
Technique	Device: EyeOP1 (Eye Tech Care, France). Two generations of probes were used. The first allowed a choice of 4 or 6 seconds of treatment time; the second used an exposure time of 8 seconds. The first generation probe was used for 71% (35/49) of eyes and the second generation probe for 29% (14/49) of eyes. All procedures were done under peribulbar anaesthesia.
Follow-up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Prospective multicentre case series. Primary outcomes were the mean IOP reduction and the rates of success after 1 year. Qualified success was defined as an IOP reduction ≥20% and 5 mmHg without adjunctive hypotensive medication. Complete success was defined as qualified success plus IOP <21 mmHg. Failure was defined as an increase in the number of postoperative daily hypotensive medications or the need for subsequent surgery during the study period.

Study population issues: 49% (24/49) of eyes had open angle glaucoma, 18% (9/49) had exfoliative glaucoma, 23% (11/49) had angle closure glaucoma and 10% (5/49) had neovascular glaucoma. 27% (13/49) of eyes had been treated previously by laser trabeculoplasty and 25% (12/49) by trabeculectomy. The mean (±SD) IOP at baseline was 27.7±9.2 mmHg. Preoperative mean best corrected visual acuity was 1.65±1.14 logMAR.

Other issues: There may be some patient overlap with Giannaccare G et al, 2017 (study 4).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **47 (49 eyes)**

Reduction in IOP during follow-up

Follow-up	Mean IOP (mmHg)	Mean IOP reduction (%)	Mean number of daily hypotensive drops	Mean number of acetazolamide tablets used
Baseline	27.7	-	3.2	0.5
1 day	17.9	35.5	0	0
7 days	17.1	38.4	0.4	0
14 days	17.9	35.4	0.7	0.1
1 month	18.7	32.7	1.2	0.1
3 months	18.5	33.2	1.8	0.2
6 months	19.0	31.7	2.1	0.2
9 months	18.7	32.6	2.1	0.2
1 year	19.8	28.7	2.3	0.2

$p<0.0001$ for reduction in IOP at 1 day and 1 year compared with baseline.

$p<0.05$ for reduction in daily hypotensive drops and acetazolamide tablets at 1 year.

Percentage of patients using acetazolamide tablets decreased at 1 year after the procedure from 53.1% to 16.7%.

Linear regression analysis showed that postoperative IOP reduction was statistically significantly related to preoperative IOP ($r^2=0.5034$, $p<0.0001$).

Percentage of IOP reduction at follow-up according to the generation of the probe used

Follow-up	First generation probe	Second generation probe
1 day	32.2	42.3
7 days	34.3	46.7
14 days	30.8	44.5
1 month	26.3	45.6
3 months	27.8	43.8
6 months	26.5	41.9
9 months	28.0	41.7
12 months	25.6	35.0

$p<0.05$ for comparison between probes

The mean IOP reduction at last follow-up visit did not statistically significantly differ according to type of glaucoma or lens status, but the highest reduction was in eyes with angle closure glaucoma (−13.3 mmHg from baseline to 1 year follow-up; 41% reduction) followed by open angle glaucoma (−7.3 mmHg; 29%), neovascular

Safety

Minor complications

- Conjunctival hyperaemia=71.4%
- Conjunctival chemosis=42.9%
- Superficial punctate keratitis=38.8%
- Subconjunctival haemorrhage=24.5%
- Transient anterior chamber uveal reaction=18.4%
- Focal areas of scleral thinning=8.2%
- Fluctuation of visual acuity within 2 lines during the first postoperative month=14.3%
- Semi-mydriasis=4% (reversed after a median time interval of 3.5 weeks)

glaucoma (−7.1 mmHg; 21%) and exfoliative glaucoma (−4.3 mmHg; 18%). **Qualified success=51.1% (25/49)** **Complete success=42.9% (21/49)** **Failure=24.5% (12/49)** Of the 12 failures, 9 eyes were treated with the first generation probe and 3 with the second generation probe. 7 eyes needed additional surgery after an average interval of 3 months (trabeculectomy in 6 eyes and implantation of Ahmed valve in 1 eye). The remaining 5 patients had to increase the number of daily hypotensive medications. 7 failures were classified as early (within 6 months of the procedure) and the other 5 were late. No patients had vision loss of 1 line of more at 1 year and postoperative final visual acuity and visual field mean deviation did not statistically significantly differ from preoperative values.	
Abbreviations used: IOP, intraocular pressure	

Study 6 De Gregorio A (2017)

Details

Study type	**Case series**
Country	Italy
Recruitment period	Not reported
Study population and number	**n=40 (40 eyes)** Patients with glaucoma
Age and sex	Mean 72 years (range 29 to 94); 50% (20/40) male
Patient selection criteria	Inclusion criteria: age 18 years or older with primary or secondary glaucoma with a baseline IOP>21 mmHg under maximal tolerated medical therapy. Exclusion criteria: pregnancy, concomitant systemic medications that could affect IOP, history of ocular tumour, ocular infection, ocular surgical or laser procedure in the previous 6 months.
Technique	Device: second generation EyeOP1. Standard parameters: 21 MHz operating frequency, 6 activated sectors, 2 to 3 W acoustic power, 8 seconds of the HIFU for each sector. All procedures were done under sub-Tenon's anaesthesia. Preoperative hypotensive medications were maintained during follow-up if IOP was >15 mmHg, otherwise they were gradually reduced. Patients were retreated with HIFU at 4 months if IOP was >21 mmHg and there were no adverse major complications related to the initial HIFU procedure.
Follow-up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: All patients were evaluated at 1, 4, 10 days and each month until 1 year after the last treatment.

Study design issues: Prospective single-centre case series. The main efficacy outcome was based on IOP reduction at 4 and 12 months from each treatment. Complete success was defined as 'final IOP higher than 5 mmHg and less than or equal to 21 mmHg without adding hypotensive medications and without major or vision-threatening complications'.

Study population issues: 35% (14/40) of patients had primary open angle glaucoma, 8% (3/40) had chronic closed angle glaucoma, 20% (8/40) had exfoliative glaucoma, 30% (12/40) had neovascular glaucoma and 8% (3/40) had uveitic glaucoma. 43% (17/40) of patients had previous filtering surgery and 63% (25/40) had previous phacoemulsification and intraocular lens implant. The mean preoperative IOP was 32.5±9.9 mmHg.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 40

Complete success after 1 procedure=45% (18/40) (with a mean IOP reduction of 44.3% at 4 months and 45.7% at 12 months)

Mean IOP after the first HIFU procedure (n=40)
<table>
<tr><th>Follow-up</th><th>Mean IOP (mmHg)</th><th>p value</th></tr>
<tr><td>Preoperative</td><td>32.5</td><td>-</td></tr>
<tr><td>1 day</td><td>23.9</td><td><0.001</td></tr>
<tr><td>4 days</td><td>18.5</td><td><0.001</td></tr>
<tr><td>10 days</td><td>18.0</td><td><0.001</td></tr>
<tr><td>30 days</td><td>20.7</td><td><0.001</td></tr>
<tr><td>60 days</td><td>20.9</td><td><0.001</td></tr>
<tr><td>120 days</td><td>23.4</td><td><0.001</td></tr>
</table>
22 eyes did not achieve complete success and 20 were retreated with HIFU (1 patient refused a second treatment and 1 had trabeculectomy surgery).

Mean IOP after the second HIFU procedure (n=20)
<table>
<tr><th>Follow-up</th><th>Mean IOP (mmHg)</th><th>p value</th></tr>
<tr><td>Preoperative</td><td>29.6</td><td>-</td></tr>
<tr><td>1 day</td><td>25.1</td><td>Not significant</td></tr>
<tr><td>4 days</td><td>20.1</td><td><0.01</td></tr>
<tr><td>10 days</td><td>17.3</td><td><0.01</td></tr>
<tr><td>30 days</td><td>21.3</td><td><0.01</td></tr>
<tr><td>60 days</td><td>23.2</td><td><0.01</td></tr>
<tr><td>120 days</td><td>23.6</td><td><0.01</td></tr>
</table>
4 months after the second treatment, 8 eyes achieved the target IOP with a mean IOP reduction of 33.1% at 4 months and 32.4% at 12 months.

Mean IOP after the third HIFU procedure (n=12)
<table>
<tr><th>Follow-up</th><th>Mean IOP (mmHg)</th><th>p value</th></tr>
<tr><td>Preoperative</td><td>26.5</td><td>-</td></tr>
<tr><td>1 month</td><td>19.7</td><td><0.01</td></tr>
<tr><td>4 months</td><td>17.5</td><td><0.01</td></tr>
<tr><td>12 months</td><td>16.8</td><td><0.01</td></tr>
</table>
Complete success=67% (8/12) of patients treated 3 times

At 12 months, complete success=85% (34/40) of treated eyes with a maximum of 3 procedures.

The mean number of hypotensive therapy classes reduced from 3.6 at baseline to 2.4 at 12 month follow-up (p<0.01).

Mean visual acuity remained statistically significantly unchanged.
</td><td>
Intraoperative ocular complications

Pain=75% (30/40)
Subconjunctival haemorrhage=37.5% (15/40)

Postoperative ocular complications

Conjunctival hyperaemia=100% (40/40)
Superficial punctate keratitis=45% (18/40)
Subconjunctival haemorrhage=30% (12/40)
Scleral thinning=25% (10/40)
Loss of visual acuity (>2 lines)=5% (2/40) (1 caused by cataract evolution and 1 caused by glaucoma disease progression)
Corneal ulcer=5% (2/40) (treated with medication)
Corneal oedema=0% (0/40)
Choroidal detachment=0% (0/40)
Phtisis=0% (0/40)
Anterior chamber reaction=0% (0/40)

</td></tr>
<tr><td colspan="2">Abbreviations used: IOP, intraocular pressure</td></tr>
</table>

Study 7 Denis P (2015)

Details

Study type	**Case series (EyeMUST 1 study)**
Country	France
Recruitment period	2011 to 2012
Study population and number	**n=52** Patients with refractory glaucoma
Age and sex	Mean 63 years (range 37 to 89); 50% (26/52) male
Patient selection criteria	Age 18 years or older, IOP >21 mmHg under maximum medical therapy, with at least 1 failed filtering surgery. Patients included in the study had not had surgical or laser treatment within the 3 months preceding the study treatment, and no previous ciliary body interventions or drainage implants were included.
Technique	Device: EyeOP1 (Eye Tech Care, France). Two consecutive groups of patients were treated with 2 different exposure times. The patients in group 1 (n=24) were treated with a 4-second exposure time and those in group 2 (n=28) were treated with a 6-second exposure time. All procedures were done under peribulbar anaesthesia (n=38), general anaesthesia (n=7) or topical anaesthesia combined with short sedation (n=7), depending on patient and physician preference. Glaucoma medication remained unchanged for the 2 months after the procedure. After the 2-month period, adjustment of medication was allowed. Also, after 2 months, retreatment was allowed for patients with either IOP remaining above 28 mmHg despite initial treatment efficacy, or for patients who did not have a 20% decrease versus preoperative values. 44 patients had 1 procedure and 8 patients had 2 procedures.
Follow-up	**12 months**
Conflict of interest/source of funding	6 authors have been consultants for Eye Tech Care.

Analysis

Follow-up issues: Patients were followed up at 1 day, 1 week and then 1, 2, 3, 6 and 12 months. Of the 52 patients, 6 (12%) were lost to follow-up and 12 withdrew from the study. 65% (34/52) of patients completed the 1-year follow-up.

Study design issues: Prospective multicentre case series. The primary efficacy outcome was based on IOP reduction at 6 and 12 months. Surgical success was 'IOP reduction from baseline ≥20% or more and final IOP >5 mmHg without adding hypotensive medications and with possible HIFU retreatment'. If a patient needed additional treatment such as filtering surgery or cyclodestruction to lower ocular pressure, the HIFU procedure was considered to have failed.

Study population issues: 69% (36/52) of patients had primary open angle glaucoma, 6% (3/52) had uveitic, 6% (3/52) had exfoliative, 2% (1/52) had pigmentary, 2% (1/52) had traumatic, 4% (2/52) had aphakic and 12% (6/52) had other types of glaucoma. The mean number of previous glaucoma surgeries was 1.5. The mean IOP at baseline was 29.7 mmHg in group 1 and 29.0 mmHg in group 2.

Other issues: this study was also included in the meta-analysis by Denis P, 2016 (study 1).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **52**

The procedure was incomplete in 2 patients; 1 patient had chemosis, impairing the ability to deliver the planned treatment and for another patient, only 4 of the 6 planned sectors were treated.

IOP results for all patients – group 1 (n=24)

Follow-up	n	Mean ±SD IOP (mmHg)	Relative IOP reduction (%)	Number of re-treated patients	Success rate, %
Baseline	24	29.7±7.7	-	-	-
Day 1	24	23.5±9.5	20.7	-	54.2
Day 7	24	18.9±7.4	36.3	-	70.8
Month 1	24	21.8±7.7	26.4	-	66.7
Month 2	21	22.4±11.4	24.5	-	66.7
Month 3	21	22.4±8.3	24.7	1	54.5
Month 6	19	21.3±6.7	28.3	2	61.9
Month 12	17	20.1±6.7	32.2	5	57.1

IOP results for all patients – group 2 (n=28)

Follow-up	n	Mean ±SD IOP (mmHg)	Relative IOP reduction (%)	Number of re-treated patients	Success rate, %
Baseline	28	29.0±7.4	-	-	-
Day 1	28	22.4±7.1	22.8	-	64.3
Day 7	28	17.6±9.2	39.4	-	85.7
Month 1	27	20.8±10.9	28.2	-	66.7
Month 2	25	21.5±7.0	25.8	1	61.5
Month 3	24	22.5±10.0	22.4	-	68.0
Month 6	22	20.2±7.4	30.2	2	65.4
Month 12	17	18.5±6.6	36.0	3	48.0

Sub group analysis – primary open angle glaucoma (POAG)

IOP results for patients with POAG - group 1 (n=14)

Follow-up	n	Mean ±SD IOP (mmHg)	Relative IOP reduction (%)	Number of re-treated patients	Success rate, %
Baseline	14	28.0±5.0	-	-	-
Day 1	14	22.3±8.5	20.2	-	57.1
Day 7	14	17.1±5.6	38.8	-	78.6
Month 1	14	19.4±5.7	30.7	-	78.6
Month 2	13	20.7±6.2	25.9	-	69.2
Month 3	13	19.3±4.3	31.1	-	76.9
Month 6	13	20.3±5.7	27.5	1	78.6
Month 12	13	19.0±5.6	32.0	2	78.6

Safety

Ocular complications

Complication	Group 1, n=24	Group 2, n=28
Intraoperative		
Pain	1 (4.2%)	3 (10.7%)
Corneal burn	0 (0%)	0 (0%)
Subconjunctival haemorrhage	1 (4.2%)	1 (3.6%)
Postoperative		
Hyperaemia	9 (37.5%)	16 (57.1%
Superficial punctate keratitis	6 (25.0%)	11 (39.3%)
Corneal oedema	2 (8.3%)	2 (7.1%)
Ocular pain	1 (4.2%)	2 (7.1%)
Anterior chamber inflammatory reaction	6 (25.0%)	7 (25.0%)
Transient hypotony, choroidal detachment	0 (0%)	1 (3.6%)
Transient macular oedema	0 (0%)	1 (3.6%)
Phthisis	0 (0%)	0 (0%)
Cataract	0 (0%)	0 (0%)
Intravitreous haemorrhage	0 (0%)	0 (0%)
Loss of visual acuity (>2 lines)	3 (12.5%)	3 (10.7%)

The superficial punctate keratitis resolved spontaneously within a few days.

For the patient with transient hypotony, antiglaucoma drugs were tapered off, additional topical steroid treatment was given, and the event resolved within 30 days.

The transient macular oedema appeared 1 month after the procedure and resolved after 1 month with topical nonsteroidal anti-inflammatory agents. There was no impact on visual acuity.

The loss of visual acuity in 2 patients in group 1 was deemed unrelated to the study treatment (1 cataract worsened after vitrectomy for retinal detachment and 1 patient had central venous occlusion at 12 months). In group 2, 1 patient with a loss of visual acuity had corneal decompensation of his corneal graft and 1 patient presented reactivation of toxoplasmosis choroiditis 1 month after the procedure.

IOP results for patients with POAG – group 2 (n=22)

Follow-up	n	Mean ±SD IOP (mmHg)	Relative IOP reduction (%)	Number of re-treated patients	Success rate, %
Baseline	22	28.7±6.8	-	-	-
Day 1	22	22.4±7.1	22.0	-	54.5
Day 7	22	16.7±7.1	41.8	-	86.4
Month 1	21	19.6±9.1	31.7	-	68.2
Month 2	20	21.1±6.6	26.6	-	54.5
Month 3	18	21.6±10.4	24.9	-	61.9
Month 6	17	18.8±5.1	34.5	1	61.9
Month 12	13	19.0±6.0	33.9	2	45.0

There was virtually no change in glaucoma medication in either group during follow-up.

Retreatments=23.1% (12/52) (4 patients in group 1 and 8 in group 2)

9 patients had trabeculectomy, 2 had diode laser cyclodestruction, and 1 had Ahmed valve surgery. These treatments were done between 6 and 12 months after the HIFU procedure.

Mean visual acuity (best corrected visual acuity logMAR)

- Baseline=0.98±1.20 (group 1); 0.94±1.18 (group 2)
- At last follow-up=1.09±1.18 (group 1); 1.24±1.36 (group 2)

p=not significant for baseline compared with follow-up

Abbreviations used: IOP, intraocular pressure; POAG, primary open angle glaucoma

Study 8 Graber M (2018)

Details

Study type	**Non-randomised comparative study**
Country	France
Recruitment period	2013 to 2014
Study population and number	**n=86 patients (99 eyes)** (70 high-intensity focused ultrasound [HIFU] cyclocoagulation, 29 transscleral diode laser cyclophotocoagulation [cyclodiode]) Patients with refractory glaucoma
Age and sex	Mean age: HIFU=65 years, cyclodiode=64 years 59% (51/86) female
Patient selection criteria	All patients treated by cyclodestruction for the first time for refractory glaucoma. Refractory glaucoma was defined by an uncontrolled high IOP despite medical treatment and at least 1 filtering surgery. Uncontrolled high IOP was defined by an IOP≥16 mmHg. The glaucoma diagnosis was confirmed by an automated visual field testing, and peripapillary retinal nerve fibre layer scans.
Technique	HIFU was done with first-generation probes. Three devices were available with different ring diameters (11, 12 or 13 mm) and equipped with 6 piezoelectric transducers. Parameters: 21 MHz frequency, 2.45 W acoustic power, with the activation of each transducer lasting 6 seconds. The procedure was done under peribulbar anaesthesia. The cyclodiode procedure was done using the Oculight SL × 810 nm diode laser photocoagulator and the Iris G-probe (Iris Medical Instrument, US). An energy of 2.0 W was used for 2 seconds, resulting in a power delivery of 4.0 Joules per application. The procedure was done under peribulbar anaesthesia. No ciliary body tracking was used.
Follow-up	**Median follow-up was 6 months for the HIFU group and 3 months for the cyclodiode group.**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: IOP results are reported for 81% (57/70) of eyes in the HIFU group and 86% (25/29) of eyes in the cyclodiode group at 1 month follow-up. At 3 months, IOP was reported for 53% (37/70) and 66% (19/29) of eyes respectively and at 6 months, it was reported for only 40% (28/79) and 35% (10/29) of eyes.

Study design issues: Retrospective, single centre, non-randomised comparative study. Treatment success was defined if 2 conditions were met: (1) postoperative IOP between 5 mmHg and 21 mmHg and (2) IOP reduction superior or equal to 20% compared with preoperative values.

Study population issues: Mean preoperative IOP was statistically significantly higher for the cyclodiode group (34.3 ± 11.1 mmHg) compared with the HIFU group (23 ± 6.8 mmHg, p<0.0001) as well as mean preoperative BCVA (1.6 ± 1.6 LogMAR for the cyclodiode group and 0.5 ± 0.6 for the HIFU group, p<0.0001) and mean preoperative number of filtering surgery (2.3 ± 1.1 for the cyclodiode group and 1.7 ± 1.1 for the HIFU group, p=0.02).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **86 (99 eyes; 70 HIFU, 29 cyclodiode)**

Follow-up	HIFU (n=70)				Cyclodiode (n=29)			
	n	Mean IOP (mmHg±SD)	Relative IOP reduction	Success rate	n	Mean IOP	Relative IOP reduction	Success rate
Baseline		23.0±6.8				34.3±11.1		
Day 1	60	22.5±8.1	2.2		24	23.0±9.2	32.9	
Day 7	60	19.5±6.6	15.2		26	18.4±9.4	46.3	
Month 1	57	19.7±6.3	14.3	38.2	25	18.2±8.2	46.9	69.0
Month 3	37	19.2±7.9	16.5	28.3	19	17.1±10.9	50.1	61.1
Month 6	28	18.1±6.9	21.3	24.2	10	23.7±10.9	30.9	38.2
Month 9	15	19.2±8.5	16.5	20.8	3	12±5.3	65.0	
Month 12	13	19.8±8.6	13.9		2	6±0	82.5	

Absolute reduction in IOP at 1 month (mmHg)

- HIFU=3.3±7
- Cyclodiode=16.1±13, p<0.0001

Treatment success rate at last follow-up

- HIFU=25%
- Cyclodiode=52%, p=0.01

Mean estimated time to failure (Kaplan-Meier)

- HIFU=3.7 month
- Cyclodiode=5.9 months, p=0.02

Safety

Complications

	HIFU	Cyclodiode	p value
Procedure related			
Uveitis	1	1	0.30
Uveal effusion	0	1	0.502
Hypotony, phthisis bulbi (defined by postoperative IOP below 5 mm Hg)	0	4	0.006
Paradoxical hypertony	9 (13%)	3 (10%)	1.00
Loss of >2 lines (Snellen Chart)	12 (17%)	9 (31%)	0.176

Significantly more patients in the cyclodiode group had at least 1 complication related to the procedure (6 compared with 1 in the HIFU group), p=0.003.

Abbreviations used: HIFU, high-intensity focused ultrasound; IOP, intraocular pressure; sd, standard deviation

Study 9 Torky M (2019)

Details

Study type	**Case series**
Country	Kuwait
Recruitment period	2017 to 2018
Study population and number	**n=62 patients (62 eyes)** Patients with moderate to advanced primary or secondary glaucoma without previous incisional glaucoma surgery
Age and sex	Mean 64 years; 68% male
Patient selection criteria	Adult patients (>18 years) with moderate to advanced primary or secondary glaucoma without previous incisional glaucoma surgery. Patients were enrolled if they had uncontrolled IOP (defined as IOP >21 mmHg despite maximal tolerated antiglaucoma drugs) and presented with a contraindication to glaucoma invasive surgery. Only patients who completed the 12 month follow-up period were included. Patients were excluded from the study if they had normal tension glaucoma or had intraocular surgery (apart from cataract extraction) or laser treatment within the previous 3 months, or had a previous cyclodestructive procedure as well as patients diagnosed with ocular infection within the previous 2 weeks. Records of patients with glaucoma surgical intervention within 12 months after the procedure were not included in the study.
Technique	The 2nd generation probe was used (EyeOP1, Eye Tech care; France). The following parameters were used for all treatments: operating frequency, 21 MHz; number of sectors activated, 6; acoustic power, 2.45 W; duration of each shot, 8 s; and time between each shot, 20 s. All procedures were done under peribulbar anaesthesia.
Follow-up	**At least 12 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were only included if they had completed the 12 month follow-up period.

Study design issues: Retrospective, single centre case series. Key outcomes were the reduction of the IOP and success rates at the end of the follow-up period. Other outcomes were intra- or postoperative complications and visual acuity. Qualified success was defined as IOP >5 mmHg and reduction by ≥30% from baseline values with or without medication. Failure was considered whenever IOP reduction was <30% despite the use of medication or the development of any devastating complications or the need of other glaucoma surgeries.

Study population issues: Neovascular glaucoma was the most frequent diagnosis (24%) followed by primary open angle glaucoma (21%).

Key efficacy and safety findings

Efficacy

Number of patients analysed: 62 (62 eyes)

IOP reductions and qualified success, mean±SD

Follow-up period	IOP (mmHg)	IOP reduction (%)	Qualified success n (%)	p
Baseline	35.2±8.3			
Day 1	11.15±0.22	67.4±5.6	62 (100)	<0.0005
Week 1	12.05±0.23	64.5±7	62 (100)	<0.0005
Month 1	13.08±0.3	61.5±8.3	62 (100)	<0.0005
Month 3	19.05±0.43	44.2±11.5	56 (90.3)	<0.0005
Month 6	18.07±0.64	48.2±10.6	59 (95.2)	<0.0005
Month 12	20.6±8.7	42.3±16.7	48 (77.4)	<0.0005

The mean number of topical anti-glaucoma medications decreased from 3.2±0.4 before treatment to 2.1±1.02 at 12 months (p<0.0005).

Of all the types of glaucoma, eyes with neovascular glaucoma and uveitic glaucoma showed the highest failure rate (60% and 45.5% respectively) with statistically significant difference compared with other diagnoses (p<0.005).

Visual Acuity (logMAR mean BCVA)

- Baseline=0.72±0.23
- 12 month follow-up=0.73±0.26, p=0.6

Safety

There were no intraoperative complications.

Postoperative complications

- Anterior chamber reaction= 100% (62/62)
- Punctate keratitis=9.8% (6/62)
- Macular oedema=4.8% (3/62)
- Mydriasis=3.2% (2/62)

Abbreviations used: HIFU, high-intensity focused ultrasound; IOP, intraocular pressure; SD, standard deviation

Validity and generalisability of the studies

- There were no randomised controlled trials.
- The evidence includes studies from Europe, India and Asia. Results from 1 country may not be generalisable to another.
- The studies included patients with different types of glaucoma. Some studies only included patients with refractory glaucoma, some included only non-refractory glaucoma and some included a combination of refractory and non-refractory.
- The evidence included patients treated by the first and second generation of a device. Treatment parameters varied between studies.
- There was variation between the studies with regard to how antiglaucoma medications were continued or not after the procedure.
- The longest follow-up period was 1 year.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma. NICE interventional procedures guidance 612 (2018). Available from http://www.nice.org.uk/guidance/IPG612

- Ab externo canaloplasty for primary open-angle glaucoma. NICE interventional procedures guidance 591 (2017). Available from http://www.nice.org.uk/guidance/IPG591

- Trabecular stent bypass microsurgery for open-angle glaucoma. NICE interventional procedures guidance 575 (2017). Available from http://www.nice.org.uk/guidance/IPG575

- Trabeculotomy ab interno for open angle glaucoma. NICE interventional procedures guidance 397 (2011). Available from http://www.nice.org.uk/guidance/IPG397

NICE guidelines

- Glaucoma: diagnosis and management. NICE guideline 81 (2017). Available from http://www.nice.org.uk/guidance/NG81

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for high-intensity focused ultrasound for glaucoma were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE did not receive any completed submissions.

Issues for consideration by IPAC

- Ultrasound has been used for cyclodestruction since the 1980s but it was not widely adopted. Interest was recently revived with the development of a circular device with miniaturised transducers to produce high-intensity focused ultrasound. This uses a higher operating frequency than the earlier device. Older papers (pre 2000) and papers reporting outcomes with the older device that is no longer available were not included.

References

1. Denis P (2016) Clinical research of ultrasound ciliary plasty and implications for clinical practice. European Ophthalmic Review 10: 108–12
2. Deb-Joardar N, Reddy KP (2018) Application of high intensity focused ultrasound for treatment of open-angle glaucoma in Indian patients. Indian Journal of Ophthalmology 66: 517–23
3. Hu D, Tu S, Zuo C et al. (2018) Short-Term Observation of Ultrasonic Cyclocoagulation in Chinese Patients with End-Stage Refractory Glaucoma: A Retrospective Study. Journal of Ophthalmology 4950318
4. Giannaccare G, Vagge A, Gizzi C et al. (2017) High-intensity focused ultrasound treatment in patients with refractory glaucoma. Graefe's archive for clinical and experimental ophthalmology 255: 599–605
5. Giannaccare G, Vagge A, Sebastiani S et al. (2018) Ultrasound Cyclo-Plasty in Patients with Glaucoma: 1-Year Results from a Multicentre Prospective Study. Ophthalmic Research 1–6
6. De Gregorio A, Pedrotti E, Stevan G et al. (2017) Safety and efficacy of multiple cyclocoagulation of ciliary bodies by high-intensity focused ultrasound in patients with glaucoma. Graefes Archive for Clinical & Experimental Ophthalmology 255: 2429–35
7. Denis P, Aptel F, Rouland JF et al. (2015) Cyclocoagulation of the ciliary bodies by high-intensity focused ultrasound: a 12-month multicenter study. Investigative ophthalmology & visual science 56: 1089–96
8. Graber M, Rothschild PR, Khoueir Z et al. (2018) High intensity focused ultrasound cyclodestruction versus cyclodiode treatment of refractory glaucoma: A retrospective comparative study. Journal Francais d Opthalmologie 41: 611-618
9. Torky MA, Al Zafiri YA, Hagras SM et al. (2019) Safety and efficacy of ultrasound ciliary plasty as a primary intervention in glaucoma patients. International Journal of Ophthalmology 12: 597-602

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	17/05/2019	Issue 5 of 12, May 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	17/05/2019	Issue 5 of 12, May 2019
HTA database (CRD website)	17/05/2019	n/a
MEDLINE (Ovid)	17/05/2019	1946 to May 16, 2019
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	17/05/2019	1946 to May 16, 2019
EMBASE (Ovid)	17/05/2019	1974 to 2019 May 16

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Glaucoma/ (34410)
2	Glaucoma, Open-Angle/ (12586)
3	glaucom*.tw. (48776)
4	Ciliary Body/ (7986)
5	(ciliar* adj4 (body or bodies)).tw. (5391)
6	POAG.tw. (2862)
7	COAG.tw. (191)

8	OAG.tw. (1377)
9	PXF.tw. (92)
10	Ocular Hypertension/ (6124)
11	Intraocular Pressure/ (35123)
12	((ocular* or intraocul* or eye*) adj4 (hypertens* or tension or pressur*)).tw. (32413)
13	IOP.tw. (14815)
14	or/1-13 (87052)
15	High-Intensity Focused Ultrasound Ablation/ (1321)
16	(High* adj4 intens* adj4 focus* adj4 ultrasound*).tw. (2166)
17	HIFU.tw. (1657)
18	(Cyclocoagulat* or Cyclo-coagulat* or "Cyclo coagulat*").tw. (41)
19	exp Ultrasonic Therapy/ (11047)
20	Ultrasonography, intervention/ (20473)
21	Ultrasonic waves/ (1278)
22	Ultrasonic surgical procedures/ (360)
23	(Ultrasound* adj4 (Cyclo-Plast* or Cycloplast* or "Cyclo Plast*")).tw. (2)
24	(Ultrasound* adj4 (Ciliary-Plast* or Ciliaryplast* or "Ciliary Plast*")).tw. (0)
25	UCP.tw. (1798)
26	(ultrasound* adj4 coagulation*).tw. (82)
27	(Cycloablat* or Cyclo-ablat* or "Cyclo ablat*").tw. (43)
28	(Focus* adj4 ultrasound* adj4 (treatment* or therap* or surger*)).tw. (1185)
29	or/15-28 (35363)
30	14 and 29 (181)
31	EyeOP*.tw. (3)
32	"Eye Tech Care".tw. (2)
33	30 or 31 or 32 (181)
34	animals/ not humans/ (4501022)
35	33 not 34 (159)
36	limit 35 to english language (118)

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Aptel F, Charrel T, Lafon C et al. (2011). Miniaturized high-intensity focused ultrasound device in patients with glaucoma: a clinical pilot study. Investigative Ophthalmology & Visual Science 52: 8747–53	Case series n=12 FU=12 months	Ultrasonic circular cyclocoagulation using high-intensity focused ultrasound delivered by a circular miniaturised device containing six piezoceramic transducers seems to be an effective and well-tolerated method to reduce intraocular pressure in patients with refractory glaucoma.	Larger or more recent studies are included.
Aptel F, Lafon C (2012) Therapeutic applications of ultrasound in ophthalmology. International Journal of Hyperthermia 28: 405–18	Review	For the treatment of glaucoma, the specific advantage of HIFU, particularly when compared to the laser, is that the energy can be focused through optically opaque media, especially through the sclera which is a strongly light-scattering medium. HIFU is therefore a possible method for partial coagulation of the ciliary body (an anatomical structure responsible for the production of the liquid filling the eye) and, hence, reducing intraocular pressure and the risk of glaucoma.	More recent studies are included.
Aptel F, Dupuy C, Rouland JF (2014) Treatment of refractory open-angle glaucoma using ultrasonic circular cyclocoagulation: a prospective case series. Current Medical Research & Opinion 30: 1599–605	Case series n=28 FU=12 months	The procedure seems to be an effective and well tolerated method to reduce intraocular pressure in patients with primary open-angle glaucoma. Studies directly comparing the efficacy and safety of the procedure with that of trabeculectomy or diode laser are needed.	Larger or more recent studies are included. Study is included in meta-analysis by Denis P, 2016 (study 1).
Aptel F, Lafon C (2015) Treatment of glaucoma with high intensity focused ultrasound. International	Review	A commercially available device was marketed in the 1980s, but later abandoned, essentially for	More recent studies are included.

Journal of Hyperthermia 31: 292–301		technical reasons. A smaller circular device using miniaturised transducers was recently developed and proposed for clinical practice. Experimental studies have shown selective coagulation necrosis of the treated ciliary body. The first 3 clinical trials in humans have shown that this device was well tolerated and allowed a significant, predictable and sustained reduction of IOP.	
Aptel F, Denis P, Rouland J et al. (2016) Multicenter clinical trial of high-intensity focused ultrasound treatment in glaucoma patients without previous filtering surgery. Acta ophthalmologica 94: e268–77	Case series n=30 FU=12 months	Intra-ocular pressure was significantly reduced ($p<0.05$) from a mean pre-operative value of 28.2 ± 7.2 mmHg (n=3.6 hypotensive medications) to 19.6 ± 7.9 mmHg at 12 months (n=3.1 hypotensive medications and n=1.1 procedures) (mean IOP reduction of 30%). Qualified success was achieved in 63% of eyes (19/30) (mean IOP reduction of 37% in these eyes) and complete success in 47% of eyes (14/30) (mean IOP reduction of 37% in these eyes) at the last follow-up. No major intra- or post-operative complications occurred.	Larger or more recent studies are included. Study is included in meta-analysis by Denis P, 2016 (study 1).
Dastiridou AI, Katsanos A, Denis P et al. (2018) Cyclodestructive Procedures in Glaucoma: A Review of Current and Emerging Options. Advances in Therapy 35: 2103–27	Review	Confirmation of the first promising data with larger studies with adequate follow-up is needed before these modalities are more widely adopted in clinical practice.	No meta-analysis – all the studies have been included in table 2 or the appendix.
Fernandez A, Raez-Balbastre J, Elipe V et al. (2017) Canthotomy and cantholysis prior to ultrasound circular cyclocoagulation (UC3® Eye Tech Care) in refractory glaucoma. Archivos de la Sociedad Espanola de Oftalmologia 92: 382–85	Case report n=1	In complex cases of refractory glaucoma in which cyclo-destructive surgery is limited for anatomical reasons, a complementary oculoplasty technique may be a good option.	Case report of patient who needed a canthotomy and cantholysis to correctly position the ultrasound probe.
Graber M, Khoueir Z, Beauchet A et al. (2017) High intensity focused ultrasound as first line treatment in patients with chronic angle closure glaucoma at risk for malignant	Case series n=7 FU=mean 6 months	The mean IOP was reduced from 18.4+/-3.5mmHg preoperatively to 14.8+/-4.1mmHg 6 months postoperatively. The	Studies with more patients or longer follow-up are included.

glaucoma. Journal Francais d Opthalmologie 40: 264–69		average number of glaucoma medications decreased from 3.4+/-1.1 at baseline to 3.3+/-0.7. Visual acuity remained stable (median 0.17 log MAR preoperatively and 0.19 log MAR at last follow-up visit). No significant side effects occurred during the follow-up period.	
Mastropasqua R, Agnifili L, Fasanella V et al. (2016) Uveo-scleral outflow pathways after ultrasonic cyclocoagulation in refractory glaucoma: an anterior segment optical coherence tomography and in vivo confocal study. British Journal of Ophthalmology 100: 1668–75	Case series n=44 FU=1 month	Ultrasonic cyclocoagulation induced anatomical modifications of sclera and conjunctiva, which suggested that the trans-scleral aqueous humor outflow enhancement is one of the possible mechanisms exploited by ultrasound to reduce IOP.	Study focuses on imaging to investigate the modifications of the uveo-scleral outflow pathway after the procedure.
Mastropasqua R, Fasanella V, Mastropasqua A et al. (2017) High-Intensity Focused Ultrasound Circular Cyclocoagulation in Glaucoma: A Step Forward for Cyclodestruction? Journal of ophthalmology 7136275	review	To date, no comparative study between ultrasound circular cyclocoagulation and other cyclodestructive procedures has been published. Therefore, whether it represents a better solution for refractory glaucoma with respect to standardised cycloablative techniques needs to be addressed.	No meta-analysis – all the studies have been included in table 2 or the appendix.
Melamed S, Goldenfeld M, Cotlear D et al. (2015) High-intensity focused ultrasound treatment in refractory glaucoma patients: results at 1 year of prospective clinical study. European Journal of Ophthalmology 25: 483–9	Case series n=20 FU=12 months	Intraocular pressure was significantly reduced ($p<0.01$) from a mean preoperative value of 36.4 +/- 5.7 mmHg to a mean postoperative value of 22.5 +/- 10.3 mm Hg at 12 months. Four patients needed to be retreated. The mean IOP reduction achieved was 38%. Surgical success was achieved in 13 of 20 eyes (65%). No major intraoperative or postoperative complications occurred.	Larger or more recent studies are included. Study is included in meta-analysis by Denis P, 2016 (study 1).
Pellegrini M, Sebastiani S, Giannaccare G et al. (2019) Intraocular inflammation after Ultrasound Cyclo Plasty for the treatment of glaucoma. International Journal of Ophthalmology 12: 338-341	Case series n=18 Follow-up=6 months	The present study confirms existing data about the safety and efficacy of ultrasound cycloplasty, with no major complications and an IOP reduction of almost 50% at 6-month follow-up. The study showed that inflammation returned to	Small case series.

		baseline values 3 months after surgery, because of the gradual recovery of blood-aqueous barrier.	
Posarelli et al. High Intensity Focused Ultrasound (HIFU) procedure: the rise of a new non-invasive glaucoma procedure and its possible future applications. Surv Ophthalmolo 2019 May 21. doi: 10.1016/j.survophthal.2019.05.001. [Epub ahead of print]	Review	High-intensity focused ultrasound induces a selective and controlled thermal ablation of the distal part of the ciliary body, and this effect is independent from the degree of tissue pigmentation with limited damage to adjacent structures. This selective and innovative treatment decreases intraocular pressure by reducing aqueous humor production and by increasing uveoscleral outflow. The current literature on the use of high-intensity focused ultrasound in glaucoma is reviewed, exploring present use, safety, efficacy, and future clinical applications.	Review with no meta-analysis.