COMPARATIVE ANALYSIS BETWEEN EXPRESS DEVICE AND XEN GEL STENT BY IOP IN OPEN ANGLE GLAUCOMA UNCONTROLLED WITH MEDICAL TREATMENT

Faculty of Medicine

A unicentre, single-blind, randomized controlled clinical trial

FINAL DEGREE PROJECT

Author: Sara Martínez Reiríz

Clinical Tutor: Dr. Joan Tarrús de Vehí

Methodological tutor: Dr. Xavier Castells Cervello

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OFTALMOLOGIC DEPARTMENT
Hospital Universitary Josep Trueta

"La ceguera también es esto, vivír en un mundo donde se ha perdido la esperanza"

Ensayo sobre la ceguera, José Saramago.

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ABBREVIATIONS

IOP: Intraocular pressure

OAG: Open- Angle-Glaucoma

AC: Anterior Chamber

MIGS: Minimally Invasive Glaucoma Surgery

AMD: Age-Related Macular Degeneration

NTG: Normal Tension Glaucoma

POAG: Primary Open-Angle Glaucoma

PACG: Primary Angle Closure Glaucoma

ITC: Intratrabecular Contact

OHT: Ocular hypertension

GDD: Glaucoma Drainage Device

RAPD: Relative Afferent Pupillary Defect

RNFL: Retinal Nerve Fiber Layer

OCT: Optic Coherence Tomography

NRR: Neuroretinal Rim

PPA: Peripapillary Atrophy

CCT: Central Corneal Thickness

VFI: Visual Field Index

C/D: Cup/Disc

ABSTRACT

BACKGROUND

Glaucoma is a leading cause of vision loss worldwide, and intraocular pressure (IOP) is the single proven modifiable risk factor for the development and progression of glaucoma. Therefore, the basis of glaucoma treatment is the reduction of IOP. Topical and oral medications, laser trabeculoplasty, and incisional surgery are used to accomplish this goal either alone or in combination. Because of the rates of complications and failure associated with filtration surgery, new implants that attempt to lower IOP in a safer fashion are constantly being explored. Many of these new surgeries fall under the heading of MIGS, most commonly defined as minimally invasive or microinvasive glaucoma surgery. The XEN Gel Stent, which is a subtype of MIGS, uses the subconjunctival space for aqueous drainage but from a novel, ab interno approach. In contrast with traditional ExPRESS device, the XEN stent is significantly smaller and shunts aqueous to the subconjunctival space without the presence of an extraocular reservoir. There is evidence enough of its efficacy in mil-to-moderate open angle glaucoma but is necessary compare the XEN Gel stent technique with an old more patented implant like ExPRESS.

OBJECTIVE

The main purpose of this study is to compare the efficacy of XEN Gel stent versus ExPRESS device in the treatment of patients diagnosed with mild-to-moderate open angle glaucoma uncontrolled with medical treatment.

DESIGN

A randomized, single-blinded, controlled clinical trial that will be perform in the Hospital Universitari Josep Trueta within the Oftalmologic unit from September of 2018 to August of 2021.

METHODS:

110 patients with mild-to-moderate open angle glaucoma will be recruited with a consecutive method. This patients will be randomly placed in one of the two treatment groups, either Xen Gel stent or ExPRESS device. T- Student test will be used for statistical analysis of the primary objective. U- Mann Whitney test and chi-square test will analyse the secondary objectives.

KEYWORDS

Surgery, Open-angle glaucoma, ExPRESS device, XEN Gel stent, MIGS, IOP

INTRODUCTION

GLAUCOMA

GLAUCOMA DEFINITION

Glaucoma is a complex disease in which damage to the optic nerve leads to progressive, irreversible vision loss.(1) Progressive neuroretinal rim loss of the optic nerve, resulting in characteristic cupping is the structural hallmark of glaucoma. Features suggestive of glaucoma include enlargement of the central cup, focal thinning or notching of the neural rim, or hemorrhages of the optic nerve.

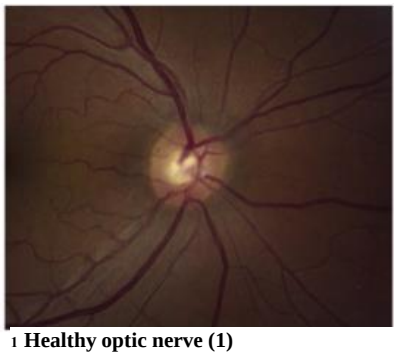
The optic nerve is the site of degenerative damage in glaucoma. Various systems to clinically denote the degree of optic nerve damage due to glaucoma have been described, including cup-to-disc ratio and disc damage likelihood scales.

The precise inciting mechanism for the cascade of cellular damage resulting in glaucomatous optic neuropathy is not clear and is likely a complex interplay of several factors, including structural susceptibility and vascular.

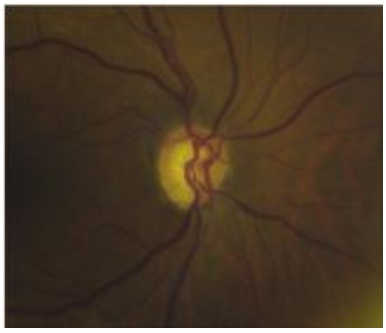
The IOP is a balance of aqueous humor production by the ciliary body and aqueous humor drainage through the internal outflow system. Elevated IOP is an important risk factor for developing glaucomatous optic neuropathy, and, furthermore, the rate at which glaucoma damage progresses is higher at greater levels of IOP. This risk factor can be modified so drugs and surgeries are focused on it.(2)

It affects 2% of the population over 40 years old and 10% of the population over 80 and 50% of glaucoma patients are not diagnosed.

Open angle glaucoma is the most frequent type of glaucoma and it is also the one we will focus on.



1 **Healthy optic nerve (1)**



2 **Glaucomatous right eye with asymetric neuroretinal rim inferiorly (1)**

EPIDEMIOLOGY

Glaucoma is a significant global health problem and the second leading cause of blindness worldwide. Worldwide, glaucoma affects 66'8 million people, 10% of whom are blind bilaterally. In the United States, more than 2 million Americans are affected, with 120,000 blind as a result, costing approximately $1.5 billion in expenses. Glaucoma is responsible for 11% of the cases of blindness and with the aging population, the incidence and burden of glaucoma are expected to rise to even more significant levels. (3)

Table 1 presents the variability in OAG prevalence by ancestry and that most studies are based on persons 40 years and older and show a marked increase in prevalence with age. The overall prevalence was 2.1% at ages 40 and older, with the highest frequencies in persons of African descent. In persons 40 years and older, studies report prevalence estimates of around 1–3% in Europe.(3)

Tabla 2 Prevalence of open-angle glaucoma and male/female comparisons by main ancestry -40+yrs; meta-analysis (3)

	Odds ratio (95% credible interval)	
Population	Prevalence-overall	Male/female prevalence
European- "white"	2.1% (1.6, 2.7)	1.5 (1.2, 1.7)
African- "black"	4.2% (3.1, 5.8)	1.3 (1.1,1.6)
Asian	1.4% (1.0, 2.0)	1.4 (1.1, 1.8)
Total	2.1% (1.7, 2.6)	1.3 (1.2, 1.5)

Rudnicka et al. IOVS 2006;47:4254–4261.

Glaucoma is the second cause of blindness in the world, mainly due to OAG, and representing 12% of global blindness. Because of the greater life expectancy of women it is consider that glaucoma affects more women than men.

Is calculated that in 2020, 80 million people will be affected by glaucoma worldwide being 74% of them OAG. Bilateral blindess will affect 8-11´2 million people.(4)

Tabla 1 Prevalence of glaucoma in Spain by communities (4)

Comunidad Autónoma	Prevalencia	Comunidad Autónoma	Prevalencia
Andalucía	3,94	**C.Valenciana**	4,18
Aragón	4,50	**Extremadura**	4,13
Asturias	2,66	**Galicia**	6,45
Baleares	2,43	**Madrid**	2,88
Canarias	3,66	**Murcia**	2,88
Cantabria	3,43	**Navarra**	5,57
Castilla y León	4,09	**País Vasco**	2,90
Castilla-La Mancha	2,94	**La Rioja**	5,40
Cataluña	3,64		

In 2008, the focus of the survey was the disability and Independence by Spanish National Stadistic Institute it showed that the first cause of blindness in Spain was firstly glaucoma, then AMD and pigmentary retinosis.

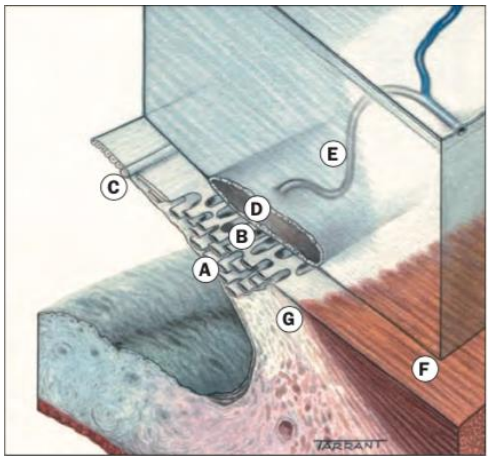
Analyzing the prevalence by communities are differences; for example, Galicia have a 6,45% of prevalence and Baleares 2,43% being Cataluña in the 9th position.(5)

ANATOMY AND PHYSIOLOGY

The aqueous humour has the function of supplying oxygen and nutrients to the avascular structures of the eye (cornea and crystalline), as well as facilitating the immune response to inflammations and infections.

AQUEOUS PRODUCTION

Aqueous humour is produced from plasma by the ciliary epithelium of the ciliary body pars plicata, using a combination of active and passive secretion. A high-protein filtrate passes out of fenestrated capillaries (ultrafiltration) into the stroma of the ciliary processes, from which active transport of solutes occurs across the dual-layered ciliary epithelium. The osmotic gradient thereby established facilitates the passive flow of water into the posterior chamber. Secretion is subject to the influence of the sympathetic nervous system, with opposing actions mediated by beta-2 receptors (increased secretion) and alpha-2 receptors (decreased secretion). (22)



2. Anatomy of outflow channels: A, uveal meshwork; B, corneoescleral meshwork; C, Schwalbe line; D, Schlemm canal; E, connector channels; F, longitudinal muscle of the ciliar body; G, scleral spur.(6)

AQUEOUS OUTFLOW

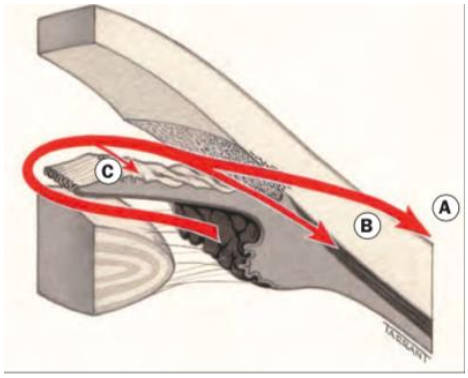
Anatomy

• The trabecular meshwork (trabeculum) is a sieve-like structure at the angle of the anterior chamber (AC) through which 90% of aqueous humour leaves the eye. It has three components: the uveal meshwork, the corneoscleral meshwork and the juxtacanalicular (cribriform) meshwork links the corneoscleral meshwork with the endothelium of the inner wall of the canal of Schlemm. It offers the major proportion of normal resistance to aqueous outflow.

• The Schlemm canal is a circumferential channel within the perilimbal sclera. The inner wall is lined by irregular spindle-shaped endothelial cells containing infoldings (giant vacuoles) that are thought to convey aqueous via the formation of transcellular pores.

Physiology and pathogenesis

Aqueous flows from the posterior chamber via the pupil into the AC, from where it exits the eye via three routes:



***3.* Routes of aqueous outflow: A, trabecular; B, uveoscleral; C, iris. (6)**

- Trabecular outflow (90%): aqueous flows through the trabeculum into the Schlemm canal and then the episcleral veins. This is a bulk flow pressure-sensitive route so that increasing IOP will increase outflow.
- Uveoscleral drainage (10%): aqueous passes across the face of the ciliary body into the suprachoroidal space, and is drained by the venous circulation in the ciliary body, choroid and sclera.
- Iris: some aqueous also drains via the iris. (6)

Retinal ganglion cell death in glaucoma occurs predominantly through apoptosis (programmed cell death). The preterminal event is calcium ion influx into the cell body and an increase in intracellular nitric oxide; glutamine metabolism is intrinsically involved. After initial injury, a cascade of events results in astrocyte and glial cell proliferation, and alterations in the extracellular matrix of the lamina cribrosa, with subsequent optic nerve head remodelling.

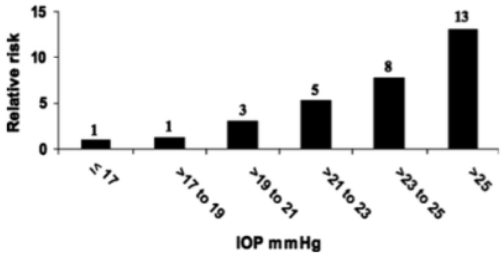
INTRAOCULAR PRESSURE IMPORTANCE AND OTHER RISK FACTORS

A. Intraocular pressure (IOP): is determined by the balance between the rate of aqueous production and its outflow, the latter in trun related to factors that include the resistance encountered in the trabeculum and the level of episcleral venous pressure.

   The average IOP in the general population is around 16 mmHg on applanation tonometry, and a range of about 11–21 mmHg – two standard deviations either side of the average – has conventionally been accepted as normal.

The IOP is a strong estabished factor, as the risk of OAG increases with increasing levels of IOP. A seen in the figure, elevated IOP is a major contributor to OAG development, with IOP levels ≥ 21mmHg increasing the 9-year relative risk to at least 5.

However, IOP has limitations as a predictor, since half of the incident cases in that study arose with baseline IOP under 21 mmHg.



***4.* 9-year incidence of Open-angle glaucoma by baseline intraocular pressure (7)**

The IOP level remains as the only major glaucoma risk factor that is known to be modifiable. For that reason, there has been long-standing interest in the potential of IOP-lowering treatment to decrease OAG risk. (7)

B. Age: Older age is associated with greater risk.

C. Central corneal thickness (CCT): The risk is greater in eyes with low CCT and lower in eyes with higher CCT. This is probably due to resultant under- and over-estimation of IOP although it has been proposed that associated structural factors, perhaps at the lamina cribrosa, might also be important

D. Cup/disc (C/D) ratio: The greater the C/D ratio the higher the risk. This may be because an optic nerve head with a large cup is structurally more vulnerable, or it may be that early damage is already present.

E. African- American race

F. Myopia

G. Diabetes

H. Family history of glaucoma: First-degree relatives of patients with POAG are at increased risk. An approximate risk to siblings is four times and to offspring twice the normal population risk, though surveyed figures vary.

CLASIFICATION OF GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA:

Is a commonly bilateral disease of adult onset. It is characterized by:

- IOP >21 mmHg at some stage.
- Glaucomatous optic nerve damage.
- An open anterior chamber angle.
- Characteristic visual field loss as damage progresses.
- Absence of signs of secondary glaucoma or a non- glaucomatous cause for the optic neuropathy.

POAG is the most prevalent type of glaucoma. POAG has been associated with at least 20 loci in the human genome, but mutations in only the MYOC gene, coding for the protein myocilin that is found in the trabecular meshwork, and the OPTN gene, which codes for optineurin, are broadly accepted as causing glaucoma.

Tabla 3 Risk factors for primary open-angle glaucoma (6)

Elevated IOP
Older age
Increased cup-to-disc ratio
Thinner central cornea
African American race
Family history

NORMAL- TENSION GLAUCOMA

Normal-tension glaucoma (NTG), also referred to as low-tension or normal-pressure glaucoma, is usually regarded as a variant of POAG. It is characterized by:

- IOP consistently equal to or less than 21 mmHg.

- Signs of optic nerve damage in a characteristic glaucomatous pattern.
- An open anterior chamber angle.
- Visual field loss as damage progresses, consistent in pattern with the nerve appearance.
- No features of secondary glaucoma or a non-glaucomatous cause for the neuropathy.

We must do a sleep study since it is related to obstructive sleep apnea

PRIMARY ANGLE- CLOSURE GLAUCOMA

The term 'angle closure' refers to occlusion of the trabecular meshwork by the peripheral iris (iridotrabecular contact – ITC), obstructing aqueous outflow. Angle closure can be primary, when it occurs in an anatomically predisposed eye, or secondary to another ocular or systemic factor. PACG may be responsible for up to half of all cases of glaucoma globally.

- ITC in three or more quadrants, with glaucomatous optic neuropathy
- Optic nerve damage from an episode of severe IOP elevation, such as acute angle closure, may not appear as typical glucomatous cupping

Tabla 4 Risk factors for angles-closure glaucoma (6)

Older age
Female gender
Asian ethnicity
Hyperopia

OTHER TYPES OF GLAUCOMA:

Are classified according to their etiology although the underlying mechanism is very similar to those mentioned above:

- Pseudoexfoliative glaucoma
- Pigment dispersion syndrome
- Neovascular glaucoma
- Inflammatory glaucoma
- Facolithic and Facomorphic Glaucoma
- Traumatic glaucoma

DIAGNOSIS OF PRIMARY OPEN-ANGLE GLAUCOMA

HISTORY

- Visual symptoms will usually be absent, unless damage is advanced.
- Previous ophthalmic history. Specific enquiry should be made about:
  - Refractive status as myopia carries an increased risk of POAG, and hypermetropia of primary angle-closure glaucoma (PACG).
  - Causes of secondary glaucoma such as ocular trauma or inflammation.
- Family history
  - POAG or related conditions such as OHT or other ocular disease in family members.
- Past medical history. Asking specifically about the following may be indicated.
  - Asthma, heart failure or block, peripheral vascular disease: contraindications to the use of beta-blockers.
  - Head injury, intracranial pathology including stroke: may cause optic atrophy or visual field defects.
  - Vasospasm: migraine and Raynaud phenomenon.
  - Diabetes, systemic hypertension and cardiovascular disease may increase the risk of POAG.
  - Oral contraceptive pill for several years may be associated with an increased risk of glaucoma.
- Current medication
  - Steroids including skin cream and inhalants.
  - Oral beta-blockers may lower IOP.
- Social history including smoking and alcohol intake, especially if toxic/nutritional optic neuropathy is suspected.
- Allergies, particularly to any drugs likely to be used in glaucoma treatment, e.g. sulfonamides.

EXAMINATION

- Visual acuity is likely to be normal except in advanced glaucoma.
- Pupils. Exclude a relative afferent pupillary defect (RAPD)
- Colour vision assessment such as Ishihara chart testing if there is any suggestion of an optic neuropathy other than glaucoma.
- Slit lamp examination. Exclude features of secondary glaucomas such as pigmentary and pseudoexfoliative.
- Tonometry prior to pachymetry, noting the time of day.
- Gonioscopy.
- Perimetry
- Optic disc examination for glaucomatous changes should always be performed with the pupils dilated, provided gonioscopy does not show critically narrow angles. Red-free light can be used to detect RNFL defects.

TREATMENTS

MEDICAL TREATMENT

There are several effective classes of topical therapies for glaucoma. A commonly used class is the topical *prostaglandin analogs*, which enhance outflow of aqueous humor. These medications are administered once daily with well-established efficacy.(1) Typical side effects with this class of medications may include increased eyelash length, potential hyperemia of the conjunctiva, potentially permanent darkening of the iris, and possible attenuation of the periorbital fat.

Beta-Blockers are another class of medication that reduces aqueous humour formation. A history of chronic obstructive pulmonary disease or asthma is clearly a relative contraindication. Furthermore, caution in patients with cardiac abnormalities/bradyarrhythmias should be used. *Carbonic anhydrase inhibitors and alfa 2-adrenergic agonists* are 2 other classes of medications that reduce aqueous formation and increase drainage, thereby, are effective for IOP lowering.

As with other common insidious chronic conditions, the effectiveness of medical therapy is limited by treatment adherence. Because of the dynamic nature of IOP fluctuation and elevation, combined with the lack of any symptomatic reminders by the silent disease itself, regular medical therapy poses a problem for many patients. Additionally, many patients may require multiple drops, which complicates dosing regimens and has a further negative impact on treatment adherence. Given that the preponderance of this disease affects the older population, there are dexterity, proprioceptive, and other issues that may limit a patient's abilities to regularly use these topical therapies.(8)

Drug class	Mechanism	Clinical use	Ocular side effects	Systemic side effects
Prostaglandin analogues –Latanoprost –Travoprost –Bimatoprost –Tafluprost	Increase aqueous humor outflow	Preferred first-line therapy (lowering of IOP by 6–7 mm Hg) Superior lowering of IOP; proof of neuroprotection pending	Blurred vision Lid changes Dry eyes Heterochromia Hypertrichosis Hyperemia	Uncommon
β-blockers –Timolol –Betaxolol –Levobunolol	Decrease aqueous humor production	Acceptable first line therapy (lowering of IOP by 5–6 mm Hg) Proof of neuropro-tection (Epstein et al. 1989)	Burning/stinging	Broncho-spasm Worsening heart failure Bradycardia Heart block Depression
α-agonists –Brimonidine	Increase aqueous humor outflow, decrease aqueous humor production	Appropriate first-line therapy (lowering of IOP by 3–4 mm Hg) Proof of neuroprotection (LoPGTS)	Hyperemia Allergic conjunctivitis	Somnolence (more common in children)
Carbonic anhydrase inhibitors –Dorzolamide –Brinzolamide	Decrease aqueous humor production	Appropriate first line therapy (lowering of IOP by 3–4 mm Hg) No proof of neuroprotection (EGPS 2005)	Burning Hyperemia Allergic conjunctivitis	Allergic reaction Angioedema (rare)

***5.* Summary of drugs used to treat glaucoma (8)**

There are no effective ways of measuring treatment adherence as well. A variety of techniques, such as patient education, reminders, videos, and medication dosing aids, have all been used to attempt to address this subject. The degree of IOP reduction for an individual patient, like any medical therapy, can vary depending on the effectiveness for that individual counterbalanced with tolerability, which in turn affects adherence. (9)

LASER THERAPY

It is a procedure that involves applying small impacts on the trabeculum. The biggest drawback is its loss of efficacy at 3-4 years and the difficulty in intervening later on these patients due to the destructuring of the mesh.

SURGICAL TREATMENT

Surgical treatment is usually required when topical medication and/or laser procedures are not tolerated and/or do not sufficiently reduce IOP. (22)

Traditionally, the gold standards for invasive surgery are trabeculectomy and implantation of a glaucoma drainage device (GDD).

- Trabeculectomy is glaucoma filtration surgery that lowers IOP by creating a fistula, protected by a superficial scleral flap, to allow aqueous outflow from the anterior chamber to the sub-Tenon space.

- Glaucoma drainage devices (GDD) it is similar to trabeculectomy and create a communication between the anterior chamber and the sub-Tenon space via a tube attached to a posteriorly explanted episcleral reservoir. Some contain pressure-sensitive valves for the regulation of aqueous flow. Reduction of IOP is due to passive, pressure-dependent flow of aqueous, limited by the wall of a tissue capsule that forms around the explant over the course of several weeks postoperatively. (6)

The Tube Versus Trabeculectomy (TVT) study reported early postoperative complications in 37% of trabeculectomy patients and 21% of tube patients, and late complications in 36% and 34%, respectively(10). The risk rate for failure during 5 years of follow-up was 46.9% in the trabeculectomy group and 29.8% in the tube group. Because of the rates of complications and failure associated with filtration surgery, new implants that attempt to lower IOP in a safer fashion are constantly being explored. Many of these new surgeries fall under the heading of MIGS, most commonly defined as minimally invasive or microinvasive glaucoma surgery.

Traditional filtration surgeries such as trabeculectomy and GDD implantation create a nonphysiologic outflow pathway by shunting aqueous into the subconjunctival space, resulting in bleb formation.

Mini glaucoma devices for external filtration may be implanted with an ab externo procedure (Ex-PRESS and In- nFocus Microshunt) or with an ab interno procedure (XEN Gel stent) (11)

- The Ex-PRESS mini glaucoma device is a miniature stainless steel implant that was developed with the intention of offering a simple and safe alternative to classic trabeculectomy. It is a minidrainage device. This is a valveless titanium MRI-compatible stent inserted under a scleral flap during a modified trabeculectomy, with a principal aim of increased standardization of drainage. (23)

- The XEN Gel Stent also uses the subconjunctival space for aqueous drainage but from a novel, ab interno approach. In contrast with traditional GDD, the XEN stent is significantly smaller and shunts aqueous to the subconjunctival space without the presence of an extraocular reservoir. (11)

JUSTIFICATION:

Glaucoma is a leading cause of vision loss in Spain and a leading cause of blindness worldwide.(12) Intraocular pressure (IOP) lowering is the only effective strategy.

Anterior filtering procedures, notwithstanding complications and failures, remain the gold standard of glaucoma surgery. However, trabeculectomy is a surgery in which we create a hole in the eye and hope that this hole will heal, albeit not too much. It is therefore not surprising that it may be affected by complications and failures. It has been investigated deeply on techniques that may surpass the efficacy and safety of the currently considered gold standard surgical approaches with the goal to achieve lower complication rates.(13)

The ExPress miniature shunt device was introduced in 2002 for the surgical treatment of glaucoma and as a modern alternative to traditional trabeculectomy. The Ex-PRESS is an FDA approved mini glaucoma device that has been developed in order to simplify anterior technic and may be implanted with an ab externo procedure. It is positioned under a scleral flap and it is introduced in the anterior chamber through a needle hole, avoiding the excision of the corneal-scleral button and the iridectomy.(14) The ExPRESS device shunts aqueous humour away from the anterior chamber through a permanently open tube (15) Like other anterior filtering guarded procedures, it may be associated with releasable sutures and with an everting suture (the safe Ex-PRESS procedure) in order to increase safety and efficacy.

In this context, the Ex-PRESS device is a useful tool in open-angle glaucoma and may avoid some intraoperative complications, such as iris prolapse or hemorrhage in the anterior chamber, which may be very disturbing during surgery and may lengthen the surgical time. Although in mild dregree, some complications still remain in this technic: hyphema, wound leakeage, bleb fibrosis, early hypotony and choroidal detachment.(16)

However, new devices are now under investigation and are highly promising for their ease of implantation, safety and efficacy.

This minimally invasive approach (MIGS) appeared as an effective alternative to glaucoma. It offers many advantages including sparing conjunctiva for future surgery and allowing for direct visualization of targeted tissues, thereby minimizing collateral tissue damage and enhancing visual outcomes. Postoperative

inflammation decrease, leading to more rapid recovery to baseline after surgery (10) and the decreases in IOP are almost equal.

A subtype of MIGS is XEN Gel stent which is an ab interno implanted soft, collagen tube that makes a permanent bypass between the anterior chamber and the subconjunctival space. It is a smart, quick, effective and simple procedure that recently gained FDA approval but there are no many data about. It has shown no induction of intraocular inflammation and nearly absent extraocular fibrotic or vascular response to the implant material, which is in stark contrast to the silicone material utilized in tube shunts. This approach is less invasive and preserves the integrity of the patient's conjunctiva which means that the patient's natural drainage pathways are intact.(17)

Similarly, the small size and high flexibility, when compared with tube shunts, provides a much more favorable force distribution to potentially reduce the risk of tissue irritation and erosion so decrease postoperative complications.(18)

Most traditional glaucoma devices essentially have zero inherent flow restriction. Techniques to limit flow include suture tension on the scleral flap (trabeculectomy and EX-PRESS) often do not prevent hypotony and it does not happen in XEN.(18) Findings might indicate that a more diffuse and controlled manner of outflow through the XEN Gel Stent could produce lower-lying and diffuse appearance blebs compared to the blebs observed after traditional trabeculectomy or an ExPRESS device (17)

The XEN Gel Stent was designed as a solution to provide several key advantages over conventional and other new glaucoma technologies:

- Minimum invasive procedure that reduces surgical risks to the patient and minimizes damage from the surgery
- Ab interno approach that eliminates incisions in the conjunctiva and the need to perform a scleral flap, therefore reducing postoperative inflammation and scarring
- Minimal damage to conjunctiva and tissues which allows multiple and repeatable implantations over the lifetime of the patient, if necessary
- Bypassing the trabecular meshwork, Schlemm's canal, and the collector channels entirely, thus eliminating the risk of reducing the efficacy of the implant due to any other outflow obstruction in the eye

- Low and diffuse outflow into intact tissue anatomy and intact drainage pathways in the conjunctiva, giving maximum efficacy pressure reduction

Another advantage of this procedure is the very simple and easy to perform surgical technique that does not requires long training, extraordinary surgical skills, or long learning curves. XEN Gel stent is easier to place for an expert surgeon so it reduces the time of the surgery and it could reduce the surgery waiting list at twice.

Due to that, it is necessary a comparative analysis of the efficacy in ExPRESS and XEN Gel stent in order to know whether the new technic is better that the older one for the treatment of glaucoma uncontrolled with medical drugs. This would allow us, offering our patients the best option in the treatment of open-angle glaucoma. Avoiding potential complications, making surgery easier and getting better results.

Another important reason for conducting the study is that ExPRESS device needs retrobulbar anaesthesic in contrast with the XEN that needs just topic anaesthesic, because it's simple technique.

Many studies claim the necessity of compare XEN Gel stent efficcy with those older techniques to introduce it in clinical practice.(13)

HYPOTHESIS

PRIMARY HYPOTHESIS:

- ◊ Patients with mild-to-moderate open-angle glaucoma uncontrolled with medical treatment have better IOP results with XEN Gel stent than with ExPRESS device.

SECONDARY HYPOTHESIS:

- ◊ Patients with mild-to-moderate open-angle glaucoma uncontrolled with medical treatment have less medication with XEN Gel stent than with ExPRESS device after surgery.
- ◊ Patients with mild-to-moderate open-angle glaucoma uncontrolled with medical treatment have better visual field with XEN Gel stent tan with ExPRESS device after surgery.

OBJECTIVES:

GENERAL:

- o This study aims to analyce the efficacy comparing XEN Gel stent technic and ExPRESS device in patients with mild-to-moderate open-angle glaucoma uncontrolled with medical treatment.

SPECIFIC:

MAIN OBJECTIVE:

- o Compare the post-surgical IOP with Goldmann tonometre in both glaucoma technics.

SECONDARY OBJECTIVES:

- o Compare the prescription of medical treatment between the two options post-surgery.
- o Compare the visual field in two option of treatment with perimetry.

MATERIAL AND METHODS

STUDY DESIGN:

The most accurate design for the study would be a prospective randomized comparative trial. We have two randomized treatment groups that compare with each other to minimise selection bias and obtain reliable results. The control group will be the patients operated by classical approach (ExPRESS device). It will be a single-blind trial because the surgeon will know the technique used to be able to perform the intervention. The oftalmologists, optometrists and statistic expert will be blinded.

POPULATION OF THE STUDY:

This study will be conducted in the Oftalmology Department at Hospital Universitario Josep Trueta, where the surgical procedure will take place. The selection and follow-up of patients will be carried out in Cap Güell. Patients diagnosed with open-angle glaucoma uncontrolled with medical treatment in Cap Güell tributaries to surgery and suitable for two types of interventions: ExPRESS and XEN Gel stent.

They must meet all of the inclusión and exclusión criteria.

INCLUSION CRITERIA:

- Age 18 or older
- Diagnosed of OAG
- Shaffer classification type III or IV superior nasal quadrant
- IOP with medical treatment ≥ 18 mmHg and ≤ 33mmHg. Measured twice with the Goldmann tonometer. It should measure 3 times if in the first two there was a difference of 3 mmHg or more. You must write the mean between the two or the three.
- Patients who use 1 to 5 medical treatments for glaucoma (active principles)
- Area of healthy and functional conjunctive in superior nasal quadrant
- Informed consent

EXCLUSION CRITERIA:

- Angle-closure glaucoma and narrow angles.(14)
- Secundary glaucoma (neovascular glaucoma, uveitic …)
- Previous fistulizing surgery / Valve in the objective quadrant
- Conjunctival damage previous to surgery or another conjunctival disease (pterygium…) in the objective quadrant.
- Active inflammation (uveitis, conjunctivitis, blepharitis….) 30 days before surgery.(14)
- Corneal surgery, corneal opacities or any other corneal disease.
- Pachymetry $\geq$ 490 microns or $\leq$ 620.
- Incisional surgery or laser, previous surgery like trabeculoplasty with laser argon, selective trabeculopasty, trabeculectomy, shunts, colagen implants or cyclodestructive procedures. Ididotomy is allowed.
- Intraocular lenses in anterior chamber
- Intraocular silicone oil
- Vitreous presence in anterior chamber. Drainage alterations of episcleritic veins (Sturge-Weber syndrome, nanophthalmos or any other evidence of high venous pressure)(4)
- Active diabetic retinopathy, proliferative retinopathy, coroidal neovascularitation or any other arterial or venous retinal occlusion.
- Allergy or hypersensitivity to implant components (porcine products or glutaraldehyde)
- Keloid formation
- Antiaggregants and anticoagulation the day of the surgery 100 mg of acetylsalicylic acid is allowed.
- Pregnant or lactant period.
- Inability to attend follow up visits

RANDOMIZATION METHODS AND MASKING TECHNIQUES:

After recruiting the patients they will be randomized in order to avoid the selection bias, assigning them to one of the two groups of intervention, A (ExPRESS device) or B (XEN Gel stent)

Before beginning the study the investigators will decided which glaucoma technique will correspond to each group and with a simple 1:1 randomization the patients will be placed in group A or B. The patients won't know in which group they fit to respect the blinding.

We must deliver two sheets of informed consent to patients (ANNEX 4 and 5), one for each intervention even if only one of them is going to be carried out since we do not know which one will be carried out.
In a trial that involves a surgical treatment is not possible to do a double-blind study and the patient will be blind in a simple-blind study.

It is important to blind the oftalmologists and optometrists who realice the follow-up of the patients after the surgery. The statistical expert who will analyse the results will also be blinded. The only specialist who knows which technique is used is the surgeon and the nurse who helps him in the operating theatre and this way the oftalmologist and the optometrist do not get influenced finding results by the approach that was performed.

SAMPLING:

SAMPLE SELECTION:

The patients will be recruited by a non-probabilistic consecutive method. When patients are diagnosed of open angle glaucoma and they do not achive a control of the IOP with medical treatment they will be potential candidates for the trial. If the patients meet all the inclusion criteria, they will receive an information sheet wich describes the study (ANNEX 2). If the patients accepts to participate in our study, we will proceed to give the informed consent form (ANNEX 3).

SAMPLE SIZE:

The size of the simple needed will be of 110 subjects to have a sample that is representative of the population of study.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test 110 subjects are needed, 55 in each group, to recognize a statistically significant difference greater or equal to 3 mmHg in IOP with a reason between the samples equal 1. The common standard deviation is assumed to be 5 mmHg. It has been anticipated a drop- out rate of 20%.

The sample size has been calculated with the GRANMO application.

ESTIMATED TIME OF RECRUITMENT

In Spain some epidemiologic studies show that over 2% of the population aged 45 and older are affected by glaucoma and every year it increases 1%.(16) . Taking into account that every year in the Hospital Universitari Josep Trueta are treated by glaucoma surgery around 100 patients in accordance with the data provided by Oftalmology department, we could estimate that we will have enought cases of OAG susceptible to surgery per year to carry out the study.

Although the sample could be recruit in a year approximately, we could extend the period of obtaining the sample until 1 year and three months anticipating patients who refuse to participate in the study.

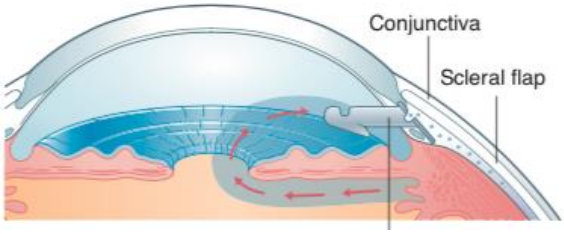
VARIABLES

INDEPENDENT VARIABLES

The independent variables of this study will be the type of surgical technique. One of the groups will be implanted the ExPRESS device and the other group will be carried out the technique using XEN Gel stent. This is considered a dichotomous qualitative variable.

THE FIRST ONE IS AN AB EXTERNO APPROACH, EXPRESS DEVICE:

The Ex-PRESS mini glaucoma device is a miniature stainless steel implant that was developed with the intention of offering a simple and safe alternative to classic trabeculectomy.(15) It is a filtration implant for glaucoma surgery, of small dimensions, which is implanted under a scleral flap in a similar manner to trabeculectomy without the need for a sclerostomy and iridectomy.(19) (24)



***6.* Ex-PRESS implant under a scleral flap (19)**

Step by step surgery:

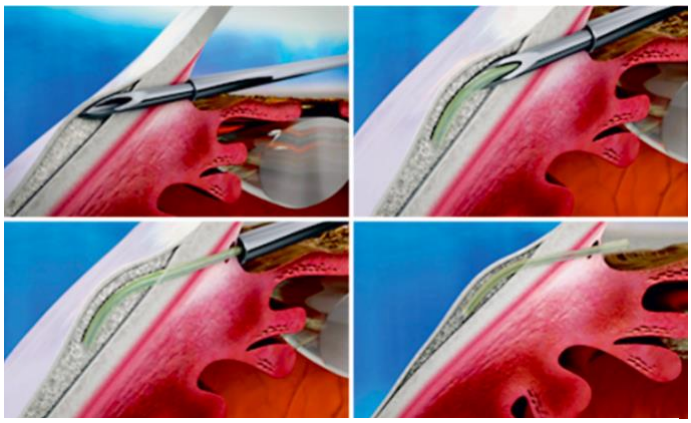
1. Dissection flap conjunctival base fornix: careful dissection of the tenon and cauterization of bleeding points.
2. Scleral flap: Dissection of the scleral flap with sclerotome until reaching the angular structures. The thickness of the flap should be 2/3 of the scleral thickness
3. Mitomycin C 2% application 2 minuts.
4. Intense washing and pre-incision with 25G needle: It is the most delicate moment of the procedure because the success of the technique will depend on it. It is in the line of transition between the scleral spur and the trabecular mesh where we will make the incision. The needle should be parallel to the iris aiming midway between the cornea and iris. Perforation with a 25 G needle, the scleral channel is narrow and is the own ExPRESS who makes the way.(20)
5. Introduction of ExPRESS device: We will place the implant that comes attached in an injector.

6. Checking the position of the implant: Using a surgical goniolens.
7. Verification of the flow: Instilling a drop of fluorescein on the scleral bed. By increasing the pressure in the anterior chamber and using the blue light of the microscope.
8. Suture of the flap with 10/0 Nylon stitches and reinsert viscoelastic.
9. Post-surgery: Drops of steroid an anthibiotic treatment.

In ANNEX 1 there are figures related to the tecnique.

THE SECOND ONE IS AN AB INTERNO APPROACH, XEN GEL STENT:

The XEN GEL Implant is a 6-mm tube of collagen-derived gelatin cross-linked with glutaraldehyde, making it permanent and non-degrading, with no foreign body reaction.(12)



***7.* The XEN Gel stent (12)**

This approach is less invasive and preserves the integrity of the patient's conjunctiva which means that the patient's natural drainage pathways are intact and the risks of fibrosis and scarring are reduced.(17)

The tube length of 6 mm was identified as the ideal length for passage ab-interno from the trabecular meshwork to the subconjunctival space at an optimal distance from the limbus. The Hagen–Poiseuille equation was then used to calculate the required internal dimensions of a tube that would prevent hypotony at average aqueous humor production. (21)

1. Intended landing zone in the superonasal quadrant of the conjunctiva is visualized and marked: after topical anesthesia, 0.05–0.2 ml MMC (0.1–0.2 mg/ml) is injected in the superonasal quadrant and massaged over the area of anticipated XEN Gel Implant insertion.
2. Corneal incisions (main and side port) are created: a conjunctival flap is made and MMC applied on sponges as in trabeculectomy. A side port and main incision are made, and viscoelastic is used to fill the AC.

3. A preloaded/single-use injector is provided to the physician, which comes individually packaged and sterile.

4. Enter main incision at peripheral cornea and direct the needle across the anterior chamber to the superonasal quadrant

5. Optional goniolens use for angle visualization: XEN Gel Implant should be placed anterior to Schlemm's canal to avoid bleeding

6. The needle is pushed to go through the sclera and into the subconjunctival space. As the needle bevel exits the sclera, an ideal 3 mm intrascleral channel is usually achieved.

7. Once the needle is out at the subconjunctival space, direct visualization of the entire needle's bevel through the surgical microscope is possible and confirms correct location

8. The XEN Gel Stent is then deployed by turning a wheel on the inserter
9. The procedure is then complete, and the surgeon simply removes this blunt sleeve from the patient's eye. The implant immediately begins shunting fluid from the anterior chamber to the subconjunctival space.

Implanting a XEN Gel Implant is a simple and short procedure which can be easily combined with phacoemulsification. (24)

In ANNEX 1 there are figures related to the tecnique.

MAIN DEPENDENT VARIABLE:

All dependent variables mesure the efficacy of the the treatments.

INTRAOCULAR PRESSURE:

According to the main objective of compare the post-surgical IOP with Goldmann tonometre in both glaucoma technics, the dependent variable are the mmHg of IOP variation between ExPRESS device and XEN Gel implant after surgery. It is a continuous quantitative variable.

The most important measure of effectiveness of the study interventions will be made after 6 months.

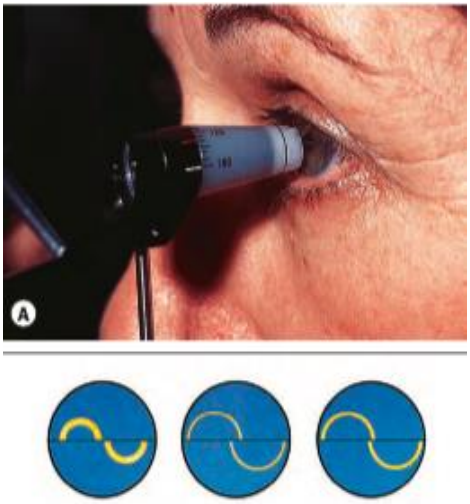
Every patient after the discharge from the hospital will have a follow-up in the first week, first month and every three months.

The IOP, which will be measured by an ofthalmologist and is going to be calculated with the gold standard method: Goldmann Applanation Tonometry.

Goldmann applanation tonometry (GAT) is based on the Imbert–Fick principle, which states that for a dry thin-walled sphere, the pressure (P) inside the sphere equals the force (F) necessary to flatten its surface divided by the area (A) of flattening (i.e. P = F/A). (6)

TECHNIQUE:

- Topical anaesthetic (commonly proxymetacaine 0.5%) and a small amount of fluorescein are instilled into the conjunctival sac.
- The patient is positioned at the slit lamp with his or her forehead firmly against the headrest and instructed to look straight ahead (often at the examiner's opposite ear) and to breathe normally.



***8.* Applanation tonometry (A) Contact between the tonometer prism and the corne; (B) fluorescein-stained semicircular mires- the diagram at right shows the correct end-point using mires of appropiate thickness (6)**

- With the cobalt blue filter in place and illumination ofmaximal intensity directed obliquely (approximately 60°) atthe prism, the prism is centred in front of the ápex of the cornea.
- The prism is advanced until it just touches the apex of the cornea
- Viewing is switched to the ocular of the slit lamp.
- A pattern of two green semicircular mires will be seen, one above and one below the horizontal midline, which represent the fluorescein-stained tear film touching the upper and lower outer halves of the prism. Mire thickness should be around 10% of the diameter of its total arc.

  Care should be taken to horizontally and vertically centre the mires so that as far as practically possible two centralized semicircles are observed.

- The dial on the tonometer is rotated to vary the applied force; the inner margins of the semicircles align when a circular area of diameter precisely 3.06 mm is flattened.
- The reading on the dial, multiplied by 10, gives the IOP; a version is available that shows IOP on a digital display.

The oftalmologists who realize the follow-up have to register the data of IOP in each patient in order to:

a) Doing the comparation with IOP before surgery (evaluating the efficacy of the technic in the same patient and patients with the same technic)
b) Comparing the IOP results of other patients with the other technic.

SECONDARY DEPENDENT VARIABLES

MEDICAL TREATMENT

The dependent variable in this study is the medical treatment after surgery of ExPRESS or XEN Gel stent that is needed to slow the progression of glaucoma. It is mesured as a discrete quantitative variable.

The more number of drugs we have to add, the less effective the surgical technique has been.

VISUAL FIELD

Visual field will be measured with Visual Field Index in the perimetry which is represented by percentages. We dichotomized the variable accepting that greater or equal to 50% is a good visual field and less or equal to 50% is a bad visual field after surgery.

COVARIATES

The covariate variables are other factors that can influence our result as they are related with our independent and dependent variables. We will include them in the multivariate anlysis in order to assess its impact in the future results.

- Gender (male or female). It is a dichotomous variable.
- Age (measured in years). It is a continuous variable.
- Race (measured in European or not). It is a dichotomous variable.
- Diabetes mellitus (yes or no). It is a dichotomous variable
- Gravity of the glaucoma disease (mild, moderate or severe). It is a discrete variable
- Apnea (yes or no). It is a dichotomous variable
- Vascular disease (yes or no). It is a dichotomous variable
- Myopia (yes or no). It is a dichotomous variable

PROCEDURES

All the professionals involved in the Oftalmologic unit have to be informed about the trial in order to fulfil the objectives. The study has a especific circuite that has to followed by all the doctors and optometrists:

VISITS:

Patients will come to Cap Güell to follow up their glaucoma and because of it, familiar history or pachymetry could be information that we previously have. We should evaluate the progression of the dissease.

- We must define what is mild-to- moderate glaucoma: optic nerve abnormalities consistent with glaucoma and glaucomatous visual field abnormalities in one hemifield, and not within 5 degrees of fixation. (25)
- Refractory: uncontrolled IOP despite medical treatment or laser.

The optometrists will realize the exploration and the tests that are explaining below but the interpretation of them is always done by the doctor, the oftalmologists:

PACHYMETRY

The measurement of corneal thickness. Corneal thickness is important because it can mask an accurate reading of eye pressure. Actual IOP may be underestimated in patients with thinner CCT, and overestimated in patients with thicker CCT.

VISUAL ACUITY

Is likely to be normal except in advanced glaucoma. It will be used a Snellen chart what is designed to be read at 6 metres.

PERIMETRY

Is the systematic measurement of visual field function. Standard automated perimetry (SAP) is the method used routinely in most clinical situations. Automated perimeters in common use include the Humphrey Field Analyser (HFA). These predominantly utilize static testing. Nerve damage in glaucoma is believed to be inflicted at the optic nerve head, and the resultant visual field defect corresponds to the pattern of fibres in the retinal area served.

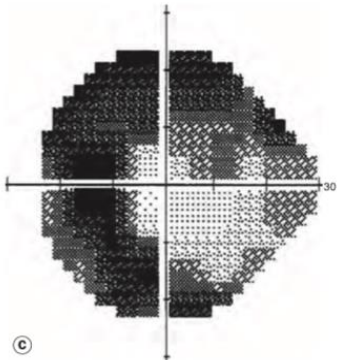
i. Early changes include increased variability of responses in areas that subsequently develop defects, and slight asymmetry between the two eyes.

ii. Small paracentral depressions can form at a relatively early stage, often superonasally.

iii. Nasal step represents a difference in sensitivity above and below the horizontal midline in the nasal field; the defect is bounded by the horizontal midline, corresponding to the retinal nerve fibre layer horizontal raphe. Inferior optic disc and OCT changes with a corresponding superior nasal step are shown in.

iv. Temporal wedge is less common than a nasal step but has similar implications.

v. Arcuate defects develop as a result of coalescence of paracentral scotomas. They typically develop between 10° and 20° of fixation as downward or upward extensions from the blind spot ('baring of the blind spot') around fixation. With time, they tend to elongate circumferentially along the distribution of arcuate nerve fibres.



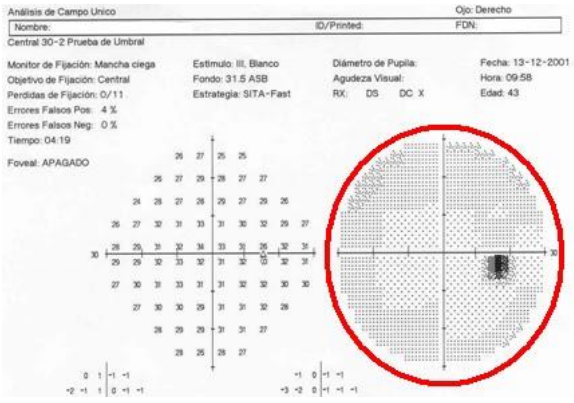
***9.* Severe glaucomatous damage (28)**

vi. A ring scotoma develops when superior and inferior arcuate defects become continuous, usually in advanced glaucoma.

vii. End-stage changes are characterized by a small island of central vision, typically accompanied by a temporal island. The 10-2 perimetry pattern facilitates monitoring of the residual central field.

viii. Summary measures should always be taken into account.

With SITA strategies, false negatives or false positives over about 15% should probably be regarded as highly significant, and with full-threshold strategies, fixation losses over 20% and false positives or negatives over 33%. In patients who consistently fail to achieve good reliability it may be useful to switch to a suprathreshold strategy or kinetic perimetry.(6)



***10.* False negatives and false positives in primetry (25)**

- *Fixation losses* indicate steadiness of gaze during the test. Methods of assessment include presentation of stimuli to the blind spot to ensure no response is recorded, and the use of a 'gaze monitor'.

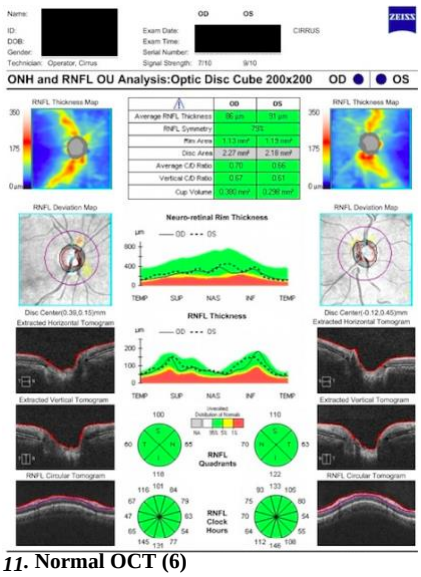
- *False positives* are usually assessed by decoupling a stimulus from its accompanying sound. If the sound alone is presented and the patient still responds, a false positive is recorded. With a high false-positive score the grey scale printout appears abnormally pale. In SITA testing, false positives are estimated based on the response time.

- *False negatives* are registered by presenting a stimulus much brighter than threshold at a location where the threshold has already been determined. If the patient fails to respond, a false negative is recorded. A high false-negative score indicates inattention, tiredness or malingering, but is occasionally an indication of disease severity rather than unreliability. The grey scale printout in individuals with high false-negative responses tends to have a clover leaf shape.

IMAGING OF THE OPTIC DISC

- OCT has become a routine part of the management of glaucoma. Sensitivity and specificity utilizing comparison with a normative database are as high as 90%.

- Peripapillary retinal nerve fibre layer (RNFL). This involves the acquisition of a circular scan of the retina around the optic nerve head. Retinal thickness is compared with normals.



11. **Normal OCT (6)**

The steps to be performed by the ophthalmologist are the following, although we must take into account that the results of the tests carried out by the optometrist will always be taken into account and thus obtain a global vision of this disease caused by multiple factors.

PUPILS.

Exclude a relative afferent pupillary defect (RAPD); if initially absent but develops later, this constitutes an indicator of substantial progression.

SLIT LAMP EXAMINATION AND TONOMETRY

Noting the time of day. The explanation of the technique is in the variable section. Sources of error:

- Inappropriate fluorescein pattern.
- Pressure on the globe
- Central corneal thickness
- Corneal oedema
- Astigmatism
- Incorrect calibration
- Wide pulse pressure
- Breath-holding

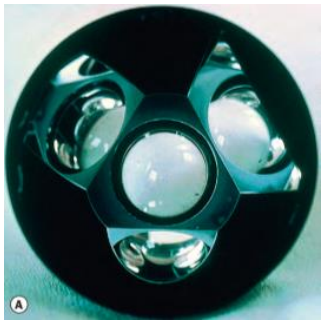
GONIOSCOPY

Is a method of evaluating the AC angle. Indirect goniolenses use a mirror to reflect rays from the angle such that they exit the goniolens at much less tan the critical angle. They provide a mirror image of the opposite angle and can be used only in conjunction with slit lamp.

TECHNIQUE:

a. It is essential that the examination takes place in a room in which the ambient illumination is very low – completely dark if possible.

b. The size and intensity of the slit beam should be reduced to the absolute minimum compatible with an adequate view, in particular avoiding any of the beam being directed through the pupil.



12. **Goldmann goniolens (15)**

c. The patient is seated at the slit lamp and advised that the lens will touch the eye but will not usually cause discomfort; the forehead must be kept against the headband and both eyes should remain open.

d. A drop of local anaesthetic is instilled.

e. A drop or two of coupling fluid is placed on the contact surface of the lens.

f. The patient is asked to look upwards and the lens is inserted rapidly so as to avoid loss of the coupling fluid. The patient then looks straight ahead.

g. Indirect gonioscopy gives an inverted view of the portion of the angle opposite the mirror.

h. Once the initial examination has been performed and the findings noted, increasing the level of illumination may help in defining the angle structures.

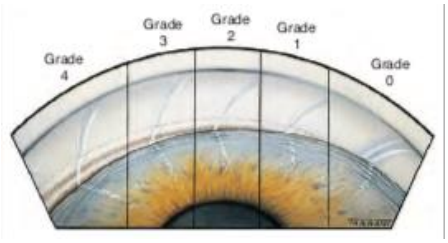
i. When the view of the angle is obscured by a convex iris, it is possible to see 'over the hill' by asking the patient to look in the direction of the mirror. Only slight movement is permissible, otherwise the structures will be distorted and a closed angle may appear open.

j. Excessive pressure with a non-indentation lens narrows the angle appearance (in contrast to the effect of pressure during indentation gonioscopy – see below). Excessive pressure also causes folds in the cornea that compromise the clarity of the view.

k. In some eyes, suction on the cornea from the lens may artificially open the angle; awareness of the need to avoid retrograde, as well as anterograde, pressure on the lens will tend to prevent inadvertent distortion.

GRADING OF ANGLE WIDTH

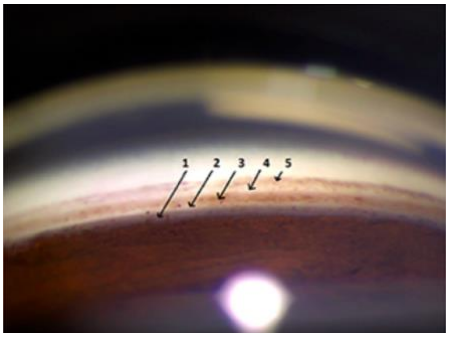
In practice, the angle is graded by many practitioners simply according to the number of structures visible, together with qualifying comments relating to the width of the iris approach.



13. **Shaffer's system of grading the angle width (6)**

SHAFFER SYSTEM

The Shaffer system records the angle in degrees between two imaginary lines tangential to the inner surface of the trabeculum and the anterior surface of the iris about one-third of the distance from its periphery. The system assigns a numerical grade to each quad- rant of the angle.



14. Grades: 5. Schwalbe's line 4. Unpigmented trabecular meshwork 3. Pigmented trabecular meshwork 2. Scleral spur 1. Ciliary body (9)

- Grade 4 (35–45°) is the widest angle, characteristic of myopia and pseudophakia; the ciliary body can be visualized without tilting the lens.
- Grade 3 (25–35°) is an open angle in which the scleral spur is visible.
- Grade 2 (20°) is an angle in which the trabeculum but not the scleral spur can be seen.
- Grade 1 (10°) is a very narrow angle in which only the Schwalbe line and perhaps the top of the trabeculum can be identified.
- Slit angle is one in which there is no obvious iridocorneal contact but no angle structures can be identified.
- Grade 0 (0°) is closed due to iridocorneal contact.
  - Indentation will distinguish appositional from synechial angle closure.

OPTIC DISC EXAMINATION

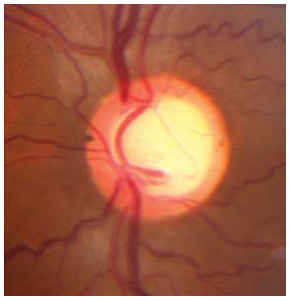
Glaucomatous changes should always be performed with the pupils dilated.

NEURORETINAL RIM

The neuroretinal rim (NRR) is the orange-pink tissue between the outer edge of the cup and the optic disc margin. The inferior rim is the broadest followed by the superior, nasal and temporal (the ‘ISNT’ rule); this has high sensitivity for glaucoma but is not very specific, i.e. eyes without glaucoma often do not respect the rule.

CUP/DISC (C/D) RATIO

The C/D ratio indicates the diameter of the cup expressed as a fraction of the diameter of the disc; the vertical rather than the horizontal ratio is generally taken. Small diameter optic discs have small cups and viceversa; only 2% of the population have a C/D ratio greater than 0.7. In any individual, asymmetry of 0.2 or more between the eyes should also be regarded with suspicion.



15. Cup-disc ratio from chronic open-angle glaucoma (6)

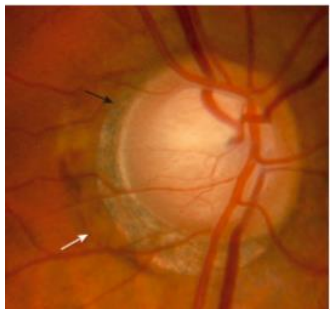
In many cases it is not possible to be certain whether an individual optic disc is glaucomatous. The clinical findings and results of investigation should be considered together to guide management. Glaucomatous damage results in characteristic signs involving (a) the optic nerve head, (b) the peripapillary area and (c) the retinal nerve fibre layer.

OPTIC NERVE HEAD

Pathological cupping is caused by an irreversible decrease in the number of nerve fibres, glial cells and blood vessels. A documented increase in cup size is always significant. If an eye with a small optic disc and correspondingly small cup develops glaucoma, the cup will increase in size, but even in the presence of substantial damage may still be smaller than that of a large physiological cup.

PERIPAPILLARY CHANGES

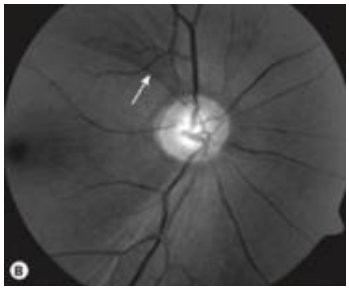
Peripapillary atrophy (PPA) surrounding the optic nerve head may be of significance in glaucoma, and may be a sign of early damage in patients with ocular hypertension.



16. **Peripapillary changes (6)**

RETINAL NERVE FIBRE LAYER

In glaucoma subtle retinal nerve fibre layer (RNFL) defects precede the development of detectable optic disc and visual field changes; their onset often follows disc haemorrhages.



***17.* Retinal nerve fibre layer defects (15)**

Two patterns occur:

(a) localized wedge-shaped defects and

(b) diffuse defects that are larger and have indistinct borders.

Defects are sometimes evident following disc haemorrhages.

After the evaluation of how the intraocular pressure and other facts that had deteriorated the optic nerve head; those people with medical treatment that does not work and the IOP is still over 21 mmHg are susceptible to surgery with ExPRESS or XEN Gel stent.

Once the patient has been identified as eligible to participate in the study by meeting all the criteria, the details of the study will be explained, the information sheet (ANNEX 2) for participants will be given and all questions will be resolved. If the patient voluntarily agrees to participate in the study, informed consent must be signed (ANNEX 3). It is important that the patients understand they will not know which technique is used to maintain the simple-blind study so they should sing two informed consent, one for each technic (ANNEX 4 and ANNEX 5)

ANAESTHESIOLOGY VISIT:

Before the surgical procedure the patients must have a visit with the anaesthesiologist who will decided if the patient can be operated and which is the operatory risk classifying he or she into the different stages of the ASA (American Society of Anaesthesiology) classification. Depending of the patient's age:

- < 40 years: Blood test and coagulability
- > 40 years: Blood test and radiography
- < 50 years: Blood test, radiography and electrocardiogram
- < 60 years: Blood test, radiography, electrocardiogram and ionogram

SURGERY:

The day of the intervention the surgeon team will receive a closed envelope with the technique that must be performed in the patient placing randomly the patient into one of the two groups of treatment. Antibiotic prophylaxis will be givem to the patient with gentamicin and vancomycin. Also paracetamol and fentanilo intravenous. During the surgery, a nurse will help the doctor and record the operation time.

FOLLOW-UP:

After the discharge we will visit the patients the week post surgery, the month after and each 3 months until the year. To evaluate the efficacy of the devices.

The most important mesure of the IOP will be done at 6 months after surgery in order to know the efficacy of the technics and compare.

Controls will be made in the Oftalmologic service of the Cap Güell in which the patient was diagnosed and proposed for surgery. During the visits, the same tests that had been done prior to the surgery will be carried out. In all the controls a exploration of visual acuity, slit-lamp, tonometry, gonioscopy, optic nerve head examination and perimetry. Just each 3 months we will evaluated OTC to have more control of the disease.

We should evaluated each test by separated but doing a global overview and completing the results sheet. (ANNEX 6)

We have to take into account that maybe some of the patients included in the study do not complet the follow up each 3 months because the loss of visual acuity is not perceivable and it does not produce pain.

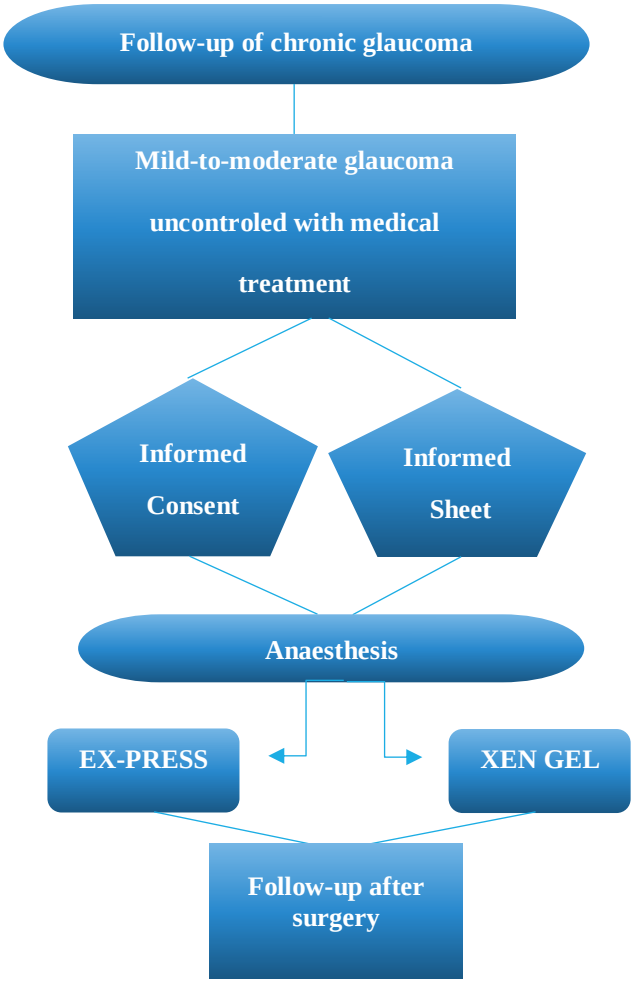
Although the results will be published at 1 year of follow-up, follow- up will be carried out year by year if the surgery success.

Tabla 5 Visit schedule and methods during all the trial

	week							
	-2	0	1	4	12	24	36	48
Informed consent	x							
Information sheet	x							
Pachymetry	x*							
Perimetry	x		x	x	x	x	x	x
OCT	x			x	x	x	x	x
Tonometry	x		x	x	x	x	x	x
Gonioscopy	x		x	x	x	x	x	x
Slit lamp	x		x	x	x	x	x	x
Anaesthesiology		x						
Surgery		x						

x* = if it is not previously done

Tabla 6 Flow chart of the patient



STATISTICAL ANALYSIS

The statistical analysis will be executed using Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, NY, US). An intention-to-treat analysis will be performed. The imputation of missing values for endpoints variables will be accomplished using the latest observed values for each variable and subject.

UNIVARIATE ANALYSIS

The result of our qualitative variables will be expressed as proportions (percentage). A table of frequencies and a bar chart will be used to represent the qualitative variables.

For the quantitative variables, they will be expressed as a mean +/- standard deviation (SD) in case of continous variables (i.e. normally distributed). For discrete variables (i.e non-normally distributed), median and interquartile ranges will be used. To represent them, we will use a bar chart for the discrete variables and a histogram for the continuous ones.

BIVARIATE ANALYSIS

Different test will be used in order to find if there is association between the independent and dependent variables. Since our independent variable is a dichotomous qualitative variable (ExPRESS device or XEN Gel Stent) the tests that will be used to analyse the association with the dependent variable will be:

- ◊ Student's t-test when the dependent variable is quantitative with a normal distribution (i.e. continuous varible). If it is not possible to assume a normal distribution because of an asymmetrical distribution of the variable in both surgical technics (i.e.discrete variables), Mann-Whitney U test will be used. It is the case of the main dependent variable: intraocular pressure (IOP).
- ◊ Mann- Whitney U test will be used in a discrete quantitative variables which is our secundary dependent variable: the number os medical treatment after surgery.
- ◊ Chi- square (x^2) test if the dependent variable is qualitative. It is the case of the visual field that is mesured as a dichotomous qualitative variable.

MULTIVARIATE ANALYSIS

Although randomization controls the presence of confounding, multivariate analysiswill be carry out, to adjust our variables for co-variables, thus we will control for potential confounding. In particular, we eill estimate a linear regression (for IOP, a continuous variable, as dependent variable), a Poisson regression (for number of drugs, a discrete variable, as dependent variable) and a logistic regression (for visual field, a dichotomous variable, as dependent variable). In the three regressions we will include the independent variable (the type of surgical technique, ExPRESS devide and XEN Gel stent) and we will adjust for the covariables.

ETHICAL ASPECTS

This study will involve humans and must respect the principles of the Helsinki Declaration and have to be approved by the Clinical Research Ethical Committee (CEIC) of the Hospital Universitari Josep Trueta. This Committee will analyse the trial and the ethical aspects to be sure they are respected. Furthermore if the CEIC give additional indication will be respected. In addition to the CEIC, the management of the centre have to approve the trial too.

The protocol must follow the Spanish law 14/2007 of 3rd of July about Biomedical Investigation involving invasive procedures. Moreover, the privacy of the participants and the personal information have to be protected according to the Spanish law 15/1999 of the 13th of December about data protection, confidentially and protection of personal data.

This clinical trial should be designed in accordance with the biomedical research law 14/2007 of July 3 for invasive procedures.

All the principles of bioethics will be respected. First of all, the patients will be informed about the interventions and the procedures of the study providing them an information document. All the questions will be answered and the potential participants will agree to participate voluntarily. To express the accordance and the understanding they will have to sign the informed consent. This way the autonomy principle will be respected. Secondly, to respect the beneficence and non-maleficence principles, the study have an exclusion criteria to do not perform a surgical treatment to a patient that the risk-benefit relation is prejudicial. Finally, all the patients will receive the same conditions and will be equally treated and respect the justice principle. To achieve this principle every participant will remain anonymous and randomly placed to one of the different groups without any differences.

It would be registered in EudraCT and will have contracta and insurance for the participants.

STRENGTHS AND LIMITATIONS

In our study there are some limitations that should be considered:

- In first place, the main limitation is the impossibility of a double-blind. The fact that the trial studies surgical procedures makes impossible to blind the surgeon who performs the intervention. This means the surgical team will know in which group is placed every patient and a detection bias can be done. To overcome this limitation the surgeon and the nurse will be the only professionals involved in the study who will know it; the optometrists, the oftalmologists and the statistician will be blinded. With this option in the follow-up tests and in the study of the results the professionals will not be influenced by which surgical technique was used.

- The second bias can be related in the recruitment of the sample. The consecutive method is a non-probabilistic and there is the risk of not obtain the most representative population. Trying to minimize this potential selection bias, very extensive inclusion criteria have been set to have a very similar sample to the reference population. With the exclusion criteria we try to reduce the confusing factors. But one of the strengths of the trial is the randomization to distribute the pation into the two groups that allowa the extrapolation of the results.

- This study will be unicentric. Dealing with surgical treatments the human factor is really relevant. In our case, only one surgeon will carry out both types of interventions because the sample and the time in which the study will be carried out is acceptable. This surgeon-dependent factor reduces the external validity of the study but we must highlight the years of experience in both techniques of the surgeon that makes both the ExPRESS and the new XEN technique comparable in terms of learning curve.

- Another limitation are losses in the duration of the study that are important in our case. We will try to correct the attrition bias by statistics (we predict a 20% of losses) and we must analyze the results by intention to treat. For those patients who do not follow all the follow-ups, we will collect the last measurements for the analysis (last observation carried for).

WORK PLAN

This intervention study will be conducted along 3-year period that will run from 2019 to the moment of the publishment and the dissemination. All the activities carried out during this period of time will be organized in five phases which are detailed bellow.

It will be led by a main investigator, Sara Martínez Reiríz, who at the moment of designing this project is a medical student cursing his last year and advised by Dr. Joan Tarrús de Vehi, associate doctor of the oftalmologic service of the University Hospital Trueta. Both are the leading investigators responsible for the study design and submission to the Clinical Research Ethics Committee, as well as the data analysis and publication of results.

The collaboration of a computer technician is required for the design and development of a database and a software to analyze it in a fast and comfortable way. An external human resources company will be required too in order to select the adequate infirmary professionals for data collection.

1- PREPARATION AND COORDINATION PHASE (3 MONTHS).

This first phase of the study will consist in the elaboration of the protocol from September 2019 to November 2019. After the approval we will review the protocol and present it to the CEIC of Hospital Universitari Josep Trueta. Once the CEIC agrees the main researcher will meet all the researchers, including oftalmologists, optometrists, anesthesiologist, statistics and every person that have a roll in the study to explain the aims of the trial. Methods and design will be explained and discussed and the instructions required will be given. The clinical research associated will coordinate and explain the patients' recruitment and organize a meeting every 6 months in order to control and asses the progression of the study.

2 - FIELD WORK

- SAMPLE RECRUITMENT (15 MONTHS):

The patients that comply with the criteria to be part of the study will be recruited by a consecutive method and randomly placed in one of the two groups of treatment. Since we need 110 patients and in the Hospital Univeritari Josep Trueta the surgeons operate 100 patients per year the sample recruitment will last 1 year

and 3 months. Athough we can obtain the simple before, we have supposed that not every people who can include in the study want to participate.

- INTERVENTION (15 MONTHS):

Due to the consecutive recruitment of the patients the sample recruitment and the intervention period will coincide in time.

- FOLLOW-UP (12 MONTHS):

The follow-up for each patient is a year. The follow-up of all the patients have to start after surgical intervention of the first patient and finish 12 months after the last patient operated. This way the follow-up will coincide with the time of recruitment and intervention.

3 – DATA COLLECTION (27 MONTHS)

In this study the data collection will start with the sample recruitment and it will last untill the last day of the follow-up. This is because from the first patient we have to collect the data, also during the surgery, and the data from the follow-up.

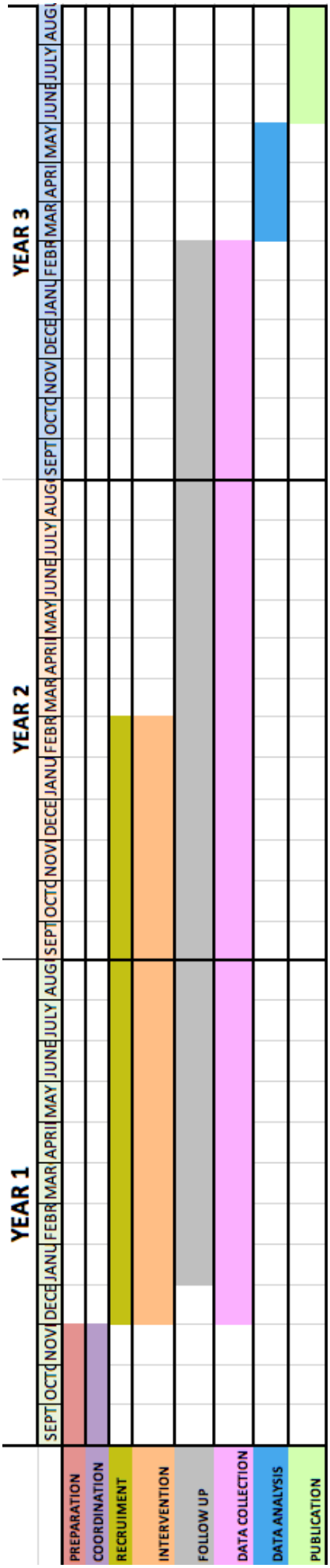
4 – DATA ANALYSIS AND INTERPRETATION (3 MONTHS)

After all the medical procedures and follow-up, the data will be analysed and the results will be materialized in the final article.

5- PUBLICATION AND DISSEMINATION (3 MONTHS)

When the study is finished and the article is written, the researches will publish the scientific paper and will inscribe it to a different congress to expand the trial results.

Tabla 7 Chronogram



FEASIBILITY

The trial will take place exclusively in the Hospital Josep Trueta de Girona. The hospital will provide everything that is necessary to carry out the study. The two devices that will be implanted to carry out the study are used today in the hospital and there is enough material for the sample that we have established.

The operating room costs and the involved surgeon and medical staff salaries will be covered by the hospital. The posterior procedures such as the oftalmologists and optometrists during the follow-up will be also provided by the health system.

The surgeon who has been choosen from the Oftalmologic unit is used to perform both of the techniques, thing that allows to ensure the reliability and quality of the surgeries. The department just needs to meet to explain and optimise the performance of the study and make consensus.

Using the same circuit that patients use in the everyday makes the study really feasible, avoiding problems with organization or payments.

BUDGET

For the realization of this study we will need an inversión of 44,265 €

The cost of the surgical intervention with the implant devices and necessary material, the anaesthesist and all the tests that we need for the follow-up are include in our National Health System (NHS). A patient diagnosed with open-angle glaucoma uncontrolled with medical treatment is operated and followed up the same way that we propose in our study. Some of the tests that we carry out commonly during the follow-up in our research will make them serve more frequently, so they have been added to the budget.

The two different surgical techniques are currently performed in the Hospital Universitario Josep Trueta consequently does not represent an additional cost.

In the everyday clinical practice patients are visited one week after surgery and every three months. In our study we will add a visit a month after the surgery that costs 52€, in which will be carried out the same tests as the every three months clinical practice.

As we are working with invasive procedures is necessary to contract an insurance for the patients, with a total os 11.000 euros.

It will be necessary a statistical expert for the randomization of the patients and to analyse the results. We will hire he or her for an estimate number of 140 hours with a salary of 25 euros/hour, that means a cost of 3,500 euros.

A part from the statistical analyses we also need a clinical research associated who will be responsible of the data monitoring and control, give assessment and coordinate the medical staff involved and the patients. This will mean 12,500€ for 500 hours in a salary of 25€ per hour.

After the study an important part is the publication and the dissemination. For the publication in national and international journals we have assigned 3000€. In the dissemination including two congresses, one in a national level and the other one in a international level with the travel and the food also computed, means a total of 3800€.

	Price	Quantity	Total
STAFF AND SERVICES			
Statistical expert	25 €/h	140h	3.500€
Clinical research associated	25 €/h	500h	12500€
Meetings	70 €	1	70€
Insurance	100 €	110	11.000€
MATERIAL AND FOLLOW-UP			
Prints	1€	110	110€
Added visit	52€	110	5720€
TCO	45€	110	4950€
Perimetry	41€	110	4510€
Drops	15€	55	825€
PUBLICATION AND DISSEMINATION			
Publication expenses	3000€	1	3000€
Inscription to national congress	300€	1	300€
Inscription to international congress	500€	1	500€
Travel accommodation and food	1500€	2	3000€

TOTAL = 49,985 €

IMPACT

The main objective of the study is to increase the knowledge of both surgical techniques, specially the XEN Gel stent, and compare the level of effectiveness between the two techniques taking into account important variables for the progression of the disease and also considering the simplicity and complications of one and the other.

Glaucoma is a very prevalent disease in our environment and its importance lies in a progressive delimitation of the visual field to remain totally blind if the only variable that we can control today to stop the progress is not controlled.

So it is important to detect significant reductions in intraocular pressure, considering the simplicity of the process to avoid complications.

If posible we would like to establish a relation between the principal objective and the second one getting to know the connection between the techniques used: which one achieve better IOP results and booster medications.

In recent years techniques have been modified to slow the progression of glaucoma, trying to do minimally invasive surgeries that produce less fibrotic tissue in the eye and reduce the complications derived from the process.

If the results obtained are relevant and validate the hypothesis, for our population of study, we will be confident to implement the XEN Gel stent as a main approach to perform the future surgeries to slow the progression of the open-angle glaucoma. (26)

In addition, important complications derived from more aggressive operations such as the ExPRESS technique compared to the new XEN technique would disappear. Regarding the community of surgeons, the benefits would be remarkable since both the process of implementing the XEN and the time of surgery will be reduced so that could decreased hospital waiting lists. (28) (29)

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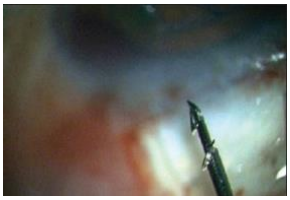
ANNEXES

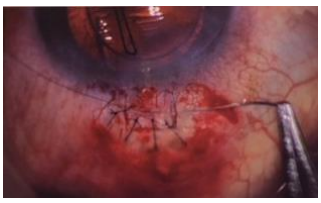
ANNEX 1

STEPS OF EXPRESS DEVICE:

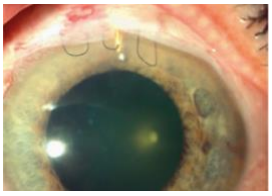


18. ExPRESS device (14)

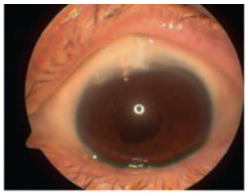
19. Scleral flap (15)



20. Suturas (15)

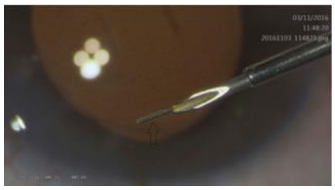


22. Vision of ExPRESS device (14)

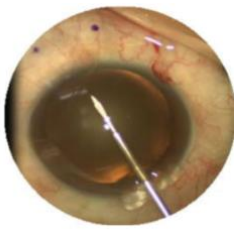


21. Bleb created (19)

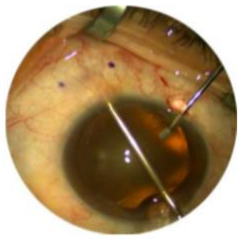
STEPS OF XEN GEL STENT:



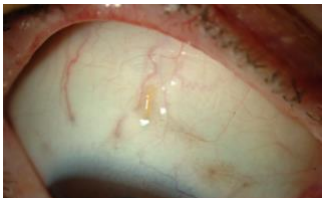
23. XEN Gel implant in the injector (24)



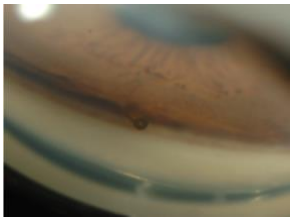
24. Needle in AC (17)



25. Xen Gel deployed in position (17)



26. Subconjuctival vision of XEN (18)



27. Image of the implant in the gonioscope (24)

ANNEX 2

HOJA DE INFORMACIÓN AL PACIENTE

TÍTULO DEL ESTUDIO: COMPARATIVE ANALYSIS BETWEEN EXPRESS DEVICE AND XEN GEL STENT BY IOP IN OPEN ANGLE GLAUCOMA UNCONTROLLED WITH MEDICAL TREATMENT

"Análisis comparativo entre la válvula ExPRESS y el stent XEN mediante la medición de la presión introcular en pacientes con glaucoma de angulo abierto no controlado con tratamiento médico"

PROPÓSITO Y OBJETIVO DEL ESTUDIO:

Su médico le invita a participar en el estudio clínico coordinado por el Hospital Universitari Josep Trueta, ya que cumple los requisitos necesarios. Este estudio consiste en la comparación de dos técnicas quirúrgicas para frenar el avance del glaucoma.

Esta intervención consiste en crear un lugar de paso artificial para el humor acuoso reduciendo así, la presión intraocular. Existen variaciones de la técnica quirúrgica estardard para reducir las posibles complicaciones y disminuír la dificultad de la intervención.

Este estudio pretende comparar dos técnicas: una técnica clásica y una técnica de cirugía minimamente invasiva mas reciente. La diferencia entre las técnicas consiste tanto en la manera como se aborda la zona anatómica como las características del propio dispositivo de implantación. En los estudios realizados hasta el momento, los resultados del nuevo dispositivo parecen a priori comparables con otras técnicas mas patentadas en cuanto a eficacia. Es necesaria la realización de este estudio para confirmar la hipótesis que se plantea.

La manera en la que se llevará a cabo el estudio es haciendo dos grupos de pacientes de características similares y hacer una técnica a cada grupo. A todos los participantes se les tratará por igual, con un estudio preoperatorio y un seguimiento igual con la única diferencia de la técnica quirúrgica.

PROCEDIMIENTOS DEL ESTUDIO

Se realizará un estudio preoperatorio estándard para determinar que se puede realizar la intervención.

En el momento de la cirugía se decidirá de forma aleatoria, con un 50% de posibilidades de recibir cada técnica, a qué grupo formará parte.

El seguimiento de la intervención se llevará a cabo a la semana de la intervención y cada 3 meses hasta año; en la que se le realizarán el mismo tipo de pruebas que habían realizado en el seguimiento del glaucoma.

INCONVENIENTES Y BENEFICIOS

Si se confirma la hipótesis del estudio, los pacientes a los que se le realice la técnica con el XEN Gel stent podrían tener mejores resultados en cuanto al control de la presión intraocular y otras variables de eficacia y menos complicaciones derivadas. En estudios realizados hasta el momento se han observado menos complicaciones en este grupo respecto al procedimiento clásico.

PARTICIPACIÓN

Su participación es totalmete voluntaria. Si decide no participar su atención médica no se verá influenciada a ninún nivel.

Si desea abandonar el estudio, en cualquier momento, es libre de hacerlo sin dar explicaciones y sin que esto afecte a su tratamiento normal o a la calidad de los cuidados que recibirá.

Su médico también podrá retirarlo del estudio en cualquier momento. Esta situación se podría dar si usted experimenta uns complicaión grave e imprevista, si experimenta cambios en su situación clínica o si no cumple con el plan establecido por el estudio.

Se le mantendrá informado de cualquier nueva información disponible o que pueda afectar a su decisión.

Este estudio ha sido analizado y aprobado por el Comité de Ético de Invertigación del Hospital Universitari Josep Trueta, que ha dictaminado que es ético y que con los resultados publicados hasta el momento en ningún momento se le puede perjudicar, ni a usted ni a su salud.

ANNEX 3

FORMULARIO DE CONSENTIMIENTO INFORMADO DE PARTICIPACIÓN AL ESTUDIO

DEL PACIENTE

CONSENTIMIENTO ESCRITO

TÍTULO DEL ESTUDIO: COMPARATIVE ANALYSIS BETWEEN EXPRESS DEVICE AND XEN GEL STENT BY IOP IN OPEN-ANGLE GLAUCOMA UNCONTROLLED WITH MEDICAL TREATMENT

"Análisis comparativo entre la válvula ExPRESS y el stent XEN mediante la medición de la presión introcular en pacientes con glaucoma de angulo abierto no controlado con tratamiento médico"

Yo,_____, con DNI _____:

He hablado con el Dr/ Dra _____

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio y se han repuesto de manera satisfactoria.
- He recibido suficiente información sobre el estudio.

Comprendo que mi participación es voluntaria

Comprendo que puedo retirarme del estudio:

- En cualquier momento.
- Sin dar explicaciones.
- Sin repercusiones en mi asistencia médica.

En consecuencia, doy libremente mi consentimiento para entrar en este estudio:

Firma del partipitante	Firma Investigador/médico
Data: __/__/_____	Data:__/__/_____

ANNEX 4

DOCMUMENTO DE CONSENTIMIENTO INFORMADO SOBRE LA TÉCNICA EXPRESS DEL GLAUCOMA DE ÁNGULO ABIERTO

Yo,_____con el diagnóstico de *glaucoma de ángulo abierto moderado no controlado con tratamiento médico*

DECLARO:

Que el Dr/ Dra_____ me ha explicado que es conveniente proceder a una cirugía de glaucoma.

1. Con este procedimiento se presentende hacer una via de paso artificial al humor acurso causante de la subida de presión intraocular, evitando las complicaciones derivadas de esta. En caso de que se pudiesen producir implicarían una intervención urgente.

2. El doctor o doctora me ha advertido que el procedimiento requiere administración de anestesia y que si fuese necesario se procedería al empleo de sangre o hemoderivados, con el riesgo que esto comporta.

3. Cabe la posibilidad de que durante la cirugía se realicen modificaiones del procedimiento debido a problemas intraoperatorios para proporcionar el tratamiento más adecuado.

4. Comprendo que, aun que la técnica se lleve a cabo de forma correcta, se pueden presentar efectos indeseados: tanto los comunes derivados de toda la intervención quirúrgica y que pueden afectar a otros órganos, como los específicos de este procedimiento. Estos pueden ser poco graves y frecuentes como el sangrado postquirugico controlable o muy graves y poco frecuentes como infecciones graves.

5. También se me ha indicado la necesidad de informar sobre mis alergias medicamentosas, alteraciones de la coagulación, enfermedades cardiopulmonares, existencia de prótesis o marcapasos, medicación actual o cualquier otra circunstacia médica.

6. La realizacion del procedimiento puede ser gravado con fines científicos o didácticos respetando la confidencialidad de acuerdo con la normativa vigente.

7. El doctor o doctora me ha explicado que es una cirugía destinada a frenar el avance de la enfermedad y no se espera una mejoría de la agudeza visual y perimetría ya perdida, si no no agrabarla.

   Comprendo las explicaciones que se me han facilitado en lenguage claro y sencillo y se me ha permitido realizar todas las preguntas y obervaciones. Todas las dudas han sido solucionadas.

   También comprendo que, en cualquier momento y sin necesidad de ninguna explicación, puedo revocar el consentimiento que estoy dando.

   Manifiesto que estoy satisfecho con la información recibida, que comprendo la intervención y los riesgos que comporta y en tales condiciones:

   DOY EL CONSENTIMIENTO a que se me realice la intervención en el Hospital Universitari Josep Trueta de Girona.

FIRMA DEL MÉDICO

FIRMA DEL PACIENTE

DNI:

ANNEX 5

DOCMUMENTO DE CONSENTIMIENTO INFORMADO SOBRE LA TÉCNICA XEN GEL STENT DEL GLAUCOMA DE ÁNGULO ABIERTO

Yo,_____con el diagnóstico de *glaucoma de ángulo abierto moderado no controlado con tratamiento médico*

DECLARO:

Que el Dr/ Dra_____ me ha explicado que es conveniente proceder a una cirugía de glaucoma.

1. Con este procedimiento se presentende hacer una via de paso artificial al humor acurso causante de la subida de presión intraocular, evitando las complicaciones derivadas de esta. En caso de que se pudiesen producir implicarían una intervención urgente.

2. El doctor o doctora me ha advertido que el procedimiento requiere administración de anestesia y que si fuese necesario se procedería al empleo de sangre o hemoderivados, con el riesgo que esto comporta.

3. Cabe la posibilidad de que durante la cirugía se realicen modificaiones del procedimiento debido a problemas intraoperatorios para proporcionar el tratamiento más adecuado.

4. Comprendo que, aun que la técnica se lleve a cabo de forma correcta, se pueden presentar efectos indeseados: tanto los comunes derivados de toda la intervención quirúrgica y que pueden afectar a otros órganos, como los específicos de este procedimiento. Estos pueden ser poco graves y frecuentes como el sangrado postquirugico controlable o muy graves y poco frecuentes como infecciones graves.

5. También se me ha indicado la necesidad de informar sobre mis alergias medicamentosas, alteraciones de la coagulación, enfermedades cardiopulmonares, existencia de prótesis o marcapasos, medicación actual o cualquier otra circunstacia médica.

6. La realizacion del procedimiento puede ser gravado con fines científicos o didácticos respetando la confidencialidad de acuerdo con la normativa vigente.

7. El doctor o doctora me ha explicado que es una cirugía destinada a frenar el avance de la enfermedad y no se espera una mejoría de la agudeza visual y perimetría ya perdida, si no no agrabarla.

   Comprendo las explicaciones que se me han facilitado en lenguage claro y sencillo y se me ha permitido realizar todas las preguntas y obervaciones. Todas las dudas han sido solucionadas.

   También comprendo que, en cualquier momento y sin necesidad de ninguna explicación, puedo revocar el consentimiento que estoy dando.

   Manifiesto que estoy satisfecho con la información recibida, que comprendo la intervención y los riesgos que comporta y en tales condiciones:

   DOY EL CONSENTIMIENTO a que se me realice la intervención en el Hospital Universitari Josep Trueta de Girona.

FIRMA MÉDICO

FIRMA PACIENTE

DNI:

ANNEX 6

HOJA DE RECOGIDA DE DATOS

DATOS GENERALES

- **Médico responsable**_____
- **Número Sobre de aleatorización**: ☐
- **Género**: Hombre ☐
  Mujer ☐
- **Fecha de Nacimiento**: ____/___/_____

ANTECEDENTES PERSONALES

- **Age**: _____
- **Historia Familiar**: SI ☐
  NO ☐
- **Race**:_____
- **IMC(kg/m^2)**: _____
- **Gravedad del Glaucoma**: BAJO ☐
  MEDIO ☐
  ALTO ☐

- **Apnea**: SI ☐

  NO ☐

- **Hábitos tóxicos**: Enolismo ☐

  Tabaco ☐

  Otras _____

- **Diabetes Mellitus**: SI ☐

  NO ☐

- **Miopía**: SI ☐

  NO ☐

EVOLUCIÓN POSTOPERATORIA

- **Grosor Corneal**:_____
- **PIO Goldmann**:_____
- **Visual Field Index**: ≥ 50% ☐

  ≤ 50% ☐

- **OCT**:

  Average RNFL Thickness: ☐

  RNFL Symmetry: ☐

Disc area: ☐

Average C/D Ratio: ☐

Vertical C/D Ratio: ☐

- **Número de tratamientos de rescate**:

1. ◯
2. ◯
3. ◯
4. ◯