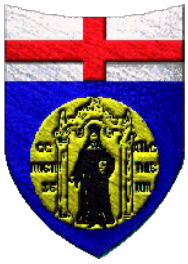

**Università degli Studi di Genova**

**Dottorato di Ricerca in**

**Biotecnologie in Medicina Traslazionale**

**CICLO XXXIII**

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# XEN gel stent for the treatment of open-angle glaucoma: real-world effectiveness and safety

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# Introduction

The term glaucoma refers to a broad group of diseases causing characteristic optic nerve damage and related visual field loss that can worse until irreversible blindness, if not adequately treated.[1,2] Glaucoma is considered a leading cause of blindness worldwide and is estimated that the number of patients will increase from 76 million in 2020 to 112 million in 2040.[2,3] Our concepts of glaucoma are continuously evolving as the understanding of the pathological processes advance, the technological diagnostic performance and the therapeutic approach become more precise, efficient and effective.[4–6] In recent years imaging technology has evolved the most, permitting accurate and precise measurement of the individual layer of the retinal tissue. Thanks to optical coherence tomography (OCT), the thickness of each layer of a large area of the retina can be recorded non-invasively in a matter of seconds and compared to a dataset of healthy subjects and to previous scans to identify changes over time.[7,8]

On the one hand, early diagnosis of glaucoma is essential to slow down the pathological process promptly and to preserve the visual field.[9] On the other hand, as clinicians, we should evaluate new technology critically keeping in mind that all these advantages are ultimately for the benefit of individual patients. For instance, when early diagnosis became over-diagnosis, it could have a negative impact on the patient' quality of life (QoL) because of physical, emotional and financial harm.[10]

Even if translational research has identified many genes, risk factors and pathological mechanism associated with glaucoma, lowering the intraocular pressure is the only treatment available for glaucoma.[11,12] Elevated IOP does not define glaucoma but has been strongly associated with the development and progression of glaucomatous damage and is currently the only modifiable risk factor.[13]

Generally, IOP is lowered with the aim of topical drugs and/or laser, and this approach is effective in the majority of glaucoma patients. When these approaches fail to maintain IOP below a value that is judged safe for the treated eye, surgical procedures are considered.

The gold standard for the surgical management of glaucoma is trabeculectomy that was described first by Cairns in 1968.[14] The operation of trabeculectomy aims to create a permanent drainage outflow channel for aqueous humor, connecting the anterior chamber to the sub-Tenon/sub-conjunctival space. Over the last five decades, the procedure slowly evolved, and minor changes to the original technique were described to enhance the functioning of the filtering bleb and to reduce the rate of complications.[15]

In the last 5-10 years, alternative surgical approaches have been introduced to offer a more predictable IOP drop and a safer profile compared to trabeculectomy with faster recovery time.[16,17]

Among new surgical procedure, the XEN gel stent implantation offers sub-conjunctival filtration by the implantation of a flexible 6mm tube with a small internal diameter of 45um. In 2016 the XEN procedure was introduced in the clinical practice and since then has partially replaced trabeculectomy because of less invasiveness and more standardization of the surgical steps.[18]

Innovations may occur faster than we can evaluate them critically. In the case of new surgical approaches for glaucoma, the long-term IOP-lowering effect of the procedure is a co-primary outcome along with the impact on the patient's QoL and with the cost-effectiveness.[19–21] QoL may be influenced not only by the maintaining of the visual field but also by visual recovery after surgery, spectacle independence, number of post-operative visits.[19] When a new surgical approach is introduced, it is also essential to identify the group of patients or the phenotype of the disease that could benefit more and the group of patients that is at more risk of complications. In the present work we have prospectively collected data on XEN implantations performed at our site with the aim to assess the efficacy and safety of the procedure. We explored demographic, peri-operative and ocular factors that permitted to IOP in a generally accepted therapeutic range 6-16mmHg without the need of additional IOP-lowering medications or additional surgeries. Proper patient's selection is the first step to achieve the best results from a new therapy or surgical procedure in terms of efficacy. When considering a new surgical intervention is also essential to focus on the safety profile. A new surgical procedure could be slightly less effective than a previous one and have an improved safety profile. In this case, the new surgical approach might be preferred to the previous one.[22] Conversely, it may be associated with previously unknown complications that are reported during post-marketing studies. The second and third part of the thesis aimed to analyse two observed complications in terms of frequency, predisposing factors and clinical outcomes: the damage of the implant and choroidal detachment. The evaluation could become even more complicated when the advantages in terms of efficacy and safety are not well established, and the cost for the patients and the healthcare system are taken into considerations. Another section of the present work aimed to compare XEN procedure to trabeculectomy in terms of clinical success, post-operative management and complications.

## The XEN Gel Stent

XEN Gel Stent is a hydrophilic tube made of porcine gelatin cross-linked with glutaraldehyde to ensure its permanence in the tissues. This material is used for a wide variety of applications in the medical field due to its high biocompatibility that does not cause foreign body reaction (Figure 1). [23–25]

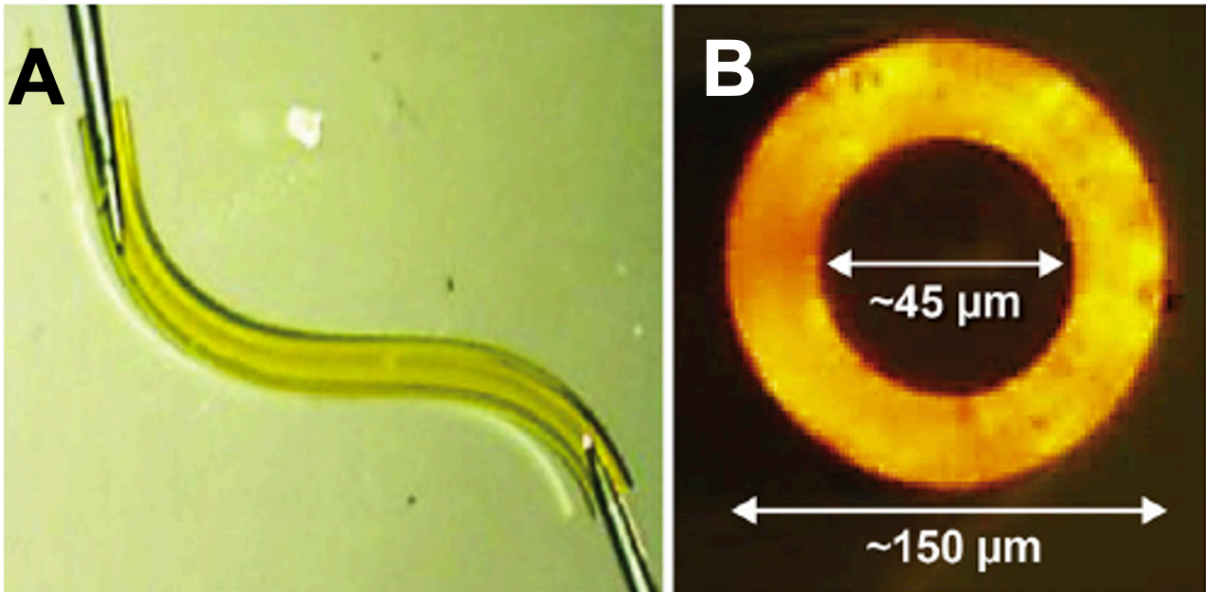


**Figure 1.** A. Longitudinal view of the XEN implant. B. Axial view of the XEN implant with the internal lumen of 45µm. Adapted from Grover et al.[26]

The implant becomes soft when hydrated, adapting perfectly to the shape of the tissue, thus avoiding possible migration and potential erosion. It has been shown that the stent is about one hundred times more flexible than the silicone tube used in traditional glaucoma drainage implant surgery. The XEN is housed in a single use preloaded inserter designed specifically for an ab interno surgical implantation [23–26].

The stent reduces intraocular pressure by creating a permanent outflow path from the anterior chamber to the sub-conjunctival space through a 2-4 mm scleral canal. The first implants proposed by Aquesys Inc. (Aliso Viejo, CA, USA) were of 3 different diameters (45, 63 and 140 µm) for different levels of IOP control. The smallest, $XEN_{45}$, the only one currently available, has an internal diameter of 45 µm, an external diameter of 150 µm, and is 6 mm long.

It was designed on the basis of the principles of laminar fluid dynamics (Hagen-Poiseuille equation) to avoid early postoperative hypotony, as demonstrated by a recent experimental study. Indeed, the aqueous humor turnover rate is estimated to be 1.0% -1.5% of the anterior chamber volume per minute, which is 2.4 ± 0.6 µL / min (mean ± SD, daytime measurements in adults aged 20 to 83 years) and $XEN_{45}$ provides 1.2 µL / min flow (at 5 mmHg pressure gradient), providing ~ 9 mmHg of flow resistance, which ultimately reduces the risk of postoperative hypotony.[24]

**Surgical technique**

Lewis first described the surgical procedure[1], which has been further reviewed by other authors. The procedure can be performed under local or topical anesthesia. Mitomycin C (MMC) is generally used at a concentration of 0.1-0.2 mg / mL (absolute dose of 10-20 µg). MMC is injected with a 30-gauge needle into the sub-conjunctival space of the supero-temporal quadrant. This induces hydro-expansion, which reduces the resistance of the tissues, preparing the space for the implant and supporting the formation of the flittering bleb. Blood vessels should be avoided during needle insertion, as bleeding can impair the visibility required for stent implantation.

Standard cataract surgery can be performed after this phase using miotic drugs after implantation of the intraocular lens (IOL) and accurate removal of the viscoelastic substance. We proceed by marking the planned positioning area in the supra-nasal quadrant, which is about 3 mm from the limbus; viscoelastic cohesive viscoelastic is injected and an infero-temporal paracentesis and the preloaded injector is inserted into the anterior chamber (27 gauge) aiming at the anterior chamber angle. The tip of the needle advance into the sclera and emerges into the sub-conjunctival space about 3.0 mm posterior to the limbus. Once the tip of the needle is visible in the sub-conjunctival space, it is rotated 90° and the stent is gently released.

Ideal stent placement should leave 2.0 mm of implant exposed in the sub-conjunctival space (preferably in a more superficial layer than the sub-tenon space), 1.0 mm in the anterior chamber (Figure 2,3), and 3.0 mm intrascleral.

The use of a gonioscopic lens during the placement could help to avoid trauma to the iris root however it is not always necessary and is used at the surgeon's discretion. The viscoelastic substance then is removed, allowing the implant, if correctly positioned, to begin sub-conjunctival filtration. All corneal incisions are finally sutured or hydrosealed.

Antibiotic drug prophylaxis is generally continued for the first two weeks and is combined with a topical corticosteroid q.i.d. for one month and then slowly taper over the following months [27,28].

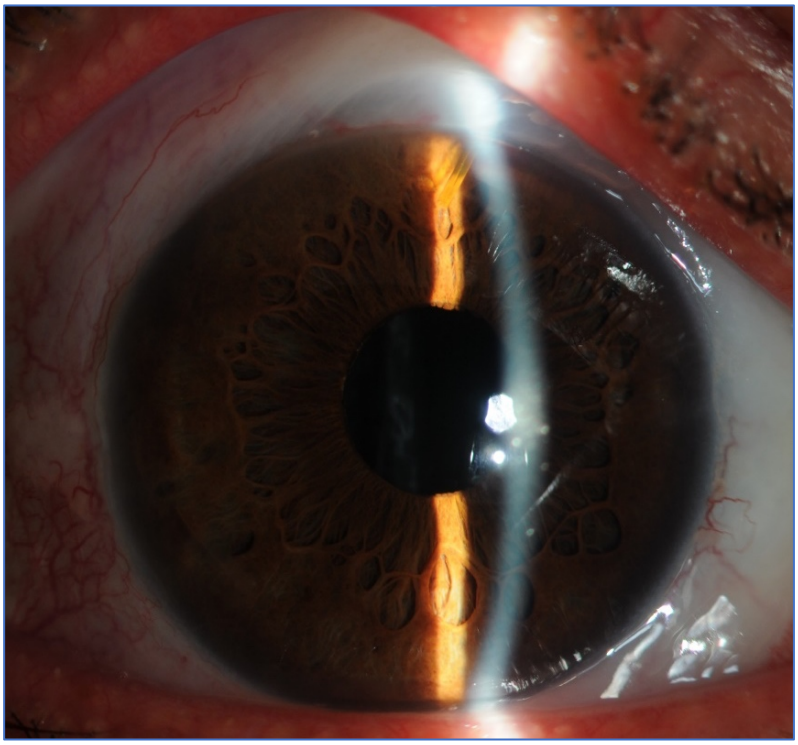

**Figure 2.** XEN visible in the anterior chamber at 12 o'clock.

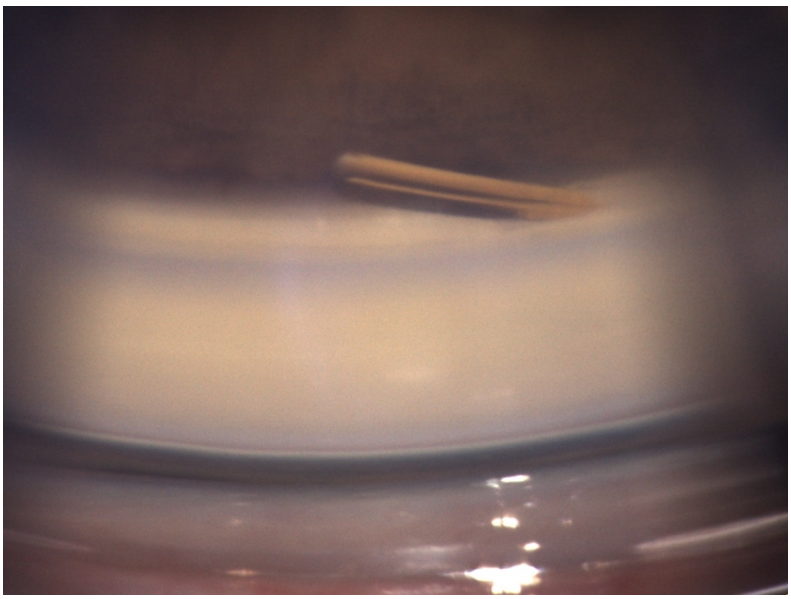

**Figure 3.** Gonioscopic view of the XEN implant

## Indications for XEN gel implant

The indications differ slightly in Europe and in the United States. In Europe, the XEN gel stent is generally used to reduce IOP in patients with primary open angle glaucoma (POAG), pseudoexfoliative glaucoma (PXFG) and pigmentary glaucoma (PG) eyes in whom medical therapy is not tolerated or is not sufficient to achieve the target pressure.

In the United States, it is also used in the management of refractory glaucoma, including cases in which previous surgical treatment had failed, cases of POAG, and PXFG or PG that do not respond to maximum tolerated medical therapy.

The XEN gel stent is generally contraindicated in the following settings or conditions: closed-angle glaucoma (gonioscopically, posterior trabecular meshwork should be visible as iris occlusion of the XEN lumen may be present in narrow angles; narrow angles can be implanted provided that the extraction of the lens has actually opened the iridocorneal angle and increased the depth of the anterior chamber); previous glaucoma surgeries with presence of conjunctival scars, previous conjunctival surgery or other conjunctival pathologies; active intraocular inflammation; neovascular glaucoma; anterior chamber IOL; presence of intraocular silicone oil; vitreous in the anterior chamber; impaired episcleral venous drainage (for example, Sturge-Weber or nanophthalmos or other causes of high venous pressure); known or suspected allergy or sensitivity to drugs required for the surgical procedure or any of the device components (e.g. glutaraldehyde).

## Previous clinical studies

Several preclinical studies were conducted using animal models and demonstrated that glutaraldehyde cross-linked porcine gelatin did not induce intraocular inflammation or significant tissue reaction, undergoing no structural changes or degradation after 1 year of follow-up.[25]

Lewis described a case in which a misplaced implant during surgery was removed 6 months after surgery and subsequently analyzed. No tissue growth was observed outside or inside the device and no signs of fibrosis were reported around the implant.[23]

In the first human clinical study, the implantation of 2 XEN gel stent models (XEN140 and XEN63) was performed in 37 eyes with OAG (although it is not specified how many XEN140 and XEN63 were implanted) combined with the cataract surgery and without intraoperative

use of MMC. Twelve months after surgery, mean IOP was significantly reduced to 15.4 ± 3.0 mmHg from 22.4 ± 4.2 mmHg before surgery (mean IOP reduction of 32.25%), with a statistically significant reduction of IOP-lowering drugs (from 2.5 ± 1.4 to 0.9 ± 1.0; 50% of patients without therapy). During the study, the authors reported no major complications; the postoperative needling rate (with MMC or 5-fluorouracil) was 32%, although the same authors suspected this rate would be lower if the procedure was performed with MMC at the time of implantation.[27]

Sheybani et al published further results of a prospective, non-randomized, multicenter cohort study of XEN140 standalone implant without intraoperative MMC in 49 eyes with refractory OAG.[28] Interestingly, 71% (35 out of 49 eyes) of the treated eyes had undergone previous procedures / surgeries: 21 eyes had undergone a previous MMC trabeculectomy, 2 eyes had undergone previous surgery with drainage implants, 3 eyes they had undergone trans-scleral cyclo-photocoagulation, and 9 eyes had been treated with laser trabeculoplasty. Only 45 eyes completed 12 months of follow-up (3 patients subsequently underwent further surgery for glaucoma), with a mean IOP reduction of 36.4% from baseline and a decrease in the number of drugs by 3, 0 to 1.3 (42% of patients were sine therapy). No serious adverse events were reported in this study, although 9% of patients were treated with viscoelastic substance injection (OVD) in the first postoperative week for athalamia associated with transient postoperative hypotony. None of the patients developed choroid detachment, chronic hypotony, or hypotony maculopathy during the study period. About 43% of patients underwent needling, a higher percentage than in current trabeculectomy studies. However, the authors speculated that, considering that more than 50% of patients had already undergone surgical procedures with conjunctival incision, the success of the device would have been greater and / or the needling rate would have been lower if the implantation of the device had been associated with intraoperative MMC injection.

Pérez-Torregrosa et al. and De Gregorio et al. published the first 2 prospective clinical studies of XEN45 gel stent implantation with adjuvant MMC combined with cataract surgery.[29,30] The first study was conducted on 30 eyes diagnosed with OAG and mild / moderate cataract, demonstrating a reduction in IOP of 29.3% at 12 months with a decrease of 94.6% of the drugs used (from 3.07 ± 0.69 to 0.17 ± 0.65). Both intra- and post-operative complications were relatively minor, often associated with the surgical maneuvers and resolved spontaneously.

In fact, a critical point reported by the authors is the final stent placement, stressing that the best solution would be 2 mm sub-conjunctival to avoid extrusion, 3 mm intra-scleral to increase resistance to reduce excessive drainage, and 1 mm in AC to limit contact with the corneal

endothelium. This prompted the study authors to reposition 6 implants and reimplant in one case. No needling was performed during follow-up and the authors reported only one case of failed bleb after 5 months of follow-up, that required to restart IOP-lowering drugs.[29] In the second study published by De Gregorio et al., XEN45 was implanted in 41 eyes with OAG in combination with cataract surgery. The results of this study indicate that the XEN45 implant is statistically effective in reducing IOP and drugs even after 12 months, with a reduction in IOP of 41.82% and 80.4% of patients without drugs. Only one patient had undergone a previous deep sclerectomy. No complications were found during all cataract surgeries and in the implant with the exception of small transient subconjunctival and / or anterior chamber haemorrhages. No patient needed postoperative refill of the anterior chamber probably due to the smaller internal diameter of the stent than those implanted in the early studies. All patients completed 12 months of follow-up, excluding 1 patient who underwent a trabeculectomy after 1 month due to stent failure due to presumed obstruction. This study reported only 1 case of bleb fibrosis that required needling (2.4%).

An international multi-centre retrospective study was recently published comparing the efficacy, safety and risk factors for XEN45 gel stent implant failure versus trabeculectomy, both with the addition of MMC.[31]

In this study, 354 eyes with uncontrolled glaucoma and without previous incisional filtering procedures underwent XEN (n = 185) or trabeculectomy (n = 169) in 4 tertiary centres. The results showed no difference in efficacy, risk of failure and safety profile between the two procedures. The most important risk factor associated with the failure of filter surgery was the presence of diabetes for both types of surgery. Black patients had statistically higher failure rates for trabeculectomy, but not for XEN implanted eyes. Eyes with preoperative visual acuity better than 0.4 logMAR showed significantly better results with XEN surgery, while those with poorer vision had good results with trabeculectomy; eyes with preoperative IOP greater than 21 mmHg had better results with the XEN, while those with IOP less than 21 mmHg had better results with trabeculectomy. A quarter of the eyes treated with XEN and a third of the eyes operated by trabeculectomy were again treated with IOP-lowering drugs in the last post-operative follow-up visit; in the trabeculectomy group 49.7% of patients had undergone laser suture lysis in the post-operative period and more needlings were recorded in the XEN group (43.2%). The trabeculectomy group had more complications albeit mostly transient, although there were no cases of long-term complications from hypotony in either group.

Despite the large sample size, multicentre design, and long follow-up (30 months) which allows for reasonable external generalizability, the authors stressed that the study has several

limitations. This was a retrospective study, with significant patient losses at follow-up, which may have either overestimated or underestimated the success rate.

The prospective multicentre study published by Grover et al. reported 12-month performance / safety results of the XEN45 implant after MMC pre-treatment in 65 eyes with refractory glaucoma.[26]

In an analysis that excluded patients with missing data (n = 4) and those requiring secondary glaucoma-related surgery (n = 9), the mean change in IOP from baseline was 27% across all postoperative visits. reaching -9. 1 mmHg (35.6% reduction in IOP) at 12 months. Compared to baseline, 36 (69.2%) patients required fewer topical medications, 16 (30.8%) required the same number, and no patient required more medications than preoperative (or oral medications). Overall, mean drug use decreased from 3.5 at baseline (n = 65) to 1.7 at 12 months; in the previously specified subgroup analysis (n = 52), 38.5% of patients did not require any postoperative medication; reported intraoperative complications and post-operative adverse events were mostly mild / moderate and transient, resolving without sequelae.

The most commonly reported postoperative complication in this study was fibrosis of the filtering bleb. The surgical technique used in this study differed from that previously reported for subconjunctival pre-treatment with MMC. The target area was treated with soaked sponges (0.2 mg / mL) for 2 minutes, assuming a conjunctival incisional approach. According to the authors, the conjunctival incision required for the application of MMC may have induced more scar formation causing an increased rate of needling (32.3%).

Although subconjunctival MMC injection is used on a large scale in XEN implant surgery, the procedure is not approved by the Food and Drug Administration in the United States.

In a further prospective study recently published by Galal et al. POAG patients were implanted with XEN45 with 0.01% subconjunctival MMC.[32] Of these eyes, 3 were pseudophakic and 10 underwent simultaneous phaco-emulsification and XEN implantation. At the end of the 12-month follow-up, patients showed a mean IOP reduction of 29.4% (from 16 ± 4 mmHg pre-operative to 12 ± 3 mmHg, p = 0.01) with a decrease 94.57% of the number of drugs (from 1.9 ± 1 in the pre-operative period to 0.3 ± 0.49, p = 0.003); 42% of the eyes had achieved complete success, defined as a 20% reduction in IOP without the use of drugs, and 66% qualified success, defined as a 20% reduction in IOP with hypotonic drugs. Complications observed were 2 cases of transient hypotony with choroidal detachment which resolved with medical therapy only, a single implant extrusion which required repositioning by conjunctival sutures, and 2 cases required surgery, trabeculectomy, due to of an uncontrolled IOP. The needling rate reported in this study was 30.7%. Post-operative adverse events reported in these studies were mostly mild

/ moderate and transient but a case of suprachoroidal haemorrhage 2 days after implantation of XEN45 was reported by Prokosch-Willing et al. [33]

## Predictors of surgical success after XEN implantation

The objective of glaucoma surgeries is to reduce IOP to prevent further glaucomatous optic nerve damage.[1] Since its introduction in 1968, trabeculectomy rapidly became the gold standard for the surgical treatment of glaucoma.[14,34] In more than 50 years, the technique underwent many advances and modifications.[15,35–37] The use of antimetabolites and the optimization of the postoperative bleb management increased the long-term efficacy.[38–43] Retrospective and observational studies also shed some light on the patient's characteristics and perioperative measures associated with the success of trabeculectomy.[44–47] Based on previous studies, factor such as low early postoperative intraocular pressure (IOP) were associated with the long-term success of trabeculectomy.[44,47] Conversely, increased preoperative exposure to ophthalmic solutions preserved with benzalkonium chloride or African descent were associated with higher failure.[48,49] Even if all these factors cannot wholly explain the prognosis and the long-term outcome of trabeculectomy, the identification of predictors of success may help the clinician to inform the patient correctly and to propose the best tailored surgical approach. Surgical procedures for glaucoma also comprise glaucoma drainage devices that are designed to divert aqueous from the anterior chamber to a retroequatorial external reservoirs; they are typically indicated for refractory glaucomas.[50] Besides, several surgical approaches generally named minimally invasive glaucoma surgical are aimed to enhance conventional or unconventional aqueous outflow. The former group of procedure is less effective than bleb-forming techniques and is generally preferred for mild glaucomas.[17] Among bleb-forming procedures, the XEN gel is a device designed to be permanently implanted and recently introduced in the clinical practice. Similar to trabeculectomy, the XEN's IOP-lowering effect is due to drainage of the humor aqueous into the episcleral space resulting in a bleb formation. The XEN gel is a 6 mm tube implanted ab-interno without requiring conjunctival incision. IOP lowering is theoretically determined by its physical dimension. To the best of our knowledge, no studies have been conducted to investigate the demographic, ocular and perioperative variables associated with the clinical outcome of the XEN procedure. The aim of this study is to identify the variables associated with the success of the XEN procedure.

## Methods

This study was part of a prospective, uncontrolled, consecutive case series involving eyes that underwent the XEN standalone procedure or combined with phacoemulsification at the Clinica Oculistica, DiNOGMI, Ospedale Policlinico San Martino IRCCS, University of Genoa. The study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. We included eyes with the diagnosis of primary open-angle glaucoma (POAG) or exfoliative glaucoma (XFG). We excluded eyes with diagnosis of other types of open-angle glaucoma, angle-closure glaucoma or history of peripheral iris iridotomy or previous ocular surgeries other than uncomplicated phacoemulsification performed more than 6 months before the study enrollment. Patients with a follow-up of <12 months were also excluded. Previous laser trabeculoplasty was not considered an exclusion criterion. For all the patients, demographic, ocular, operative and perioperative factors were recorded. Namely, glaucoma type, type of procedure (standalone or combined), type of anesthesia (peribulbar or topical), surgical duration, preoperative and post-operative IOP, number of IOP lowering drugs, postoperative bleb care (number of needlings and antimetabolites subconjunctival injections), visual acuity, adverse events and complications.

### Surgical procedure

Informed consent was obtained from all patients after a thorough explanation of the procedure and its risk. All surgical procedures were performed in topical or peribulbar anesthesia. About 20 minutes before surgery, 0.12 ml of mitomycin C 0.2 mg/mL was injected subconjunctivally in the target area using a 30-gauge needle. Standard ophthalmic surgical procedures, consisting of skin disinfection, proper field dressing, and speculum insertion, were used to prepare patients and eyes. In combined procedures, phacoemulsification and intraocular lens insertion were always performed before the XEN implantation. The conjunctival tissue of the target area was marked 3 mm from the limbus. After the anterior chamber was filled with viscoelastic, the XEN injector beveled needled tip was advanced through a clear corneal incision toward the opposite supero-nasal target quadrant. The use of intraoperative gonio-lens was at the discretion of the surgeon and was adopted only in a few cases. An adequately positioned device should be visible for approximately 1 mm in the anterior chamber and for 2 mm in the subconjunctival space, exiting the sclera 3 mm posteriorly to the limbus. In case of suboptimal stent position, the XEN was reinserted in the injector and the implantation repeated. Then,

viscoelastic was carefully removed from the anterior chamber and intracameral cefuroxime was applied. The postoperative management included topical corticosteroids and antibiotics for one week followed by topical corticosteroids slowly tapered down over four to six months. During the follow-up, needling procedure and MMC subconjunctival injection were performed at the slit lamp, the details of the procedure are described elsewhere.[37,51]

Outcome measure. Success criteria were: an off-medication IOP of 6 to 16 mmHg 12 months after surgery; no additional glaucoma surgery; no visual threatening complications (endophthalmitis, aqueous misdirection, XEN extrusion), no visual acuity loss greater than 1 Snellen line. Postoperative bleb management was not considered a failure criterion.

Statistical analysis. One eye per patient was considered for statistical analysis. In descriptive statistics, variables were summarized with median and interquartile range for continuous variables without normal distribution and absolute value and percentage for frequency of categorical variables. In order to obtain clinically interpretable and statistically fitting results, continuous variables were converted to categorical. A univariate Cox's proportional hazard regression analysis was performed to identify potential risk factors for surgical failure. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Then, a multivariate cox model was built. Criteria for model selection were guided by the univariate analysis and clinical significance of the variables. Model diagnostics included testing the proportionality assumption with the global Schoenfeld test and plotting log(−log[survival]) versus log(time). One-year surgical success was estimated using Kaplan–Meier analysis. All statistical analyses were performed with Stata version 15.1 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05 for all analysis.

**Results**

Based on the inclusion and exclusion criteria, the study population consisted of 123 patients whose demographic, ocular and perioperative characteristics are summarized in Table 1. All the surgical procedures were performed from March 2016 to July 2018. 93 patients underwent XEN implantation alone whereas 30 the combined procedure with phacoemulsification and IOL implantation. The mean IOP changed from 26.4±8.2 mmHg pre-operatively to 13.4±6.2 mmHg at 1 year ($p<0.001$). The mean number of IOP-lowering drugs changed from 2.9±1.0 pre-operatively to 0.38±0.95 at 1 year ($p<0.001$). Table 2 reports the HR and CI for all the

explored variables associated with the failure of the surgical procedure. Figure 5, 6 and 7 show the overall survival curves and the curves for the IOP at 24h and number of needlings, respectively. The value of 9 mmHg was chosen as cut-off for the IOP at 24h because it is close to the theorical pressure drop of the device and because it maximises the product of the sensitivity and specificity. Univariate cox regression showed that the day after surgery IOP greater than 9 mmHg was associated with surgical failure as defined in the methods section ($p=0.02$). A postoperative number of needlings greater or equal to 2 in the follow-up was also predictive of surgical failure ($p<0.01$).

In the multivariable analysis the following variables were included: age and combined surgery, because in the literature it has been shown to be predictor of efficacy, while IOP at 24 h and number fo needlings because they were significant in the univariant analysis. Table 3 shows the multivariate model. After controlling for age, type of procedure and number of postoperative needling, IOP $\leq$ 9mmHg at the 24-hours remains associated with a reduced hazard of having surgical failure during one-year follow-up. Figure 8 shows the box-plot of the IOP at 24h for the patients that experienced failure or not during the 1-year follow-up. The median IOP (IQR) was 8 mmHg (5 to 12 mmHg) and 12 mmHg (9 to 16 mmHg) for the non-failure and failure group respectively ($p=0.02$). We observed more cases of numerical hypotony, defined as IOP < 6 mmHg, in the group of patients that experienced success (25%) compared to the group of patients that failed (11%). The surgical success criteria at 1-year were satisfied in 76% and 43% in the group with 24-hour IOP below or equal and above 9mmHg respectively ($p=0.026$).

| | N = 123, n (%) |
|---|---|
| Demographics | |
| Age (y) | 74.5 (67.1-81.3) range = 19-92 |
| Sex | |
| Women | 58 (47.2) |
| Men | 65 (52.8) |
| Ocular characteristics | |
| Diagnosis | |
| POAG | 106 (52.8) |
| XFG | 14 (11.4) |
| Missing | 3 (2.4) |
| Preoperative IOP (mm Hg) | 25 (20-31) |
| Preoperative number of IOP lowering drugs, n | 3.0 (2-4) |
| Operative and perioperative factors | |
| Anesthesia | |
| Topical | 86 (69.9) |
| Peribulbar | 37 (30.1) |
| Type of procedure | |
| Standalone | 93 (75.6) |
| Combined | 30 (24.4) |
| Surgical duration (min) | 16 (12-25) |
| Standalone | 15 (10-20) |
| Combined | 25 (20-30) |
| IOP at 24 h | 9 (6-13) |
| Postoperative needling | |
| 0 | 60 (48.8) |
| 1 | 32 (26.0) |
| ≥ 2 | 28 (22.76) |
| Missing | 3 (2.4) |

Data are number (%) or median (IQR).
IOP indicates intraocular pressure; POAG, primary open-angle glaucoma; XFG, exfoliative glaucoma.

**Table 1.** Baseline characteristics, operative and perioperative factors.

| Variable | Categories | HR | 95% CI | *P* |
|---|---|---|---|---|
| Age (y) | | | | 0.87 |
| | ≤65 | Reference | | |
| | 65-80 | 0.81 | 0.36-1.82 | |
| | ≥80 | 0.83 | 0.36-1.93 | |
| Sex | | | | 0.1 |
| | Women | 1 | | |
| | Men | 1.75 | 0.88-3.50 | |
| Primary diagnosis | | | | 0.76 |
| | POAG | Reference | | |
| | XFG | 1.17 | 0.45-3.00 | |
| Anesthetic | | | | 0.86 |
| | Topical | 1 | | |
| | Peribulbar | 1.07 | 0.53-2.17 | |
| Surgical duration | | | | 0.57 |
| | ≤15 | 1 | | |
| | >15 | 0.81 | 0.40-1.65 | |
| Type of procedure | | | | 0.41 |
| | Standalone | 1 | | |
| | Combined | 0.7 | 0.29-1.68 | |
| Preoperative IOP (mm Hg) | | | | 0.79 |
| | <25 | | | |
| | >25 | 0.91 | 0.47-1.77 | |
| Preoperative number of IOP lowering drugs, n | n≤2 | 1 | | 0.91 |
| | n>2 | 0.96 | 0.47-1.97 | |
| IOP at 24 h (mm Hg) | ≤9 | 1 | | 0.02 |
| | >9 | 2.24 | 1.10-4.56 | |
| Postoperative needling | 0 | 1 | | <0.01 |
| | 1 | 1.40 | 0.52-3.74 | |
| | ≥2 | 5.80 | 2.55-13.18 | |

CI indicates confidence interval; HR, hazard ratio; IOP, intraocular pressure; POAG, primary open-angle glaucoma; XFG, exfoliative glaucoma.

**Table 2.** Association between failure of the XEN procedure and demographic, ocular and perioperative variables, Univariate analysis

| Variable | Categories | HR | 95% CI | *P* |
|---|---|---|---|---|
| Age (y) | ≤65 | 1 | | |
| | 65-80 | 0.71 | 0.28-1.79 | 0.467 |
| | ≥80 | 0.71 | 0.30-1.72 | 0.455 |
| Type of procedure | Standalone | 1 | | |
| | Combined | 0.85 | 0.34-2.12 | 0.720 |
| IOP at 24 h (mm Hg) | ≤9 | 1 | | |
| | >9 | 2.28 | 1.03-5.09 | 0.043 |
| Postoperative needling | 0 | 1 | | |
| | 1 | 1.94 | 0.69-5.44 | 0.206 |
| | ≥2 | 5.00 | 2.08-11.78 | <0.001 |

CI indicates confidence interval; HR, hazard ratio; IOP, intraocular pressure.

**Table 3.** Association between failure of the XEN procedure and demographic, ocular and perioperative variables, Multivariate analysis

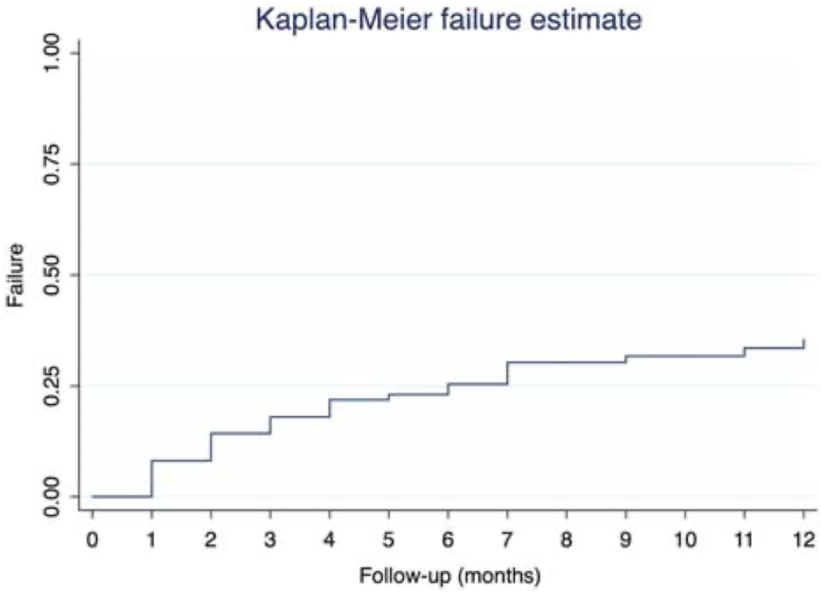


**Figure 5.** Overall failure during the follow-up.

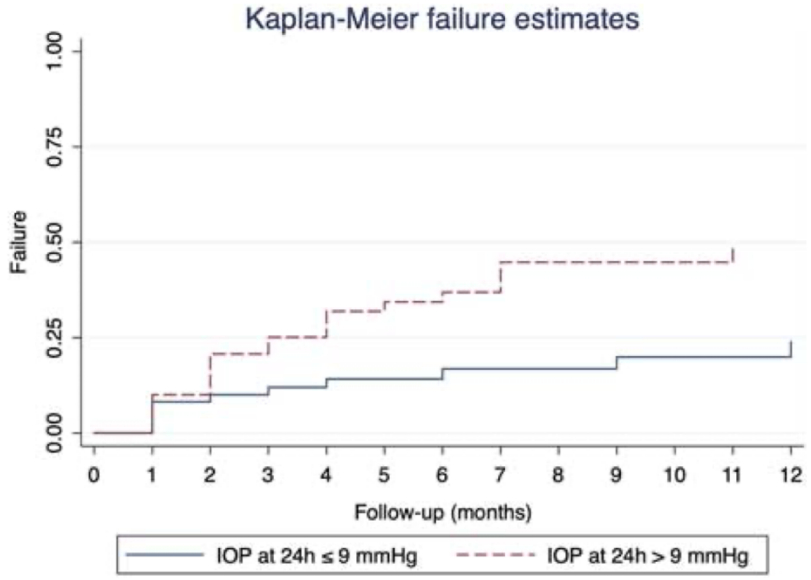


**Figure 6.** Failure curves for intraoculare pressure (IOP) ≤ 9 mmHg 24-hour postoperatively (P=0.026)

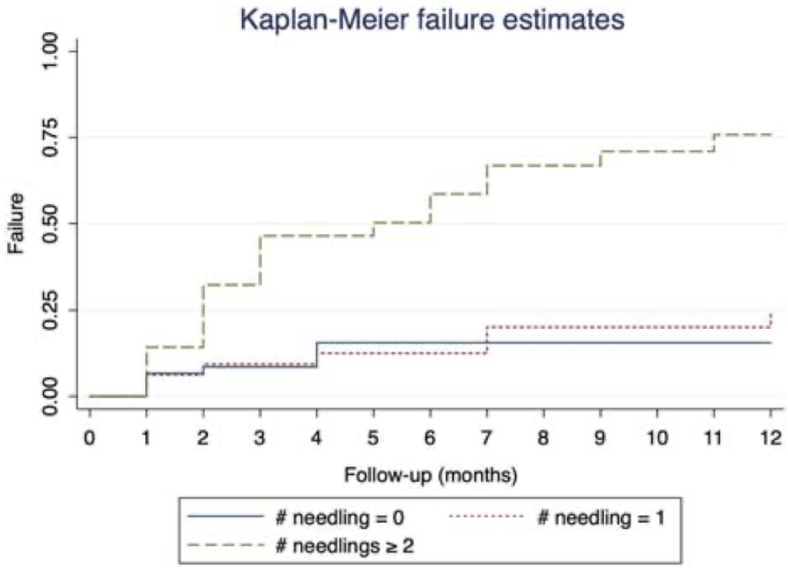


**Figure 7.** Failure curves for different number of needling procedures. Needling 0 0 versus needling = 1 (P= 0.504); needling = 0 versus needling ≥ 2 (P<0.001).

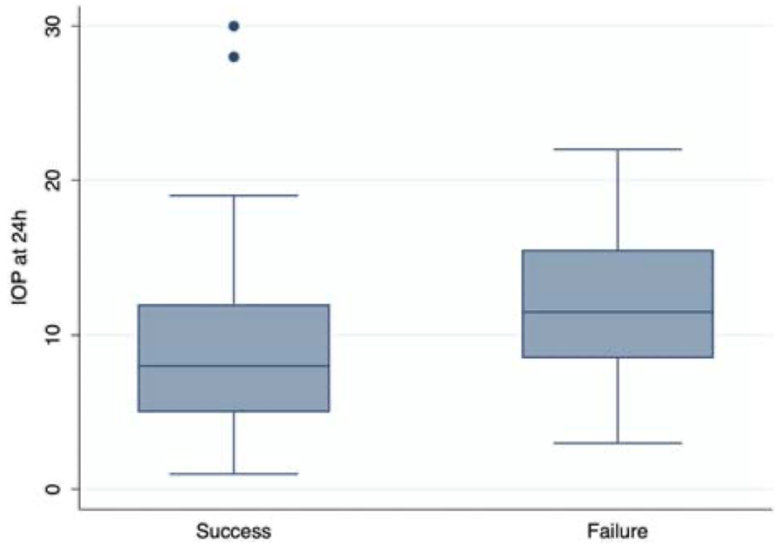


**Figure 8.** Box plot showing the intraocular pressure (IOP) at 24 hours for the group that underwent failure or not during the 12-month follow-up. The difference was statistically significant (P=0.034).

## Discussion

Our results showed that a low IOP in the early postoperative period after XEN implantation is associated with surgical success at 1 year defined as an off-medication IOP between 6 and 16 mmHg. Conversely to trabeculectomy, the XEN has been designed to achieve bleb filtration through a small tube of collagen-derived gelatine. The commercially available version of the XEN implant has a fixed internal diameter of 45 um with a length of 6 mm. By its physical dimensions, holding constant the aqueous production and aqueous viscosity, it's possible to estimate the pressure drop along with the device.[25] Hence, the pressure drop along the XEN device is assumed at about 9 to 10 mmHg. Ideally, this is the IOP level expected if the XEN device is patent, well-positioned and no viscoelastic is retained in the anterior chamber. The cases of numerical hypotony observed at the day 1 visit could be caused not only by overfiltration but also by transient decrease of aqueous production. In bleb-forming surgical procedures, the conjunctival resistance to filtration tends to be minimal in the early postoperative period. An early IOP higher than 9 mmHg may indicate that the aqueous flow through the XEN device is partially limited by factors other than its physical dimension. Causes of external flow limitations are supposed to be increased viscosity by viscoelastic, internal ostium occlusion, or external flow limitation.[52–54] Lenzhofer et al. found that the qualified surgical success of the XEN gel implant placed intra or sub-tenon group was higher than the success of the implant placed more superficially in the intra-conjunctival position. Additionally, a lower trend of secondary needling procedures and lowering IOP medications burden was encountered in the intra and sub-tenon placement group in the first post-operative year.[55] Midha et al. showed that a high day 1 IOP after standalone XEN implantation is a predictor for needling.[56] As shown by figure 4, we also found an association between early IOP and number of needling. Moreover, we observed that a number of postoperative needlings greater or equal to two is associated with surgical failure. Olivari et al. recently described three cases of XEN fracture occurred after needling, and multiple needlings may increase the risk of this adverse event.[51] Probably, the association between the number of needlings and XEN failure is explained by the fact that failing blebs require aggressive postoperative care that sometime is not possible to perform during a needling at the slit-lamp. Furthermore, to break the fibrous adhesions around the XEN by passing the 30 gauge needle over and under the tube, it could not be sufficient and this procedure if repeated sometimes, could stimulate a more accentuated fibrosis, besides the possility to break the XEN.[51]

The success was defined as an off-medication IOP between 6 to 16 mmHg to compare our results to previous study on predictors of trabeculectomy efficacy that used the same criteria. [44] Even if the statistical criterion of success does not always reflect the therapeutic success targeted for each individual patient. Conversely, mild glaucoma patients may show no progression with IOP above 16mmHg.

The CAT-152 trabeculectomy study group found that the success of trabeculectomy was negatively affected by African descent, suture or lysis intervention and by bleb needling.[46] Nguyen et al. reported that African descent was associated with higher failure rates and higher incidence of bleb leaks after trabeculectomy compared with European descent.[49] In our study we did not analyze this demographic characteristic on the XEN efficacy because only one patient was African descent. The study sample characteristics reflects the Italian population affected by glaucoma.

In a retrospective study, Awitry et al. reported that a low early postoperative IOP measurement was a predictive factor for surgical success one-year length follow-up in patients that underwent trabeculectomy surgery augmented with MMC. Of note, 88% of success of trabeculectomy was predicted when IOP was lower than 16mmHg and 55% of failures when IOP was higher than the cut off level on the first day post-operative.[44] Okimoto et al. also showed that in trabeculectomy, an early postoperative IOP below 8mmHg was associated with a long-term follow-up with IOP constantly below or equal to 15mmHg.[47] Previously, Downes et al., defining success an IOP under of 21 mmHg, found that a day 1 IOP below 17 mmHg predicted 92.6% of surgical success.[57]

In conclusion our study shows that an early IOP below or equal to 9 mmHg, which is the theoretical IOP pressure drop provided by the XEN's dimensions, is predictive of the efficacy of the procedure during 1-year follow-up. Besides from our data in the post-operative period if the patient needs more than 2 needlings this could predict a failure of the surgery and the physician could start to take in consideration a different approach to avoid to loose time.

## Postoperative management: XEN implant fracture occurred during the needling procedure

Clinical studies as well as our experience have shown that bleb needling is often needed also in case of XEN implant.[58] In general, bleb needling after a filtering procedure should always be performed with caution since possible complications include flat anterior chamber, hyphema, choroidal effusion, conjunctival buttonhole and blebitis.[59]
In case of needling after XEN procedure, the implant may be damaged.[60] In our study, we describe three case of XEN implant fracture occurred during the needling procedure and we describe the long-term follow-up of such cases.

**Methods**

This is a retrospective review carried on the charts prospectively collected for all the patients operated at Clinica Oculistica, University of Genoa. Among all the patient files, we selected the cases in which the XEN implant resulted damaged after the needling procedure. Of the 170 XEN implanted in the last two years, a needling procedure was performed in 98 eyes (57.6%) and the XEN fracture was observed in 3 cases (3.1%).

### Needling procedure used in our clinical practice:

After obtaining informed consent, 1-2 drops of benoxinate hydrochloride 0.4% (Alfa Intes, Italy) were applied five times at one-minute intervals directly over the superior bulbar conjunctiva. Then, 1-2 drops of 5% povidone-iodine ophthalmic solution (Oftasteril, Alfa Intes, Italy) were applied three minutes before the needling. A sterile technique was used for the entire procedure. With the patient seated at the slit lamp, a lid speculum permitted to expose the superior conjunctiva. A 30-gauge needle placed on a 1.0 ml syringe was used to enter the conjunctiva supero-temporally and approximately 10 mm from the XEN implant. The tip of the needle was gradually advanced under the conjunctiva and used to perforate the fibrosis around the tube with sideways sweeping movements to and from over and under the XEN implant aiming to free the tip of the from adhesions. A freely moving implant under conjunctiva is considered a favorable sign. After needling, 1 drop of 5% povidone-iodine ophthalmic solution was administered and dexamethasone-netilmicin q.i.d was prescribed for one week.

## Case descriptions

### Case 1

An 89 years old Caucasian woman affected by primary OAG (POAG) underwent an uneventful XEN procedure with mitomycin C (MMC) in the right eye and the IOP remained below 16 mmHg with no medications until the six months follow-up visit. Then, the IOP increased to 24 mmHg; gonioscopy revealed a well-positioned XEN implant free from any visible internal occlusion. The conjunctiva appeared adherent to the implant and needling was scheduled. During the procedure, a subconjunctival hemorrhage impaired the clear view of the implant. One week after the needling, the subconjunctival hemorrhage was reabsorbed and the XEN was noted to be cut in its distal part. The fractured fragment measured 0.7 mm (Figure 9, 10). No other complications were recorded. The IOP, at last, follow up, after 11 months from the event, was 10mmHg with the bleb well formed.

### Case 2

A 57 years-old woman with diagnosis of high myopia, dense posterior cortical cataract and quiescent uveitic glaucoma in right eye was submitted to phacoemulsification with intraocular lens implantation combined with XEN implant with MMC. Before surgery, best correction visual acuity (BCVA) was LogMAR +1.3 in the right eye and LogMAR 0 in left eye. Before surgery, the IOP of her right eye was uncontrolled (27mmHg) despite brinzolamide/timolol fixed combination b.i.d. and acetazolamide 250mg t.i.d. After surgery, tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% was administered q3h for 1 week. Then, topical dexamethasone was slowly tapered down. After 3 months, a recurrence of anterior uveitis associated with IOP elevation up to 30 mmHg caused by episcleral fibrosis was observed. Intraocular inflammation was reduced by topical dexamethasone and a bleb needling was performed. During the procedure, due to a sudden movement of the patient, an accidental rupture of the implant was observed. The distal part of the fragment was 0.8 mm. At the last follow-up visit, 18 months from XEN fracture, the BCVA was LogMAR +0.2 with no signs of uveitis, IOP was 14mmHg on medications: timolol 0.5% b.i.d. and brimonidine/brinzolamide fixed combination b.i.d.

### Case 3

A 76 years-old woman with POAG underwent XEN implantation with MMC in her left eye without any complication. The day after surgery IOP was 10 mmHg and remained below 15

mmHg for 2 months without any IOP-lowering drug. At the 3-months follow-up visit, IOP increased to 21 mmHg and the bleb appeared hyperemic and flat. Needling followed by subconjunctival injection of 0.1 ml MMC 0.02% was scheduled. During the needling procedure, extensive episcleral fibrosis around the XEN was noted and the maneuver to free up the distal portion of the implant resulted in an accidental break. The fragmented part measured 1 mm. At last follow up, after 17 months from rupture, the IOP was 12 mmHg without any ocular medication.

| | Age (years) | Sex | Glaucoma type | Surgery | Follow-up (months) | IOP before needling (mmHg) | IOP at the last follow-up visit | Theoretical IOP* | Fragment length (mm) | Associated feature |
|---|---|---|---|---|---|---|---|---|---|---|
| **#1** | 89 | F | POAG | XEN alone | 11 | 24 | 10 | 9.4 | 0.7 | Subconjunctival hemorrhage |
| **#2** | 57 | F | Uveitic | Phaco-XEN | 18 | 30 | 14* | 9.2 | 0.8 | Lack of cooperation |
| **#3** | 76 | F | POAG | XEN alone | 17 | 21 | 12 | 8.9 | 1 | Extensive fibrosis over the implant |

**Table 4.** Summary of the cases. *with anti-glaucoma medications. POAG= Primary open-angle glaucoma; IOP= Intraocular pressure; *Values entered in the Hagen-Poiseuille equation: aqueous production= 2µl/min; aqueous viscosity[10] = $0.7 \times 10^{-3}$ Ns/m$^2$.

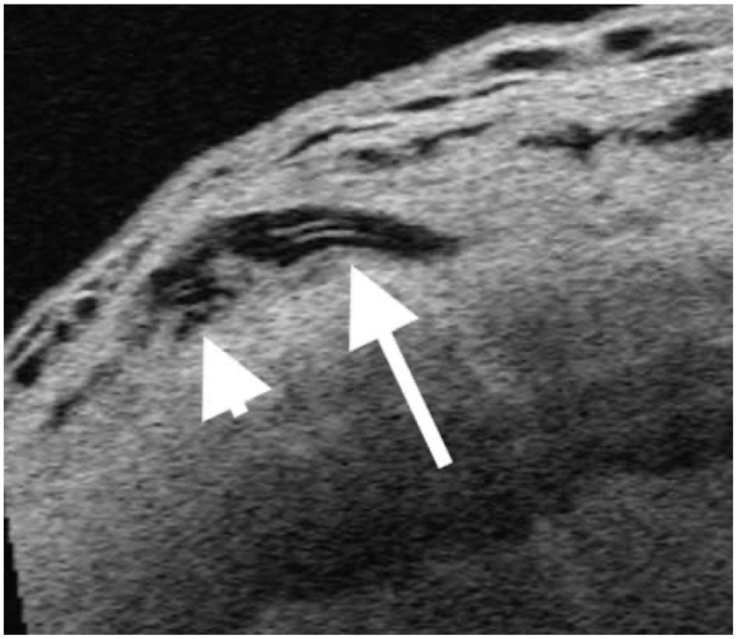

**Figure 9.** Anterior segment tomography of the XEN's bleb showing the episcleral portion of the implant (arrow) ant its distal fracture fragment (arrowhead)

**Figure 10.** XEN fracture imaged by slit-lamp. XEN gel stent and its distal fracture fragment.

**Discussion**

The XEN implant was proposed to standardize and facilitate filtering surgery. Since filtration occurs through eye tissues which are continuously remodelling, careful postoperative bleb observation and care as needed is indicated. Up to 40% of patients implanted with XEN were reported to require a needling procedure during the follow-up.[31] The XEN implant is a small hydrophilic tube composed of a porcine gelatin cross-linked with glutaraldehyde designed to be implanted permanently. When implanted, the device is hard but it becomes flexible and soft rapidly after hydration. These characteristics reduce the risk of conjunctival erosion.

The needling procedure is usually performed with a small gauge hypodermic needle made of stainless-steel with a beveled, sharp pointed tip. The tip design allows the needle to easily penetrate the skin or, in case of needling procedure, the conjunctiva. Moreover, the sharp tip is used to cut the fibrotic strands of tissue that occur in a failing bleb. Our cases highlight the fact that the small XEN implant is fragile and can be easily cut or damaged during the needling. Particularly, this may happen if the XEN implant is not always well visible during all the steps of the procedure. Poor visualization of the implant may be caused by abnormally thick conjunctiva and Tenon's capsule overlying it or by subconjunctival hemorrhage caused by previous anti-metabolites injection or occurring during the needling.

The commercially available version of the XEN implant has a fixed diameter of 45 μm with a length of 6 mm. By its physical dimensions, it's possible to estimate the pressure drop along the device using the Hagen-Poiseuille equation. When the XEN gel is damaged in its distal part, the length is shortened, and the pressure drop is reduced linearly. In particular, for a length of 5 mm the estimate pressure drop is about 8.8 mmHg that means a pressure drop reduction of -16.7% from the about 10.6 mmHg of the intact implant.

The resistance determined by a XEN implant is especially crucial during the first post-operative period to avoid hypotony and shallow anterior chamber. However, in the long-term, the subconjunctival bleb may cause itself a resistance to the aqueous drainage. As a matter of fact, the long-term IOP of XEN procedure is frequently higher that the IOP determined by the Hagen-Poiseuille equation.

Bustros et al. reported a case of inadvertent damage to the XEN implant occurred during needling procedure performed at the operating room.[60] In the previously reported case, the fragment measured 1.1 mm and was removed because extruded. The 1-month follow-up was favorable with formed bleb even if the XEN was not visible under the conjunctiva but identified by OCT in the sclera.[9] In our cases, the fragments remained in the subconjunctival space without signs of specific tissue reaction.

Theoretically, altering the physical characteristics of the device may cause a reduction in the pressure drop caused by the XEN implant (Table 4). However, in our cases, we haven't observed any hypotony or swallow chamber.

As observed by Bustros et al. subconjunctival hemorrhage can cause of loss of XEN visibility theoretically favoring its damage. Compared to trabeculectomy, the patients' cooperation is more important when needling a XEN bleb because of the presence of the soft device. In case of extensive fibrosis, the XEN is less visible and considerable force is required to free the implant from the tenacious tissues. In this case, surgical revision should be considered.

In conclusion, XEN fracture related to needling procedure should be considered as a possible adverse event of the bleb management. Because XEN is composed of a soft and flexible material, it could be easily damaged by the needle. In our cases the fracture did not to impair the efficacy of the draining device. Despite our positive results, it is recommended to preserve the integrity of the implant.

# Risk of Choroidal detachment after XEN gel stent implantation and associated factors

Among the complication of glaucoma filtration surgeries, choroidal detachment (CD) is frequently observed. The estimated incidence varies from 3% to 34% and changes accordingly to the surgical technique, to the ocular and the demographic characteristics of the patients, and the diagnostic technique accuracy.[61–66] A limited CD can be asymptomatic, resolve spontaneously, and remain undetected if not adequately investigated.[67]

CD refers to an abnormal accumulation of either blood or serum in the suprachoroidal space, between the choroid and the sclera. In normal conditions, the suprachoroidal space is a potential volume because of the close apposition of the choroid to the sclera. In pathologic circumstances, alterations of ocular fluid dynamics, namely the balance between hydrostatic and oncotic pressure, fluids can accumulate in this space. CD may be associated with hypotony of any aetiology or exudation of serum, most frequently caused by inflammation.[67,68] Previous reports have identified many factors associated with CD after trabeculectomy and glaucoma drainage devices (i.e. age, hypotony, exfoliation, corneal thickness, pseudophakia, and hypertension).[64,67,69] With the aim to reduce complications of glaucoma surgeries, novel devices that permitted more predictable filtration have been introduced in the clinical setting.[17]

CD has also been described after XEN gel stent implantation with incidences varying from 0 to 15%.[26,70–74] To the best of our knowledge no studies have investigated the demographic and ocular characteristics associated with the occurrence of CD in patients implanted with the XEN gel stent. The purpose of this study was to estimate the occurrence of CD after XEN gel implantation surgery and to investigate the associated factors.

**Material and methods**

We retrospectively reviewed the medical records of 126 patients with glaucoma who underwent XEN gel stent implantation with mitomycin C (MMC) at Clinica Oculistica, San Martino Hospital IRCCS of Genoa between March 2016 and December 2018. This study was part of a prospective, uncontrolled, consecutive case series.[75] The study followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Eyes with the diagnosis of primary open-angle glaucoma or exfoliative glaucoma were included in the analysis. Other types of glaucoma or eyes with history of previous ocular surgeries other than uncomplicated phacoemulsification were excluded.

For all the patients, we considered demographic and ocular characteristics. Namely age, gender, systemic and ocular history, refractive status, intraoperative factors, complications during or after surgery, onset time of serous choroidal detachment, visual acuity, and IOP were recorded and analysed. According to the clinical practice, postoperative visits were scheduled at days 1, 7, 14, 30. Additional visits were scheduled when clinically required. Postoperatively, the following findings were recorded: visual acuity, IOP, bleb status, wound leaks, anterior chamber (AC) depth, hyphema, anterior chamber inflammation, choroidal detachment, and other complication after surgery. In the case of numerical hypotony (IOP<6 mmHg), choroidal detachment detected during dilated fundus examination or in doubtful cases, ocular ultrasonography and ultra-widefield imaging (Optos, Dunfermline, UK) were performed to confirm and follow-up the disease. Surgical and postoperative managements were described in detail elsewhere.[51,75]

### Statistical Analysis

In descriptive statistics, variables were summarized as means and standard deviation. Absolute value and percentage for frequency were used for categorical variables. Logistic regression analysis was performed to examine the association of the occurrence of post-operative CD and the ocular, demographic, and perioperative factors. A multivariate logistic regression model was built to investigate which characteristics better predict the development of CD. Variable selection for the multivariate model was based on statistical significance and biological plausibility. In case of bilateral surgery, only the first eye was considered for the analysis. The A p-value <0.05 was considered statistically significant. Statistical analysis was performed using Stata 15.1 (StataCorp LLC, College Station, TX).

## Results

The demographic and ocular characteristics of the sample are summarized in Table 5.

Of the 126 patients included in the analysis, 25 (19.8%) developed a CD in the postoperative period. CD was diagnosed 5.84 ± 1.77 days after surgery and was serous in 22 (88%) eyes, while 3 (12%) eyes developed a mixed serous haemorrhagic CD. The mean IOP at the time of

diagnosis was 6.4 ± 3.1 mmHg. In all the cases, the CD did not extend to the posterior pole. All the patients with CD received medical treatment with a topical steroid, cycloplegic eye drops, and oral glucocorticoids (prednisone 1 mg tapering off the dose until resolution). CD resolved successfully in 15.52 ± 7.15 days in all cases.

A shallow anterior chamber (AC) was noted in 9 (36%) of CD cases on day 1 and was managed with intracameral air and/or viscoelastic injection. Ultrasonography and ultra-widefield imaging were used to document the diagnosis and follow-up the CD until resolution.

Table 6 reports the results of the univariate analysis and table 7 reports the results of the multivariate analysis. CD resulted significantly associated with older age (OR=1.10; p= 0.019), lower IOP in the first postoperative days (OR= 0.70; p< 0.001) and higher number of IOP-lowering drugs before surgery (OR= 5.70; p< 0.001).

**Table 1** – Ocular, demographic, and perioperative characteristics.

| Ocular and demographic characteristics | N= 126 |
|---|---|
| **Female** | 63 (50) |
| **Age, years** | 71.3 ± 14.8 |
| **Glaucoma type** | |
| **POAG** | 95 (75.4) |
| **XFG** | 31 (24.6) |
| **Laterality of the eye** | |
| **Right** | 50 (39.7) |
| **Left** | 76 (60.3) |
| **History of cataract surgery** | |
| **No** | 67 (53.2) |
| **Yes** | 59 (46.8) |
| **Preoperative IOP** | 25.7 ± 8.2 |
| **Mean IOP, 1 to 7 days after surgery** | 9.8 ± 5.2 |
| **Type of procedure** | |
| **Standalone** | 96 (76.2) |
| **Combined** | 30 (23.8) |
| **Preoperative IOP-lowering drugs, n** | 3 ± 0.9 |

**Table 5** – Ocular, demographic, and perioperative characteristics. Data are mean ± sd or number (%). POAG= Primary open-angle glaucoma; XFG= exfoliative glaucoma; IOP= Intraocular pressure.

| Predictor variable | Odds ratio | 95% CI | P value |
|---|---|---|---|
| **Age, years** | 1.04 | 1.00 to 1.10 | **0.03** |
| **Preoperative IOP, mmHg** | 1.03 | 0.97 to 1.08 | 0.35 |
| **Preoperative IOP-lowering drugs, n** | 3.49 | 1.94 to 6.28 | **<0.001** |
| **Glaucoma type** | 1.17 | 0.79 to 1.73 | 0.43 |
| **POAG** | 1.00 | | |
| **XFG** | 3.27 | 0.92 to 11.58 | |
| **Mean IOP, 1 to 7 days after surgery** | 0.77 | 0.66 to 0.89 | **<0.001** |
| **Procedure** | 0.55 | 0.17 to 1.75 | 0.31 |
| **Standalone** | 1.00 | | |
| **Combined** | 0.59 | 0.18 to 1.90 | |

**Table 6** - Univariate analysis results. Factors associated with the occurrence of choroidal detachment after XEN gel stent surgery. IOP= Intraocular pressure; POAG= Primary open-angle glaucoma; XFG= exfoliative glaucoma.
Bold means that the value is statistically significant.

| Predictor variable | Odds ratio | 95% CI | P value |
|---|---|---|---|
| **Age, years** | 1.10 | 1.01 to 1.19 | **0.019** |
| **Preoperative IOP-lowering drugs, n** | 0.99 | 0.89 to 1.09 | 0.855 |
| **Preoperative drugs, n** | 5.70 | 1.98 to 16.36 | **0.001** |
| **Glaucoma type** | 1.23 | 0.59 to 2.58 | 0.576 |
| **Mean IOP, 1 to 7 days after surgery** | 0.70 | 0.56 to 0.87 | **0.001** |
| **Procedure** | 0.72 | 0.10 to 5.27 | 0.749 |

**Table 7** - Multivariate analysis results. Factors associated with the occurrence of choroidal detachment after XEN gel stent surgery. IOP= Intraocular pressure. Bold means that the value is statistically significant

**Discussion**

Choroidal detachment is a common complication of any filtering surgery, and hypotony and uveal inflammation are deemed to be notable causes.[76,77] In our study, we have identified two patient's characteristics and one postoperative factor associated with CD development following the XEN gel stent implantation.

We observed that CD occurrence increased progressively with age, being more frequent in older patients. Jampel et al. also found that older patients were more likely to experience serous choroidal detachment after trabeculectomy in the collaborative initial glaucoma treatment study.[78] Older individuals might have relatively fragile connective tissue, which promotes fluid movement through the uveal tissue and the vascular barrier. The altered sclera of the older subject may also promote the compression of the vortex veins with an increase in the venous pressure and vessels leaking.[64]

The present study identified lower postoperative IOP in the first week as a significative factor associated with CD occurrence. Low IOP is a well-known factor for CD after filtering surgeries.[64,69,76,77][3,10,21,23] XEN gel stent has been designed to produce a pressure drop of about 8 mmHg.[25] Theoretical pressure drop can be calculated with the Hagen-Poiseullie equation taking into account XEN's physical dimension and assuming a constant aqueous production. In the first postoperative period, aqueous production may be impaired by surgical trauma and antimetabolite toxicity to the ciliary body, reducing the theoretical pressure drop.[77] Moreover, a small amount of aqueous may flow around the implanted XEN. In a previous report, we found that low IOP in the post-operative factor is associated with better IOP control at 1 year.[75] The clinical success of glaucoma surgery is a trade-off between a IOP that sufficiently low to slow glaucomatous damage and no sign and symptoms of hypotony.

In our study, we found that eyes treated with a higher number of preoperative IOP-lowering drugs were at higher risk for CD. There is a theoretical possibility that a higher number of preoperative medications together with postoperative hypotony increases ocular inflammation and exacerbate the end uveal effusion. Previous studies reported that IOP-lowering drugs were associated with CD occurrence in eyes with or without previous filtering intervention.[79–84] The pathophysiology of CD, induced or associated with medicaments, is not completely understood. It is deemed that low IOP and inflammation play a role in CD.[80] The ciliary body can be damaged by long-term use of drugs, and in case of surgery, aqueous production may be impaired, causing marked hypotony. On the other hand, prostaglandins (PGA) may permanently alter the level of collagen in the uveo-scleral outflow pathway predisposing to

post-surgical hypotony, and may alter capillary permeability favouring uveal exudation.[79,85]In addition, MMC may cause direct toxicity to the ciliary epithelium, resulting in hyposecretion.[86,87]

In our cases, all patients received medical treatment with topical, oral steroid and cycloplegic, and showed a complete resolution of the CD between 5 and 30 days after surgery. In few cases when the AC was too shallow, an air or viscoelastic bubble was injected in the AC through the surgical paracentesis in the infero-temporal quadrant.

In our experience, CD following filter surgery using XEN gel stent was a transient complication and did not have a negative effect on the final outcome of the surgery.

This study is limited because of its retrospective nature. Randomized clinical trials on XEN gel stent are lacking. Further prospective studies could help to confirm the validity of our retrospective analysis.

In the case of CD diagnosis or suspect, we found clinically meaningful the use of wide-field imaging that permits non-contact and non-dilated 200-degree imaging of the retina for diagnosis, documentation, and follow-up of CD. Unfortunately, no study has determined yet the accuracy of this technique to detect CD.

MIGS, as the XEN gel stent has been the introduced to reduce post-operative complications and facilitate the surgical procedure.[88] Another advantage of MIGS is faster visual recovery and shorter surgical time compared to trabeculectomy. Postoperative complications may still limit the safety of these surgical procedure and the identification of prognostic factors may permit to select the most suitable group of patients to offer the procedure.

## Comparison between XEN procedure and trabeculectomy

The aim of the study is to compare the results of two filtering procedures: trabeculectomy with mitomycin C (MMC) as adjuvant and XEN gel stent implantation with MMC in patients with open angle glaucoma.

**Study design**

Retrospective chart analysis of patients treated at the Ophthalmology Clinic, DiNOGMI, of the San Martino Polyclinic Hospital in Genoa from March 2016 to September 2020. All procedures were conducted in accordance with institutional ethical standards and the Declaration of Helsinki. All patients received informed consent which they subsequently signed.

**Participants**

Patients were selected using the following inclusion criteria:

- XEN implant
- Age > 45
- IOP above target despite maximum tolerated medical therapy
- healthy conjunctiva in the upper sector
- gonioscopically open angle
- presence of glaucomatous optic neuropathy
- Visual field loss suggestive of glaucoma
- Follow-up of at least 36 months
- Previous laser treatment such as trabeculoplasty was not considered as an exclusion criterion

Patients were excluded from the study in the presence of:

- Angle closure or angle closure suspect (irido-trabecular contact over 180 ° in gonioscopy)
- Secondary glaucoma except PXFG
- previous eye surgery except for phacoemulsification of the lens with uncomplicated intraocular lens (IOL) implantation and performed at least six months prior to enrolment.

On the basis of the inclusion and exclusion criteria, the data of 34 patients that underwent filtering surgery with XEN gel stent were analysed. A control group of patients that underwent trabeculectomy homogeneous for demographic and ocular characteristics to the XEN group was formed.

At the baseline visit, the following variables were recorded for each patient: age, sex, systemic and ocular history, refractive status, visual field damage expressed as Mean Deviation (MD), anaesthesia used (local or topical), duration of the intervention in minutes, pre- and post-operative IOP values, best corrected visual acuity (BCVA), complications occurred during or after surgery and days of hospitalization.

Table 8 shows the characteristics of the two cohorts of patients under study which are homogeneous for all the variables reported.

| | XEN (n=34) | Trabeculectomy (n=34) | p value |
|---|---|---|---|
| Age, years | 72.7 (±9.5) | 74.2 (±7.7) | 0.462 |
| Female, % | 55.9(19) | 70.6. (24) | 0.107 (*) |
| Baseline IOP, mmHg | 23 (19-28) | 22 (17-28) | 0.640 |
| Baseline IOP-lowering medications | 2.91 (±0.82) | 2.72 (±1.16) | 0.5089 |
| Glaucoma type, % | | | |
| POAG | 85.3 (29) | 91.2(31) | 0.709(*) |
| PXFG | 14.7 (5) | 8.8 (3) | |
| Visual field, dB | -13.2(±10.2) | -13.4 (±8.8) | 0.946 |
| Lens status, % | | | |
| Pseudophakia | 67.7(23) | 41.2(14) | 0.051 |
| Clear lens | 32.3 (11) | 58.8 (20) | |
| BCVA | 0.78 (±0.22) | 0.68 (±0.32) | 0.202 |

**Table 8.** Demographic characteristics

(*) Who squared. Data are mean (SD) or percentage (number), or median (interquartile range).

Preoperative intraocular pressure (IOP) median interquartile range (IQR).

Drugs pre: number of IOP-lowering medication before surgery

POAG: Primary open angle glaucoma

PXFG: Primary pseudoexfoliative glaucoma

MD: mean deviation

dB: decibel

IQR: interquartile range

SD: standard deviation

BCVA: Best corrected visual acuity

In the postoperative period the following variables were recorded: IOP, visual acuity, bleb characteristics, complications, depth of the anterior chamber, number of IOP-lowering drugs, number of additional surgical or laser procedures.

Goldmann's applanation tonometer was used for every IOP measurement. Hypotony was defined as a reduction in IOP of less than 6 mmHg. The type of anesthesia used during the

surgical procedure such as topical or peribulbar, the duration of the surgery, the days of hospitalization were recorded and are shown in Table 9.

| | XEN | TRAB | P value |
|---|---|---|---|
| Anaesthesia % (n) | | | <0.001 (*) |
| Topical | 52.9 (18) | 0 (0) | |
| Peribulbar | 47.1 (16) | 100(34) | |
| Surgical time, minutes (SD) | 14'9'' (5'.5'') | 39'4'' (7.8') | <0.001 |
| Hospitalization days | 1 (0) | 1.9 (0.9) | <0.001 |

**Table 9.** Type of anaesthesia, operating times, days of hospitalization. *Chi squared

### Success and failure criteria

Based on the World Glaucoma Association guidelines on clinical trial design and reports, three success criteria were defined on IOP value. Criterion A is defined by IOP values 6 mmHg ≤ IOP ≤ 12 mmHg, criterion B with 13mmHg ≤ IOP ≤ 15mmHg and criterion C with 16 mmHg and ≤18 mmHg. Failure for the specific criterion was defined with an IOP measurement greater than the upper limit or less than the lower limit for two consecutive visits.
Complete failure was considered in the presence of visual acuity equal to no light perception, the need for additional glaucoma surgical procedures, the need to restart IOP-lowering drugs. Additional postoperative procedures such as suture lysis, Nd: YAG laser procedures, bleb needling, and MMC injection were not considered as failure.

### Statistical analysis

In the descriptive statistics, the variables were summarized as mean and standard deviation. The absolute value and the percentage of frequency were used for the categorical variables. For comparisons between groups, the Wilcoxon test was used for continuous data and the chi-squared test was used for categorical variables. Kaplan-Meier curves were used to compare survival defined by criteria A, B, C for the two interventions. Log rank test was used to compare the survival distributions of the two samples. The p-value 0.05 was considered statistically significant. Statistical analysis was performed using Stata 15.1 (StataCorp LLC, College Station, TX).

**Results**

In our case series (N= 68), 34 patients underwent filtering surgery with XEN Gel Stent implantation and 34 trabeculectomy.

The demographic and ocular characteristics of the two groups are summarized in Table 8. The population under examination was homogeneous between the two groups in terms of mean age, gender, preoperative IOP, number of IOP-lowering drugs, type of glaucoma, visual field loss. A marginally significant difference was found in the status of the lens. The population undergoing XEN gel stent implantation had more pseudophakic status while trabeculectomy patients were predominantly phakic ($p = 0.051$).

Table 9 report the type of anaesthesia used during the surgical procedure, the duration of the surgery and the days of hospitalization. 100% of trabeculectomy surgeries were performed under peribulbar anaesthesia and 52% of XEN gel implant surgeries were performed with topical anaesthesia. The surgical times are significantly longer for trabeculectomy surgery as well as for the days of hospitalization following the surgery.

In the analysis of the postoperative management, we examined the number of postoperative visits performed and we found a marginally significant difference between the group of patients undergoing trabeculectomy and XEN implantation. The first group showed fewer visits at 24 months but not at 12 months. The measures of the IOP during the 48 months after surgery are shown by figure 11. The group of patients undergoing trabeculectomy experienced a more stable and lower IOP profile than the XEN group.

The number of needling procedures performed and MMCs performed are reported in Table 10 and do not show a statistically significant difference between the two groups.

Additional surgery such as trabeculectomy and revision of the filter bleb were 20% and 2.9% in the XEN group, respectively; in the group of patients undergoing trabeculectomy we found 5.88% of cases of revision of the filtering bleb.

Table 11 reports the complications observed in the two groups. The statistical analysis of the survival curves expressed with the Kaplan Meier curves were tested with the Log rank test for criterion A ($P = 0.006$), B ($P = 0.065$) and C ($P = 0.23$). They are shown by figures 12-14.

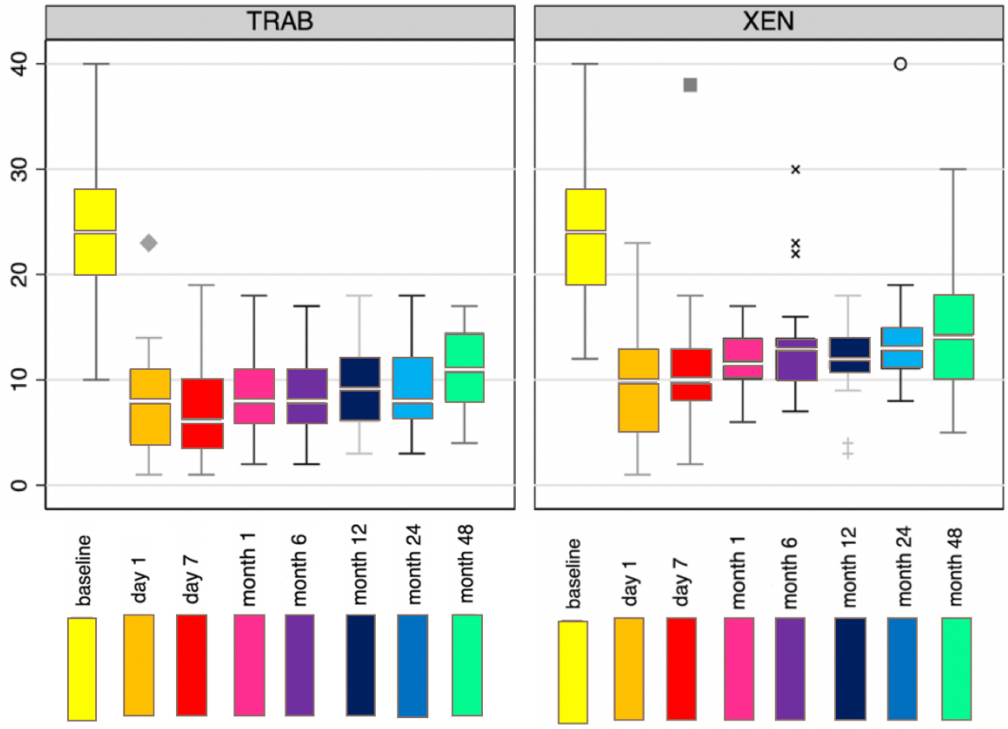


**Figure 11.** IOP values in the Trabeculectomy and XEN groups, 48 months of follow up

| | XEN (n=34) | Trabeculectomy (n=34) | p value |
|---|---|---|---|
| Visit in the first 12mo | 12.76 ± 4.41 | 10.88 ±4.87 | 0.15 |
| Visit in the first 24mo | 22.04 ±8.87 | 17.20 ±8.87 | 0.055 |
| Surgical adjustments | | | |
| Suture lysis | 0 | 15 (44.1%) | |
| Nd:YaG | 2 (5.8%) | 0 | |
| MMC* | 1,2 ±0,9 | 0.9±1,5 | 0.3815 |
| Needling* | 2.7 ± 2.8 | 1.7±3.05 | 0.2722 |
| Additional surgery | | | |
| Bleb revision | 1 | 2 | |
| Trabeculectomy | 7 | | |

* multiple procedure for single patient

Table 10: post-operative management

| | XEN (n=34) | Trabeculectomy (n=34) | p value |
|---|---|---|---|
| Choroidal detachments | 6 (17.6 %) | 2 (5.9%) | 0.13 |
| (Posterior pole not involved) | | | |
| Seidel | 1 (2.9) | 3 (8.8%) | 0.30 |
| Flat anterior chamber | 0 | 5 (14.7) | |
| Hyphema | 2 (5.9%) | 0 | |

Table 11: post-operative complications

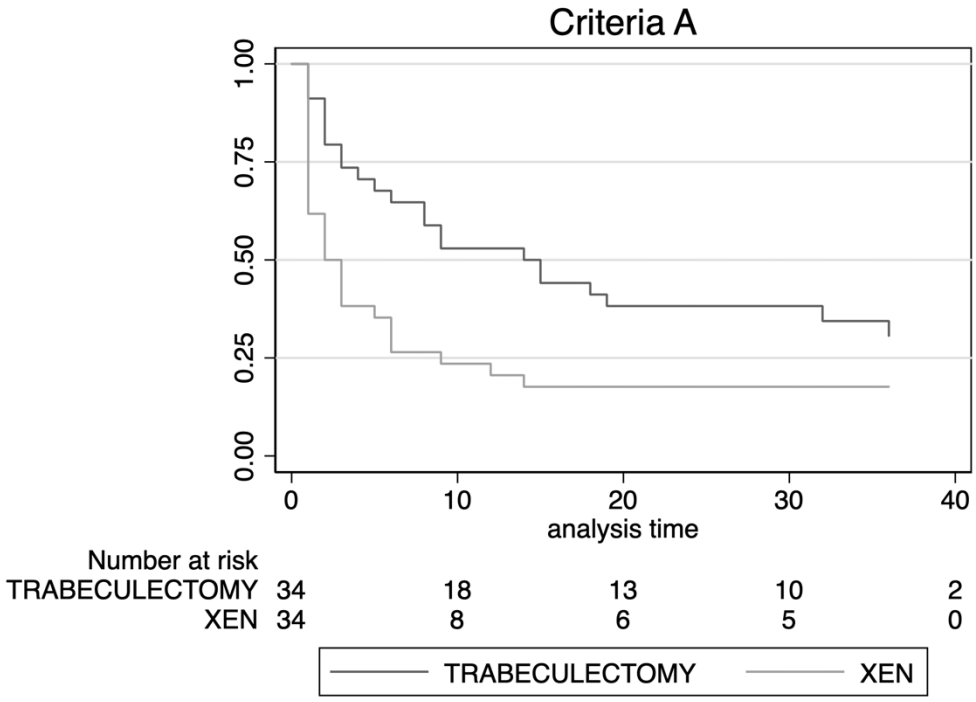


**Figure 12.** Criterion A= 6 mmHg ≤ IOP ≤ 12 mmHg. P-value= 0.006

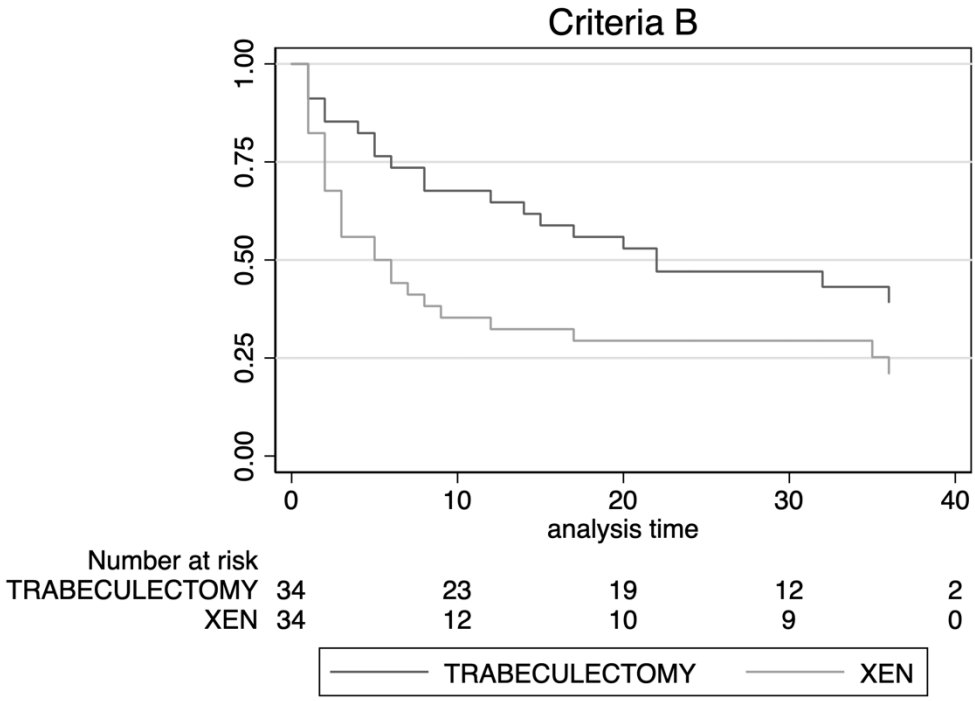


**Figure 13.** Criterion B= 13mmHg ≤ IOP ≤ 15mmHg. P-value= 0.065

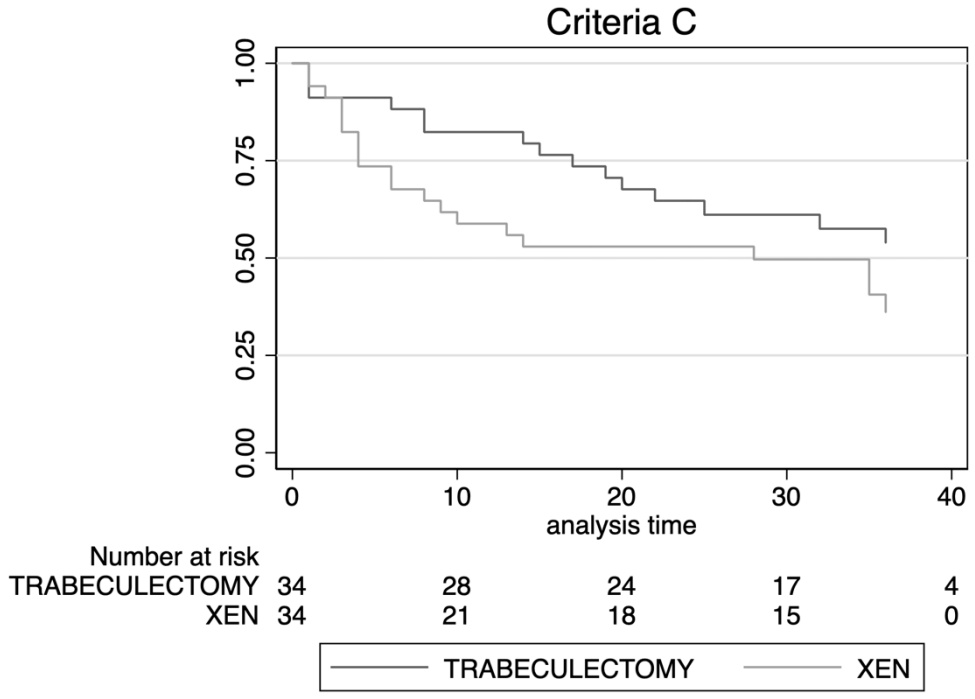


**Figure 14.** Criterion C= 16 mmHg and ≤18 mmHg. P-value= 0.23

## Discussion

Our results showed that the two cohorts of patients analysed resulted similar in terms of preoperative ocular and demographic characteristics except for the lens phakic status that was more frequently observed in the trabeculectomy group ($p = 0.051$). This difference may be due to the surgeon's personal choice. Similar preoperative IOP values and number of IOP-lowering drugs were found in the multicentre study led by Schlenker et al. Compared to this study performed on 185 patients undergoing XEN gel stent implantation and 169 with trabeculectomy our research is characterized by having a longer follow-up and a lower dropout rate.[31]

The data collected on the type of anaesthesia, on the duration of the surgery and the days of hospitalization show statistically significant differences, shown in table 9. 100% of the trabeculectomy operations were performed under peribulbar anaesthesia by choice of the surgeon and 52% of XEN gel implant surgeries were performed with topical anaesthesia. The operating times are significantly longer for trabeculectomy surgery as well as for the days of hospitalization following the surgery. This difference may be caused by the more complex surgical procedure of trabeculectomy surgery compared to XEN gel stent implantation. The longer duration of hospitalization may be due to the immediate complications of trabeculectomy such as the greater frequency of hypotonia to XEN implant surgery, as shown in Table 10 or to individual patient’s needs not related to the surgery.

In the analysis of the postoperative management of the two groups (table 10), the number of postoperative visits performed showed a marginally significant difference between the group of patients undergoing trabeculectomy or XEN implantation. The first group showed fewer visits at 24 months while the difference was not significant at 12 months. This can be justified by the greater stability of the IOP ensured by the trabeculectomy and the consequent need for fewer controls in the long-term follow-up. This hypothesis can also be supported by the analysis of mean IOP profile over 48 months and represented and graphically showed by figure 11.

The lysis value of the sutures shown in the table refers only to the group of patients operated on for trabeculectomy due to the intrinsic characteristics of the operation that requires the application of sutures, which are absent in the XEN gel stent ab internal implant. 44.1% of patients underwent suture lysis with the frequency concordant with the Schlenker study.[31]

The laser procedures performed with Nd:Yag laser application near the internal lumen of the XEN gel device were performed in 5.8% of patients. The number of procedures we performed was lower than the data in other studies.[89,90]

The number of needling procedures and MMCs performed per patient are shown in table 7 and show no statistically significant difference between the two groups under examination. Our values of filter bleb management procedures, for both groups, appear to be greater than the data described by Schlenker and more similar with the data described by the group of Midha et al.[56] The difference may probably be attributable to a more intensive and interventional management of the bleb in the post-operative period by our clinic. [29–31,56]

Additional surgery interventions such as trabeculectomy and bleb revision were 20% and 2.9% in the XEN group, respectively, and the rate of additional surgery or reoperation was generally higher in our study than in previous studies. This value can be influenced by the duration of our follow up, which was longer than in other previous similar studies.

In both study groups, we did not observed the occurrence of malignant glaucoma, endophthalmitis and exposure of the gel stent implant in the postoperative period.

The results of the survival curves show that trabeculectomy surgery offers a higher chances of maintaining a lower IOP profile in the long-term compared to XEN, in particular when the IOP target is in the low teens.

With regard to the failure and success criteria, it is important to consider that they do not represent clinical failure or success, but only statistical criteria set for data analysis. For instance, we excluded from the success criterion patients with IOP of 4-5mmHg without hypotony complications that clinically may represented a therapeutic success.

# Conclusions:

Since its introduction in the clinical practice, the XEN procedure gained popularity among glaucoma surgeons, even if a randomized control trial comparing XEN to trabeculectomy is still lacking. The XEN implantation is considered a fast and relatively minimally invasively method to achieve subconjunctival filtration and reduce IOP where the physical dimensions of the implant permit flow regulation by design.

During the last five years, observational studies have permitted to increase experience regarding long-term outcome and safety. In this scenario, our analysis has allowed identifying predictors of efficacy. We found that a post-operative IOP below or equal to 9 mmHg, which is the theoretical pressure drop of the implant, is also predictive of long-term efficacy of the procedure. These observations are meaningful for the clinician because they may permit to stratify patients for the risk of failure.

Complications denote another critical peculiarity regarding a new surgical device. We reported and analysed two relevant complications regarding the XEN implantation. CD has been associated with higher patient's age and with an increased number of IOP-lowering drugs, and the possible biological mechanisms have been extensively discussed.

We also reported cases where the implant appeared damaged during the follow-up and we described the clinical course and discussed the predicted effect of a shorter XEN device on IOP. In the last report, comparing XEN with trabeculectomy, we found that the two procedures are comparable when the success criterion is in the mid-teens but is favourable to trabeculectomy when a very low IOP target is needed.

## Acknowledgements

I would like to thank all the "XENs team" at Clinica Oculistica that, during the last 3 years, helped in the collection and analysis of data. I desire to acknowledge the director and coordinator of my doctorate, Prof. Rodolfo Quarto for his precious time and for all the support. I would also like to thank my tutor Prof. Carlo Traverso, for sharing part of his knowledge with me. A special thanks also to Prof. Iester for helping me prepare the manuscripts. In alphabetical order I would like to thank all my collaborators and colleagues: Dr. Alessandro Bagnis, Dr. Chiara Bonzano, Dr. Carlo Catti, Dr. Chiara Pizzorno, Dr. Sara Olivari, Dr. Letizia Negri, Dr. Riccardo Scotto.

## List of published articles related to this thesis:

Cutolo CA, Iester M, Bagnis A, Bonzano C, Negri L, Olivari S, Cappelli F, Testa V, Sindaco D, Pizzorno C, Scotto R, Saccheggiani M, Traverso CE. Early Postoperative Intraocular Pressure is Associated With Better Pressure Control After XEN Implantation. J Glaucoma. 2020 Jun;29(6):456-460. doi: 10.1097/IJG.0000000000001501. PMID: 32205829.

Olivari S, Cutolo CA, Negri L, Cappelli F, Testa V, Iester M, Traverso CE. XEN Implant Fracture During Needling Procedure. J Glaucoma. 2019 Dec;28(12):1086-1089. doi: 10.1097/IJG.0000000000001360. PMID: 31478952.

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