Article

XEN glaucoma implant for refractory glaucoma management: results and complications during a 2-year follow-up

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Abstract: The aim of this study was to analyze surgical and refractive outcomes of XEN glaucoma implant (Allergan, an Abbvie company, Irvine, CA, USA), a minimally invasive surgical device for the treatment of refractory glaucoma. A retrospective chart review of eyes that received XEN Gel Stent placement from December 2014 to October 2019 was conducted. Intraocular pressure (IOP) change, best corrected visual acuity (BCVA), change in glaucoma medications, frequency of slit lamp revision procedures, and frequency of secondary glaucoma surgeries were the primary outcomes. Seventy-two subjects were included in the study: 32 (44%) males and 40 (56%) females. The mean follow-up time was 26.87 ± 15.33 months. The mean IOP before surgery was 24.82 ± 8.03 mmHg and decreased to 17.45 ± 5.84 mmHg at the end of the study, MD = -7.48, CI95 [-10.04; -4.93], $p < 0.001$. The mean decrease from baseline was 23%. Before surgery BCVA was 0.38±0.30 and at the end of the follow-up period it had improved to 0.47±0.37, MD = 0.09, CI95 [0.04; 0.13], $p < 0.001$. Additional procedures (fluorouracil injection, Bleb needling) were performed in 11/72 patients (15%). Further glaucoma surgery was necessary for 23.9%% of the patients. Implantation of XEN Gel Stent is both safe and effective for lowering IOP in refractory glaucoma patients.

Keywords: refractory glaucoma; XEN implant; management; retrospective study, MIGS, glaucoma surgery, bleb, subconjunctival stent

1. Introduction

Glaucoma remains the second leading cause of blindness in the world [1], and the only known factor that can slow the progression of this disease is reduction of the intraocular pressure (IOP). Despite advanced pharmacological and surgical treatments, many cases of this disease progress to blindness [2]. Refractory glaucoma (RG) poses a challenge for the glaucoma surgeon [3]. It is defined as having an uncontrolled IOP level with associated visual field deterioration, despite maximum tolerated anti-glaucoma treatment and previous unsuccessful anti-glaucoma procedures [4]. In clinical practice, these are usually cases of neovascular glaucoma (NVG), congenital glaucoma (CG) or juvenile glaucoma (GJ), post-inflammatory glaucoma (UG), traumatic glaucoma (TG), or glaucoma resulting from previous vitreoretinal procedures (oil-induced glaucoma).

In such cases, glaucoma drainage devices (GDD) are the treatment of choice. Their effectiveness is comparable to trabeculectomy, however, they carry a relatively high risk of complications such as anterior chamber shallowing, choroidal detachment, filtering bleb leakage, blood in the anterior chamber, chronic corneal endothelial loss, hypotony, and macular edema [5, 6]. In addition, these procedures are time-consuming and require great operating skill, especially when fibrosis of the conjunctiva after previous surgeries forces the use of other quadrants of the sclera than the superior ones.

Therefore, it is imperative to search for new surgical methods that lower intraocular pressure safely and effectively. In 2016 the US Food and Drug Administration (FDA) approved the new XEN® Gel Stent implant (XEN 45 Gel Stent; Allergan plc, Dublin, Ireland)

for the treatment of open-angle glaucoma (OAG), GJ, UG and RG (CE certified in 2011). This implant belongs to the category of Minimally Invasive Glaucoma Surgery (MIGS) and its mode of action, like trabeculectomy and GDD, is to create a new route of outflow for the aqueous humor from the anterior chamber, bypassing the potential site of increased outflow resistance in the Schlemm's canal (SC) and using the subconjunctival outflow route. Similar to trabeculectomy, it is a filtration-bleb-dependent procedure. This 6 mm long gelatin implant with internal cross-sections of 140, 63, and 45, (in XEN140, XEN63, XEN45, respectively) was designed based on the Hagen-Poiseuille law, with the pressure difference along the implant depending on its length and cross-section [7]. It can be implanted with both the *ab interno* and *ab externo* approaches, with similar efficacy [8]). It is constructed with a non-absorbable, soft, cross-linked collagen tube, which is supposed to provide better biocompatibility and reduce inflammatory reactions to foreign bodies and reduce fibrosis. It hydrates within 1-2 minutes (the external dimension increases, and the internal dimension remains unchanged), which allows it to maintain the intended implant position without shifting and having to adapt to surrounding tissues. In contrast to trabeculectomy and GDD, the advantages of the implant include microinvasive *ab interno* access, sparing of the sclera and conjunctiva, eliminating the need for iridectomy and sutures, and short procedure time.

The latest MIGS procedures are routinely performed in eyes with incipient or intermediate-stage glaucoma to reduce drug burden, or as an early intervention to lower the IOP without the use of a drug or laser [9]). However, XEN is the only one among this category of procedures to use subconjunctival drainage of the aqueous humor in its mechanism of action, a pathway of aqueous humor outflow that has been the foundation of glaucoma surgery for over a century. Due to this quality, it can compete with trabeculectomy, which is considered as the gold standard in glaucoma surgery and is burdened with a high risk of complications often resulting in unpredictable outcomes and deterioration of vision [10]. Studies comparing the two treatments demonstrate similar hypotensive efficacy with a better safety profile for XEN [11-13].

The efficacy of the XEN implant was demonstrated in intermediate and incipient glaucoma [14, 15]. However, there are few studies evaluating their efficacy in refractory glaucoma [16-18] and the longest follow-up period in these studies was 12 months. Therefore, our aim was to retrospectively evaluate the efficacy of XEN implantation in 72 patients with RG, during a 24-month follow-up period.

2. Materials and Methods

This study was performed with approval from the Bioethics Committee of the Military Institute in Warsaw, in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki, and its later amendments or comparable ethical standards. All the subjects gave written and fully informed consent for the examination and the use of their clinical data for publication.

We retrospectively analyzed the data of patients undergoing XEN implantation for refractory glaucoma defined as IOP ≥21 mmHg, with a history of previous unsuccessful anti-glaucoma procedures, subject to surgeries performed by the same experienced surgeon (MR) from December 2014 to October 2019. Inclusion criteria were defined as the following: (1) patients ≥ 18 years of age with RG defined as prior treatment with surgical or cyclodestructive procedures, and (2) failure to achieve target IOP with maximally tolerated topical IOP-lowering treatment or intolerance to drugs. Both primary and secondary open- and closed-angle glaucoma cases were included in the study. If a clinically significant cataract was also observed in a phakic patient, the patient qualified for a combined procedure with phacoemulsification and implantation of an artificial intraocular lens. Other inclusion criteria were presence of healthy mobile conjunctiva in at least one quadrant and Best Corrected Visual Acuity (BCVA) better than light perception. Exclusion criteria were clinically significant inflammation or infection within 30 days prior to

surgery, history of corneal refractive surgery, corneal deposits or haze preventing intraoperative viewing of the anterior chamber, presence of an anterior chamber lens, advanced Age-Related Macular Degeneration (AMD), known or suspected allergy or sensitivity to porcine products or glutaraldehyde, pregnant or nursing women, and lack of consent to participate in the study. If the patient was taking anticoagulants before surgery, they were discontinued as supervised by the general practitioner, changed to low-molecular-weight heparin injections perioperatively, and then continued after surgery. If both eyes were eligible for surgery, the eye with the worse BCVA and visual field was operated on first.

The number of previous surgical procedures was not an exclusion criterion.

During the procedure, depending on the availability of the surgical field, the surgeon used the *ab interno* or *ab externo* technique following previously described techniques [17, 19]. In cases where only the lower quadrants were accessible, *ab externo* access was the technique of choice. All treatments were performed with 40 micrograms of Mitomycin C (MMC), which was injected under the conjunctiva at least 6 mm from the corneal limbus in the projection of the future filtering bleb (MOVIE file 1). The eyes were treated postoperatively with topical medication containing steroids (Loteprednol) three times daily for four weeks (which then where tapered to BID for a week), an antibiotic (Moxifloxacin) three times daily for two weeks, and NSAIDs three times daily for 4 weeks [20].

At the preoperative visit, the following information was obtained from the patient: age, sex, previous surgical procedures, BCVA (according to Snellen chart), IOP (measured using Goldmann applanation tonometry), mean deviation (MD) of the visual field (using the 24-2 algorithm of the Humphrey Visual Field Test), the number of IOP-lowering medications, counted as single substances or oral acetazolamide. For instance, 3 medications would be counted for an eye that was prescribed acetazolamide tablets and dorzolamide-timolol drops.

The number of anti-glaucoma medications, IOP, and BCVA were analyzed before the surgery, as well as 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, and 2 years after the surgery. From the day of the surgery, the patients had all anti-glaucoma drugs discontinued, which were restarted according to the AGIS rule if the target IOP was not achieved after surgery [21]. The final MD value at the end of the follow-up period was compared to that achieved at the first visit.

Moreover, injections with 5-fluorouracil (5FU), transconjunctival needling, and subsequent anti-glaucoma surgeries were recorded as they occurred. Additional procedures were applied when the following criteria were met: for 5FU injection (5 mg in 0.2 mL)– progressive increase in the IOP greater than 16 mmHg, the development of subconjunctival fibrosis (manifested in engorged and tortuous blood vessels above the scleral flap); for needling – diagnosing of fibrosis (based on the clinical signs above), insufficient subconjunctival outflow, the increase in the IOP or the flattening of the bleb (Figures 1-5). Injections were given for 5 consecutive days or until the fibrosis was abated and the IOP stabilized, provided that no anti-metabolite-related adverse effects occurred [22].

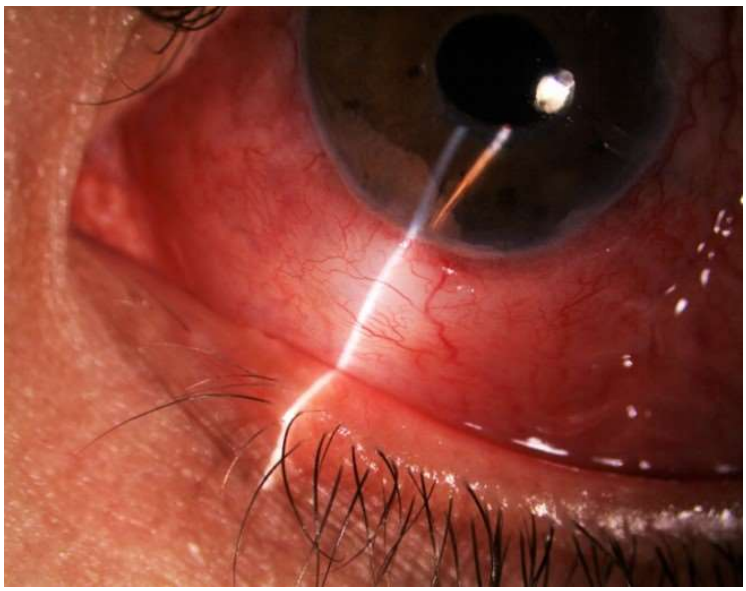

Figure 1. Bleb before needling

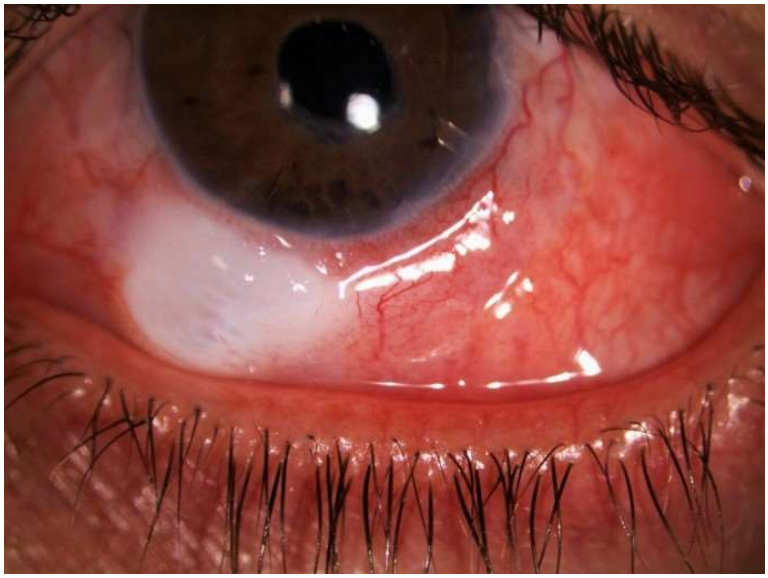

Figure 2. Bleb after needilng

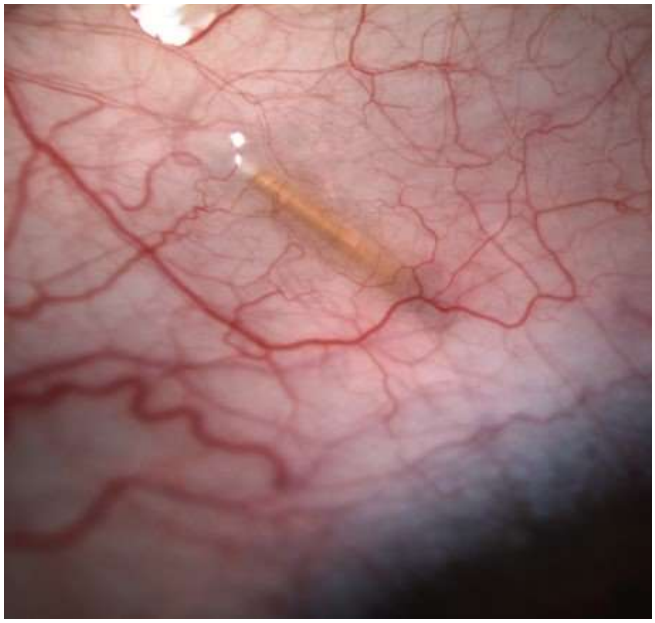

Figure 3. Fibrosis of filtering bleb

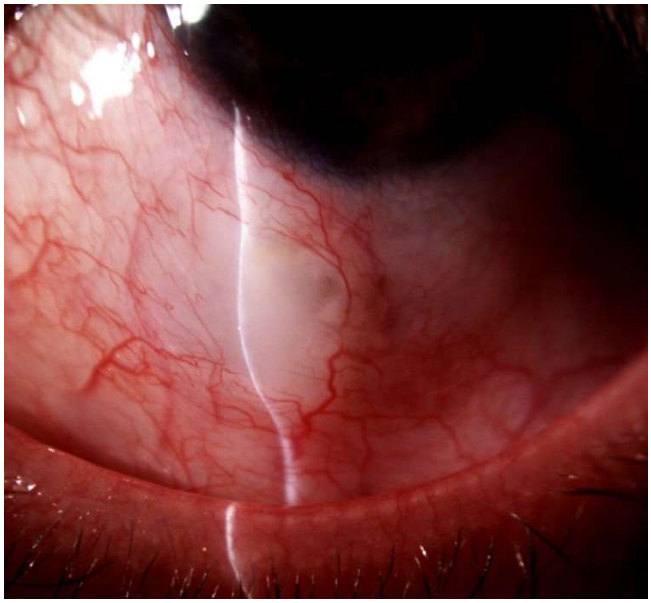

Figure 4 Filtering bleb 1 month post-op

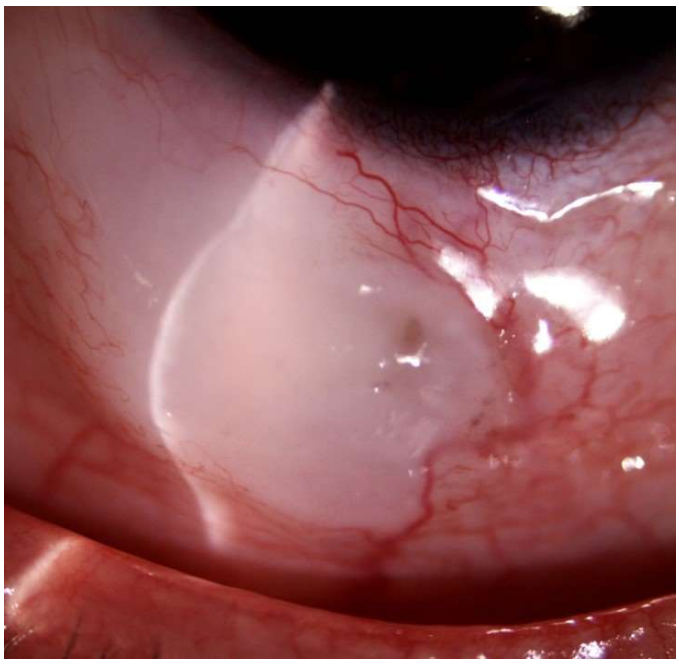

Figure 5. Filtering bleb 12 months post op

The number of complications in the form of hypotony, choroidal detachment, corneal edema and keratopathy, improper positioning (Figure 6), leakage of the filtering bleb (Figure 7), implant displacement or occlusion (Figures 8,9), bleeding into the anterior chamber (Figure 10), malignant glaucoma, and intraocular inflammation were noted. Hypotonia was defined as IOP ≤5 mmHg in two consecutive measurements at any stage of the follow-up period.

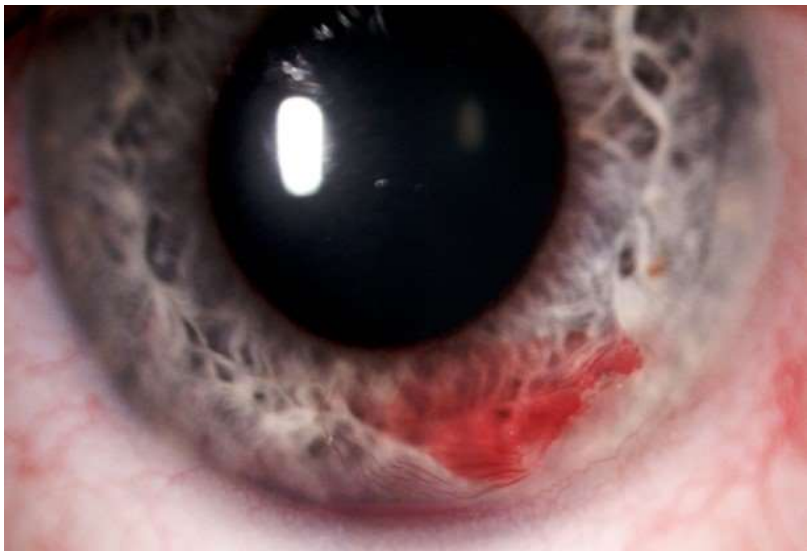

Figure 6. Complications of XEN - bleeding into anterior chamber

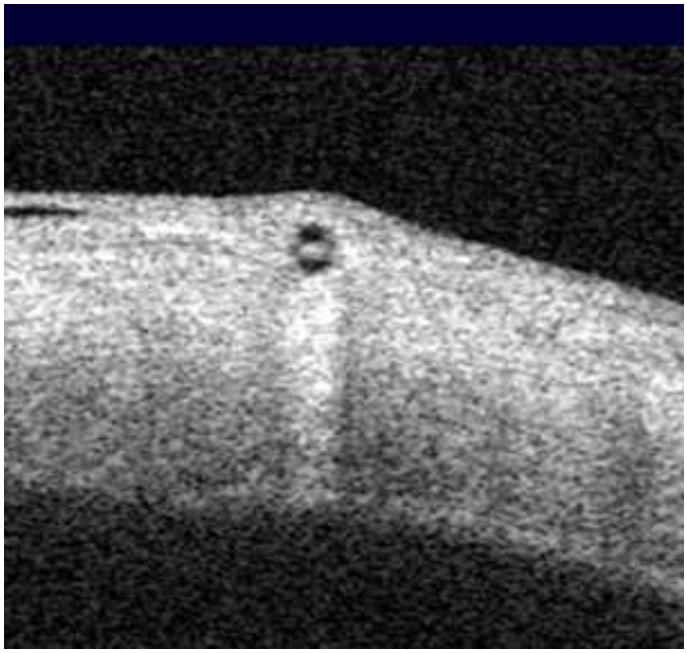

Figure 7. Complications of XEN - protrusion under the conjunctiva. OCT image

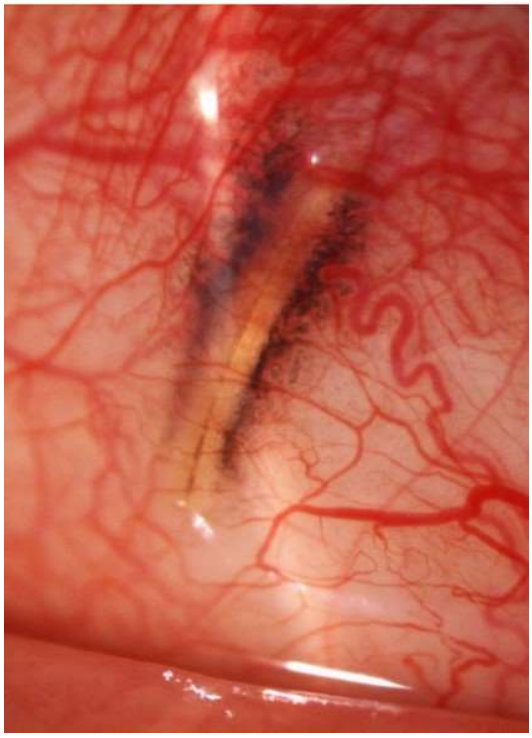

Figure 8. Complications of XEN - protrusion under the conjunctiva

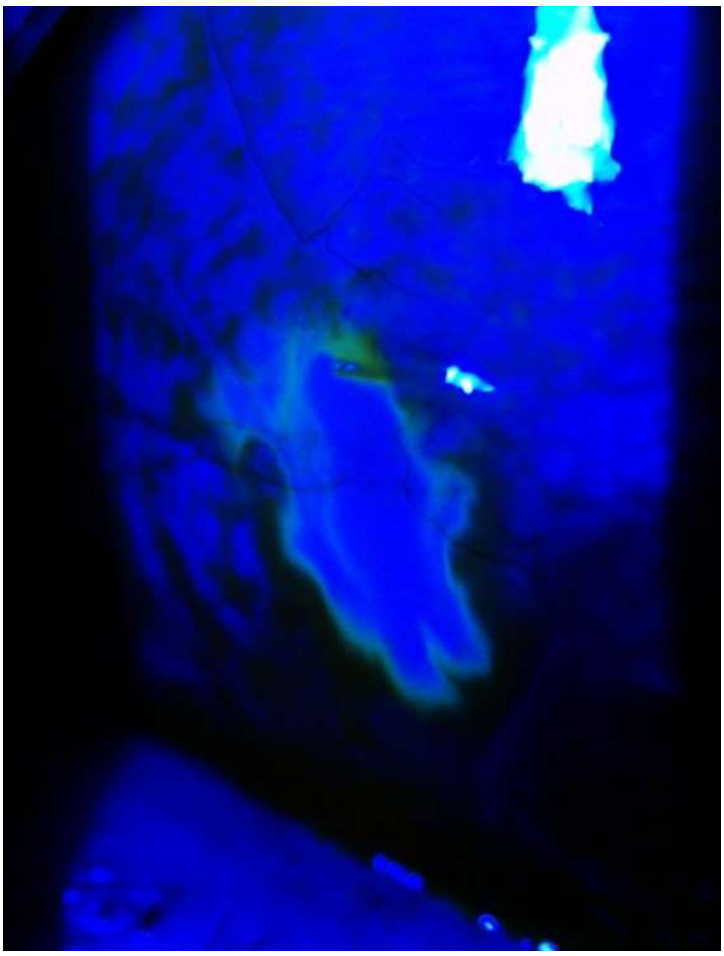

Figure 9. Complications of XEN- bleb leaking

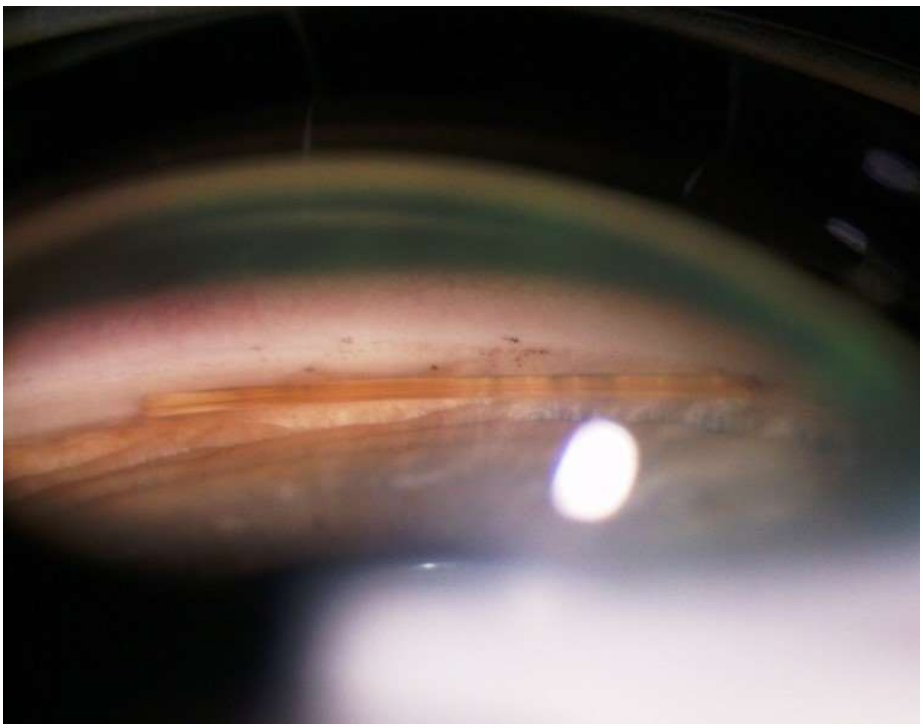

Figure 10. Complications of XEN - protrusion of XEN into anterior chamber

Total surgical success was defined as a decrease of 20% in IOP, or IOP ≤ 15 mmHg without medication. Satisfactory success was defined as a decrease of 20% in IOP, or IOP ≤ 15 mmHg with up to 2 anti-glaucoma medications.

Statistical analysis was performed using the R software, version 3.5.1. The study variables were presented using descriptive statistics. The normality of the distribution of quantitative variables was assessed using the Shapiro-Wilk test, data skewness, kurtosis indicators, and visual assessment of the histograms. The equality of variance was checked by Bartlett's test. Comparative analysis of the results between the beginning and the end of the study was performed with the Student's t-test for dependent measurements. Mean difference (MD) with 95% confidence level was also calculated. Additionally, the cumulative incidence of complete success and cumulative incidence of satisfactory success were calculated using the Kaplan-Meier survival analysis. Missing values were omitted when analyzing individual variables. A significance level of $\alpha = 0.05$ was used, and all tests were two-sided.

3. Results

3.1. Demographics

Seventy-two subjects were included in the study, including 32 (44%) males and 40 (56%) females. The mean follow-up time was 26.87 ± 15.33 months. 25 patients (35%) had POAG, 12 (17%) had PXG, 8 (11%) had glaucoma associated with developmental anomalies (Cogan syndrome, Axenfeld-Rieger syndrome), 7 (10%) had oil-induced glaucoma after vitrectomy, 6 (8%) had NG, 4 had (5%) UG, 3 (4%) had closed-angle glaucoma, 3 (4%) had secondary traumatic glaucoma, 3 (4.5%) had secondary pigmentary glaucoma, and 1 patient (1.5%) had glaucoma after choroidal melanoma treatment.

The mean age of patients at the time of surgery was 59.51 ± 18.22 years and ranged from 23 to 88 years. The duration of the subjects' glaucoma ranged from 2 months to 56

years (mean 14.38 ± 13.97 years). The median number of prior surgery was 1, with a range of 1 to 6 operations (Table 1). The treatments performed previously were: 73% of eyes had a history of trabeculectomy, 66% had undergone sclerectomy, 43% had undergone cyclodestructive procedures, 25% had undergone canaloplasty, 21% had undergone vitrectomy, 12% had undergone buckling, 10% had undergone ExPress seton implantation, 8% had undergone Ahmed glaucoma valve implantation, and 65% of patients had a history of laser trabeculoplasty.

Table 1. Characteristic of study group

	n	%	Mean (SD) / Median (Q1;Q3)	Range
N	72			
Sex				
Male	32/72	44.4		
Female	40/72	55.6		
Age at surgery, years	70		59.51 (18.22)	23 to 88
Disease time, years	66		14.38 (13.97)	2 months to 56 years
Number of earlier surgeries	68		1 (1; 2.25)	1 to 6

3.2 Intraocular pressure

The mean IOP before surgery was 24.82 ± 8.03 mmHg and decreased to 17.45 ± 5.84 mmHg at the end of the study, MD = -7.48, CI95 [-10.04; -4.93], p < 0.001. The mean decrease from baseline was 23% (Table 2).

3.3 Visual acuity

Before surgery BCVA was 0.38±0.30 and at the end of the follow-up period it had improved to 0.47±0.37, MD = 0.09, CI95 [0.04; 0.13], p < 0.001.

Table 2. Visual acuity and interocular pressure mean values, median values, standard deviations, and range before and after surgery

	n	Mean (SD)	Median	Range	MD (95% CI)	p
Visual acuity (BCVA)						
Pre-op	69	0.38 (0.30)	0.30	0.001 to 1.00	0.09 (0.04; 0.13)	<0.001
Final	59	0.47 (0.37)	0.40	0.00 to 1.00		
Change	59	0.09 (0.18)	0.05	-0.30 to 0.60		
Intraocular pressure (IOP)						
Pre-op	68	24.82 (8.03)	22.00	17.00 to 45.00	-7.48 (-10.04; -4.93)	<0.001
Final	64	17.45 (5.84)	17.00	7.00 to 38.00		
Change	64	-7.48 (10.24)	-5.00	-36.00 to 21.00		
Change (%)	64	-23.3% (32.5%)	-24.2%	-81.6% to 123.5%		

SD: standard deviation; Pre-op: pre-operatively; MD: mean difference calculated as final level minus pre-op level with 95% confidence interval; paired t-test.

Kaplan-Meier cumulative incidence of satisfactory success was 59.4% after 24 months, CI_{95} [48.2%; 73.1%], while cumulative incidence of complete success after 2 years of observation was 13.4%, CI_{95} [6.7%; 26.7%].

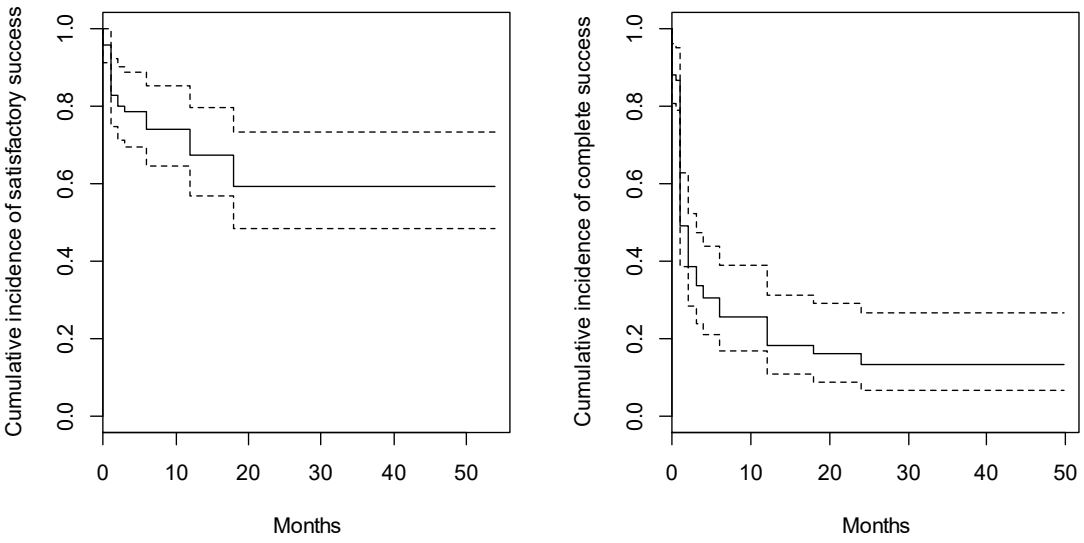

Figure 11. Kaplan-Meier cumulative incidence of satisfactory success and complete success. Dotted lines indicate 95% confidence interval. Complete success defined as IOP < 15 mmHg without drugs, satisfactory success defined as IOP < 15 mmHg with or without drugs.

At the end of the follow-up period, a decrease in BCVA compared to baseline was observed in 12/59 subjects (20%), while an increase was observed in 34/59 subjects (58%). The cases of decrease in BCVA were caused by secondary glaucoma (6 subjects – 10%), development of AMD (3 subjects – 5%), and progression of glaucomatous neuropathy (3 subjects – 5%). On the other hand, decrease in IOP level at the end of the study in relation to the baseline value took place in 49/64 subjects (77%); increase was noted in 10/64 subjects (16%). A decrease in IOP equal to or greater than 20% occurred in 9/64 patients (14.1%), representing 18% (9/49) of all patients with a decrease in IOP. A final IOP level of less than 15 mmHg affected 31/64 (48%) patients.

3.4 Additional interventions and medications

Additional procedures were performed in 11/72 patients (15%). Massage was recommended to 13/72 (18%) people. Needling was performed in 43/64 patients (67%), the median number of procedures per patient was 2 (IQR: 1.5-3), with a range of 1 to 12. A subconjunctival injection of 5-FU was required in 14/72 (19%) patients. The median for patients who took medication before surgery was 4 (IQR: 3-5), with a range of 1 to 5, while the median for medication taken after surgery was 2 (IQR: 1-4). The first drug was included after 49.5 days (IQR: 20.5-137.5).

Table 3. Clinical characteristic of study group

Characteristic	n	%	Median (Q1;Q3)	Range
BCVA change, n (%)				
Decline	12/59	20.3		
No change	13/59	22.0		
Increase	34/59	57.6		
IOP change, n (%)				
Decline	49/64	76.6		
No change	5/64	7.8		
Increase	10/64	15.6		
Decline ≥ 20%	9/64	14.1		
Decline < 20%	40/64	62.5		
IOP final level ≤ 15 mmHg	31/64	48.4		
Massage recommendation, n (%)	13/72	18.0		
Needling, n (%)	43/64	67.2		
Number of needlings	43		2.00 (1.50; 3.00)	1 to 12
Number of drugs before surgery	67		4.00 (3.00; 5.00)	1 to 5
Time to inclusion of first drug, days	54		49.50 (20.50; 137.50)	0 to 764
Final number of drugs	67		2.00 (1.00; 4.00)	0 to 4
Additinal procedures, n (%)	11/72	15.3		
Complications, n (%)	23/69	33.3		
Reoperations, n (%)	17/71	23.9		

Complications occurred in 23/69 patients (33%) and reoperations were performed in 11/72 patients (24%).

Table 4. Postoperative complications

Postoperative complications	n	%
Dellen	1	1.4
Malignant glaucoma	1	1.4
Bleeding under the choroid	1	1.4
Migration of the implant into the anterior chamber	1	1.4
Filtering bleb leakage	1	1.4
Implant occlusion	1	1.4
Bleeding into the anterior chamber	2	2.8
Incorrect placement of the implant tip under the conjunctiva	2	2.8
Corneal edema and keratopathy	2	2.8
Corneal epithelial defects and erosion	2	2.8
Inflammation of the inside of the eyeball	2	2.8

Recurrence of uveitis	3	2.8
Implant extrusion	3	4.1
Serous choroidal detachment	3	4.1
Hypotonia	4	5.5
Revision / another anti-glaucoma surgery	11	15.2
Increase in IOP > 21 mmHg	35	58

Reoperated patients (11 patients) had the following procedures: implantation of second XEN in 6 cases, trabeculectomy in 3 cases, and 2 patients had revision of fistula after XEN. Two of these patients had 2 subsequent procedures: the first one had a second XEN implanted 2 months after the procedure and trabeculectomy after another 10 months, and the second one had trabeculectomy 4 months after the procedure, and implantation of a second XEN implant after another 7 months.

4. Discussion

XEN gel implant is gaining more and more popularity among glaucoma surgeons as a natural alternative to trabeculectomy. According to our knowledge, there are few clinical trials evaluating its use in refractory glaucoma. This retrospective analysis confirms that XEN implantation effectively decreases both IOP and the number of anti-glaucoma medications in patients with this type of glaucoma, with a relatively favorable safety profile.

Grover et al. (17), in his multi-center study on advanced glaucoma (14.3% of patients) and refractory glaucoma (84.6% of patients) achieved similar results in a group of 65 eyes, over a period of 12 months. In his study, 67.6% of patients had POAG, 9.2% had PXG, 1.5% had PDG and 1.5% had mixed-mechanism glaucoma. 76.3% of eyes in his study achieved surgical success in reducing IOP ≥ 20% compared with baseline at 12-month follow-up, with the same or less medications as before the surgery. In his group, 84.6% of patients also had previous surgery. 38.5% of people in this study used no medications at the end of the follow-up period, and the mean number of medications dropped from 3.5 to 1.7 per patient. The most common complications in this study included: needling, a 2-line decrease in BCVA, transient hypotonia, and IOP spikes. No cases of intraocular inflammation were observed in this group, unlike our study, where there were two such cases. This is probably due to the surgical technique, as all procedures were performed using ab interno approach used by Grover et al. The two cases of filtering bleb inflammation that we observed in our study were in the lower quadrants, which are at increased risk of infection. Both cases showed good response to treatment; after excision of the inflamed conjunctiva and antibiotic therapy, they resolved without leaving a decrease in BCVA.

In the study, Tan et al. (23) presented an analysis of 39 cases with XEN as a solo procedure with previous treatments (30.8% cataract surgery, 7.7% trabeculectomy, 5.13% iStent). Most of his patient group had POAG, (71%), while the remaining had PXG (5.1%), UG (10.3%) PDG (2.5%), NVG (2.5%), and steroid-induced glaucoma (2.5%). Initial IOP in this group was the same as in our group (24.9±7.8 mm Hg and 24.82 ±8.03 mmHg, respectively), and final IOP after 12 months of follow-up was lower than in our group (14.5±3.4mmHg vs 17.45±5.84 mmHg, respectively); the number of medications decreased from 3 before the surgery to 0.7 after 12 months of follow-up ($p<0.005$), compared to our

group, where it was 4 before the surgery (IQR: 3-5) and 2 after the surgery (IQR: 1-4). The surgical success was higher at 62%, and total and satisfactory success was 64% , in his study. All the previous studies have a more favorable hypotensive effect compared to our results, but have half the duration of the follow-up period. In addition, given the stage of glaucoma in our study group, the target IOP was set at a relatively low level (15 mmHg), in contrast to other investigations, where an IOP of 18 mmHg was set for surgical success.

There are many papers that also analyze the efficacy of XEN in a combined procedure with cataract surgery. There are conflicting reports in the literature regarding the superiority of the solo procedure over the combined procedure with cataract surgery (24-27). Hengerer et al.(28) compared XEN 45 solo (n = 200) with XEN 45 combo (n = 39) in a retrospective single-center single-surgeon analysis of 117 patients with POAG (48.3%), 62 with PXG (25.6%), 21 with Primary Angle-Closure Glaucoma (PACG) (8.7%), 14 with NVG (5.8%), and 10 with inflammatory glaucoma (4.2%) with a 12-month follow-up period. One hundred and seventy eyes (70.2%) were subject to prior intervention, with 53 eyes (21.9%) having a prior iStent implanted, and 52 eyes (21.5%) having undergone prior trabeculectomy. The mean initial intraocular pressure treated in the XEN solo group was 31.5 ± 8.4 mmHg, with 3.1 ± 1.0 medications, decreasing to 14.3 ± 4.2 mmHg with 0.3 ± 0.7 medications, and in the XEN combo group it was 35.7 ± 12.0, with 3.3 ± 1.0 medications, decreasing to 13.9 ± 2.5 mmHg for 0.4 ± 0.7 medications at postoperative month 12. Complete success was achieved in 55.4% of eyes, and qualified success in 73%, with no significant difference between the two groups. In our opinion, as is the opinion of other authors as well (15, 26),combining the procedure with cataract surgery, as opposed to trabeculectomy, does not impair the effectiveness of the procedure. Therefore, we did not separate solo procedures and procedures combined with cataract surgery in our group.

The retrospective nature and lack of a control group are potential weaknesses of this study. However, based on our knowledge, this is the only study involving patients with a history of 1-5 anti-glaucoma surgeries with a 24-month follow-up period. It would be difficult to select a group for comparison with this material. Our group is characterized by extremely diverse cases and different mechanisms of glaucoma in different patients. Another limitation may be the fact that our study focused only on the Caucasian population. While this may be a weakness on one hand, such material is homogeneous and relates to a specific ethnic group in a given country.

5. Conclusions

Postoperative IOP increase and the need for reoperation were the most common complications of XEN implantation at 24-month follow-up. In long-term follow-up, the applied surgery appears to show promising results in patients with difficult-to-treat glaucoma and is a good alternative for patients with refractory glaucoma, owing to its minimal invasiveness. Pharmacoeconomic and quality-of-life studies in different groups of glaucoma patients are necessary to enable presenting this treatment method to patients as an alternative.

Supplementary Material: Video S1: Implantation of XEN.

Author Contributions: KL collected data from the patients. JK worked on the main text. JJ worked on figures and video. ZM reviewed whole article. MR operated patients and worked on the main text. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Institutional Review Board Statement: is study was performed in line with the principles of the Declaration of Helsinki. The protocol was approved by the Local Bioethics Committee at the Military Institute in Warsaw under the number: 5/WIM/2021

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Data Availability Statement: Readers can access the data supporting the conclusions of the study upon an e-mail request on corresponding author. The names and personal data of the participants cannot be released due to ethical aspects.

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