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ORIGINAL PAPER

Efficacy of postoperative management with 5-fluorouracil injections after XEN Gel Stent implantation

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Abstract

Purpose To evaluate the efficacy of postoperative management with 5-fluorouracil injections after XEN Gel Stent implantation.

Methods Prospective real-world evidence study included 39 eyes (of 36 patients) with primary open-angle glaucoma without previous glaucoma surgery and with uncontrolled intraocular pressure (IOP), glaucoma progression, or intolerance to IOP-lowering therapy. Patients underwent mitomycin C-augmented XEN implantation either as a stand-alone procedure or combined with cataract extraction. 5-Fluorouracil subconjunctival injections were a first-choice therapy for bleb failure and were administered according to predetermined criteria (analogous to pro re nata regimen in age-related macular degeneration treatment). Primary outcome was unqualified success, defined as postoperative IOP < 18 mmHg and $> 20\%$ reduction from medicated baseline without any antiglaucoma medications and no detected glaucoma progression.

Results At median follow-up of 8 months (range 3–24 months), IOP decreased from a medicated baseline value of 23 mmHg (95% CI 21–24 mmHg) to 13 mmHg (95% CI 12–15 mmHg) and number of medications decreased from 3 (95% CI 2–3) to 0 ($p < 0.0001$ for both). Median number of 5-fluorouracil injections per eye was 3 (95% CI 2–3), and median time to first injection was 0.5 months (95% CI 0.25–3 months) after surgery. Thirteen eyes (33.3%) underwent ≥ 1 needling, and surgical revision was performed in three cases (7.7%). The primary outcome measure, which allows performing additional procedures, was achieved in 27 eyes (69%).

Conclusions 5-Fluorouracil subconjunctival injections are safe and effective in postoperative management of bleb failure after XEN implantation and represent a viable alternative to other methods.

Keywords Glaucoma · XEN · 5-Fluorouracil · Minimally invasive glaucoma surgery · Stent

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Introduction

The introduction of minimally invasive glaucoma surgery (MIGS) devices is a recent innovation that has changed the therapeutic perspective in glaucoma surgery. One MIGS device is the XEN Gel Stent (Allergan plc, Irvine, CA), a 6-mm-long stent of collagen-derived gelatin cross-linked with glutaraldehyde [1]. In similarity with trabeculectomy, the stent allows outflow of aqueous humor from the anterior chamber (AC) into the subconjunctival space. It is placed ab interno with less damage to the ocular surface than with traditional methods, and with an inner lumen diameter of 45 μm, it limits postoperative hypotony. The procedure is often augmented with subconjunctival injection of mitomycin C (MMC) [2, 3]. The XEN Gel Stent received approval from the United States Food and Drug Administration in 2016 [4].

Although the ab interno approach prevents both the conjunctiva and Tenon's capsule from disruption, scarring and fibrosis of the bleb remain common problems. The diminished surface of the bleb limits outflow and results in increased intraocular pressure (IOP). Approaches to address this problem include 5-fluorouracil (5-FU) subconjunctival injection to inhibit wound healing, decrease scarring potential, and allow mechanical separation of the layers with the injected fluid [5, 6]; needling with or without adjunctive antimetabolite injection (to mechanically rupture tissue adhesions between the sclera and conjunctiva) [7, 8]; and surgical revision with or without adjunctive MMC to release the implant from fibrotic tissue and recreate the filtering bleb [9, 10].

As bleb needling may damage the stent [11, 12], a less invasive option than needling or surgical revision is needed for postoperative management. 5-Fluorouracil is a pyrimidine analogue and an antimetabolite used widely in oncology. Considering its proven antiproliferative effects, off-label 5-FU applications have, in recent years, become an essential adjunct in ocular and periorbital surgeries [13]. Management focused on 5-FU injections after MIGS has not been reported in the literature. Based on our experience using 5-FU injections to maintain the bleb after deep sclerectomy or trabeculectomy, we used 5-FU injections as a first-choice therapy after stent implantation in this study, with needling or surgical revision performed as needed.

The purpose of this study was to evaluate the efficacy and safety of postoperative management with 5-FU injections in the follow-up period after XEN Gel Stent implantation and to determine factors correlating with the number of interventions.

Materials and methods

Study design

This was an investigator-initiated, single-center, prospective, real-world evidence study conducted at the Department of Ophthalmology, Wroclaw Medical University, Poland. The study was approved by the local ethics committee (Approval Number KB 563/2017).

Study population

Patients with primary open-angle glaucoma (POAG) were prospectively enrolled in the study between January 2016 and February 2018 (EW, IH). Patients were included if they had any of the following characteristics: uncontrolled IOP, glaucoma progression, or intolerance to IOP-lowering therapy. Detailed inclusion and exclusion criteria for XEN implantation are shown in Supplemental Digital Content Table 1. Prostaglandin analogues, if used at enrollment, were discontinued at least 3 weeks before the surgery. All patients underwent a complete ophthalmological examination including slit-lamp biomicroscopy, fundoscopy, gonioscopy, visual field testing using standard white-on-white perimetry (Humphrey Field Analyzer [HFA] II 750; 24-2 Swedish interactive threshold algorithm; Carl Zeiss Meditec, Dublin, CA), and retinal nerve fiber layer (RNFL) thickness measurement using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). The following baseline data were recorded: age, gender, best-corrected visual acuity, preoperative IOP with Goldmann applanation tonometry, and number of different glaucoma medications. The schedule of visits and measurements is shown in Supplemental Digital Content Table 2.

Surgical technique

Patients underwent MMC-augmented XEN Gel Stent implantation either as a stand-alone procedure (in both

Table 1 Baseline demographic and clinical characteristics of the study population

	All $N = 39$ eyes	XEN (phakic) $n = 9$ eyes	XEN (pseudophakic) $n = 15$ eyes	Combined surgery $n = 15$ eyes
No. of patients	36	8	15	13
Age, years [median (95% CI)]	67 (63–69)	55 (45–69)*	69 (66–77)	68 (63–69)
Female sex, %	51	25	67	46
Preoperative medicated IOP, mmHg [median (95% CI)]	23 (21–24)	25 (19–29)*	19 (19–20)	19 (18–21)
Number of IOP-lowering medications [median (95% CI)]	3 (2–3)	3 (2–4)	2 (2–3)	3 (2–3)
Duration of follow-up, months [median (95% CI)]	8 (5–16)	4 (3–7)*	8 (5–23)	18 (9–24)

IOP intraocular pressure

*$p < 0.05$; differences between the three groups were evaluated with Kruskal–Wallis test

Table 2 Postoperative 5-fluorouracil use after XEN Gel implantation

	All $N = 39$ eyes	XEN (phakic) $n = 9$ eyes	XEN (pseudophakic) $n = 15$ eyes	Combined surgery $n = 15$ eyes
No. of eyes receiving 5-FU	30	6	12	12
No. of 5-FU injections, median (95% CI)	3 (2–3)	1 (0–2)*	3 (1–3)	3 (2–5)
Time to first 5-FU injection, months [median (95% CI)]	0.5 (0.25–3)	2 (0.25–5)	2 (0.25–4)	0.25 (0.25–2)

5-FU 5-fluorouracil

*$p < 0.05$; differences between the three groups were evaluated with Kruskal–Wallis test

phakic and pseudophakic eyes) or in combination with cataract extraction, performed by the same surgeon in all cases (IH). Under local anesthesia, 0.1 mL of MMC (concentration, 0.15–0.2 mg/mL) was injected in the superonasal quadrant, preferably under the Tenon's capsule, or subconjunctivally, if this was not possible, and was massaged over the area of anticipated implantation; the ocular surface was then rinsed.

For a stand-alone procedure, the superior nasal conjunctiva was marked 3 mm from the limbus and an inferotemporal main incision and a temporal paracentesis were created. After carbachol was applied intracamerally and the anterior chamber (AC) was filled with viscoelastic agent, the injector was placed in the main incision and a goniolens was used to confirm the exact location of the apex of the injector. With a second instrument used to provide counterforce, the injector was pushed through the area above the trabecular meshwork and sclera. As the bevel was fully visible in the previously marked area, the injector was rotated 90 °, the stent was deployed, and the injector was withdrawn. The placement and mobility of the implant in the subconjunctival space, its location in the AC, and the presence of the bleb were confirmed.

For a combined procedure, the main incision was made in the temporal quadrant and two paracenteses were created. After standard phacoemulsification and intraocular lens (IOL) implantation, the viscoelastic material beneath the IOL was removed. The remainder of the procedure was performed as described above.

Postoperative management

All local and oral antiglaucoma medications were discontinued. Patients were prescribed combined steroid and antibiotic drops six times daily for 1 week and then five times daily up to the month 1 follow-up visit. Antibiotics were then stopped, and steroids were tapered according to the morphology and

vascularization of the filtering bleb and also according to the necessity of 5-FU injections.

Follow-up examinations after surgery were scheduled with one of the authors (EW, JPD) on day 1, day 7, months 1, 3, and 6, and every 6 months thereafter up to month 24. In addition to the standard ophthalmological examination, visual field and RNFL thickness examinations were performed at the month 3 visit and each visit thereafter to assess progression of glaucoma. Extra interim visits were scheduled at the discretion of the treating ophthalmologist. IOP-lowering medications were reintroduced no earlier than 3 months after surgery, after steroids had been tapered and there was no inflammatory reaction that could affect the IOP. IOP-lowering medications were reintroduced only when 5-FU injections did not change the bleb morphology enough to decrease IOP to its target values or if the bleb morphology was ideal and there was no need for further anatomical changes. The first choice in pharmacotherapy was preservative-free prostaglandin analogues or if these were contraindicated, preservative-free beta blockers.

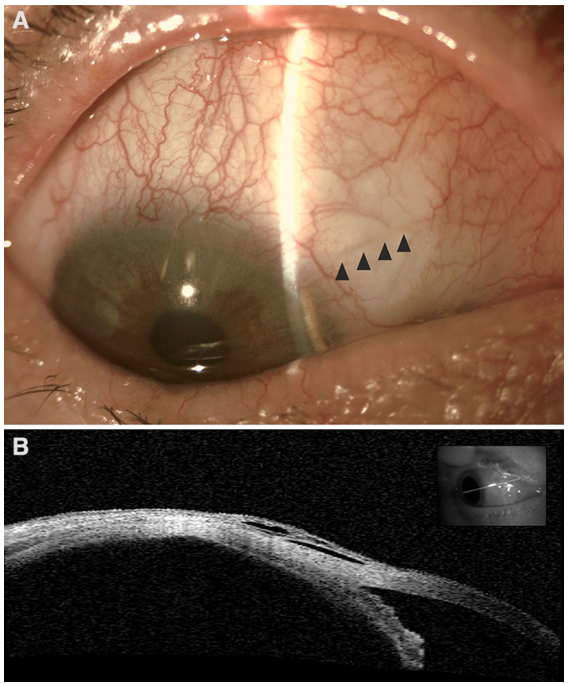

Fig. 1 **a** A vascularized bleb (arrows indicate the placement of the stent). **b** Anterior segment optical coherence tomography image of a flat bleb

5-Fluorouracil injection

Patients received subconjunctival injections of 5-FU if they met either of the following two predefined criteria: (1) the IOP spiked relative to either the immediate postoperative IOP or to postoperative IOP in the stabilization period and also exceeded target values or (2) on morphologic evaluation the bleb was flat, cystic, fibrotic, or heavily vascularized (Fig. 1). Proposed study protocol can be compared to pro re nata regimen in age-related macular degeneration treatment using anti-VEGF injections.

5-FU was prepared by the hospital pharmacy (5 mg in 0.1 ml) and was administered as a subconjunctival injection (IH). Following local anesthesia and disinfection (povidone-iodine 5%), a sterile speculum was placed and the patient was asked to look down. A 30-G needle was inserted in the margin of the bleb and moved under the conjunctiva (without sweeping movements), and 5-FU was injected into the bleb. While the needle was being removed, the insertion point was pressed with a sterile cotton swab. Following thorough rinsing to ensure that no 5-FU remained on the ocular surface, povidone-iodine 5% and dexpanthenol gel were applied and the eye was covered with dressing. After the procedure, steroid drops were applied at least three times a day [or more frequently if 5-FU was administered in the early postoperative period (first 6 weeks)], and a follow-up examination was conducted within the next 7–10 days.

If the IOP increased despite 5-FU injections and there was evidence of excessive fibrosis [for example, conjunctiva enwrapping the implant ("hot-dog" bleb morphology)] or there was difficulty applying 5-FU injections, needling was performed with a 25- to 30-G needle depending on conjunctival thickness. If neither 5-FU injection nor needling was effective and IOP was still high, revision of the bleb without MMC was performed. For safety reasons, the revision was limbus-based (with a fornix incision) to prevent any possibility of conjunctival perforation above the implant.

Outcome measures

The primary outcome measure was unqualified success of glaucoma treatment, defined as a postoperative IOP < 18 mmHg and $> 20\%$ reduction compared with the baseline value, achieved without use of any

antiglaucoma medication and with no detected glaucoma progression as assessed at the final follow-up visit (3–24 months). Glaucoma progression was evaluated with the Hodapp–Parrish–Anderson glaucoma grading scale (GGS) at months 3 and 6 after surgery and every 6 months thereafter. Additionally, the thickness of the retinal nerve fiber layer (RNFL) and rate of change in RNFL thickness were evaluated. The secondary outcome measure was qualified success, with three score categories: score A, IOP < 21 mmHg and $> 20\%$ reduction; score B, IOP < 18 mmHg and $> 20\%$ reduction; and score C, IOP ≤ 15 mmHg and $> 40\%$ reduction, with or without antiglaucoma medications and no progression in GGS in each group [14]. Therapeutic failure was specified as loss of light perception, necessity for additional glaucoma surgery, $< 20\%$ IOP reduction from baseline, or two consecutive IOP measurements > 21 mmHg at the follow-up visits.

Statistical analysis

Three patient groups were defined within the study population based on the surgical procedure: XEN implantation in phakic patients, XEN implantation in pseudophakic patients, and combined surgery. The effect of 5-FU injections on primary and secondary outcomes, the number of 5-FU injections, and time of first administration were analyzed. The primary and secondary outcome measures were assessed by a researcher (JPD) not involved with either XEN implantation or 5-FU injections. There were no missing data in the study.

Descriptive statistics including median and 95% confidence intervals (CIs) for median were used. Comparisons between two independent samples were made with the Mann–Whitney test, and for multiple independent samples, the ANOVA Kruskal–Wallis test was used; repeated measurements were analyzed with the ANOVA Friedman test. To calculate the number needed to treat (NNT) with 5-FU for any level of success, the risk difference between 5-FU treated and untreated eyes was first determined; NNT was calculated as 1/risk difference. Kaplan–Meier survival curves were used to assess the likelihood of requiring no 5-FU injection, requiring a further 5-FU injection, or requiring an additional procedure. Records were considered censored or uncensored based on the predefined success score. Statistical significance was recognized if the p value was < 0.05 for the primary outcome measure and < 0.001 for all other outcome measures. Statistical analyses were conducted using MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017) licensed by University of Science and Technology in Wroclaw. Spearman rank correlation was used to identify possible associations between primary outcome, secondary outcomes, and number of 5-FU injections and variables such as age, gender, overall preoperative medication score, different types of medication, or type of surgery, with a p value < 0.001 considered significant. The next step, linear regression analysis, was performed using the stepwise model builder from Statistica Software version 13.3 (TIBCO Statistica 1984–2017 TIBCO Software Inc.) in which each successive variable was added only if the overall fitness of the model was improved at a significance of $p < 0.05$.

Results

Patient demographics

A total of 39 eyes (from 36 patients) without previous glaucoma surgery were included in the study; two patients had combined surgery in both eyes; and one patient had a stand-alone phakic procedure in both eyes. The mean (SD) age was 65 (10) years [median, 67 years (95% CI 63–69 years)], 51% of patients were female, and all were Caucasian. Twenty-four eyes underwent XEN Gel Stent implantation alone [phakic, nine eyes (eight patients); pseudophakic, 15 eyes (15 patients)] and 15 eyes (13 patients) underwent combined surgery with phacoemulsification, performed by one surgeon in all cases. Baseline demographics of the whole group and according to type of surgery are shown in Table 1. Phakic patients who underwent implantation alone were younger, had higher preoperative medicated IOP, and were followed up for a shorter duration compared with pseudophakic patients and those who underwent combined surgery (Table 1).

5-FU use

At a median follow-up of 8 months (range 3–24 months), a median of three 5-FU

subconjunctival injections had been administered per patient, and the median time to the first injection was 0.5 months (95% CI 0.25–3 months) after stent implantation (Table 2). The requirement for 5-FU injections was significantly lower in phakic eyes that received the XEN Gel Stent (median of one injection) compared with pseudophakic eyes and eyes that had undergone a combined procedure (median of three injections for each) ($p < 0.05$). Kaplan–Meier survival analyses for attaining score B in the three groups are shown in Fig. 2. The percentages indicate the probability for a single patient to attain score B qualified success without any 5-FU injection. Combined surgery was characterized by the lowest probability (13%) of attaining score B without any 5-FU injection (observation made up to the 24 months), whereas the XEN only (phakic) had the highest probability (22%) (observations to 6 months). The median time to first 5-FU injection was significantly shorter after combined surgery (0.25 months) compared with stand-alone surgery (2 months for both phakic and pseudophakic eyes) ($p < 0.05$) (Fig. 2). Overall, nine eyes received no 5-FU injection, 20 received 1–3 injections, and ten received ≥ 4 injections.

Figure 3 shows the probability of not requiring a further injection of 5-FU in order to remain within score B for eyes that received from 0 to > 4 5-FU injections. Within a 24-month period, the probability of not requiring a further 5-FU injection was highest in patients who had received three or four injections (40% and 53%, respectively), but was considerably lower after receipt of ≤ 2 injections (range 15–19%), and lowest with > 4 injections (11% within 12 months), suggesting a lack of benefit of 5-FU administration beyond four injections.

Postoperative IOP and antiglaucoma medication use

At a median follow-up of 8 months (range 3–24 months), both IOP and number of glaucoma medications were significantly reduced ($p < 0.0001$) from preoperative values (Table 3). Median IOP decreased from 23 mmHg (95% CI 21–24 mmHg) under medication at baseline to 13 mmHg (95% CI 12–15 mmHg) postoperatively. The median number of different glaucoma medications decreased from 3 to 0. Antiglaucoma medication was still required for 11 eyes (28%); 25 of 36 patients (69%) remained medication-free.

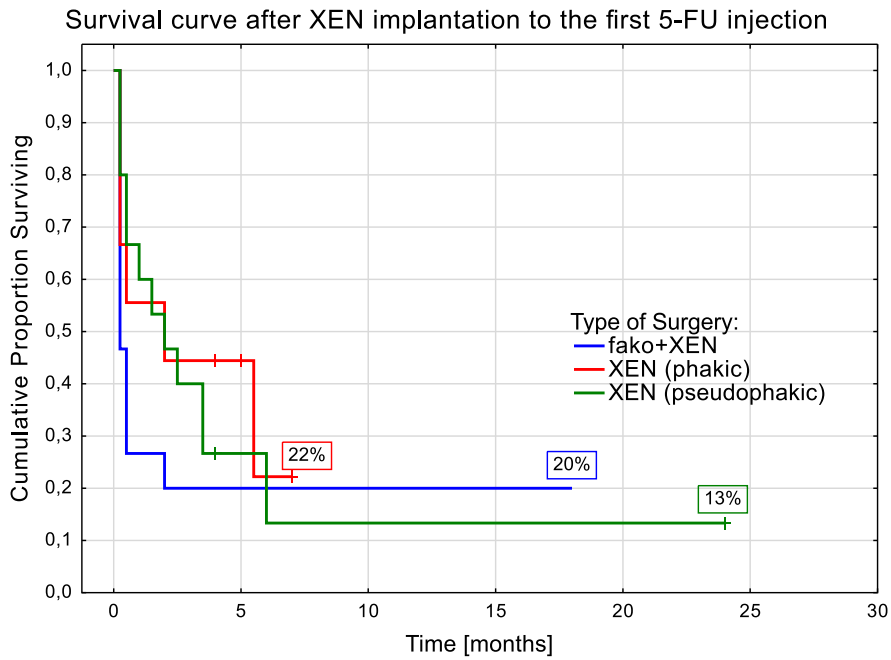

Fig. 2 Kaplan–Meier survival analysis of requirement for a first 5-fluorouracil injection after XEN Gel Stent implantation in patient subgroups, based on score B. Percentages indicate the probability of not requiring any 5-FU injection

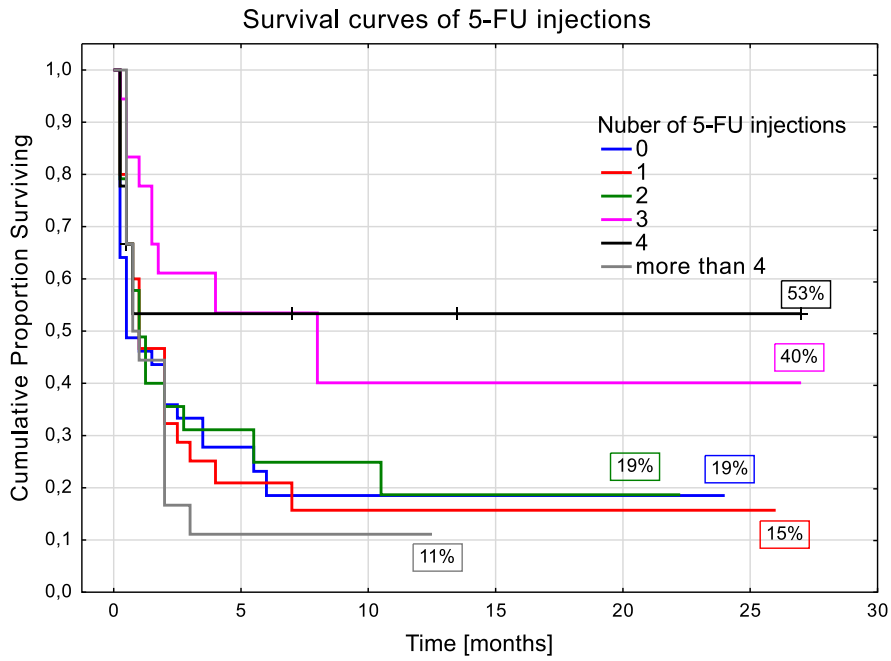

Fig. 3 Kaplan–Meier survival analysis by number of 5-Fluorouracil injections received, based on score B. Percentages indicate the probability of not requiring any further 5-FU injections

Table 3 IOP and use of IOP-lowering medications after postoperative follow-up

	All $N = 39$ eyes	XEN (phakic) $n = 9$ eyes	XEN (pseudophakic) $n = 15$ eyes	Combined surgery $n = 15$ eyes
IOP, mmHg [median (95% CI)]				
Baseline medicated IOP	23 (21–24)	25 (19–29)	19 (19–20)	19 (18–21)
Follow-up	13 (12–15)***	13 (11–15)***	13 (11–17)**	13 (12–18)*
No. of IOP-lowering medications [median (95% CI)]				
Baseline	3 (2–3)	3 (2–4)	2 (2–3)	3 (2–3)
Follow-up	0***	0*	0 (0–1)	0 (0–1)***
No. of eyes requiring IOP-lowering medications, *n* (%)	11 (28%)	0 (0%)	7 (46%)	4 (26%)

IOP intraocular pressure

*$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$, postoperative value vs preoperative value evaluated by Friedman ANOVA test

Primary and secondary outcomes

The primary outcome (unqualified success), which allows performing additional procedures, was achieved in 27 eyes (69%) (Table 4). Nine of these eyes (in nine patients) with outcome of IOP < 18 mmHg and IOP reduction > 20% did not require any additional postoperative management. In the overall group with unqualified success, the median number of 5-FU injections per eye was 1 ($p = 0.0098$) and the median number of needlings and revisions was both 0 ($p = 0.043$ for both). Unqualified success rate was higher in phakic eyes that underwent a stand-alone procedure ($n = 9$; 100%) than in pseudophakic eyes ($n = 8$; 53%) or in eyes after combined surgery ($n = 10$; 67%). Using the risk difference, the chance of unqualified success was 39% (95% CI 29–57%) lower among eyes that did not receive 5-FU ($p < 0.01$); the NNT to achieve unqualified success was 2.5.

Table 4 Primary and secondary outcomes

	All $N = 39$ eyes	XEN (phakic) $n = 9$ eyes	XEN (pseudophakic) $n = 15$ eyes	Combined surgery $n = 15$ eyes
Primary—unqualified success (IOP < 18 mmHg and > 20% reduction), *n* (%)	27 (69.0)	9 (100.0)	8 (53.0)	10 (67.0)
Secondary—qualified success, *n* (%)				
Score A (IOP < 21 mmHg and > 20% reduction)	36 (92.3)	9 (100.0)	12 (80.0)	15 (100.0)
Score B (IOP < 18 mmHg and > 20% reduction)	31 (80.0)	9 (100.0)	11 (73.0)	11 (73.0)
Score C (IOP ≤ 15 mmHg and > 40% reduction)	20 (51.0)	6 (67.0)	6 (40.0)	8 (53.0)
NNT for 5-FU injection				
Unqualified success	2.5***	ND	ND	ND
Qualified (score A)	10	ND	ND	ND
Qualified (score B)	4*	ND	ND	ND
Qualified (score C)	11	ND	ND	ND

ND not done, *NNT* number needed to treat, *IOP* intraocular pressure

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; differences in percentages in chi-square evaluated by *Z* statistics

The secondary outcome (qualified success) according to scores A, B, or C was achieved in 92.3%, 80%, and 51% of eyes, respectively (Table 4). Phakic eyes had the highest qualified success rates with all scores. Based on risk difference, the chance to achieve qualified success score B was 25% (95% CI 20–31%) lower in the group that did not receive 5-FU ($p < 0.05$); the NNT to achieve score B success was 4.

Therapeutic failure was observed in three subjects who required further glaucoma surgery (non-penetrating deep sclerectomy in two cases, cyclodiode in one case).

Factors influencing 5-FU injection and outcomes

Factors such as age, gender, overall preoperative medication number, or different types of medication did not influence either the primary or the secondary outcome. However, there was a correlation between number of 5-FU injections and both age ($r = 0.45$, $p < 0.001$) and type of surgery ($r = -0.36$; $p < 0.01$). These were confirmed in a linear regression model (age, $r^2 = 0.1$, $p < 0.01$; type of surgery, $r^2 = -0.39$, $p < 0.01$). A multiple regression model revealed that only the type of surgery was an independent prognostic factor, resulting in 40% reduction in number of 5-FU injections after a stand-alone phakic procedure.

Additional procedures

Thirteen subjects (33.3%) underwent at least one needling, whereas surgical revision was performed in three cases (7.7%) (Fig. 4). In the first case (stand-alone implantation in a pseudophakic eye), the IOP spiked to 40 mmHg but stabilized following revision at 4 months. In two cases, the stents eroded the conjunctiva (one case at 9 months after combined surgery and one case at 7 days after stand-alone implantation in a pseudophakic eye). In both cases, the implants were left in place, but were covered with a rotated conjunctival flap and were tightly sutured to avoid further leakage. The case of erosion after 7 days required deep sclerotomy 4 months later.

Complications

No major complications after 5-FU injections, such as bleb leakage, postoperative shallowing of the anterior chamber, choroidal effusion, or suprachoroidal hemorrhage, occurred. One patient with XEN in both eyes presented with binocular transient corneal edema and superficial punctate keratitis after the injections. However, these changes were due to a reduced endothelial cell count, a condition that may increase sensitivity to 5-FU injections.

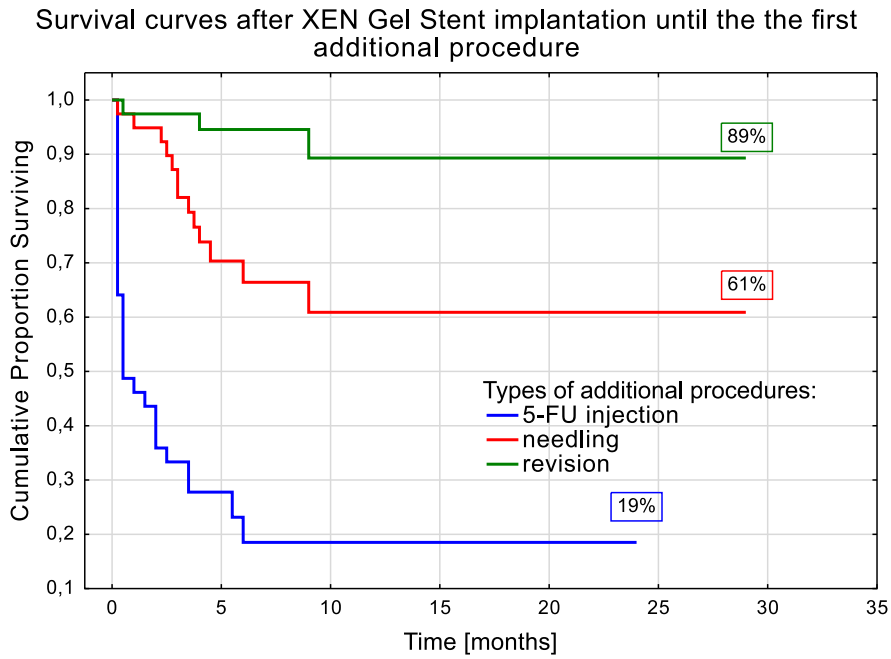

Fig. 4 Kaplan–Meier survival analysis of requirement for an additional procedure after XEN Gel Stent implantation in patient subgroups based on score A. Percentages indicate the probability of not requiring any additional procedure

Discussion

This investigator-initiated, single-center, prospective, real-world evidence study is the first study to provide data on the postoperative management of XEN implantation with 5-FU subconjunctival injections. Unqualified success, defined as achieving postoperative IOP of < 18 mmHg and $> 20\%$ IOP reduction from baseline without any antiglaucoma medications but allowing additional procedures, was achieved in 27 of 39 eyes (69%).

The efficacy of 5-FU injections in the postoperative period after different glaucoma surgeries remains to be established. A 2014 Cochrane review that examined randomized trials of postoperative 5-FU injections compared with placebo or no treatment after trabeculectomy showed that the dosage and frequency of injections were highly variable [5]. The analysis revealed that the mean risk of failure was reduced by postoperative 5-FU application both in patients after primary trabeculectomy and in those with high risk of failure (patients with previous glaucoma drainage surgery or with secondary glaucoma); there was no significant difference in the combined surgery subgroup (cataract extraction with trabeculectomy). The authors concluded that the current practice of ad hoc use of 5-FU injections in the postoperative period needs to be evaluated. Our study addresses this need and was designed for 5-FU to be administered according to predefined recommended criteria; however, we did not have defined time points for administration. As mentioned earlier, proposed study protocol is analogous to pro re nata regimen used in exudative age-related macular degeneration treatment based on anti-VEGF injections.

In our study, the lowest number of 5-FU injections was administered in phakic eyes (median of one injection, $p < 0.05$) and all achieved unqualified success. Pseudophakic eyes and eyes undergoing combined surgery not only required more 5-FU injections (median of three injections in both cases) but also had lower unqualified success rates of 53% and 67%, respectively. This finding may indicate that irrespective of the time of cataract extraction, previous intraocular surgery activates a stronger inflammatory reaction, which makes the bleb more difficult to maintain. The median time to the first 5-FU injection following combined surgery (0.25 months) was also significantly shorter, compared with a median of 2 months following stand-alone surgeries, again suggesting that a rapid inflammatory reaction quickly leads to bleb flattening and fibrosis after combined surgery, whereas the reaction is delayed after stand-alone surgery.

In the absence of a standard protocol for bleb management, a variety of interventions have been used postoperatively, including reintroduction of antiglaucoma medications in case of IOP increase. The needling rate with the XEN Gel Stent varies widely, [15] from < 3% with MMC [16, 17] to approximately 50% when performed without antimetabolites [18] or with MMC in a few cases [3]. A recent retrospective study reported that needling with 5-FU after XEN implantation resulted in a substantial IOP-lowering effect (preneedling IOP of 26.2 ± 9.5 mmHg and postneedling IOP at last follow-up of 15.4 ± 3.7 mmHg) [19].

In an evaluation of XEN implantation in which postoperative management was limited to needling with MMC, bleb revision, and reintroducing antiglaucoma medications, Mansouri et al. [20] showed that at 1 year of follow-up, median medicated IOP decreased from 19 mmHg at baseline to 13 mmHg ($p < 0.01$) and median medication rate was reduced from 2 preoperatively to 0 ($p < 0.001$). In 37% of eyes, needling was performed at least once over the follow-up period, and 28.7% of eyes required antiglaucoma medications at 1 year. In another study of the XEN Gel Stent in which postoperative management was limited to revisional surgeries only, primary success (defined as postoperative IOP of < 18 mmHg and > 20% IOP reduction with no revision) after a mean follow-up of 8.5 months (range 1–23) was achieved in 59% of subjects [21]. Qualified success, which additionally allowed one revisional surgery, was achieved in 77%; however, the mean time interval between revision and the last follow-up visit was short [5.2 months (SD 4.8)]. The rate of surgical revision was 34%.

The decrease in antiglaucoma medications in our study was comparable to that reported in the described studies, but the IOP reduction was higher. This suggests that using 5-FU in postoperative management not only increases the IOP-lowering potential of XEN, but also keeps the majority of patients medication-free, which can influence their quality of life. Based on an NNT of 2.5 for unqualified success, two of five patients will require treatment with 5-FU after XEN Gel Stent implantation to remain free of IOP-lowering medications. Compared with surgical revision, 5-FU injection is a less invasive, shorter, and easier to perform (even at the slit lamp) procedure that consumes fewer human and financial resources and does not require an operating room to be available. Thus, with similar outcomes as surgery, 5-FU injection reduces the risk of another surgery in approximately one-third of patients.

Although 5-FU is an antimetabolite with possible serious adverse effects [5, 8, 13], our study shows it can be used safely when performed meticulously as described, particularly ensuring that no 5-FU remains on the ocular surface. In our series, only one patient with XEN in both eyes developed binocular transient corneal edema and superficial punctate keratitis after the injections.

The main limitation of our study is a variable follow-up time, which was shorter in phakic patients as this kind of surgery was conducted after gaining some experience in typical procedures. Phakic patients were also significantly younger than pseudophakic patients and patients undergoing combined surgery. Additionally, as the vast majority of 5-FU injections was required in the first months after XEN implantation, we decided to include three eyes with a fairly short follow-up time (3 months) in the study—one phakic eye and two eyes after combined surgery. All patients in the first 3 months demanded a close follow-up, and that is why this period gave us a lot of essential information concerning the postoperative management. Later on the need for 5-FU injections significantly decreased. Other limitations are a small group size and lack of a control group. Defining postoperative management in a control group is difficult, and because of our positive experience with 5-FU injection after filtering surgeries, we decided to collect data on 5-FU management without a control group.

As current practice is to use 5-FU ad hoc, the results of our study have clinical implications for improving the plan of postoperative care. It is crucial to examine patients at key time periods such as the first fortnight and the second month. In our clinical practice, we inform patients that after XEN implantation, there is a 77% chance of requiring 5-FU injection postoperatively, but also a 69% medication-free IOP success rate. Because the number of 5-FU injections is correlated with both age and type of procedure, fewer interventions should be expected in younger patients after stand-alone phakic procedures. Our data also suggest that there is limited clinical benefit beyond four 5-FU injections and that needling should be considered if there are indications for additional injections.

In conclusion, this study demonstrates that 5-FU subconjunctival injections are a viable option for postoperative management after XEN implantation. 5-FU injection is a safe and effective alternative to more traditional approaches such as reintroducing antiglaucoma medication, needling, and/or revisional surgery. It does not replace other methods, but should be considered a complementary management approach. As a first-choice treatment, 5-FU injection has the potential to improve quality of life by reducing the need for IOP-lowering medications and decreasing the number of more risky interventions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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