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XEN® Gel Implant for Glaucoma; Prospective Cohort Study in a High-Volume Department

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Abstract

Purpose: To evaluate the 3-year efficiency and safety of XEN® 45 gel stent implantation in a heterogenous group of open angle glaucoma patients. **Methods:** In this prospective, non-randomized observational study we identified patients who had undergone either stand-alone XEN® implantation (XEN solo) or XEN® implantation in combination with phacoemulsification (XEN combi). All patients who had undergone an implantation during the period 01.04.17-31.10.19 at the Department of Ophthalmology, Drammen Hospital, Norway, were asked to participate. Success was defined as IOP between 5 - 18 mmHg and 20% pressure reduction without medications. Qualified success required the same pressure interval and reduction but allowed medications. The procedure was deemed as failure if pressure requirements were not met, vision was reduced to light perception or worse, or if there was a converion to secondary glaucoma surgery. **Results:** Out of 115 patients and 133 eyes identified, 87 patients and 99 eyes consented to participate. All patients were Caucasians with a mean age of 73.6 years. The study had a mean (range) follow-up of 38.9 (28 - 54) months. The mean medicated baseline (SD) was reduced from 22.6 (7.9) mmHg on 3.2 (1.1) medications to 14.2 (5.6) mmHg on 1.4 (1.6) medications. Success and qualified success were achieved in 22.2% and 21.2%, respectively. Needling was performed in 34 eyes. **Conclusion:** XEN® 45 gel stent implantation is a safe procedure, offering a significantly lower IOP and number of medications in a subset of patients with open angle glaucoma.

Keywords

Long Term Outcome after XEN® Gel Stent, Open Angle Glaucoma, OAG, Pseudoexfoliative Glaucoma, Minimally Invasive Glaucoma Surgeries, MIGS

1. Introduction

Glaucoma is globally the leading cause of irreversible blindness. As the world's population continues to grow older the incidence of glaucoma will increase. Current predictions estimate an expansion from 76 million glaucoma patients in 2020 to 111.8 million in 2040 [1]. The only known modifiable risk factor is elevated intraocular pressure (IOP) [2]. Consequently, treatment aims at reducing the IOP via medications, laser or surgery. Although effective, hypotensive drops are limited by the number of available substances, patients' compliance and adverse effects (AEs) such as ocular surface irritation and allergy [3] [4]. Laser treatment shares a low threshold for treatment, but the effect may be short lived [5]. Incisional surgeries, *i.e.*, trabeculectomy and tube-shunt surgery (Baervelt glaucoma implant and Ahmed glaucoma valve), lower the IOP by creating an alternative route for the aqueous humour (AH) to the subconjunctival space. Trabeculectomy has long been regarded as first line surgical treatment [6]. Though effective at reducing IOP and the number of medications, trabeculectomy is associated with initial volatile pressures and a significant risk of hypotony, maculopathy, choroidal detachments, bleb fibrosis and infection [7] [8]. This necessitates a close follow-up regime [9], generally leaving trabeculectomy reserved for patients with more advanced glaucoma.

Minimal invasive glaucoma surgeries (MIGS) are a novel group of IOP lowering procedures. MIGS aims at reducing IOP with minimal intraoperative tissue damage, thus causing fewer AEs and a more rapid recovery. Several products are on the market, including the XEN®45 Gel Stent (Allergan, CA, USA). This device was FDA approved in 2016 for primary open angle glaucoma (POAG), pseudoexfoliative glaucoma (PXG) and pigmentary glaucoma (PG) on maximum tolerated medical therapy. The XEN® stent is a 6 mm tube with a 45 μm lumen draining AH from the anterior chamber to the subconjunctival space. At physiological AH production the steady-state IOP is calculated to be 7.56 mmHg, preventing numerical hypotension without the need for valve mechanisms [10]. An increasing number of publications have demonstrated the efficacy and safety of the XEN® stent [11]. Most of these papers focus on the first post-operative year [12] [13] [14] [15] [16]. Recently, however, several studies have been published with up to 3 years of follow-up [17] [18] [19]. The aim of the current study was to evaluate the XEN®45 gel stent's efficiency and safety, with a mean (range) follow-up time of 39 (28 - 54) months.

2. Methods

Approvals

Study design was granted by The Regional Committee for Medical and Health Research Ethics of Health Region South-East, Norway (201124). Inclusion was by written and oral informed consent after explaining the nature and the possible consequences of the study. The study was conducted in compliance with the tenets of the Declaration of Helsinki.

Experimental design and study population

In this prospective and observational study, the target group was in house or referred patients with established OAG who had previously undergone XEN®45 Gel stent implantation. Inclusion criteria was patients treated with XEN® stent, either as a stand-alone procedure or combined with phacoemulsification, at the Department of Ophthalmology, Drammen Hospital, Norway, during the period 01.04.17-31.10.19. We identified 115 consecutive patients and 133 eyes. No patients were excluded. 12 patients died prior to inclusion, and 5 patients were unable to be reached. Due to long travel distance and/or poor general health 11 patients declined to participate. A total of 87 patients and 99 eyes, consented to participate in the study, granting us access to their medical records. They were invited back to the clinic for an additional study follow-up mean (range) 39 (28 - 54) months after primary surgery. This last follow-up was performed in the out-patient clinic by the first (HWM) or the corresponding author (TS).

Baseline measurements

Prior to operation each patient was evaluated and cleared for surgery by an experienced glaucoma surgeon. In addition to a slit lamp examination, the following parameters were registered: IOP (one-time Goldman applanation tonometry), number of glaucoma medications, best corrected visual acuity (BCVA) and spectral-domain optical coherence tomography (OCT) examination. The latter used Canon OCT-HS 100 (Canon Inc., Tokyo, Japan) to evaluate the mean retinal nerve fiber layer and central ganglion cell layer. The auto-tracking function permits scanning of the same area in follow-up visits and offers the possibility of future comparisons. Images were viewed and processed with the CR-2 RX platform software.

Surgical Technique

The XEN® gel stent is usually placed by an ab-interno approach leaving the conjunctiva untouched. The procedure may be performed isolated (XEN solo) or in combination with cataract surgery (XEN combi). At our department all study patients were treated by one of three experienced surgeons with a similar technique (ab-interno approach). The superior nasal conjunctiva was marked 2.5 mm posterior to the limbus and 0.1 mL of 0.2 mg/mL mitomycin C (MMC) was injected subconjunctival to reduce postoperative fibrosis. Clear corneal incisions, a main and a side-port, were created, and the anterior chamber filled with cohesive viscoelastica. The injector was inserted through the main corneal incision and directed across the CA towards the superonasal quadrant. Position was checked via a goniolens before entering just superior to the trabecular meshwork (TM) to minimize bleeding. The needle was advanced through the sclera into the subconjunctival space while the eye was stabilized using a Vera-hook in the side-port incision. Once the bevel was clearly visible in the subconjunctival space, the gelatin stent was released, and the injector withdrawn. Adequately placed, 2 mm of the stent would reside in the sub-Tenon space, 3 mm in the scleral wall and 1 mm freely in anterior chamber. Finally, the viscoelastica was washed out, creating a bleb.

Follow up

All participants had their postoperative consultations in accordance with department guidelines. Appointments were scheduled for day 1, week 1 - 4, as well as the 2nd and 3rd month. Study data was retrieved from the patient records on the 1st day, 1st week, 1st month, 3rd month and from the additional study follow up mean 39 months after surgery. IOP, number of glaucoma medications, AEs, needlings and secondary surgeries were recorded. In addition, OCT and BCVA was performed at the additional study follow-up.

Outcome definitions

Success was defined as IOP between 5 - 18 mmHg and 20% pressure reduction without medications. Qualified success was set to the same pressure interval and percentual IOP reduction but allowed pressure lowering drops. Failure was defined as less than 20% pressure reduction, IOP below 5 or above 18 mmHg, vision loss to light perception or worse, or conversion to secondary glaucoma surgery.

Statistics

Continuous data were described as mean with standard deviation (SD) when distribution followed a normal curve, and median and interquartile range were used for non-normally distributed values. Comparison was performed using Pearson's Chi-square test for categorized data and paired sample t-test for continuous data. Binary logistic regression was used to explore the impact of a set of predictors (age, sex, needling-rate, baseline IOP, baseline number of medications and type of glaucoma) on a categorical dependent variable (outcome). For the statistical analyses, we used SPSS version 28. Statistical significance was accepted at the 0.05 level.

3. Result

Demographics and baseline characteristics

The study included data from 99 eyes of 87 patients. The gender distribution was even, with a slight weight towards females (53.5%). All patients were Caucasians averaging 73.6 years of age with the majority having an underlying POAG diagnosis (51.5%). PXG was the second leading diagnosis, 1 patient had PG and ten patients were classified as "other" which included uveitic glaucoma. Approximately one-third of the eyes had undergone previous glaucoma surgery, mainly High Frequency Deep Sclerotomy (18 eyes) and trabeculectomy (16 eyes). XEN solo was performed in 82% of the eyes. Mean (SD) medicated IOP at baseline was 22.6 (7) mmHg on a mean (SD) of 3.2 (1.2) IOP-lowering medications. For further details see Table 1.

Treatment outcome

The study had a mean (range) follow-up of 39 (28 - 54) months with a baseline pressure of 22.6 mmHg on 3.2 medications. Preoperative oral acetazolamide was used in 22% of the patients. On day 1 the mean pressure was reduced to 9.3 (8.5) mmHg on no drops. As Table 2 and Figure 1 show, the IOP steadily increased

during the first 3 months to 15.9 (7.0) mmHg on 1.0 (1.3) medication. At follow-up mean 39 (28 - 54) months after surgery the pressure was 14.2 (5.6) mmHg on 1.4 (1.6) medications. (Table 2, Figure 1). This equates to a 36% reduction in

Table 1. Patient demographics and baseline characteristics.

Demographics/characteristics	*N = 99 eyes*
Mean age, y (SD)	73.6 (8.9)
Sex, n (%)	
Female	53 (53.5)
Male	46 (46.5)
Ethnicity, n (%)	
Caucasian	99 (100)
Type of glaucoma, n (%)	
POAG	51 (51.5)
PXG	37 (37.4)
PG	1 (1.0)
Other	10 (10.1)
Eye that received XEN, n (%) *right/left*	42 (42.4)/57 (57.6)
Operating method, n (%)	
XEN solo + MMC	81 (81.8)
XEN combi + MMC	18 (18.2)
Prior cataract surgery, n (%)	61 (61.6)
*Prior glaucoma procedure**, n (%)	35 (35.2)
Prior LTP/SLT	67 (67.7)
Mean medicated IOP, mmHg (SD)	22.6 (7.0)
Range, mmHg	11 - 45
Mean IOP lowering medications, n (SD)	3.2 (1.2)
Total number, n (%)	
1	3 (3.0)
2	14 (14.1)
3	33 (33.3)
4	40 (40.4)
5	5 (6.1)
No IOP lowering medications:	3 (3.0)
Diamox, n (%)	22 (22.2)

SD = Standard Deviation, IOP = Intraocular pressure, POAG = Primary open-angle glaucoma, PXG = Pseudoexfoliative glaucoma, PG = Pigmentary glaucoma, MMC = Mitomycin-C, LTP = Laser trabeculoplasty, SLT = Selective laser trabeculoplasty, * Prior glaucoma procedure: Several patients had undergone multiple procedures prior to XEN (e.g., I-stent (n = 5), HFDS (n = 18), Trabeculectomy (n = 16), Cyclodiode laser (n = 3)).

Table 2. Mean intraocular pressure and mean number of IOP-lowering medications at each visit.

Visit	*IOP*				*Number of IOP-lowering medications*			
	n (%)	Mean (SD), mmHg	Range, mmHg	95% CI	n (%)	Mean (SD)	Range	95% CI
Baseline	99 (100)	22.6 (7.0)	11 - 45	21.2 - 24.0	99 (100)	3.2 (1.1)	0 - 5	3.0 - 3.5
Day 1	97 (98.0)	9.3 (8.5)	1 - 50	7.6 - 11.0	98 (99)	0 (0.0)		
Week 1	99 (100)	10.7 (6.9)	1 - 42	9.3 - 12.1	99 (100)	0.2 (0.8)	0 - 5	0 - 0.3
Month 1	94 (94.9)	15.0 (7.1)	2 - 43	13.5 - 16.4	93 (93.9)	0.2 (0.8)	0 - 4	0.1 - 0.4
Month 3	56 (56.6)	15.9 (7.0)	4 - 42	14.0 - 17.8	55 (55.6)	1.0 (1.3)	0 - 4	0.6 - 1.3
Follow up (*Mean* 39 *months*)	68 (68.7)	14.2 (5.6)	3 - 50	12.9 - 15.6	68 (68.7)	1.4 (1.6)	0 - 5	1.0 - 1.8

IOP = Intraocular pressure, SD = Standard deviation, CI = Confidence interval.

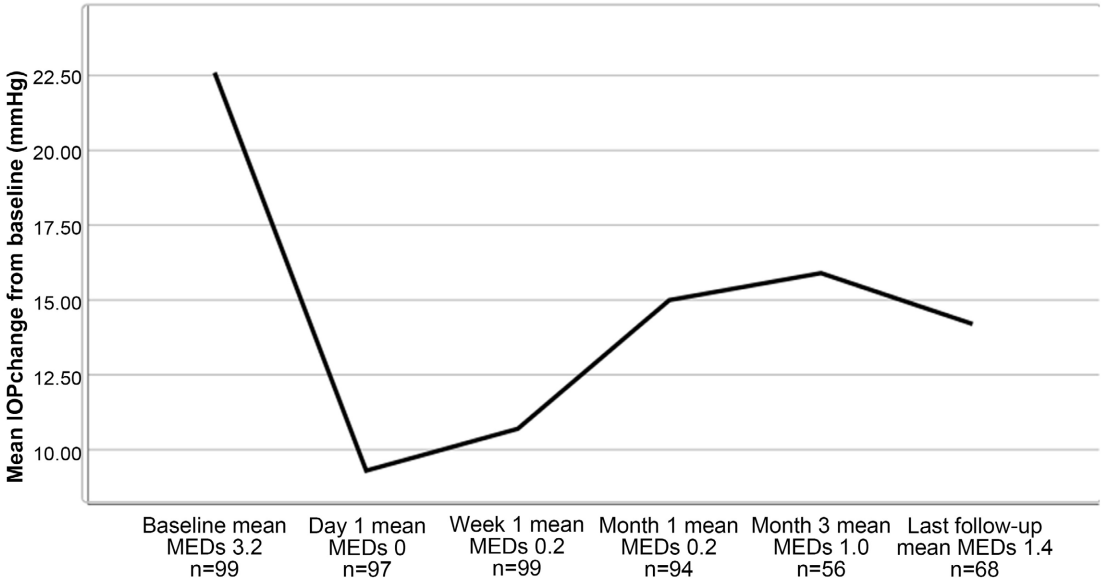

Figure 1. Mean intraocular pressure and mean number of IOP-lowering medications at baseline and at each visit after XEN® 45 gel stent implantation excluding participants who had failure requiring secondary glaucoma surgery. IOP = intraocular pressure, MEDs = number of medications, n = number of participants.

IOP as compared to the preoperative level, and a 56.3% reduction in the number of medications. Participation was steadily high during the first postoperative period. Subsequently, participation dropped to 56.6% at the third month due to a combination of follow-ups by patients own ophthalmologist elsewhere and conversion to secondary surgery intervention (SSI). The missing data at the follow-up were all due to conversion to SSI. Hence, Table 2 and Figure 1 exclude patients who had failure requiring secondary glaucoma surgery.

After mean 39 (28 - 54) months, success (as defined in the methods section) was achieved in 22.2% of patients and qualified success (as defined in the methods section) in 21.2% (Table 3). The mean changes from baseline in IOP (−8 mmHg) and IOP lowering medications (−1.8) were statistically significant (Table 4).

Table 3. Outcome as defined by success, qualified success, or failure.

Outcome	*Follow-up* (*mean* 39 *months*)
	n (%)
Success	22 (22.2)
Qualified success	21 (21.2)
Failure	56 (56.6)
	99 (100)

Table 4. Outcome.

	Baseline	*Follow-up* (*mean* 39 *months*)	
Mean IOP (*mmHg*)	22.2	14.2	p = 0.000 (paired sample t-test)
Mean number of IOP lowering medications	3.2	1.4	p = 0.000 (paired sample t-test

IOP = Intraocular pressure.

Adverse effect and intervention

Of the 99 eyes included in the study 23 (23.2%) experienced intraoperative complications and 65 (65.7%) developed postoperative complications (Table 5). Postoperative hyphema (28.3%) and transient hypotension (20.2%), defined as IOP below 6 mmHg for less than 4 weeks, was the most prevalent complications. Four eyes developed transient choroidal effusions and one eye had bleb leakage. No eyes developed serious complications *i.e.*, endophthalmitis, malignant glaucoma or retinal detachment. Mean BCVA remained unchanged at last follow-up as compared to baseline measurement and there was no significant decrease in mean retinal nerve fiber layer.

A total of 34 eyes were needled, of which 32 were needled one time and two eyes were needled twice. There was no significant difference in needling rate dependent on type of procedure (XEN solo vs XEN combi), (Chi-square, p = 0.266). Failure (defined in the methods section) was registered in 56 patients (56.6%), 31 (31.3%) were due to SSI. The remaining 25 failures did not reach the criteria of >20% pressure reduction (20 eyes) or had medicated IOP > 18 mmHg at follow-up (5 eyes).

Risk factors

Binary logistic regression was preformed to assess the impact of age, sex, needling-rate, baseline IOP, baseline number of medication and type of glaucoma on the likelihood of failure. We found a greater likelihood of failure amongst patients with a high number of medications at baseline and in those who were needled; however, only needling proved to be statistically significant (Chi-square p = 0.04).

4. Discussion

XEN® gel stent has since its approval by the FDA been increasingly recognized

Table 5. Rates of all adverse events recorded during the mean 39 months follow-up (entire population, n = 99). AC = Anterior chamber.

Adverse Effect/ Diagnosis	n (%)
*Needling**	34 (34.3)
No complication	45 (45.5)
Intraoperative complication	
Subconjunctival bleeding	3 (3)
AC bleeding	10 (10.1)
Dislocation	4 (4)
Reimplantation	6 (6.1)
Postoperative complication	
Subconjunctival bleeding	6 (6.1)
Hyphema	28 (28.3)
Corneal problems	6 (6.1)
Transient hypotension (<6 mmHg < I month)	20 (20.2)
Persisting hypotension	0
Hypotensive maculopathy	0
Choroidal effusion	4 (4)
Flat AC	0
Bleb leak	1 (1)
Blebitits	0
Endophthalmitis	0
Malignant glaucoma	0
Retinal detachment	0

*In the American Academy of Ophthalmology's (AAO) Preferred Practice Pattern for Primary Open Angle Glaucoma, bleb needling is listed as a recommended action "as necessary" in the perioperative care in glaucoma surgery to maximize the chances of successful long-term results.

as a safe and efficient device, rivaling traditional surgical options. An increasing number of papers are being published on its efficacy and safety, but few evaluate the long-term results in a clinical setting. This prospective, non-randomized observational study was conducted to evaluate the longevity and efficacy amongst a heterogenous group of OAG patients seen in a typical secondary ophthalmological department. We enrolled 99 eyes who had undergone ab-interno XEN® stent implantation with or without phacoemulsification during the interval 01.04.17 - 31.10.19, excluding no patients. Our baseline of 22.6 mmHg on 3.2 medications was significantly reduced by 8 mmHg and 1.8 medications to a new mean of 14.2 mmHg on 1.4 medications after mean 39 (28 - 54) months. Data on IOP and medications of patients with need of secondary glaucoma surgery were excluded

at the time of secondary surgery. Complete success was achieved in 22.2% of patients, and qualified success in 21.2%.

These findings are in the same range as comparable publications. Gabbay, Goldberg [19] published a three-year retrospective study including 205 eyes with XEN® implant. They included both POAG and angle closure glaucoma. The baseline IOP was reduced from 22.6 (±7.0) mmHg on 2.6 (±1.1) medications, to 14.0 (±2.9) mmHg on 0.6 (±1.0) medications. The previous year Gillmann, Bravetti [18] published a study of 149 eyes treated with XEN® implant as a standalone procedure or in combination with phacoemulsification. The study had a baseline IOP of 20.8 (±7.4) mmHg on 1.9 (±1.3) medications. After a three-year follow-up data from 92 eyes showed a reduction to a new mean of 13.1 (±3.4) mmHg on 0.4 (±0.9) medications. Similarly, Reitsamer, Vera [17] evaluated 174 eyes with a mean pressure of 20.7 mmHg on 2.5 medications. Three years after the XEN® implantation 85 eyes were reevaluated showing a new mean of 13.9 mmHg on 1.1 medications.

It is difficult to compare success-rates between studies as differences in inclusion/exclusion criteria and in the definition of success varies and have a great impact on outcome. We chose a rather strict definition of success, as defined in the method section, in combination with liberal inclusion criteria without exclusions. On this basis, we found complete success in 22.2% of patients while additional 21.2 % achieved qualified success. Gillmann, Bravetti [18] had an identical definition of outcome and found that 29% achieved complete success and 31% qualified success. In contrast to our study, Gillmann excluded all patients with terminal or refractory glaucoma, and eyes with previous history of filtering surgery. Gabbay, Goldberg [19] had a broader definition of success. They required IOP below 18 mmHg in combination with either 20% pressure reduction or any decrease in number of hypotensive drops. In their study, 61.5% were deemed as complete success, while 92.3% as qualified success. The latter allows hypotensive drops in order to meet the target. Reitsamer, Vera [17] had, in a subset of their population a similar definition of success and qualified success as we used in our study and found complete success in 35.5% and qualified success in 30.3%. They excluded all patients who required more IOP drops at any time from the data set. Further analysis shows that a relatively large proportion of our patients had medicated IOP ≤ 15 mmHg at baseline (14%), and 35% had medicated IOP ≤ 19 mmHg. This makes it challenging to achieve a 20% IOP reduction, even if IOP at follow-up lies between 5 - 18 mmHg. Eliminating the requirement of 20% IOP reduction, the percentage of patients with success and qualified success in our population was 63.6%. Subsequently, failure rate was reduced from 57.6% to 36.4%.

Our study, in synchrony with previous published studies, indicates that although there is a high complication rate, most complications are minor, transitory and self-limited. One or more intraoperative complications affected 19.2% of the patients. Furthermore, 46.5% experienced postoperative complications, none of which were serious. Most complications were associated with intraoper-

ative bleeding and postoperative hyphema, respectively 10.1% and 28.3%. Current literature present variable numbers of complications. Grover, Flynn [20] evaluated 65 patients after XEN® implantation. The study reported no intraoperative bleeding, and postoperative hyphema in 4.6%. In contrast to our study, they defined hyphema as the presence of ≥2 mm layered blood at any time. Reitsamer, Vera [17] reported a similar low intra- and postoperative AC bleeding of 3.8%, but the bleeding in the AC was only counted if occurring at more than one consecutive visit. In contrast Perez-Torregrosa, Olate-Perez [21] found a slight intra-cameral hemorrhage in 86.6% of their patients. This suggests that a slight, subclinical anterior chamber bleeding is common.

The second leading postoperative complication in our study, transient hypotony, affected 28.2% of the patients. This seems to be in finding with other studies. Tan, Walkden [15], Grover, Flynn [20] and Reitsamer, Vera [17] described hypotony in respectively 20.5%, 24.6% and 20.2% of their patients. Tan defined hypotony as pressure below 5 mmHg, while Grover and Reitsamer used the same definition as used by us in this study. As a result of hypotony, 4% of our patients developed transient choroidal effusion, none of which affected the macula. Comparable literature from Gillmann, Bravetti [18] and Widder, Dietlein [22] found choroidal effusion in 2.7% and 3.4%. Macular complications seem overall rare and were reported by Karimi, Lindfield [23] as 1.9%, and in the meta-analysis by Chen, Liang [24] as 0.91%. As seen in **Table 5** none of our patients developed serious complications. Reitsamer, Vera [17] reported one patient with retinal detachment (1.1%); Karimi, Lindfield [23] one late onset endophthalmitis and Heidinger, Schwab [25] one patient with malignant glaucoma. Overall, serious complications to XEN® gel stent implantation seem rare.

Consistent with previous reports, our study also indicates that needling may be required in a proportion of eyes with fibrosis. In our patient group needling was performed in 34.3% of the eyes. The result is comparable with current literature showing a needling-rate of 22.1% - 51.3% amongst one-year follow-up studies [12] [14] [15] [20] [22] [23] [25]. Gabbay, Goldberg [19] evaluated the needling rate after a 3-year follow-up period and found a comparable 36.6%. Our findings are, however, lower than the 36-month study by Gillmann, Bravetti [18], showing a needling-rate of 55.4%. Reitsamer, Vera [17] performed needling in 37%, 42% and 43% after respectively 1, 2 and 3 years. As there are no defined international guidelines for needling, the decision is often based on the physician's own discretion. This could in part explain the variability in needling-rates between studies.

In our data set 31 patients (31.3%) were deemed as failure due to SSI. Previous publications with one-year surveillance report a lower rate of SSI in the range of 2.4% - 16.7% [12] [13] [14] [15] [20] [23]. Gabbay, Goldberg [19] reported that 14% required SSI after one year, 22% after two years and 25% after three years. Similarly, Gillmann, Bravetti [18] reported 26.1% conversion to SSI after three years of follow-up. Reitsamer, Vera [17], however, performed a secondary oper-

ation in 12.3% of their patients. This discrepancy in SSI is possibly due to a difference in the patient population secondarily to variations in inclusion and exclusion criteria.

Our study has some limitations. The design was based on previously operated patients. This limits the use of standardized journals, leading to a risk of underreporting AEs. Moreover, our patient demographic was in several regards homogenous. The ethnicity was exclusively Caucasians with a similar age span, and with a majority suffering from either POAG or pseudoexfoliative glaucoma. Care must be employed when understanding the outcome as populations not sharing these characteristics may respond differently.

Conflicts of Interest

No conflicting relationship exists for any author.

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Abbreviations

IOP = intraocular pressure; AH = aqueous humour; POAG = primary open angle glaucoma; OAG = open angle glaucoma; PXG = pseudoexfoliative glaucoma; PG = pigmentary glaucoma; BCVA = best corrected visual acuity; OCT = optical coherence tomography; SSI = secondary surgery intervention; AEs = adverse effects; MIGS = minimal invasive glaucoma surgeries; SD = standard deviation.