ORIGINAL ARTICLE

XEN45 Gel Stent implantation in eyes with primary open angle glaucoma: A study from a single hospital in Taiwan

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Abstract

Background: To evaluate the effectiveness and safety of the XEN45 Gel Stent in East Asian patients with primary open angle glaucoma (POAG).

Methods: We retrospectively reviewed 37 medically uncontrolled POAG patients who received XEN45 Gel Stent. The primary outcomes were reduction in intraocular pressure (IOP) and in the number of glaucoma medications 12 months after surgery. The secondary outcomes were requirement for intervention and further glaucoma surgery. The adverse intraoperative and postoperative events were investigated.

Results: At the 12-month postoperative follow-up, the mean IOP was significantly reduced from the preoperative value of 21.7 ± 7.7 mmHg to 15.0 ± 2.0 mmHg ($p = 0.001$). The mean number of glaucoma medications decreased from 3.4 ± 0.9 to 1.3 ± 1.5 ($p < 0.001$). Seventeen patients (45.9%) required postoperative interventions. Four patients (10.8%) received additional glaucoma surgery. Postoperative IOP at month 1 was significantly associated with outcomes at the 12-month follow-up and the need for subsequent intervention and additional glaucoma surgery.

Conclusion: The XEN45 Gel Stent effectively reduced the IOP values and number of glaucoma medications in East Asian patients with POAG. No major complications were observed, but almost half of the eyes in the study required intervention for wound healing modification. Postoperative IOP at month 1 was a predictor of surgical success at 12 months after surgery.

Keywords: Asian Continental Ancestry Group; Glaucoma; Glaucoma, open angle

1. INTRODUCTION

Trabeculectomy has long been the gold standard procedure for the effective reduction of intraocular pressure (IOP) in patients with medically refractory glaucoma. Despite its efficacy and relative safety, the postoperative course and final outcome of trabeculectomy remain unpredictable; unpredictable visual loss reportedly occurs in up to 8% of eyes operated on.[1] Clinically, many patients postpone surgery due to fear until they reach advanced stage of glaucoma, where only limited visual functions remain. Thus, to improve the preservation of visual functions in the surgery options available to patients with medically uncontrolled glaucoma, minimally invasive surgical procedures with superior predictability and postoperative recovery are required as an alternative to trabeculectomy.

The XEN45 Gel Stent (Allergan, Dublin, Ireland) is a biocompatible hydrophilic tube composed of porcine gelatine cross-linked with glutaraldehyde. It is 6-mm long with an inner diameter of 45 μm.[2] It drains aqueous humor from the anterior chamber (AC) to the subconjunctival space. Based on the principles of laminar fluid dynamics, the XEN45 Gel Stent provides resistance of approximately 6–8 mmHg at a flow rate of 2–2.5 μL/min, thus minimizing the risk of persistent postoperative ocular hypotony.[2] The implantation of the XEN45 Gel Stent requires no incision of the conjunctiva, dissection of the sclera, or cutting part of the corneoscleral and the iris. Compared with trabeculectomy, XEN45 implantation surgery yields superior results in surgical time, patient comfort, and postoperative visual recovery time.[3,4] More reports on this minimally invasive glaucoma surgery technique have been published since 2016, but most have focused on patients of European descent. The literature is sparse regarding the efficacy and safety of XEN45 surgery for Asian patients.[5]

The prevalence of myopia is higher in East Asian individuals than in individuals of European descent,[6] and myopia was reported as a risk factor for primary open angle glaucoma (POAG).[7] Considering that trabeculectomy may be more challenging in highly myopic eyes,[8,9] a study should investigate whether a minimally invasive surgery technique, such as

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Conflicts of interest: C. Jui-Ling is the principal investigator (PI). Y.-C. Ko and M.-J. Chen are the co-PI of a study sponsored by Allergan, Protocol 1924-701-007—A Prospective, Multicenter Clinical Trial Designed to Evaluate the Safety and Effectiveness of the XEN45 Glaucoma Treatment System in Patients with Angle Closure Glaucoma. C. Jui-Ling, Y.-C. Ko, and M.-J. Chen have received honorarium from Allergan. Allergan has no role in the conduct, design, or analysis of this study.

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XEN45, renders glaucoma filtration surgery less challenging in eyes with myopia. In addition, East Asian individuals were reported to experience lower success rates and higher complication rates after trabeculectomy.[10] Therefore, the efficacy and safety of XEN in Asian populations require further evaluation.

In this study, we reviewed consecutive patients with POAG who received XEN45 Gel Stent implantation in our hospital, and we compared our results with those of other reports.

2. METHODS

2.1. Design and participants

This is a retrospective study from a single referral centre. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional review board of Taipei Veterans General Hospital. We reviewed medical records of all patients with POAG who had received standalone implantation of XEN45 Gel Stent from March 2018 to April 2019. Patients who had received prior trabeculectomy, glaucoma drainage device implantation, or cyclophotocoagulation were excluded.

All patients had undergone a comprehensive preoperative ophthalmic examination, whose measurements included the spherical equivalent and best-corrected visual acuity (BCVA) (measured using standard Snellen charts and recorded in terms of the logMAR charts with conversion) as well as results from slit lamp biomicroscopy, Goldmann applanation tonometry, and fundoscopy. The Humphrey visual field (Carl Zeiss Meditec AG, Dublin, CA) SITA Standard 24-2 protocol had been performed within 6 months of surgery. The axial length was measured using LenStar LS-900 (Haag-Streit AG, Koeniz, Switzerland) or IOLMaster (Carl Zeiss, Jena, Germany) biometers. The following data were also recorded: age, sex, laterality of the operated eye, number of glaucoma medications taken, duration of glaucoma medical therapy, and history of ocular laser treatment or surgery. Fixed-combination glaucoma medications, such as timolol-dorzolamide, were counted as two medications.

The number and type of intraoperative complications were recorded. As for postoperative data, the IOP and number of glaucoma medications were recorded during the follow-up period from day 1 to month 12. Postoperative refractive error, BCVA, and visual field tests at the 6- and 12-month follow-up visits as well as the occurrence of adverse events, interventions, and further glaucoma surgeries were recorded. If additional glaucoma surgery or XEN stent removal was conducted, the data after these surgeries were excluded from the final analysis.

Complete success was defined as a patient being medication-free, having $6 \leq IOP < 18$ mmHg, and not needing additional glaucoma surgery at 12-month postoperative follow-up. Qualified success was defined as a patient with or without glaucoma medication and, as complete success, having $6 \leq IOP < 18$ mmHg, and not needing additional glaucoma surgery at 12-month postoperative follow-up. Failure was defined as a patient having IOP ≥ 18 mmHg or < 6 mmHg at the 12-month follow-up, requiring additional glaucoma surgery such as trabeculectomy, or receiving XEN stent removal. The occurrence of subsequent interventions, such as focal laser iridoplasty for tube occlusion and subconjunctival injection of mitomycin C (MMC) with or without needling revision, was recorded but not defined as surgical failure. Mitomycin C injection was performed when increasing fibrotic activity was noted, and needling would be performed simultaneously if there was visible traction or occlusion by fibrotic tissue around XEN opening. The selection of 18 mmHg as the cut-off value was based on the findings of the Advanced Glaucoma Intervention Study, in which patients with an IOP of <18 mmHg at all visits exhibited the lowest risk of visual field deterioration.[11]

Statistical analysis was conducted using SPSS (version 20; IBM Corporation, Armonk, NY). A Wilcoxon signed-rank test was used to compare preoperative and postoperative values of mean IOP, number of glaucoma medications, BCVA, spherical equivalent, and mean deviation of visual field. A Cox regression and log-rank test were used to evaluate the associations between each patient characteristic, namely, age, lens status, preoperative BCVA and IOP, number and duration of preoperative glaucoma medications, preoperative visual field mean deviation, axial length, and postoperative IOP, and the success rates, the probability of subsequent interventions and additional glaucoma surgery. A p value of <0.05 indicated statistical significance.

2.2. Surgical technique

Operations were performed under topical anesthesia. A subconjunctival injection of 0.1 mL of MMC 0.2 mg/mL was administered over the superior nasal quadrant, at least 5 mm away from limbus, at the beginning of the surgery. The MMC solution was massaged away from the limbus using a cotton swab. A temporal corneal incision and a side-port incision were made. The AC was filled with Healon GV Ophthalmic Viscoelastic Device (OVD) (Abbott Medical Optics, Santa Ana, CA). The injector preloaded with the XEN45 Gel Stent was advanced to the target angle (superior nasal quadrant of the eye), and the stent was placed in the designated position with the internal entry anterior to the trabecular meshwork. The position of the stent was confirmed through gonioscopy, the mobility of the distal portion of the stent beneath the conjunctiva was verified, and the OVD was removed.

Topical steroid prednisolone acetate ophthalmic suspension 1% (Pred Forte; Allergan, Inc., Irvine, CA) was applied after the operation, administered every 2 hours initially and then gradually tapered over the following 2-3 months according to the degree of intraocular inflammation and conjunctival hyperemia. Topical antibiotic eye drops were used for the first two postoperative weeks.

3. RESULTS

A total of 37 eyes from 37 patients (24 of whom were men, and 13 of whom were women) were eligible for the study. All patients were Chinese ethnicity, with a mean age of 53.4 ± 13.6 years. The preoperative baseline ocular characteristics of all the eyes are listed in Table 1. All patients maintain follow-up in our hospital, but only 30 patients completed 12-month follow-up while we started statistical analysis of this study.

The mean IOP decreased from 21.7 ± 7.7 mmHg preoperatively to 13.4 ± 8.6 mmHg at 1 day, 10.3 ± 3.5 mmHg at 1 week, 15.0 ± 5.7 mmHg at 1 month, 16.2 ± 5.0 mmHg at 3 months, 15.4 ± 4.9 mmHg at 6 months, and 15.0 ± 2.0 mmHg at 12 months after surgery (all $p < 0.05$) (Fig. 1). The mean number of glaucoma medications reduced from 3.4 ± 0.9 preoperatively to 1.3 ± 1.5 at the 12-month follow-up visit ($p < 0.001$). The preoperative and postoperative BCVA, spherical equivalent, and mean deviation of the visual field did not significantly differ.

Data on adverse events and postoperative procedures are listed in Table 2. Bleeding from the needle insertion site of the chamber angle was mild and transient; only one eye had layered hyphema of <1 mm postoperatively. Eleven eyes had shallowing of AC during the first two postoperative weeks, and nine had numerical hypotony, but none developed hypotony maculopathy. A transient IOP spike of ≥30 mmHg occurred in three eyes at postoperative day 1, which resolved after ocular massage, and none required further intervention or surgery to control the IOP. The average IOP on day 1 was 11.2 ± 4.5 mmHg after removal of the three extreme values. Exposure of the XEN45 Gel Stent was noticed at the 8-month follow-up visit on one 72-year-old

Table 1

Patient demographics and baseline ocular characteristics (n = 37)

Operated eye, n (%)	
Right	16 (43.2%)
Left	21 (56.8%)
Lens status at operation	
Phakic	28 (75.7%)
Pseudophakic	9 (24.3%)
Best-corrected visual acuity, logMAR	
Mean ± SD	0.38 ± 0.57
Range	0.00 to 3.00
Spherical equivalent, diopter	
Mean ± SD	–5.13 ± 4.44
Range	–13.63 to +2.88
Intraocular pressure, mmHg	
Mean ± SD	21.70 ± 7.72
Range	12.0 to 50.0
Number of glaucoma medication	
Mean ± SD	3.43 ± 0.87
Range	2.0 to 5.0
History of glaucoma medical therapy, mo	
Mean ± SD	87.7 ± 68.9
Range	12.6 to 359.7
Visual field mean deviation, dB	
Mean ± SD	–13.09 ± 8.06
Range	–27.51 to +1.54
Axial length, mm	
Mean ± SD	26.67 ± 1.65
Range	23.00 to 29.34
Previous laser treatment or surgery, n (%)	
Argon laser trabeculoplasty	5 (13.5)
LASIK	2 (5.4)

LASIK = laser-assisted in situ keratomileusis surgery.

patient who had received glaucoma medications for almost 20 years. The stent was removed before any sign of infection was observed.

Among the eyes of the 30 patients who were included in the 12-month follow-up analysis, complete success was achieved in 11 eyes (36.7%) at month 12, qualified success was achieved in 23 eyes (76.7%), and failure in 7 eyes (23.3%) (Fig. 2). Among the eyes with treatment failure, four eyes received trabeculectomy, one eye received XEN stent removal, and two eyes had IOP exceeding 18 mmHg despite the use of multiple antiglaucomatous medications. The failure rate did not differ between eyes that received wound modification procedure or not (p = 0.400 by Pearson's chi-squared test).

Complete success was more likely for eyes with a better preoperative visual field mean deviation and lower IOP at day 1, week 2, and month 1 (Table 3). Qualified success was more likely for eyes with lower preoperative IOP and lower IOP at month 1. Notably, eyes with lower IOP at month 1 and month 2 were less likely to require subsequent intervention, and eyes with a lower preoperative IOP and lower IOP at month 1 were less likely to require additional glaucoma surgery.

In short, a lower IOP at the month-1 visit was associated with a higher complete and qualified success rate as well as a lower need for further intervention and additional glaucoma surgery. These associations remained statistically significant after multivariate analysis. When the two eyes that received subsequent intervention within the first postoperative month were excluded from the analysis, the association of IOP at month 1 with the need for subsequent intervention remained statistically significant.

4. DISCUSSION

Our study investigated the efficacy and safety of the XEN45 Gel Stent in East Asian patients with POAG. At the 12-month postoperative follow-up, the mean IOP dropped 30.9% and mean number of glaucoma medications reduced 2.1 from their preoperative counterparts. The complete success rate was 36.7%, and the qualified success rate was 76.7% 12 months after surgery.

There were several studies regarding XEN45 Gel Stent with at least one-year follow up.[3,4,12–28] Direct comparisons among these studies are impossible because of differences in factors such as patient characteristics, study designs, surgical techniques, and definitions of success. The above-mentioned studies demonstrated a postoperative IOP reduction of 19.8% to 65% at the last follow-up visit and a decrease in glaucoma medication ranging from 0.87 to 3.07 (Supplementary Table 1 http://links.lww.com/JCMA/A61).[3,4,12–28] Regardless of how high the preoperative IOP was, a mean IOP around mid-teens was achieved after XEN surgery, with a substantial decrease in the number of glaucosma medications throughout the first year.[22]

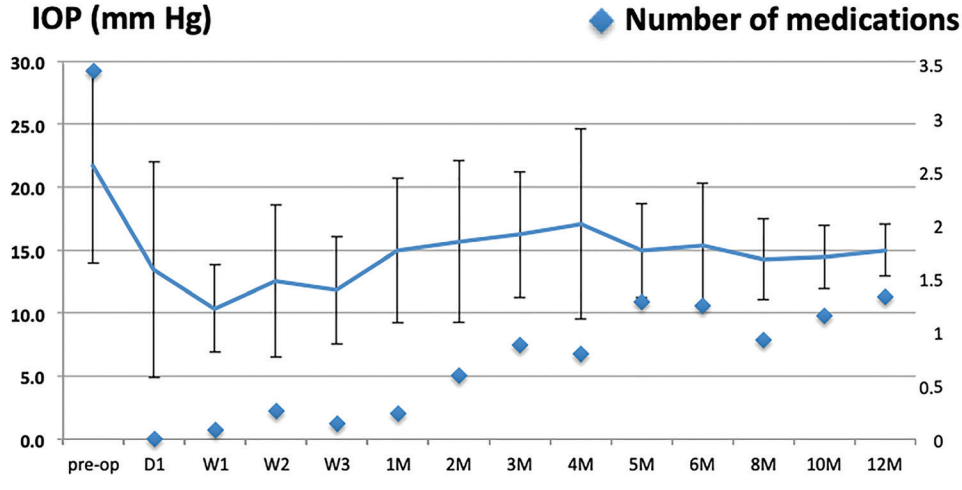

Fig. 1 Changes in the mean intraocular pressure (IOP) and mean number of glaucoma medications from baseline to 12 mo' follow-up. Error bars indicate the SD of the mean IOP. Triangles denote the mean number of medications used at each time point. If additional glaucoma surgeries or XEN stent removal were required, the data after the surgeries were not included in this analysis.

Table 2

Intraoperative and postoperative adverse events, subsequent interventions, and additional glaucoma surgery

Intraoperative adverse events, n (%)	
Subconjunctival hemorrhage	16 (43.2)
Anterior chamber angle bleeding	5 (13.5)
Stent malposition requiring repositioning	4 (10.8)
Postoperative adverse events, n (%)	
Transient shallow anterior chamber	11 (29.7)
Transient numerical hypotony (≤6 mmHg)	9 (24.3)
IOP spike (≥30 mmHg) at day 1	3 (8.1)
Hyphema	1 (2.7)
Exposure of XEN Gel Stent	1 (2.7)
Subsequent interventions, n (%)	
Total number of cases	17 (45.9)[a]
Subconjunctival injection of MMC	6 (16.2)
Subconjunctival injection of MMC with needling revision	12 (32.4)
Laser iridoplasty for tube occlusion	1 (2.7)
Additional glaucoma surgery, n (%)	
Trabeculectomy	4 (10.8)

IOP = intraocular pressure; MMC = mitomycin C.
[a]Two patients received both subconjunctival MMC injection and subconjunctival MMC injection with needling revision.

The success rate for IOP control following XEN45 gel implantation varied across studies. The qualified success rate of 76.7% in this report falls in the average of many other studies. However, the rate of intervention for wound healing modification in this study was 45.9% during the 1-year follow-up, which is comparable with the rate reported by Fea et al. (50%),[14] Sng et al. (62.5%),[18] Tan et al. (51.3%),[4] and Reitsamer et al. (67.5%)[24] but higher than the rates reported in other studies (ranged from 5% to 44.1%).[3,12,13,15–17,19–23,25–28] The relatively high revision rate could possibly be attributed to the relatively young age (53.4 years) and East Asian ethnicity of our study population. Young age has been shown to be a significant risk factor for trabeculectomy failure.[29–31] The average ages for most previous studies ranged from 65 to 78 years old,[3,4,12–16,18–24,26–28] but only five patients (13.5%) in our study were older than 65 years of age. A Singaporean study including patients with uveitic glaucoma with a mean age of 46 years found a high intervention rate (62.5%).[18] By contrast, a United Kingdom study that also included patients with uveitic glaucoma of a similar average age (45.3 years) demonstrated an intervention rate of 13.5%.[26] These findings have indicated that ethnicity may influence the rate of intervention following XEN surgery. Although Schlenker et al.[13] reported that the correlation between the surgical success of XEN surgery and ethnicity (European descent vs non-European descent) was not apparent, their study included 148 (80%) patients of European descent and only 18 (9.7%) patients of Asian descent. Further studies are warranted to clarify the effects of ethnicity on the surgical success of XEN surgery.

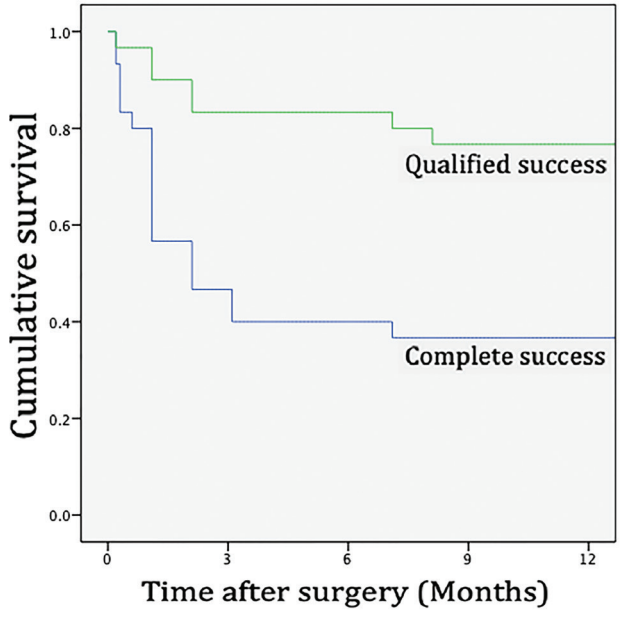

Fig. 2 Kaplan-Meier survival plots for eyes achieving complete success and qualified success in patients undergoing XEN surgery (n = 30).

Several hypotheses have been proposed regarding the causes of and countermeasures against the fibrotic process following XEN45 gel implantation. Smith et al. reported that loss of IOP control owing to subconjunctival fibrosis is more commonly exhibited in XEN surgery than in trabeculectomy.[22] Midha et al.[32] noted that, in eyes undergoing trabeculectomy, the subconjunctival and episcleral tissue are dissected intraoperatively, resulting in low resistance to aqueous outflow in the immediate postoperative period. By contrast, in eyes undergoing XEN implantation, because manipulation of the subconjunctival and episcleral tissues is minimal, needling may be required to reduce tissue resistance in the early postoperative period.[31] Therefore, placing the distal part of the XEN Gel Stent superficial to Tenon's capsule may be advisable, particularly in Asian patients who are more prone to hypertrophic scar formation than patients of European descent are.[33] However, Lenzhofer et al. evaluated the surgical outcomes of XEN surgery based on the position of the distal lumen, through optical coherence tomography, and noted better surgical outcomes when the stent was implanted deeper in the Tenon layer.[34] The optimal placement of the XEN implant (either subconjunctival or subtenon) is nonetheless controversial and requires further investigation. And the implant placement should potentially be individualized, with the patients' ages, ethnicities, and conjunctival conditions taken into consideration. We suggest that patients be informed in advance regarding the possibility of needle revision during the early postoperative period.

We found that postoperative IOP at month 1 was a predictor of (1) complete and qualified success at 1 year and (2) the requirement of bleb intervention or further glaucoma surgery. This remained true even when two eyes that received bleb intervention within the first month were excluded from the analysis. Failure to control IOP occurred mostly within the first 2 months in our study (5 out of 7, 71%), and 52.9% of postoperative interventions were performed within this time period. Our findings are consistent with those of another 1-year study in which the authors discovered that eyes undergoing postoperative bleb intervention after XEN surgery exhibited a significantly higher IOP at month 1 than did eyes receiving no intervention.[4] Elevated IOP has been postulated to increase the stretch of the bleb wall, where the stretch force activates fibroblasts with subsequent fibrosis.[35] In contrast to the report by Midha et al,[32] we did not find that IOP at day 1 was a useful predictor of outcomes or of the requirement of further intervention. Karimi et al.[36] also demonstrated that day 1 IOP is an unreliable indicator of long-term outcomes after XEN surgery. Because the first few months after XEN surgery seems to be a critical period for long-term IOP control, we suggest frequent follow-ups and meticulous postoperative care to obtain a desirable IOP during the first 1-2 months.

Our study population included many myopic eyes, with a mean spherical equivalent of −5.13 ± 4.44 dioptres and mean axial length of 26.67 ± 1.65 mm (up to 29.34 mm). Eleven (29.7%) eyes experienced transient postoperative hypotony,

Table 3

Factors associated with complete success, qualified success, subsequent intervention, and additional glaucoma surgery

	OR (95% CI); *p*			
	Complete success	**Qualified success**	**Subsequent intervention**	**Additional surgery**
Age	0.999 (0.964-1.035); 0.976	1.014 (0.958-1.075); 0.619	0.977 (0.937-1.020); 0.288	0.954 (0.888-1.025); 0.196
Lens status[a]	...; 0.806	...; 0.614	...; 0.333	...; 0.301
Baseline BCVA	1.230 (0.554-2.732); 0.611	1.198 (0.303-4.739); 0.798	1.085 (0.519-2.270); 0.829	1.208 (0.312-4.678); 0.784
Baseline IOP	0.935 (0.871-1.002); 0.058	0.870 (0.796-0.951); **0.002**	1.092 (0.991-1.203); 0.076	1.181 (1.049-1.330); **0.006**
Number of preoperative glaucoma medications	0.611 (0.329-1.135); 0.119	0.432 (0.151-1.239); 0.118	1.024 (0.504-2.079); 0.948	3.066 (0.716-13.12); 0.131
Duration of glaucoma medical therapy	1.004 (0.997-1.011); 0.287	1.009 (0.993-1.027); 0.266	0.997 (0.989-1.006); 0.544	0.977 (0.946-1.010); 0.167
Visual field mean deviation	1.070 (1.008-1.135); **0.026**	1.041 (0.944-1.147); 0.422	0.989 (0.925-1.058); 0.756	0.950 (0.836-1.080); 0.435
Axial length	1.082 (0.831-1.410); 0.559	0.659 (0.355-1.222); 0.186	0.959 (0.687-1.337); 0.803	1.382 (0.669-2.857); 0.382
IOP at day 1	0.935 (0.889-0.984); **0.010**	0.976 (0.912-1.043); 0.465	0.969 (0.900-1.044); 0.413	1.024 (0.935-1.121); 0.613
IOP at week 1	0.907 (0.792-1.040); 0.162	1.043 (0.816-1.333); 0.738	1.042 (0.889-1.221); 0.612	0.960 (0.677-1.362); 0.821
IOP at week 2	0.924 (0.855-0.999); **0.048**	1.053 (0.883-1.255); 0.057	1.057 (0.969-1.152); 0.021	0.908 (0.663-1.245); 0.550
IOP at week 3	0.939 (0.821-1.074); 0.359	1.063 (0.839-1.346); 0.617	1.019 (0.841-1.235); 0.848	0.906 (0.650-1.261); 0.557
IOP at month 1	0.928 (0.875-0.984); **0.012**	0.885 (0.796-.0985); **0.025**	1.210 (1.089-1.345); <**0.001**	1.245 (1.050-1.475); **0.012**
IOP at month 2	0.939 (0.876-1.005); 0.069	0.987 (0.885-1.101); 0.817	1.113 (1.037-1.193); **0.003**	1.001 (0.846-1.183); 0.992

Bold values denotes statistical significance at the $p < 0.05$ level.

BCVA = best-corrected visual acuity; IOP = intraocular pressure; OR = odds ratio.

[a]Factors were determined using the log-rank test; others were determined using a Cox regression model.

but none developed hypotony maculopathy during the study period. Other studies have demonstrated that the rate of hypotony maculopathy may be as high as 18% following trabeculectomy,[37] and young myopia is a significant risk factor of this vision-threatening complication.[8] Although more studies are required to clarify whether the risk of hypotony maculopathy is lower after XEN surgery than after trabeculectomy, especially in young patients with high myopia, data support the perception that XEN surgery is promising in this regard.

This study is limited by the inherent disadvantages of retrospective studies. Another limitation is that this study is a small case series with a 12-month follow-up period. Studies with long-term follow-ups and more participants from Asia are crucial to understand the long-term safety and efficacy of the XEN Gel Stent in Asian patients.

In conclusion, the XEN45 Gel Stent effectively reduces IOP and the number of glaucoma medications required throughout the 12-month follow-up in East Asian patients with POAG. Complications are minor and mostly transient. Close follow-up and meticulous postoperative wound modification during the first month are recommended to ensure the long-term success of XEN surgery.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

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