Efficacy and safety of XEN45 implant in Thai eyes with primary open angle glaucoma; one year result

Tosaporn Yodmuang

Department of Ophthalmology, Phayao Hospital, Thailand

Purpose: To report the efficacy and safety of the XEN45 implant in Thai patients with primary open angle glaucoma (POAG).

Method: Retrospective study of POAG patients who underwent XEN45 implant glaucoma surgery in June 2019 or later and completed 12 months of follow up. Primary outcome measures were intraocular pressure (IOP) reduction and number of glaucoma medications at 12 months postoperatively. Secondary outcome measures were surgical complications and success rate of surgery at 1 year. Complete success was defined as a postoperative IOP drop of ≥ 20% from preoperative baseline at 12 months without any glaucoma medications. Qualified success was defined as a postoperative IOP reduction of ≥ 20% at 12 months with glaucoma medications. Failure was defined as < 20% reduction of IOP from baseline at 1 year, visual loss of light perception, or need for additional glaucoma surgery. Needling with 5-fluorouracil (5-FU) injection of the XEN conjunctival bleb was not considered to constitute a surgical failure.

Results: Thirteen eyes of 10 patients were included in the study. The mean IOP dropped from 23.2 ± 4.5 mmHg preoperatively to 13.7 ± 2.9 mmHg at 12 months, a 40.9% IOP reduction ($P < 0.0001$). Mean number of glaucoma medications reduced from 2.5 ± 0.9 preoperatively to 1.1 ± 1.1 at 12 months ($P < 0.0001$). Success rate was 76.9% at 12- month follow up, 46.1% (6 eyes) achieved complete success and 30.8% (4 eyes) achieved qualified success. Seven eyes (53.8%) required bleb needling with 5-FU injection. Seven eyes (53.8%) required glaucoma medications. Three eyes (23.1%) exhibited numeric hypotony which resolved without intervention by 1 week. There were no serious complications and required glaucoma surgery at 12-month follow up.

Conclusion: The XEN45 implant proved to be an effective treatment with a good safety profile at 1-year follow up period in Thai patients with POAG. Patients considering this procedure should be warranted that by 1 year postoperatively there is a significant chance of requiring postoperative bleb needling and glaucoma medications.

Conflicts of interest: The author reports no conflicts of interest.

Key Words: Xen45 implant, glaucoma surgery, efficacy, safety

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Correspondence to:
Tosaporn Yodmuang, *Department of Ophthalmology, Phayao Hospital, Thailand*
Email: tosaporn.yo@cpird.in.th
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Background

Glaucoma is one of the leading causes of irreversible blindness worldwide. Primary open angle glaucoma (POAG) accounts for approximately 70% of all glaucoma. The

pathogenesis of POAG is not yet fully understood, but elevated intraocular pressure (IOP) is considered the only modifiable risk factor.[1] The mainstay of glaucoma treatment is IOP reduction with IOP lowering drugs, laser treatments and surgery.[2] First-line treatment typically involves IOP lowering drops, which are effective, but cause local side effects such as ocular surface irritation or allergy.[3, 4] Laser treatments have been proven to significantly reduce IOP, but the effect may be short-lived or ineffective in some cases.[5, 6] Trabeculectomy have a long track record of IOP reduction, yet carries significant long-term risks of hypotony and infection.[7, 8]

Minimally invasive glaucoma surgery (MIGS) has attracted substantial interest within the glaucoma community in recent years. There has been particular interest in developing microstents, which can lower intraocular pressure (IOP) in a similar manner to traditional glaucoma drainage surgeries, but with a better safety profile and shorter surgical time.[9] The iStent (Glaukos Corporation, Laguna Hills, CA,USA) and Hydrus microstent (Ivantis Inc.,Irvine, CA, USA) are Schlemm's canal stents, designed to allow aqueous humor to egress into Schlemm's canal more efficiently directly from the anterior chamber. Studies have shown that these stents have the potential to safely lower IOP to the 15-20 mm Hg range in open-angle glaucoma patients.[10-13] Where a lower IOP may be required due to advanced glaucomatous change, these stents may not be the intervention of choice. The suprachoroidal stents, Cypass (Transcend Medical, Menlo Park, CA, USA) and iStent Supra (Glaukos Corporation), provide direct communication between the anterior chamber and suprachoroidal space. Studies examining these stents are still limited but initial results showed a similar IOP reduction to the other stents mentioned above.[14]

Subconjunctival outflow has been proven to deliver the greatest IOP reduction and has been the traditional outflow pathway for glaucoma drainage surgery. XEN45 gel implant (Aquesys/ Allergan Inc., Irvine, CA, USA), made of a soft, permanent, collagen-derived gelatin, is 6 mm long and with an internal lumen of 45 μm. It is injected ab internally, through the trabecular meshwork via a scleral tunnel into the subconjunctival space. The implant is designed to regulate the outflow of aqueous from the AC into the non-dissected tissue of the subconjunctival space. It simulates traditional drainage surgery, but has the potential benefits of being minimally invasive and safer to perform.[15]

The XEN gel stent has been widely available since 2016 in Europe and its approval by Thai FAD in 2017. Previous studies reported 22.7-54.1% IOP reduction and 37.9-94.6% glaucoma medications reduction.[19, 26-30, 34-35] Although several studies have been carried out to assess the efficacy of XEN45 implant,[16-35] there is no data reported in Thai patients. This study is the first to report the efficacy, safety profile, and postoperative management of XEN 45 implants in Thai patients.

Method

This study was a retrospective study involving patients who underwent XEN45 implantation (Allergan, Inc) in June 2019 or later by a single, experienced glaucoma specialist in Phayao Hospital, Thailand. The study had the approval of the local Institutional Review Board of waiver of consent, complied with the guidelines of Good Clinical Practice and adhered to the tenets of the Declaration of Helsinki.

The medical record charts were reviewed. Patients with gonioscopically confirmed open-angle glaucoma, who were taking at least one IOP-lowering medication, medicated IOP of ≥ 18 mmHg and ≤ 35 mmHg, age 18 years

or older with an area of healthy, free and mobile conjunctiva at the superior nasal quadrant were included in the study. Patients with angle closure glaucoma, uveitis glaucoma, neovascular glaucoma, active infection or inflammation, anterior chamber intraocular lens, presence of intraocular silicone oil and any secondary glaucoma were excluded from the study. Any previous glaucoma surgeries such as trabeculectomy and glaucoma drainage device implantation also were excluded.

All cases were performed under topical anesthesia by a single, glaucoma specialist with extensive experience in traditional filtration surgery and bleb management. Topical 2% pilocarpine was applied to the eye every 15 minutes for 4 times preoperatively. After anesthesia and skin disinfection, superior nasal conjunctiva was marked 3 mm from the surgical limbus. A standard dose of 0.1 ml of 0.2 mg/ml of mitomycin-C (MMC) was injected using a 28-gauge needle into the subconjunctival space at 12 o'clock 5 mm behind the surgical limbus and spread with a surgical sponge. Corneal paracentesis was performed using a 21-gauge and a highly cohesive viscoelastic was injected into the anterior chamber.

A clear corneal wound incision was then made inferotemporally. The XEN45 was implanted via an ab interno approach using a preloaded injector, superior to the trabecular meshwork via a scleral tunnel into the subconjunctival/subtenon space. Ocular Hopkins Barkan GonioLens was used to see the angle during the operation. The viscoelastic was then removed and intracameral 0.5% Moxifloxacin was given. Finally, the clear corneal incisions were hydrated with balance salt solution (BSS). Attention was paid to ensure the implant was inserted correctly, with subsequent bleb formation noted at the end of surgery. If combined with the cataract surgery by a standard phacoemulsification technique, the XEN45 implantation was performed following insertion of the intraocular lens.

Postoperatively, patients were advised to discontinue all glaucoma medications on day 1 and given 0.5% Moxifloxacin eye drops 4 times/day for 1 week and 1% prednisolone acetate 4 times/day at least 4 weeks then tapered according to the degree of inflammation present. All patients were reviewed at 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months. Further follow-ups were arranged between these dates as required. Complications and bleb intervention were recorded.

Bleb needling with 5-fluorouracil (5-FU) injection of the XEN conjunctival bleb was not considered to constitute a surgical failure. Postoperative bleb interventions were carried out at the discretion of the same surgeon who performed the surgery. The indications for these interventions were similar to post-trabeculectomy management and decision was based on bleb morphology, conjunctival injection and IOP. In this study, bleb needling was performed with a standard dose of 0.1 ml of 50 mg/ml 5-fluorouracil (5-FU) injections at the slit lamp.

Patient demographics, best-corrected visual acuity (BCVA), IOP measured with Goldmann tonometry, number of glaucoma medications, type of interventions, and complications were recorded for each study visit. Primary outcome measures were intraocular pressure (IOP) reduction and number of glaucoma medications at 12 months postoperatively. Secondary outcome measures were surgical complications and success rate of surgery at 1 year. Complete success was defined as a postoperative IOP drop of ≥ 20% from preoperative baseline at 12 months without any glaucoma medications. Qualified success was defined as a postoperative IOP reduction of ≥ 20% at 12 months with glaucoma medications. Failure was defined as

< 20% reduction of IOP from baseline at 1 year, visual loss of light perception, or need for additional glaucoma surgery. Bleb intervention was not considered as failure.

Statistical analysis was performed using IBM SPSS statistic version 19.0 (IBMcorp, Armonk, NY, USA) and using Stata version 11.1 (StataCrop., College Station, TX, USA). Data were statistically described in terms of mean ± standard deviation (SD) and percentages when appropriate. Comparisons of numerical variables were done using Wilcoxon sign-rank test, Friedman's two way analysis test, and Kaplan-Meier survival analysis. A p values less than 0.05 was considered statistically significant.

Results

A total of 13 eyes of 10 patients were included and completed a 12- month follow up. Seven patients (70%) were male and 3 patients were female (30%). Mean age was 71.8 ± 5.4 years (Range 64 to 82). Three patients (30%; 2 male and 1 female) had undergone XEN45 implant bilaterally at different times. Only one eye had XEN 45 implant and phacoemulsification with intraocular lens implantation on the same session. Seven eyes were pseudophakic (53.8%), 6 eyes were phakic (46.2%). The patient demographics are shown in Table1.

The mean preoperative IOP was 23.2 ± 4.5 mmHg on at least one drop of IOP lowering medications. The IOP reduced to 6.8 ± 1.3 mmHg on day 1, 8.6 ± 2.1 mmHg on week 1 and 13.7 ± 2.9 mmHg at month 1 using no IOP lowering medications. Mean IOP was 15.1 ± 5.1 mmHg at month 3 on 0.5 ± 0.7 medications, 16.9 ± 5.6 mmHg at month 6 on 0.8 ± 1.2 medications and 13.7 ± 2.9 mmHg at month 12 on 1.1 ± 1.1 medications (P < 0.0001) (Figure 1 and 2). A 40.9% IOP reduction was achieved at month 12 from baseline (p < 0.0001). Mean number of glaucoma medications dropped from 2.5 ± 0.9 (2-4) preoperatively to 1.1 ± 1.1 (0-2) at 12 months of follow up (P < 0.001). Glaucoma medication was not required for 8 eyes (61.5%) and 6 eyes (46.1%) at 6 months and 12 months, respectively.

Overall success rate was 76.9% in this study, 46.1% (6 eyes) achieved complete success and 30.8% (4 eyes) achieved qualified success at 12-month follow up. The 12 months cumulative Kaplan-Meier survival probability was 53.9% (95% CI = 0.2-0.7) (Figure 3). Three eyes (23.1%) met the criteria of failure in this study. All of the three eyes were male and phakic. Two failure eyes required 2 bleb needling with 5-FU injection, one eye required 3 needling intervention.

One eye (7.7%) who underwent XEN45 implant combined with the cataract surgery by a standard phacoemulsification technique achieved qualified success at 12 months follow up and required 1 bleb needling with 5-FU injection.

Six eyes (46.2%) required no bleb intervention at all during the 12-month follow up period. Seven eyes (53.8%) had fibrotic bleb and raised IOP which required bleb needling with 5-Fluorouracil (5-FU) injection. The median number of bleb needling with 5-FU injection was 1.1 ± 1.1 (Range 1-4). The first bleb needling with 5-FU injection was performed as early as 1 month and as late as 6 months postoperatively. There were a higher number of phakic patients in bleb needles with 5-FU injection (6 phakic eyes and 1 pseudophakic eye).

None of the patients developed severe intraoperative complication and severe postoperative inflammation. There was no obstructed XEN45 implant by iris tissue and hyphema requiring anterior chamber washout in this study. None of eyes developed loss of two or more lines of BCVA, blebitis, bleb leak, persistent corneal edema, endophthalmitis, suprachoroidal hemorrhage, or choroidal detachment. Three eyes

(23.1%) had numerical hypotony (IOP < 6 mmHg) on day 1 which resolved without intervention by 1 week. All patients had steady of their visual acuity and no required cataract surgery due to visual disturbance from cataract. There was no patient required glaucoma drainage device, trabeculectomy and selective laser trabeculoplasty at the final follow up visit.

Table 1: Patient demographics

Demographics	Number (%)
Number of eyes	13 eyes
Gender	
• Male	7 (70%)
• Female	3 (30%)
Laterality	
• Unilateral XEN45 implantation	7 (70%)
• Bilateral XEN45 implantation	3 (30%)
Mean age	71.8 ± 5.7 (Range 64-82)
Best corrected visual acuity	
• 20/30 or better	4 (30.7%)
• 20/40 or better	6 (46.2%)
• 20/100 or better	2 (15.4%)
• Worse than 20/200	1 (7.7%)
Lens status	
• Phakic	6 eyes (46.2%)
• Pseudophakic	7 eyes (53.8%)
Mean cup: disc	0.8 ± 0.1
Underlying disease	
• No disease	3 (30%)
• Hypertension and dyslipidemia	2 (20%)
• Hypertension and diabetes mellitus	3 (30%)
• Ischemic heart disease	1 (10%)
• Chronic kidney disease	1 (10%)

Discussion

Minimally invasive glaucoma surgery (MIGS) aims to provide a safer, less invasive means of reducing IOP than traditional glaucoma surgery to reduce dependency on medication. XEN45 implant is inserted through minimum corneal incision and requires mitomycin C injection and the formation of filtering bleb beside the necessary intraocular manipulation. The implant utilizes subconjunctival filtration creating a non-physiologic route for aqueous outflow which is the basis of traditional trabeculectomy and aqueous shunt glaucoma surgery.[19, 20]

A prospective multicenter study of XEN gel implant in predominantly Caucasian eyes with medically uncontrolled primary open angle glaucoma (POAG) shows that it effectively

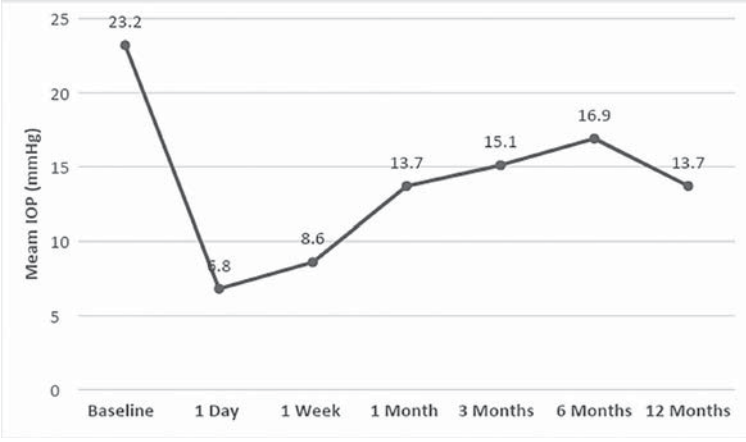

Figure 1: Mean intraocular pressure (mmHg) pre- and post XEN45 implant over 12-month follow up visits.

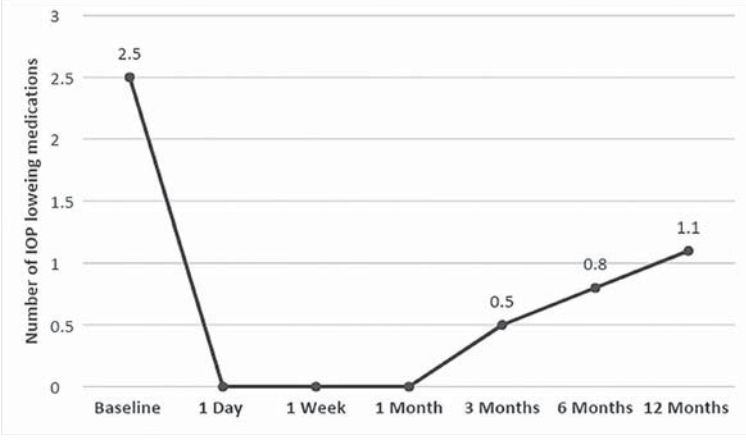

Figure 2: Mean number of IOP lowering medications pre- and post XEN45 implant over 12-month follow up visits.

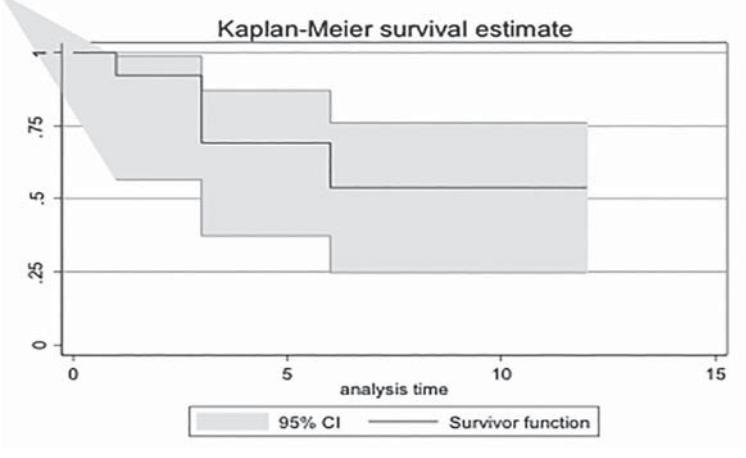

Figure 3: Kaplan–Meier survival curve showing time to failure the cumulative probability of survival was 53.9% at 12 months (95% CI = 0.25-0.75)

decreased IOP and glaucoma medications at 24 months compared with baseline, with an acceptable safety profile.[21] The outcome of XEN implantation has not been reported in East Asian eyes, particular Chinese eyes[22], also included Thai eyes. This retrospective study is the first study to have evaluated the XEN45 implant as a new modality shunt device with an ab interno approach sparing conjunctiva in Thai patients. In this study exhibited a significant mean IOP reduction from 23.2 ± 4.5 mmHg preoperatively to 13.7 ± 2.9 mmHg at 12 months, a drop of 40.9% IOP reduction (Delta 9.4 mmHg). The mean number of glaucoma medication significantly reduced from 2.5 ± 0.9 preoperatively to 1.1 ± 1.1 at 12 months (Delta 1.4 medications), with 53.8% of cases required back on glaucoma medications by 12 months. Over half of cases (53.8%) required bleb needling with 5-FU injection. There were no serious complications and required glaucoma surgery at 12-month follow up, 23.1% exhibited numeric hypotony which resolved without intervention by 1 week.

Previous studies reported 22.7-54.1% IOP reduction (Delta 4.0-17.9 mmHg) and 37.9-94.6% glaucoma medications reduction (Delta 1.1-2.9 medications)[19, 26-30, 34-35] The results from Thai eyes in this study were similar and supported the efficacy of XEN45 implant from previous studies which mostly Caucasian eyes.

The results of 40.9% IOP reduction in this study are similar to the study by Chelvin C et al, which reported 45% IOP reduction at 1 year of combine XEN implantation and phacoemulsification in Chinese eyes.[22] Although the study by Chelvin C et al performed XEN45 implantation in both primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG), surgical outcomes of XEN implant with phacoemulsification in PACG eyes did not differ significantly from POAG eyes in IOP or glaucoma medications reduction. The low rate postoperative complications in Chinese eyes also were similar to Thai eyes from this study, our results supported XEN implant is effective and favorable safety profile in Asian eyes.

Definition of clinical success is not standardized in the literature, it is difficult to directly compare studies results, also the different study length, patient demographics and sample size are different in each study. In this study, complete success was defined as a postoperative IOP drop of ≥ 20% from preoperative baseline at 12 months without any glaucoma medications. Qualified success was defined as a postoperative IOP reduction of ≥ 20% at 12 months with glaucoma medications. Success rate was 76.9% at 12- month follow up, 46.1% (6 eyes) achieved complete success and 30.8% (4 eyes) achieved qualified success. Previous studies with the similar to the definition of success in our study and 12 months follow up period reported the success rate of 65.8-92% at 12 months follow up.[19, 29, 30, 33, 34]

Hypotony is a rare complication in other MIGS devices such as Hydrus and iStent, although transient hypotony has been reported in 15.4% of eyes with Cypass stents.[36] Overall complication rate was low with XEN45 implant in this study. Three eyes (23.1%) had numerical hypotony (IOP < 6 mmHg) on day 1 which resolved without intervention by 1 week, supports the safety of MIGS. Tan SZ et al has been reported 20.5% of postoperative hypotony of XEN45 implant which required anterior chamber reformation at 3 week.[30] Jeremy Y Hu et al reported 25.4% postoperative hypotony on day 1 in both XEN45 gel implant surgeries with or without concurrent cataract surgery in Chinese eyes and 4.8% required viscoelastic reformation of anterior chamber but all eyes had the hypotony resolve by 3 months postoperatively.[24] Chelvin C et al reported 12.9% of transient hypotony and resolved spontaneously within 3 weeks in

all affected eyes.[22] The result from our study supports a small transient hypotony of XEN45 implant from previous studies.[22, 24, 30]

This study did not find any bleb related complications such as blebitis, blebitis associated endophthalmitis, bleb leakage which have been reported at a rate of 0.5%, 0.5% and 14% respectively in documented trabeculectomy cases.[37] There was no hyphema requiring anterior chamber washout in this study. None of eyes developed loss of two or more lines of BCVA, blebitis, bleb leak and persistent corneal edema. All patients had steady of their visual acuity and no required cataract surgery due to visual disturbance from cataract. Overall complication rate was low with XEN45 implant in our study maybe due to patient selection in only primary open angle glaucoma which did not include severe type of secondary glaucoma such as neovascular glaucoma.

There was no implant blockage and hyphema in our study. This was due to a careful intraoperative gonioscopy in all cases to ensure that the implant is anterior to pigment trabecular meshwork especially in the phakic eye patients and discontinued systemic anticoagulant or antiplatelet medications in all cases preoperatively.

The bleb intervention is needed to achieve IOP goal similar to traditional filtration procedure, XEN 45 implant required understanding of the conjunctival health and healing, and experience in postoperative bleb assessment and management.[30] The needling rate with or without antimetabolite reported in the different studies is variable from 0 to 51.3%.[19, 26-33] Seven eyes (53.7%) in our study required at least once of bleb needling with 5-FU injection as early as 1 month to 6 months postoperatively. Chelvin C et al reported 35.5% of bleb needling without adjunctive antimetabolites in Chinese eyes at 1 year follow up.[22] Jeremy Y et al. reported 61.9% of bleb needling with 5-FU or MMC injection in Chinese eyes at 6 months follow up.[24] A high rate of bleb needling may be due to East Asian eyes having a greater propensity for scarring.[25] Although an experienced surgeon performing the procedures, there was an inevitable learning curve associated with any new intervention, which might account for the initial complications such high needling rates. Based on published results, however, it appears that 25-50% of patients require bleb intervention following XEN surgery.[16] Studies with a higher success rate seem to correlate with more aggressive bleb management.[30]

Although this study included only naïve primary open angle glaucoma patients and excluded all secondary glaucoma and previous glaucoma surgery, there were some limitations in retrospective nature. In addition, this case series represents the first XEN45 implant cases undertaken by one glaucoma specialist and therefore may include a learning curve effect in the procedure technically challenging. The relatively small sample size of this study could have resulted in inadequate statistical power for subgroup analysis of success and failure. The 1-year follow-up period did not detect long term complications of XEN45 implants such as blebitis, which have been reported in other studies.[21, 23] The long-term efficacy, cost-effectiveness, and quality-of-life improvement are yet to be established. The prospective study with long term and large sample size is required in the future.

Conclusions

The XEN45 implant proved to be an effective treatment with a good safety profile at 1-year follow up period in Thai patients with POAG. Patients considering this procedure should be warranted that by 1 year postoperatively there is a significant chance of requiring postoperative bleb needling and glaucoma medications. The

results from this study will be invaluable in guiding clinicians' decision on the surgical management of glaucoma in this modern era in Thai eyes. The long-term efficacy, cost-effectiveness, and quality-of-life improvement are yet to be established.

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