



A Retrospective Analysis of Safety and Efficacy of XEN 45 Microstent Combined Cataract Surgery in Open-Angle Glaucoma over 24 Months

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Abstract

Objectives: To evaluate the effect on intraocular pressure (IOP) reduction and safety of ab interno gelatin microstent (XEN 45 Gel Stent; Aquesys, Inc, Aliso Viejo, CA, USA) microincisional glaucoma/cataract surgery in open-angle glaucoma (OAG).

Materials and Methods: In this retrospective study, 30 eyes of 25 patients with OAG which underwent XEN 45 implantation combined with simultaneous phacoemulsification were clinically evaluated. Clinical outcomes analyzed included IOP, percent of IOP reduction, medication use, complications, best corrected visual acuity, and surgical outcomes at 24-month follow-up.

Results: After the XEN 45 combined cataract surgery procedure, IOP dropped from 20.37 ± 4.80 mmHg with a mean of 3.07 ± 1.04 medication classes preoperatively to 14.83 ± 1.91 mmHg with a mean of 0.94 ± 1.11 medication classes at 24 months ($p=0.001$ for both). At 24 months, 55.6% of patients had IOP ≤ 18 mmHg without medication, 94.4% of patients had IOP ≤ 18 mmHg with or without medication, and 61.1% of patients reached $\geq 20\%$ IOP reduction from baseline.

Conclusion: XEN 45 is an effective minimally invasive surgical treatment for OAG with significant reduction in IOP and glaucoma medications and minimal complications in long-term follow-up.

Keywords: Cataract surgery, microincisional glaucoma surgery, open-angle glaucoma, XEN 45 Gel Stent

Introduction

Glaucoma is an important cause of blindness and affects 3.54% of people worldwide.¹ The purpose of treatment is to reduce intraocular pressure (IOP) via various treatment strategies in order to halt optic nerve injury.² The most common surgeries are traditional incisional surgeries which provide the drainage of aqueous fluid to the subconjunctival space with an ab externo approach.³ Although these methods have been successful in reducing IOP, both trabeculectomy and

aqueous tube shunts come with a range of short- and long-term complications like hypotony, leakage, scarring, foreign body sensation associated with blebs, astigmatism, secondary cataracts, blebitis, endophthalmitis, and choroidal hemorrhage.^{3,4,5,6}

Minimally invasive glaucoma surgery (MIGS) is less invasive than traditional incisional surgeries and offers more modest results with the benefit of a safe risk profile in patients with mild to moderate glaucoma.⁷ The four main approaches to IOP reduction include increasing trabecular outflow, increasing

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uveoscleral outflow via suprachoroidal pathways, reducing aqueous production from the ciliary body, and creating a subconjunctival drainage pathway via an ab interno incision.⁷

The XEN 45 Gel Stent (Aquesys, Inc., Aliso Viejo, CA, USA) is a hydrophilic tube composed of gelatin crosslinked with glutaraldehyde, with the smallest model having an inner diameter of 45 μ m and a length of 6 mm, which creates subconjunctival drainage like traditional incisional glaucoma surgeries with an ab interno microincisional approach.^{8,9} It was created with adequate length, tube rigidity, and lumen diameter to limit flow and avoid hypotony by using the Hagen-Poiseuille equation.^{8,10}

This retrospective analysis aimed to assess the results of combined glaucoma/cataract surgery using the smallest diameter XEN 45 Gel Stent in regard to IOP-lowering effect, visual acuity, and postoperative complications in open-angle glaucoma (OAG) patients.

Materials and Methods

Patients and Assessments

We retrospectively analyzed 30 eyes of 25 patients who were treated with XEN 45 implantation with mitomycin C (MMC) combined with cataract surgery by the same surgeon at the Kocaeli University Department of Ophthalmology between January 2016 and January 2018. The Local Ethics Committee of the Kocaeli University approved the study, which was conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria for the Diagnostic Innovations in Glaucoma Study of primary OAG (POAG) were glaucomatous optic neuropathy in clinical examination including thinning of neuroretinal rim with retinal nerve fiber layer loss, visual field (VF) defect, and open angle confirmed with gonioscopy.¹¹ The diagnosis of pseudoexfoliation glaucoma (PXG) was based on clinically visible criteria on slit-lamp examination (accumulated extracellular material in the anterior segment of the eye) with the parameters mentioned above.¹² This study included eyes with primary and secondary (pseudoexfoliation) OAG and previously diagnosed cataract that had not reached target IOP or showed progressive VF loss with maximum medical therapy, as well as eyes of patients with medication intolerance or nonadherence.

Exclusion criteria were angle-closure, congenital, and neovascular glaucoma, prior uveitis or endophthalmitis, ocular surgery history (except glaucoma surgery), and aphakia. The patients who fulfilled these inclusion criteria and underwent combined cataract surgery and XEN 45 microstent implantation were evaluated in this retrospective case study.

Complete ophthalmic examination including visual acuity, gonioscopic evaluation, IOP measurement by Goldmann applanation tonometry, anterior and posterior segment evaluation, cup/disc ratio, central corneal thickness (CCT) with a fully automatic tonometer (Canon TX-20P, Tokyo, Japan), VF testing 30-2 strategies with a Humphrey Field Analyzer model 750I (Carl Zeiss Meditec, Dublin, CA, USA), and optical coherence tomography (SD-OCT, Heidelberg Engineering,

Germany) were performed preoperatively (baseline) and at 1, 3, 6, 12, and 24 months postoperatively. Thirty eyes completed 12 months and 18 eyes completed 24 months of follow-up. None of the patients were excluded from analysis. Glaucoma staging was done according to mean deviation values (mild: >-6 dB, moderate: -6 to -12 dB, and severe: <-12 dB) as described in the European Glaucoma Society Guidelines.¹³

Primary outcome measures included IOP, mean IOP reduction, percentage of IOP reduction, the number of antiglaucoma medications used and their changes in repeated measures, IOP reduction $\geq 20\%$, the mean categorized IOP (8-12 mmHg, $>12-15$ mmHg, $>15-18$ mmHg, >18 mmHg), postoperative complications, logarithm of the minimal angle of resolution (LogMAR) best corrected visual acuity (BCVA), and vision changes (gain of ≥ 2 lines, stable, or loss of ≥ 2 lines; clinically significant change in BCVA was defined as 0.2 units of logMAR) during 24-month follow-up.¹⁴

Secondary efficacy outcomes were determined as the rate of needling and complete and qualified success rates. Complete success was defined as a postoperative IOP ≤ 18 mmHg but not < 5 mmHg with $\geq 20\%$ reduction in IOP without medication. Qualified success was defined as a postoperative IOP ≤ 18 mmHg but not < 5 mmHg with $\geq 20\%$ reduction in IOP with or without medication.¹⁵

Surgical Technique

A single surgeon performed all surgical procedures under peribulbar anesthesia. After skin disinfection, the superior nasal conjunctiva was marked 3 mm from the limbus, then 0.1 mL of MMC (0.02%) was injected subconjunctivally using a 27-gauge needle and spread with a microsponge in the superior nasal quadrant. The surgeon performed cataract surgery using a 2.8-mm main incision at the 12 o'clock position and two 1.2-mm sideport incisions at the 10 and 2 o'clock positions. At the end of cataract surgery, the anterior chamber was filled with a cohesive viscoelastic device. A new incision was made for XEN implantation. The new clear corneal incision of 1.2 mm opposite the site (inferior temporal quadrant) of the desired XEN implantation (superior nasal quadrant) was performed using a metal keratome. The XEN handheld disposable injector was inserted through the opposite clear corneal incision. We used gonioscopy to verify correct placement and avoid iris insertion. The injector needle penetrated the angle and formed a tunnel through the sclera, emerging approximately 3.0 mm posterior to the limbus. The implant remained in position with further rotation of the dial. Having 2 mm of exposed implant in the subconjunctival space and 1 mm in the anterior chamber was accepted as ideal placement. The cohesive viscoelastic device was irrigated and the sideports and main incision were hydrated. The anterior chamber was pressurized. Bleb formation was readily visible.

All glaucoma medications were discontinued on the day of surgery, prednisolone acetate 1.0% drops (Pred Forte, Allergan) were used 6 times a day for 1 month and then tapered over 1 month. Moxifloxacin 0.5% drops (Vigamox, Alcon) were used

4 times a day for 15 days. Postoperatively, additional glaucoma medications were used as necessary.

If postoperative IOP was higher than target and flat or cystic bleb formation was observed, needling with MMC was performed. A 27-gauge angled needle was advanced subconjunctivally to the tip of the stent and the fibrous tissue around it. Using the tip of the needle, adhesions around the stent were disintegrated and the tip of the implant was released in flat blebs. In cystic blebs, the cyst was opened with the tip of the needle and all its walls were lysed. Then 0.1 ml of MMC (0.02%) was injected subconjunctivally in all needlings (Figure 1A-D).

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp, Armonk, NY, USA). Kolmogorov-Smirnov test was used to assess the assumption of normality. Numerical variables were expressed as mean \pm standard deviation, and categorical variables were summarized as count (percentage). Preoperative values were defined as baseline values. The changes in variables between time periods were analyzed by paired t test and Wilcoxon Signed Rank Test for normally and non-normally distributed variables, respectively. A two-sided p-value less than 0.05 was considered statistically significant.

Results

Baseline Parameters

Thirty eyes of 25 patients were included in our retrospective study. Seventeen patients (56.7%) were male and 13 patients (43.3%) were female. The mean age of the patients was 66.1 ± 8.1

(49-81) years. Nineteen eyes (63.3%) had POAG and 11 eyes (36.7%) had PXG. In 4 patients, both eyes were included in the study and bilateral surgery was performed. Mean CCT was 562 ± 21.71 μ m and the mean cup/disk ratio was 0.52 ± 0.24 . The mean preoperative IOP was 20.37 ± 4.80 mmHg with a mean of 3.07 ± 1.04 medications. There was no statistically significant difference in preoperative IOP and medication use between POAG and PXG groups. Eleven patients (36.7%) had mild, 9 patients (30%) had moderate, and 10 patients (33.3%) had severe glaucoma. There was no statistically significant difference between POAG and PXG groups in terms of cup/disk ratio ($p=0.611$) and glaucoma stage ($p=0.226$). There were no major complications during implantation surgery and all cataract surgeries were uneventful. All patients completed the 12-month examination and 18 of them completed the 24-month follow-up. The mean follow-up time was 22.90 ± 8.22 months. All demographic and clinical baseline parameters are shown in Table 1.

IOP and Medication Use

At 12 and 24 months, mean IOP decreased significantly to 15.0 ± 1.91 mmHg and 14.83 ± 1.91 mmHg ($p < 0.001$ for both) with a mean of 0.87 ± 1.13 and 0.94 ± 1.11 medication classes ($p < 0.001$ for both). None of the patients was using more medications compared to preoperative medication count. The mean number of medications used at 12 months was 1.05 ± 1.22 and 0.55 ± 0.93 in the POAG and PXG groups, respectively ($p=0.350$). At 24 months, there was a statistically significant difference in terms of medication use between POAG and PXG groups (1.63 ± 1.06 , 0.40 ± 0.84 , respectively) ($p=0.043$). IOP was reduced by a mean of 23.3% and 27.2% at 12 and 24 months of follow-up, respectively (Figure 2a-c). There was no statistically significant difference between PXG and POAG patients according to postoperative IOP or mean IOP reduction at 12 and 24 months. At 12 and 24 months, mean IOP reduction from baseline was -6.16 ± 0.92 mmHg (95% confidence interval [CI]: -4.22 , -8.11) and -6.44 ± 1.19 mmHg (95% CI: -3.91 , -8.96), respectively.

Surgical Success

The distribution of patients according to the surgical success parameters is shown in Table 2. At 12 and 24 months, 96.7% and 94.4% of patients had IOP ≤ 18 mmHg, and 70% and 61.1% of patients achieved $\geq 20\%$ IOP reduction from baseline with or without medication, respectively. The qualified success rate of the procedure was 70% and 61.1% and the complete success rate was 40% and 33.3% at 12 and 24 months, respectively. There was no statistically significant difference in terms of complete and qualified success rates between the PXG and POAG groups.

BCVA Results

The mean preoperative LogMAR BCVA was 0.38 ± 0.52 , which improved significantly to 0.21 ± 0.46 and 0.31 ± 0.56 at 12 and 24 months ($p < 0.001$, $p=0.004$, respectively) (Figure 2d). At month 12, 46.7% of patients gained ≥ 2 lines of BCVA, 53.3% had stable BCVA, and none lost ≥ 2 lines of BCVA. At month 24, 44.4% of patients gained ≥ 2 lines of BCVA, 55.6% had stable

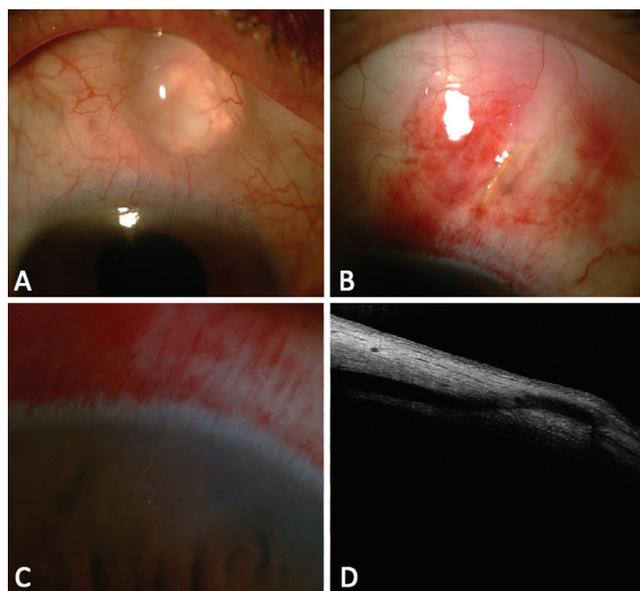


Figure 1. Color photograph showing cystic bleb formation requiring needling (A), the placement of the device subconjunctivally after needling (B), scanning of the suitable placement of the apparatus in the angle and anterior chamber (C). Anterior segment optic coherence tomography image showing the presence of XEN implant through the sclera (D)

Table 1. Evaluation of the baseline parameters and primary surgical outcomes	
Demographic and clinical data	
Age (years), mean ± SD	66.17±8.19
Male/female, n (%)	17 (56.7)/13 (43.3)
Right/left eyes, n (%)	16 (53.3)/14 (46.7)
Bilateral cases, n (%)	4 (13.3)
Primary open angle, n (%)	19 (63.3)
Pseudoexfoliation, n (%)	11 (36.7)
Central corneal thickness (µm), mean ± SD	562.0±21.71
Baseline BCVA LogMAR (mean ± SD)	0.38±0.52
Baseline IOP (mmHg), mean ± SD (25 th -75 th percentile)	20.37±4.80 (17.0-23.0)
Baseline medications, mean ± SD	3.07±1.04
M12 BCVA (LogMAR), mean ± SD	0.21±0.46
M12 IOP (mmHg), mean ± SD (25 th -75 th percentile)	15.0±1.91 (14.0-16.0)
M12 medications, mean ± SD	0.87±1.13
M24 BCVA (LogMAR), mean ± SD	0.31±0.56
M24 IOP (mmHg), mean ± SD (25 th -75 th percentile)	15.17±3.31 (13.75-16.0)
M24 medications, mean ± SD	0.94±1.11
SD: Standard deviation, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution; IOP: Intraocular pressure, M12: Postoperative month 12, M24: Postoperative month 24	

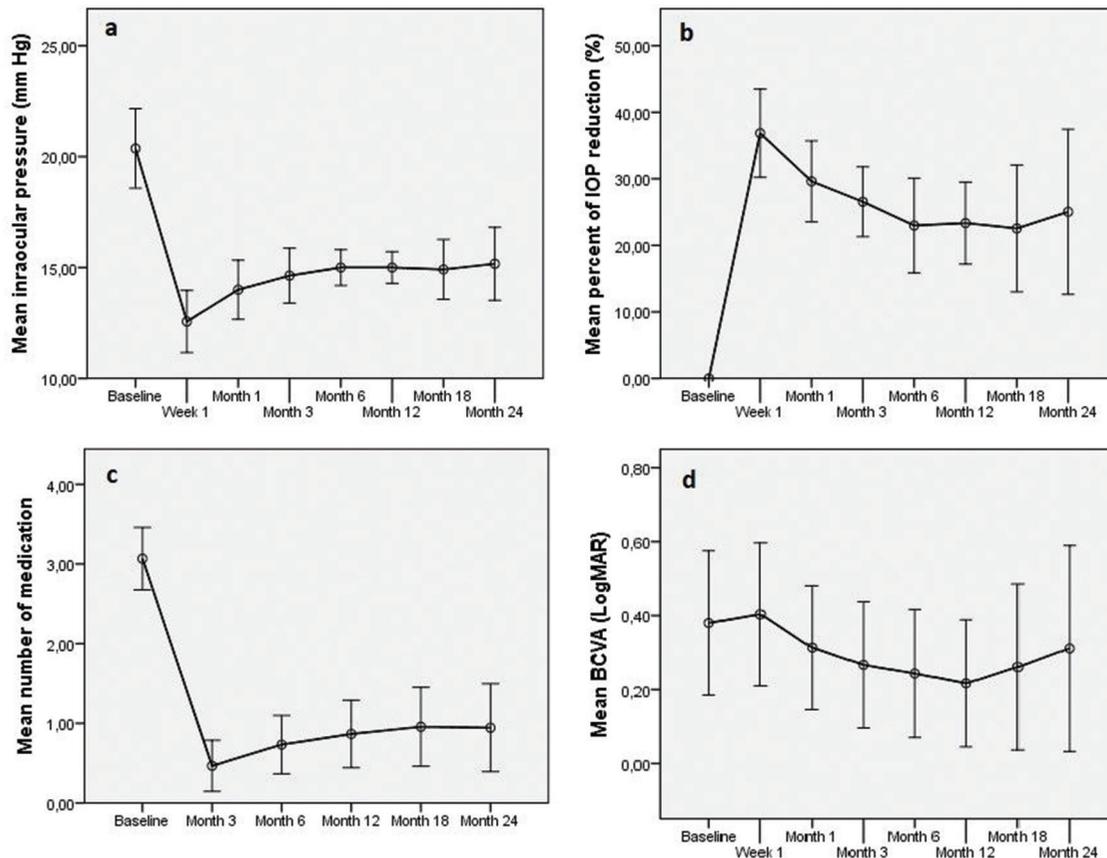


Figure 2. Mean IOP (a), mean percentage of IOP reduction (b), mean number of IOP lowering medication (c) and the change of mean BCVA LogMAR (d) over 24 months after XEN 45 Gel Stent implantation with cataract surgery. Error bars represent two standard deviations
 IOP: Intraocular pressure, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimal angle of resolution

BCVA, and none lost ≥ 2 lines of BCVA. The change in BCVA values was similar in PXG and POAG patients, and there was no significant difference between them according to BCVA values at 12 and 24 months ($p=0.497$, $p=0.068$, respectively).

Needling Intervention

Thirteen patients (43.3%) required needling during follow-up. Needling was needed in the first week in 1 patient (7.7%), between 1 week and 3 months in 11 patients (84.6%), and after 3 months in 1 patient (7.7%). Seven patients required needling procedure twice and 1 patient required it 4 times. The patient requiring needling 4 times needed additional glaucoma surgery due to stent insufficiency. This patient had trabeculectomy history and the etiology of glaucoma was POAG. The mean IOP was 25.9 ± 5.3 mmHg pre-needling and was 18.2 ± 5.3 mmHg after needling ($p < 0.001$). No patient had hypotony or anterior chamber shallowing after needling. The rate of needling intervention was 47.4% in PXG and 36.4% in POAG patients. There was no statistically significant difference in needling requirement between PXG and POAG patients ($p=0.708$).

Surgical Complications

There were no cases of endophthalmitis, wound leak, device exposure or migration, macular edema, choroidal effusion or hemorrhage, iritis, or retinal detachment over 24 months. One patient had hyphema on postoperative day 1 that resolved completely by 1 week with topical steroid and cycloplegic eye drops. One patient had additional glaucoma surgery (aqueous tube shunt) at postoperative 3 months because of stent insufficiency. This patient had trabeculectomy history and the etiology of glaucoma was POAG. In terms of complications, there was no statistically significant difference between the POAG and PXG groups ($p=1.000$).

Discussion

Although cataract surgery provides a decrease in IOP, additional glaucoma surgery is required in some glaucoma patients.^{16,17,18} Combined procedures with traditional surgery

methods had additional risks related to the surgery type.^{4,19} Because of this, new MIGS techniques were adopted. The XEN 45 Gel Stent is an apparatus that shunts aqueous to the subconjunctival space via a minimally invasive ab interno approach. This type of subconjunctival drainage avoids the risk of outflow obstruction while lowering IOP, and the XEN Gel Stent is the only filtering MIGS device that works in this way. The ab interno installation of the device provides safety with a low rate of long-term complications. Although some complications have been reported as case reports, rates of serious complications are lower than in traditional surgery.²⁰

In a prospective clinical study with XEN 45 Gel Stent combined cataract surgery, 80.4% of patients had IOP ≤ 18 mmHg at 12 months.²¹ In a multicenter open-label study, 75.4% of patients had $\geq 20\%$ IOP lowering from baseline on the same or fewer medications at 12 months, while this rate was 70.0% in our study.²² Similar to the literature, 61.1% of patients reached $\geq 20\%$ IOP reduction from baseline and 94.4% of patients had IOP ≤ 18 mmHg at 24 months in our study. The percentage of IOP reduction could differ according to baseline IOP and the indication (medication intolerance or nonadherence). Moreover, almost all patients had IOP ≤ 18 mmHg with a lower number of medications at 12 months and this benefit continued over 24 months.

IOP reduction of 36.4% and 30% was reported in clinical studies with XEN 140 without MMC and with XEN 140 and XEN 63 combined with cataract surgery without MMC, respectively.^{23,24} In a prospective study of the XEN 45 microimplant with MMC, 29.4% reduction in IOP was reported.²⁵ Our IOP reductions were 23.3% and 27.2% at months 12 and 24, respectively. Different degrees of IOP reduction could be related to the proportion of patients with well-controlled IOP in study populations and the distribution of patients with different types of OAG. The results vary depending on many factors such as the type of XEN stent used, whether glaucoma surgery is applied in conjunction with cataract surgery, and the use of MMC, but sufficient IOP lowering and decreased

Table 2. Surgical success parameters

	Preoperative (n=30), % (n)	Month 12 (n=30), % (n)	Month 24 (n=18), % (n)
IOP category			
8-12 mmHg	0.0 (0)	0.0 (0)	0.0 (0)
>12-15 mmHg	16.6 (5)	63.3 (19)	66.7 (12)
>15-18 mmHg	23.3 (7)	33.3 (10)	27.8 (5)
>18 mmHg	60.0 (18)	3.3 (1)	5.6 (1)
$\geq 20\%$ IOP Reduction			
Without medication		40.0 (12)	33.3 (6)
With or without medication		70.0 (21)	61.1 (11)
≤ 18 mmHg the mean of IOP			
Without medication		60.0 (18)	55.6 (10)
With or without medication		96.7 (29)	94.4 (17)
Qualified success		70.0 (21)	61.1 (11)
Complete success		40.0 (12)	33.3 (6)

medication use are reported in all studies. Ozal et al.²⁶ reported that the patients who underwent cataract surgery with XEN implantation and those who underwent only XEN implantation were similar in terms of IOP reduction. In our study, combined cataract surgery with XEN implantation was applied to all patients because they had cataracts and glaucoma. Therefore, no comparison was made in terms of these conditions in our study. When evaluated in the light of the literature data, as XEN implantation is an ab interno surgery that does not cause conjunctival damage, it is thought that inflammation induced by cataract surgery will not affect surgical success as much as trabeculectomy. Combined surgery also decreases the burden of multiple surgeries.

At 12 and 24 months, the qualified success rates of our procedure were 70% and 61.1%, and complete success was achieved in 40% and 33.3%, respectively. Using the same criteria for complete and qualified success, Gillmann et al.²⁷ reported complete success rates of 24.5% and 36.4% and qualified success rates of 30.6% and 38.6% at 24 months in their POAG and PXG groups, respectively. Many factors can determine surgical success, including low baseline and postoperative IOP and higher number of baseline medications, because the success rate calculations are based on both postoperative IOP 5-18 mmHg and $\geq 20\%$ IOP reduction.²⁷

The rate of needling was 43.3% in our study, 47% in a study by Sheybani et al.²³ in which MMC was not used, 30.7% in a study by Galal et al.²⁵, 27% in a study by Hengerer et al.²⁵ in which MMC was used during implantation, and 43.0% in the study by Gillmann et al.²⁷ in which MMC was used. We thought that the difference between percentages could be related to MMC use and the profile of the study groups (PXG, POAG, and pigmentary glaucoma). According to our results, PXG patients required more needling interventions than POAG patients, but this difference was not statistically significant. Average needling times were reported as 4.5 months by Mansouri et al.²⁸ and between 1 week and 3 months by Hengerer et al.²⁴ In our study, the mean time to needling was between 1 week and 3 months in 84.6% of patients.

Conclusion

This study has limitations such as the small sample size and noncomparative design. Nevertheless, we provided valuable data for clinicians when choosing the procedure for their patients. This retrospective study demonstrated that XEN 45 implantation in patients with inadequately controlled IOP despite maximum medical therapy or in patients with medication intolerance or nonadherence provided significant reductions in IOP and medication use and improved visual acuity with high success rates and low complication rates during follow-up.

Ethics

Ethics Committee Approval: The Local Ethics Committee of the Kocaeli University approved the study, which was conducted in accordance with the tenets of the Declaration of Helsinki.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Y., Concept: S.S., N.Y., Design: S.S., F.Ö., Data Collection or Processing: S.S., F.Ö., Analysis or Interpretation: S.S., B.Y.T., Literature Search: S.S., D.P., Writing: S.S.

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