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1. **Please confirm the section headings are correctly identified.**

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2. **Please check the whether the intended meaning of the sentence 'In terms of mean...follow-up visit data' is clearly conveyed.**

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3. **Please check the edit made in the sentence 'In two of those...using the dry-lake technique'.**

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Medium-term clinical outcomes following Xen45 device implantation

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Abstract

Purpose

To evaluate medium-term clinical outcomes with microstent XEN® 45 Gel Stent (Allergan Dublin, Ireland) for treatment of primary open-angle glaucoma (POAG).

Material and methods

This is a retrospective, descriptive and observational study involving 93 eyes from 63 patients who had undergone POAG surgery with a XEN® 45 Gel Stent implantation and had been followed up and controlled between 12 and 36 months.

Results

IOP dropped from 18.23 ± 5.00 mmHg pre-op to 14.16 ± 2.14, 14.47 ± 2.16 and 14.63 ± 1.91 at 1, 2 and 3 years after surgery ($p = 0.000$, 0.000 and 0.001) consecutively. Mean number of medications dropped from 1.87 ± 0.94 preoperatively to 0.31 ± 0.69, 0.34 ± 0.63 and 1.00 ± 0.88 ($p = 0.000$, 0.000 and 0.017) at 12, 24 and 36 months. Mean visual field deviation values never turned out to be significant for any of the follow-up visit data. A total of 94.6% of the surgical procedures turned out to be complication-free. In one surgery, the procedure failed and 18 months later other device was implanted.

Conclusion

POAG surgical procedures with XEN® 45 Gel Stent implants are a safe and effective treatment approach.

Keywords

Glaucoma
MIGS
Xen45

Introduction

Glaucoma surgery has changed significantly in the past few years with the advent of the novel MIGS (micro-invasive glaucoma surgery) devices. The development of new surgical techniques for glaucoma is, in itself, a fact that provides very relevant information about the pathology. Interest in micro-incisional or micro-invasive surgery has emerged due to the need for surgical options that have lower complication rates than classic surgical procedures. Besides, having a relatively simple and safe surgical technique may help to prevent the effects associated with the chronic use of topical medication and to tackle the issue of low adherence to glaucoma medical treatments. The main feature of these minimally invasive devices is the very limited surgical damage they cause [1, 2, 3, 4].

The way most MIGS devices work is by improving the outflow of aqueous humor through the Schlemm's canal or supraciliary space rather than following the non-physiological subconjunctival route chosen by traditional glaucoma drainage surgery. This is likely to be the reason why former studies suggest that MIGS devices are less effective than these standard procedures; nonetheless, it must be said that they have the merit of showing lower rates of hypotony-related complications [5].

The present study shows the outcomes of a XEN® 45 Gel Stent (Allergan Dublin, Ireland) implantation in a set of patients, where the follow-up ranged between 1 and 3 years.

Materials and methods

This is a retrospective, descriptive and observational study involving patients who had undergone primary open-angle glaucoma (POAG) surgery with a XEN® 45 Gel Stent implantation and had been followed up and controlled for at least 1 year.

All patients belong to the IOA Madrid database and were operated at our clinic by the same experienced surgeon between 2014 and 2017.

The inclusion criteria were: patients with open-angle glaucoma who had a XEN® 45 Gel Stent implanted in a stand-alone surgery or in the context of a combined glaucoma–cataract surgery and whose medical history

included at least 1 year of follow-up data.

The exclusion criteria were: other relevant ophthalmic conditions other than glaucoma, eye trauma or a history of eye surgery other than cataract.

The following metrics to assess surgical outcomes were chosen and pre- vs. postsurgical values were compared: intraocular pressure (IOP), visual field mean defect (MD), retinal nerve fiber layer (RNFL) thickness, number of glaucoma drugs the patient was treated with and intra-surgical or postoperative complications.

Intraocular pressure was measured by means of Goldmann tonometry, whereas visual-field mean defect was evaluated using an Octopus perimeter (Haag-Streit Inc, Koeniz, Switzerland), G1x strategy. Finally, nerve fiber layer thickness was measured with the Cirrus HD-OCT platform (Carl Zeiss Meditec, Inc, Dublin, CA, USA), which relies on optical coherence tomography.

The study was approved by the Ethics Committee of the Clínico San Carlos Hospital (Madrid), and they granted us a waiver of informed consent, since the study entailed no intervention except for data collection; the surgical procedures themselves had been performed several years before the study was initiated. The study is in compliance with the tenets of the Declaration of Helsinki.

XEN® 45 Gel Stent

The XEN® 45 Gel Stent implant is a small—6 mm long, 45 micron inner diameter—hydrophilic tube made of biocompatible porcine gelatin that has been cross-linked with glutaraldehyde, so as to provide it with certain rigidity [6, 7].

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Subconjunctival flow creates a non-physiological pathway for aqueous humor drainage; it is the basis of traditional trabeculectomy and aqueous shunt glaucoma surgeries. The XEN® 45 Gel Stent device follows Poiseuille's law for laminar flow, which states that flow velocity depends on the tube's length and diameter. Hypotony is avoided thanks to the resistance to flow. This procedure can only be performed on eyes that do

not have any conjunctival scars; at the same time, it remains to be determined whether trabecular atrophy can limit the IOP drop achieved with this surgical approach, although it is worth mentioning that this XEN® 45 Gel Stent is already EC- and FDA-approved.

This device remains hard while dry, but once it comes into contact with the aqueous humor, within less than 2 min it becomes soft and flexible, thus allowing a total adaptation to the tissues it goes through. The XEN® 45 Gel Stent is typically inserted via an *ab interno* approach using a preloaded injector, which allows us to place it in its final position closely following the procedure's protocol. The surgery is performed under topical anesthesia, either as a stand-alone procedure or combined with cataract surgery.

This *ab interno* approach generally makes use of a clear cornea incision located opposite the implantation quadrant.

Surgical technique

Under topical anesthesia, 0.1 ml of mitomycin C (having a concentration of 0.02 mg/ml) were introduced 5 mm away from the limb—in the area where the XEN® 45 Gel Stent was to be implanted—and it was spread toward the back, never toward the limb so as to avoid limbic toxicity. An incision—a temporal one for right eyes and a temporal-lower one for left eyes—was made with a diamond knife; it was oriented toward the location where the device was to be inserted. After filling the anterior chamber with viscoelastic, lidocaine with adrenaline was introduced into the adjacent conjunctival area in order to create a conjunctival bleb and to further anesthetize the area, so as to produce a slight vessel vasoconstriction. The implant was introduced into the target zone, exiting through the sclera 3 mm away from the limb. After seeing the injector's lumen in full—through the conjunctiva without injuring it—the injector is turned clockwise in right eyes and counterclockwise in left eyes and, without retracting the injector and by exerting a slight pressure on the angle, the implant is finally introduced.

It has to be verified that the implant lies linearly, without undesired bends, and totally mobile below the conjunctiva. A suction irrigator is then introduced into the anterior chamber in order to suck in the viscoelastic

and to create the necessary pressure within the chamber to confirm the implant's permeability. Due to the device's resistance, the bleb does not form quickly but slowly having an extension surface of about 4 h (120°). To conclude the surgical procedure, the corneal incision was then hydrated and the patient received intracameral cefuroxime.

Statistical analysis

Data analysis has been performed with the statistical software package SPSS Statistics v. 22.0 (IBM, Armonk, NY, USA).

A descriptive analysis has been carried out, involving all the sociodemographic and clinical variables collected at the beginning (preoperative, baseline data), as well as the intra-surgical and postoperative data, such as postoperative complications or the need for reintervention (secondary surgeries). As for categorical variables, absolute and relative frequencies were determined, while for continuous variables, mean, standard deviation, median and minimum and maximum values were chosen as descriptors (including the total number of valid values).

To compare pre- and post-glaucoma surgery outcomes, either parametric test (paired *t* test or ANOVA) or nonparametric test (Wilcoxon or Friedman test) was applied for continuous variables, while the Chi-square test was used for categorical variables.

For all tests, the threshold for statistical significance was assumed to be $p = 0.05$.

Results

Preoperative data

Once the database analysis was completed, we included in the study a total of 93 eyes—45 right eyes, 48 left eyes—from 63 patients, where 65.5% of them were female and the remaining 34.5% were male. Mean patients' age was 74 ± 8 years (range 45–91 years).

Mean preoperative best-corrected visual acuity (BCVA) was 0.79 ± 24 in a decimal scale (range 1–0.1). Mean IOP was 18.23 ± 5.00 mmHg (range 40–9), with a mean central corneal thickness (as measured with corneal

pachymetry) of 538.40 ± 32.94 μm (range 593–396). As for the number of medications that patients were being treated with for their glaucoma prior to surgery, the mean number of IOP-lowering medications was 1.87 ± 0.94 (range 4–1). During the preoperative period, 33.3% of the patients included in the study had received just one treatment, 32.3% two different treatments, and 34.4% had received three or more treatments.

As for the visual field assessment, mean deviation (MD) was 8.44 ± 6.53 (range 25–0.3). Finally, mean retinal nerve fiber layer (RNFL) thickness amounted to 66.12 ± 12.56 μm (range 103–36 μm).

Regarding surgical procedure type, 87.1% of the procedures were combined ones, i.e., performed in conjunction with cataract surgery.

Pre- vs. postoperative result comparison

Table 1 shows for each follow-up visit the pre- vs. postoperative changes in intraocular pressure (IOP), visual field mean deviation (MD), retinal nerve fiber layer (RNFL) thickness and number of IOP-lowering medications required by the patient.

Table 1

Preoperative (baseline) and postoperative (for each follow-up visit) intraocular pressure (IOP), visual field mean deviation (MD), retinal nerve fiber layer (RNFL) thickness and number of IOP-lowering medications required by the patient

Measurement time point	***N* (number of eyes)**	**Mean value ± SD**	**Range**	***p* (vs. pre-op values)**
IOP (mmHg)				
Pre-op (baseline)	93	18.23 ± 5.00	9–40	
12 months	93	14.16 ± 2.14	10–21	0.000
24 months	45	14.47 ± 2.16	11–21	0.000

The last column also shows the corresponding *p* value for the pre- vs. postoperative comparison. Significance threshold was set at 0.05

SD standard deviation

Measurement time point	*N* (number of eyes)	Mean value ± SD	Range	*p* (vs. pre-op values)
36 months	24	14.63 ± 1.91	12–18	0.001
Visual field mean deviation (MD)				
Pre-op (baseline)	93	8.44 ± 6.53	0.3–25	
12 months	47	7.58 ± 6.83	− 0.10–24.60	0.37
24 months	29	7.86 ± 6.97	− 0.30–22.80	0.58
36 months	21	9.11 ± 5.52	0.30–16.20	0.70
Nerve fiber layer (microns)				
Pre-op (baseline)	93	66.12 ± 12.56	36–103	
12 months	41	63.24 ± 9.94	41–84	0.752
24 months	24	62.21 ± 10.90	47–83	0.011
36 months	20	62.60 ± 10.10	49–87	0.924
Number of glaucoma medications				
Pre-op (baseline)	93	1.87 ± 0.94	1–4	
12 months	93	0.31 ± 0.69	0–3	0.000
24 months	38	0.34 ± 0.63	0–2	0.000
36 months	14	1.00 ± 0.88	0–2	0.017

The last column also shows the corresponding *p* value for the pre- vs. postoperative comparison. Significance threshold was set at 0.05

SD standard deviation

The comparison reveals that the implantation of a XEN® 45 Gel Stent led

to a drop in intraocular pressure (Fig. 1) and in the number of drugs used to treat glaucoma (Fig. 2), the differences emerging in every follow-up visit and being statistically significant in all cases. Regarding the retinal nerve fiber layer, a progressive decrease in thickness was observed, although it only reached significance levels 2 years after surgery. In terms of mean visual field deviation values, the pre- vs. post-changes never turned out to be significant for any of the follow-up visit data.

Fig. 1

Change in mean IOPs over 12-, 24- and 36-month follow-up visits

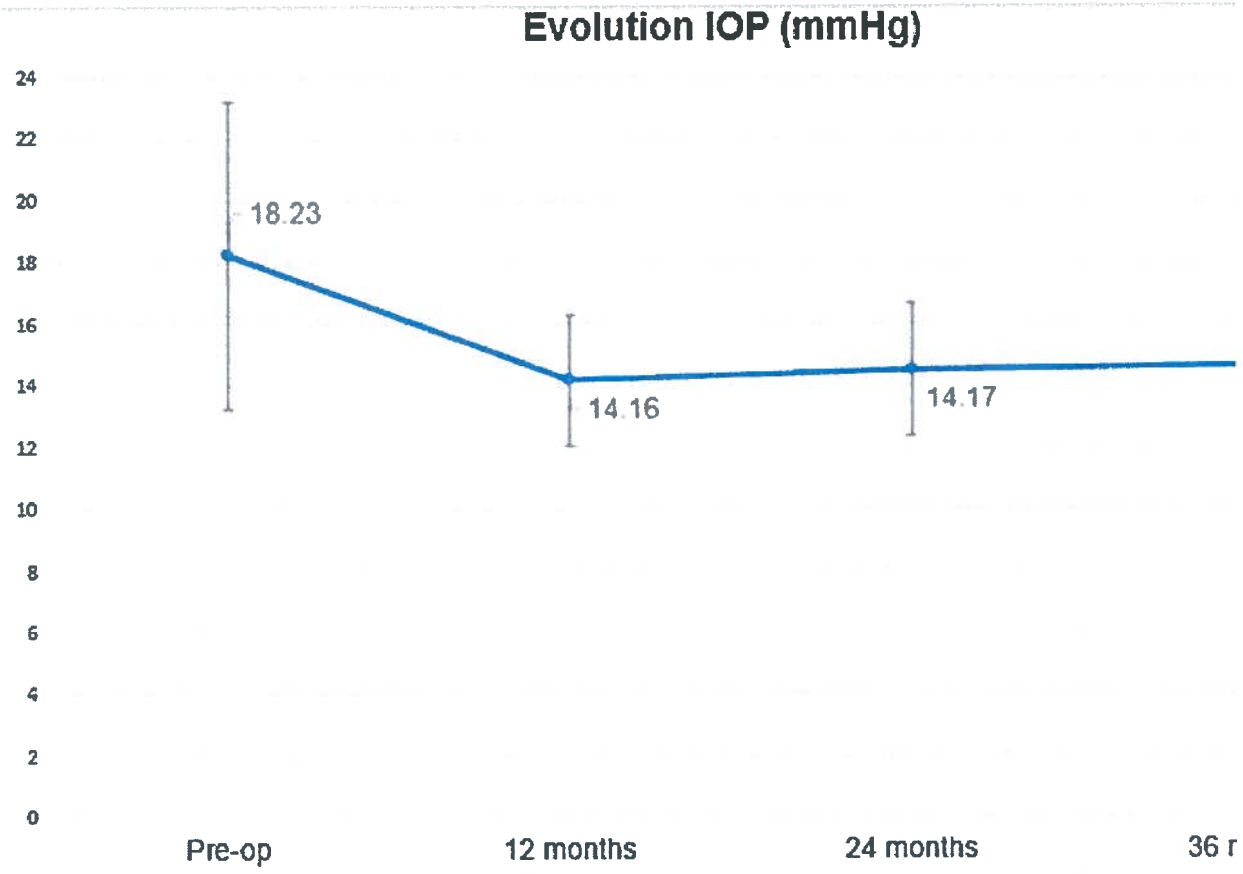
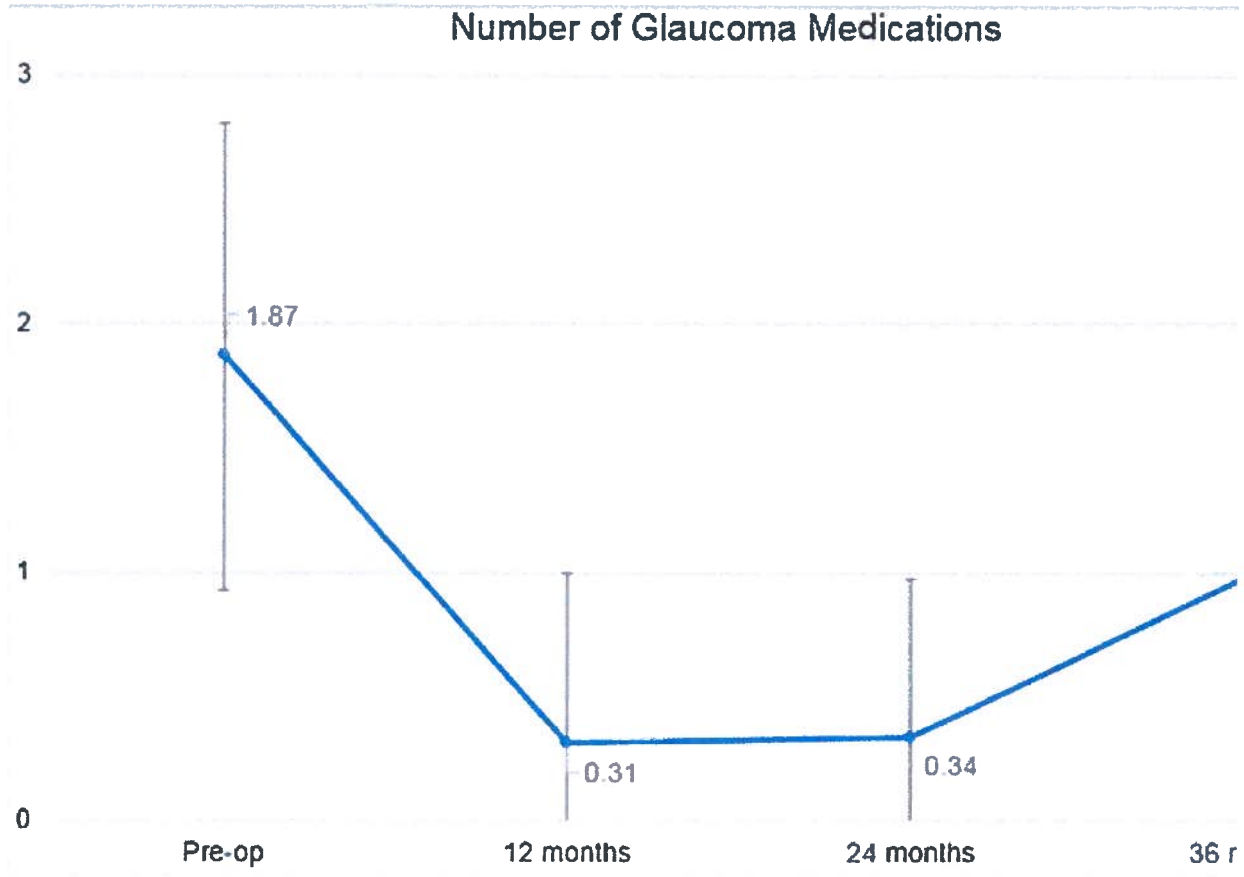


Fig. 2

Change in number of IOP-lowering medications required by the patient over 12-, 24- and 36-month follow-up visits



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Complications

A total of 94.6% of the surgical procedures turned out to be complication-free.

As much as 98.9% of the procedures required just one attempt to get the XEN® 45 Gel Stent implant inserted in place. In two procedures, a dellen occurred.

In 95.7% of the procedures, there was no anterior chamber bleeding. For 94.6% of the patients, no postsurgical bleb needling was required. In two of those cases, the bleb was reconverted using the dry-lake technique.

In just one of the surgeries, the procedure failed and 18 months later the patient had an ExPress (Alcon, Fort Worth, Texas, USA) system implanted.

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Discussion

MIGS glaucoma surgery is increasingly widespread among glaucoma specialists due to the benefits it offers over other many traditional techniques, such as trabeculectomy, although not all patient cases are eligible for this less invasive technique [8]. Our study shows the evolution of a group of 63 patients (93 eyes) with primary open-angle glaucoma who underwent the surgical implantation of a XEN® 45 Gel Stent.

When evaluating the changes resulting from the XEN® 45 implant, it is worth highlighting the relevant drop in intraocular pressure (around 24.5%), the difference being significant throughout the years of follow-up and remaining stable since the initial decrease occurred right after surgery. Mansouri [9] also found a significant decrease, although it is worth pointing out that his study focuses only on the first year of post-implantation follow-up, as did De Gregorio's [10], who reported in their study a 44% IOP drop. In Smith's research, which included the use of mitomycin [5], the 1-year IOP reduction amounted approximately to 33%. Sheybani [6], in his pilot study in patients undergoing Xen implantation combined with cataract surgery (with no use of mitomycin), also reported a mean decrease in IOP of around 20% at 12 months. Our study is the only one—up to date—that has followed up XEN® 45-implanted patients for 36 months, since in Lenzhofer's [11], doing 4-year follow-up and finding also significantly lower IOP values after surgery (40%), they chose a XEN® 63 (that is, a Xen Stent having 63 μm of inner diameter) as implanted device.

Regarding how visual field mean deviation (MD) has changed as a result of surgery, there are very few authors who have followed up this parameter. This is probably due to the high number of combined surgeries that are performed and to the fact that this factor, particularly in advanced-stage cataracts, can be affected by both the lens' loss of transparency and glaucoma. In our study, we found that values had decreased at 12- and 24-month follow-up visits, although the changes were not statistically significant. This is in good agreement with Lenzhofer's [11] findings: In his study on XEN® 63 implantation, he found no changes in visual field mean deviation (MD).

Similarly, retinal nerve fiber layer (RNFL) thickness has not been reported either in other papers found in the literature, whereas in our study, we

observed a slight decrease. Nonetheless, this RNFL thickness drop, although it remained stable over time—indicating that glaucoma was well controlled following the XEN® 45 device implantation—did not turn out to be statistically significant.

Our study reveals that the number of glaucoma medications required by the patient decreases after XEN® 45 implant surgery, and, most importantly, that this reduction is maintained over time. Similar findings were reported by Karimi [12], although their study focused on secondary surgeries—the same XEN® 45 Gel Stent implantation—after failed trabeculectomy. Other authors [5, 9, 10] also observed a drop in the number of IOP-lowering medications being used, although their findings are limited by their short-term (1-year) post-implantation follow-up.

Regarding complications, our study had a much higher number of event-free procedures than other studies in the literature; namely, in our study, there were only 5% of cases where a bleb needling had to be reviewed, which is a considerably lower rate than that seen in De Gregorio's [10] (53%) and in Mansouri's[9] (36%) work. Our study's low rate probably has to do with the fact that the correct postsurgical target IOP was achieved, not with the filtration bleb's filtering features (elevation, microcysts). Other data that can support this high success rate is the team's extensive experience with the device—XEN® 63—that preceded the advent of the XEN® 45 Gel Stent, as well as the systematic use of subconjunctival mitomycin prior to surgery. Maintaining 4–5 weeks of intensive corticosteroid and anti-inflammatory treatment as part of our postsurgical protocol may also prevent fibroblasts proliferation and, therefore, early fibrosis.

Probably, the low reintervention rate seen in our study is due to the experience and expertise of the surgeon who performed all the procedures: He had a wide experience—over 50 XEN® 63 implantation surgeries —before switching to the XEN® 45 Gel Stent implants analyzed in this study.

Two hypertrophic bleb reconversions were performed using the technique described by us [13]. In two patients, a surgical review had to be undertaken due to hypofiltration of the device.

Bleeding occurred in two of our study cases. Bleeding upon angle puncture is frequent although in the vast majority of cases, it remains self-limited and is quickly blocked by the viscoelastic material.

As for the procedures that failed at some point in time, there was only one case where we had to resort to a reconversion of the technique: A filtering surgery involving an ExPress valve and Ologen in the same exploration was performed. De Gregorio [10] showed an 11.8% failure rate, whereas in Lenzhofer's study 10% of surgeries failed (although the device in this case was a XEN® 63) [11].

Our study's limitations are: the fact that it is retrospective, and that not all cases completed the 2- and 3-year follow-up. A prospective and longer-term follow-up study should be conducted to confirm the results found in our study.

Conclusions

The results of this study give clear proof that XEN® 45 Gel Stent implantation is a safe procedure for glaucoma treatment. More specifically, more than 90% of the procedures included in the study were completed without any noteworthy complications. In addition, in 94.6% of the cases, no secondary surgery was required following the implantation of this XEN® 45 device.

On the other hand, the pre- vs. post-surgery data reveal that this surgical approach is significantly effective in terms of reducing intraocular pressure and the number of glaucoma medications required by the patient. This decrease was maintained at 12, 24 and 36 months post-surgery.

Hence, this study outcomes support the hypothesis that POAG surgical procedures with XEN® 45 Gel Stent implants are a safe and effective treatment approach.

Publisher's Note

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Compliance with ethical standards

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

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