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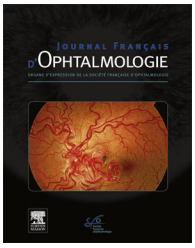

ORIGINAL ARTICLE

Real-world comparison of efficacy and safety of XEN45 implant with phacoemulsification versus iStent inject® W with phacoemulsification

Comparaison en situation réelle de l'efficacité et de la sécurité de l'implant XEN45 avec phacoémulsification versus iStent inject® W avec phacoémulsification

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KEYWORDS
Minimally invasive glaucoma surgery ;
XEN implant ;
iStent inject ;
Gel stent ;
Ab interno ;
Phacoemulsification

Summary
Purpose. — To compare iStent inject® W + phacoemulsification with XEN45 implant + phacoemulsification over 12 months in mild to moderate glaucoma patients needing cataract surgery at the Hospital General Universitario Dr. Balmis, Alicante, Spain.
Methods. — Retrospective clinical cohort study. Consecutive patients who underwent phacoemulsification either combined with XEN45 implantation or iStent inject® W from 2020 to 2022 were included. The main outcome measure was surgical success at 12 months postoperatively. Intraocular pressure (IOP), number of antiglaucoma medications, intraoperative and postoperative complications, number of revision surgeries, use of the operating room and required visits were also evaluated.

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Results. — A total of 167 eyes were included in the study, with 101 eyes of 61 patients undergoing iStent + PHACO and 66 eyes of 46 patients undergoing XEN45 + PHACO. The proportion of patients achieving a complete success (IOP $\geq$ 5 and $\leq$ 18 mmHg without medication) at the conclusion of the 12-month follow-up was 47.9% (35/73) in the iStent + PHACO and 48.2% (27/56) in the XEN45 + PHACO surgery group, $P = 1.000$. The mean (95% CI) IOP reduction at the conclusion of the study follow-up was −2.4 (−3.5 to −1.3 mmHg, $P < 0.001$, iStent + PHACO) and −3.10 (−4.8 to −1.4 mmHg, $P < 0.001$, XEN45 + PHACO). The mean number of antiglaucoma medications was significantly reduced in both study groups. Rates of intraoperative complications (5 vs. 15.2%), postoperative complications (1 vs. 46.2%), reoperations (0 vs. 24.6%), mean number of operating room visits (1 vs. 1.41), and mean number of required postoperative visits (4.50 vs. 11.13) were all statistically significantly higher in the XEN45 + PHACO group (< 0.001).
Conclusions. — Both procedures achieved similar surgical success rates, with comparable reductions in IOP and the number of antiglaucoma medications. After one year, a modest IOP reduction of 10.83% was observed in the iStent group and 13.65% in the Xen group. However, the iStent inject® W demonstrated a better intraoperative and postoperative safety profile.

MOTS CLÉS
Chirurgie du glaucome mini-invasive ;
Implant XEN ;
iStent inject ;
Stent en gel ;
Ab interno ;
Phacoémulsification

Résumé
Objectif. — L'objectif était de comparer l'iStent inject® W associé à une phacoémulsification avec l'implant XEN45 associé à une phacoémulsification sur une période de 12 mois chez des patients atteints de glaucome léger à modéré nécessitant une chirurgie de la cataracte à l'Hôpital General Universitario Dr Balmis, à Alicante, en Espagne.
Méthodes. — Étude clinique rétrospective de cohorte. Des patients consécutifs ayant subi une phacoémulsification combinée avec l'implantation du XEN45 ou de l'iStent inject® W entre 2020 et 2022 ont été inclus. La principale mesure de résultat était le succès chirurgical à 12 mois postopératoires. La pression intraoculaire (PIO), le nombre de médicaments antiglaucomateux, les complications peropératoires et postopératoires, le nombre de chirurgies de révision, l'utilisation de la salle d'opération et les visites nécessaires ont également été évalués.
Résultats. — Au total, 167 yeux ont été inclus dans l'étude, avec 101 yeux de 61 patients ayant subi la procédure iStent + PHACO et 66 yeux de 46 patients ayant subi la procédure XEN45 + PHACO. La proportion de patients ayant atteint un succès complet (PIO $\geq$ 5 et $\leq$ 18 mmHg sans traitement) à la fin des 12 mois de suivi était de 47,9 % (35/73) dans le groupe iStent + PHACO et de 48,2 % (27/56) dans le groupe XEN45 + PHACO, $p = 1{,}000$. La réduction moyenne de la PIO (IC 95 %) à la fin de l'étude était de −2,4 (−3,5 à −1,3 mmHg, $p < 0{,}001$, iStent + PHACO) et de −3,10 (−4,8 à −1,4 mmHg, $p < 0{,}001$, XEN45 + PHACO). Le nombre moyen de médicaments antiglaucomateux a été significativement réduit dans les deux groupes de l'étude. Les taux de complications peropératoires (5 vs 15,2 %), de complications postopératoires (1 vs 46,2 %), de réinterventions (0 vs 24,6 %), le nombre moyen de visites en salle d'opération (1 vs 1,41), et le nombre moyen de visites postopératoires nécessaires (4,50 vs 11,13) étaient tous significativement plus élevés dans le groupe XEN45 + PHACO ($p < 0{,}001$).
Conclusion. — Les deux procédures ont atteint des taux de succès chirurgicaux similaires, avec des réductions comparables de la PIO et du nombre de médicaments antiglaucomateux. Après un an, une réduction modeste de la PIO de 10,83 % a été observée dans le groupe iStent et de 13,65 % dans le groupe XEN-45. Cependant, l'iStent inject® W a démontré un meilleur profil de sécurité peropératoire et postopératoire.

Introduction

Glaucoma encompasses a group of eye disorders characterized by optic nerve degeneration and visual field impairments, remaining a prominent global cause of blindness [1]. The prevalence of glaucoma stands at approximately 3—5% among individuals aged 40 and above worldwide, with projections estimating an increase to 112 million cases by 2040, primarily fueled by the aging global population [2]. The primary objective in managing glaucoma is to enhance the patient's overall well-being and quality of life while ensuring

the sustainability of healthcare resources [1]. Presently, the only modifiable factor to impede glaucoma's progression is intraocular pressure. Surgery typically becomes a consideration when medication or laser treatment fails to control the disease, or when issues related to medication adherence or adverse effects arise [1]. Nevertheless, surgery may be prioritized as the initial therapy for individuals diagnosed with advanced vision loss [1]. Recent years have witnessed a significant shift towards Minimally Invasive Glaucoma Surgeries (MIGS) as the preferred approach over traditional incisional glaucoma surgeries. This preference arises from MIGS' favorable safety profile and swift postoperative recovery, particularly in patients with mild to moderate glaucoma [3]. The definition of MIGS includes procedures performed ab interno, with minimal disruption of normal anatomy, high safety profile, good efficacy, and quick recovery time [3—5].

The iStent inject® W was launched in 2020. It represents a modification of the second-generation iStent inject and consists of two preloaded trabecular micro-bypass stents with a single entry [6,7]. These stents are constructed from implant-grade titanium and are coated with heparin [6,7]. Each stent features an 80 μm diameter central inlet and outlet, in addition to four supplementary side flow outlets measuring 50 μm in diameter [6,7]. The distinguishing feature of the iStent inject® W is the base, which has a diameter of 360 μm. The iStent inject® W optimizes the trabecular outflow pathway and fits the definition of MIGS [4—7]. It has been demonstrated that the iStent, when combined with cataract surgery, significantly reduces intraocular pressure and the required number of medications, all without any serious adverse events [8—10].

The ab interno XEN45® gel stent (Allergan, Dublin, Ireland), introduced in 2016, is a hydrophilic tube measuring 6 mm in length with a 45 μm lumen [11,12]. It is constructed from porcine gelatin cross-linked with glutaraldehyde [11,12]. This implant is injected ab-internally, establishing an outflow pathway from the anterior chamber into the subconjunctival/sub-Tenon space [11,12]. There remains some debate about whether the XEN gel stent belongs to the realm of minimally invasive glaucoma surgeries (MIGS). Some authors propose that the XEN gel stent should be classified as part of Minimally Invasive Bleb Surgery (MIBS) or MIGS-plus [4,13]. Numerous studies have consistently validated the XEN implant as an effective and secure method for reducing intraocular pressure (IOP) and diminishing the reliance on topical antiglaucoma treatments [14,15]. Nevertheless, there is still controversy regarding whether the association of XEN implantation with cataract surgery affects its ability to lower IOP effectively, probably due to a higher grade of ocular inflammation and subsequent scarring [16]. A meta-analysis, encompassing ten studies and a total of 1117 eyes, found the superiority of standalone XEN45 implantation compared to its combination with phacoemulsification (XEN45 + PHACO) within the initial six months post-surgery [17]. Similarly, prior investigations have indicated that the combined procedure involving trabeculectomy and phacoemulsification may yield superior outcomes compared to the combination of XEN45 implantation and phacoemulsification [14,18]. We only found one retrospective study that directly compares iStent inject in combination with phacoemulsification to XEN in combination with phacoemulsification over a 6-month period [19].

The aim of this study was to assess and compare the outcomes in terms of success, efficacy, and safety between combined XEN45-phacoemulsification and combined iStent inject® W-phacoemulsification procedures over a one-year follow-up period at a tertiary-level hospital in Alicante, Spain.

Methods

This is a retrospective cohort study of consecutive patients diagnosed with both open-angle and closed-angle glaucoma, who underwent two different surgical procedures: gel stent implantation (XEN45® gel stent Allergan, Dublin, Ireland) with Mitomycin C (MMC), or trabecular Micro-Bypass stent implantation (iStent inject W Glaukos Corp, Laguna Hills, CA), in combination with phacoemulsification between January 2020 and August 2022. These surgeries were performed by two highly experienced glaucoma surgeons (M.M.P. and M.C.H.) at Hospital General Dr. Balmis, Alicante, Spain.

Patient identification was conducted chronologically using an electronic surgical case register, with subsequent verification through manual chart review. To ensure patient data protection, all data were pseudonymized prior to access.

Inclusion and exclusion criteria

Patients aged 40 years and older diagnosed with both mild-moderate glaucoma and cataract, and who had undergone combined surgery were included. The glaucoma staging was based on the simplified classification by Hodapp, as proposed by the European Glaucoma Society, considering only the mean deviation (MD) of the visual field [1]. Early glaucoma is defined as MD $\leq$ 6 dB, moderate glaucoma as MD > 6 dB but $\leq$ 12 dB, and advanced glaucoma as MD > 12 dB [1]. Those not meeting these eligibility criteria or having a history of prior glaucoma surgery were excluded. Postoperative data were systematically gathered at specific time points: day 1, month 1 (± 1 week), months 3 and 6 (± 2 weeks), and month 12 (± 1 month) following the surgical intervention. The collected postoperative data encompassed measurements of intraocular pressure (IOP), changes in the number of prescribed antiglaucoma medications, and the occurrence of adverse events.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent

The local ethics committee waived the need for written informed consent of the participants. Ref. CEIm: PI2023-094 — Ref. ISABIAL: 2023-0247.

Study groups

For statistical purposes, the eyes were divided into two groups: Group 1 (iStent + PHACO) and Group 2 (XEN45 + PHACO).

Surgical techniques

XEN45 implant combined with phacoemulsification

Under local anesthesia and following disinfection with povidone-iodine, reference points on the superior-nasal conjunctiva, 2 and 3 millimeters away from the limbus were marked. Then 0.1 mL of Mitomycin C (MMC) 0.02% (0.2 mg/mL), and 0.1 mL of Lidocaine using a 27-gauge hypodermic needle were administered. The injection was made beneath the conjunctiva and the Tenon capsule, just behind the intended site for the gel stent insertion. Afterward, gentle massaging of the fluid was performed to displace it further away from the limbus. The solution remained in place for 8 to 10 minutes before commencing a standard phacoemulsification.

After the phacoemulsification and intraocular lens implantation, the surgeon created a 1.2-mm side-port inferotemporal corneal paracentesis. The anterior chamber was then filled with highly cohesive viscoelastic material. Using a 27-gauge preloaded injector, she inserted the needle across the anterior chamber, creating a puncture in the sclera above the trabecular meshwork under gonioscopy. The XEN45 implant was carefully positioned in the superonasal part of the anterior chamber angle, with the ideal placement being 1 millimeter within the anterior chamber, 2 millimeters within the sclera, and 3 millimeters within the subconjunctival space.

The viscoelastic material was subsequently removed from the anterior chamber, and balanced salt solution (BSS) with constant irrigation was employed to assess the formation of a bleb. Finally, the surgeon hydrated the corneal incisions, deepened the anterior chamber with balanced salt solution, and initiated postoperative care. This care regimen included antibiotic prophylaxis administered four times daily for one week and a gradual tapering of corticosteroids (dexamethasone 0.1%) over the course of two months.

iStent inject W combined with phacoemulsification

Device implantation followed standard phacoemulsification. After the insertion of intraocular lens, the surgeon adjusted the patient's head, positioning it up to 25° away from her, and tilted the microscope up to 35° toward her to ensure a proper view of the anterior chamber angle. Subsequently, the microscope was fine-tuned to magnifications of 10—12x, enabling the identification of the trabecular meshwork. After pupillary miosis with acetylcholine chloride intraocular solution, a cohesive viscoelastic was used to deepen the anterior chamber as needed.

Under direct-gonioscopic guidance, the surgeon entered the eye through a temporal clear corneal incision with an inserter. The inserter was advanced beyond the pupillary margin, and the surgeon carefully positioned the trocar through the central or slightly anterior part of the trabecular meshwork, reaching the back wall of Schlemm's canal. Once the device was properly situated within Schlemm's canal, the inserter button was pressed to release the first device. Afterward, the surgeon moved 2 to 3 clock hours away to implant the second stent. The viscoelastic substance was then rinsed out from the anterior chamber. The postoperative care regimen included antibiotic prophylaxis administered four times daily for one week and a gradual tapering of corticosteroids (dexamethasone 0.1%) over the course of one month.

Bleb needling

Under a slit lamp microscope, the bleb area was disinfected with povidone-iodine. Subsequently, topical lidocaine 2% gel was applied over the bleb intended for needling. A sterile lid speculum was then inserted. Following this, 0.1 mL of a solution (consisting of non-preserved 1% lidocaine, MMC 0.02% [0.2 mg/mL], or 5-Fluorouracil [5 mg in 0.1 mL]) was injected beneath the conjunctiva using a 30-gauge needle. The needle was inserted bevel up, approximately 5 to 10 mm away from the temporal edge of the bleb, and directed posteriorly to release subconjunctival scar tissues. To ensure proper distribution away from the limbus, the bleb was gently massaged using a cotton swab, applying pressure in a rolling motion over the conjunctiva near the injection site.

Outcomes

The primary outcome variable assessed surgical success at the one-year mark, with success categorized into three distinct groups:

- strict success was defined as achieving a reduction in intraocular pressure (IOP) of at least 20% compared to the preoperative IOP, maintaining an IOP between 5 and 18 mmHg during follow-up, not requiring any antiglaucoma medication, and avoiding the need for revision surgery [20];
- complete success entailed maintaining an IOP between 5 and 18 mmHg during follow-up, without any use of antiglaucoma medication, and without requiring revision surgery;
- qualified success meant achieving an IOP between 5 and 18 mmHg during follow-up, even with the use of antiglaucoma medication, and without requiring revision surgery.

Failure was determined if the IOP was either less than 5 mmHg (with signs of hypotony maculopathy) or greater than 18 mmHg, or if revision surgery was deemed necessary. Any data collected after surgical failure was not included in the study analysis.

Secondary outcome measures included assessing IOP at various time points (day 1, month 1, month 3, month 6, month 12), the number of antiglaucoma medication (NOAM), intraoperative and postoperative complications, number of revision surgeries, use of the operating room and required visits. Revision surgery was considered necessary when the IOP exceeded the individual target IOP, and topical therapy was insufficient in achieving these target values post-surgery. Needling was not classified as a revision surgery. The required visits were noted just for the last

operated eye in the case that both eyes of a patient underwent surgery.

Statistical analysis

We employed IBM SPSS Statistics version 28 (IBM Corp, New York, USA) for the statistical analysis. Statistical significance was defined as a *P*-value less than 0.05. Data were presented as follows: number (percentage %), mean (standard deviation or 95% confidence interval), and median (interquartile range). We assessed data for normal distribution using both the Kolmogorov-Smirnov and Shapiro-Wilk tests. To evaluate changes in IOP and the number of glaucoma medications from the preoperative baseline to month 12 within each group, we employed the Wilcoxon signed rank test. Additionally, we utilized the Mann-Whitney U test to compare these changes between the two groups. Adverse events were assessed using the Fisher exact test. Survival analysis was conducted using Kaplan-Meier curves. Furthermore, Cox regression analysis was carried out to examine the impact of potential factors on the likelihood of surgical failure at POM12. The model included variables such as the type of intervention (iStent-PHACO vs. XEN45-PHACO), age, gender, ethnic group, presence of underlying diabetes mellitus, preoperative IOP, preoperative number of antiglaucoma medications, and type of glaucoma.

Results

This study encompassed a total of 167 eyes, with 101 eyes from 61 patients undergoing iStent + PHACO procedures and 66 eyes from 46 patients undergoing XEN45 + PHACO procedures. The baseline and glaucoma characteristics were generally comparable between the two groups, but differed in the prevalence of diabetes mellitus and the average number of antiglaucoma medications (NOAM). The iStent + PHACO group had a higher prevalence of diabetes mellitus and a higher mean NOAM compared to the XEN45 + PHACO group (as shown in Table 1).

By the twelfth month, strict success was achieved in 21.9% of patients in the iStent + PHACO group, while the XEN45 + PHACO group achieved a rate of 23.2% (Table 2). There were no statistically significant differences between these two groups ($P < 0.473$). However, statistically significant differences were evident only at the first month ($P = 0.001$) and the third month ($P = 0.042$), where the XEN45 + PHACO group had higher rates of strict success. When comparing complete success between both groups, no statistically significant differences were observed at any time point (Table 2). At the twelfth month, complete success was attained by 47.9% of patients in the iStent + PHACO group and by 48.2% in the XEN45 + PHACO group ($P = 1.000$ between the groups). The rates of qualified success were not significantly different between both groups across the study's time points (Table 2).

Significant differences in intraocular pressure (IOP) between pre- and postoperative assessments were observed consistently across all time points for the XEN45 + PHACO group (Table 3). The most pronounced IOP reduction was evident immediately on the first day post-surgery, with a notable mean decrease of −5.95 mmHg, corresponding to a substantial 30.04% reduction. This reduction trend persisted at the sixth month, where a mean decrease of 3.23 mmHg was recorded, equating to a 14.27% reduction from the preoperative baseline. These statistically significant differences in IOP between pre- and postoperative measurements also remained evident at the first, third, and twelfth months. Similarly, within the iStent + PHACO group, the most significant IOP reduction was noted at the sixth month, showing a mean decrease of 2.4 mmHg, which represented a 10.83% reduction from the preoperative baseline. Interestingly, no statistically significant difference was observed on the first day postoperative when compared to the preoperative IOP levels.

The XEN45 + PHACO group exhibited a significantly greater mean IOP reduction solely on the first day postoperative (< 0.001), with a 5.02 mmHg difference compared to the iStent + PHACO group. However, beyond the immediate postoperative period, no statistically significant disparities in IOP reduction were observed between both groups at subsequent time points. By the twelfth month, the iStent + PHACO group displayed a mean IOP reduction of −2.4 mmHg, equivalent to a 10.83% mean decrease from the preoperative value, while the XEN45 + PHACO group showed a mean IOP reduction of −3.10 mmHg, constituting a 13.65% mean decrease from the preoperative value. Importantly, there were no statistically significant differences between the two groups at this twelve-month mark ($P = 0.332$).

Both groups exhibited a significant reduction in the number of antiglaucoma medications following surgery at each time point ($P < 0.001$, Table 3), and there were no statistically significant differences observed between the two groups. Nevertheless, this reduction in the mean number of antiglaucoma medications (NOAM) displayed a tendency to diminish over time. By the twelve-month mark, the iStent + PHACO group had experienced a reduction of −1.67 NOAM, while the XEN45 + PHACO group had a reduction of −1.43 NOAM ($P = 0.102$ between groups).

Excluding the rates of failure and loss to follow-up, at the month 12 endpoint, the percentage of patients achieving low-teen IOP ($\leq$ 12 mmHg, complete and qualified success) were 25.4% in the iStent + PHACO group and 23.4% in the XEN45 + PHACO group ($P = 1.00$, Fischer exact test); mid-teen IOP ($\leq$ 15 mmHg, complete and qualified success) were 50.7% in the iStent + PHACO group and 55.3% in the XEN45 + PHACO group ($P = 0.707$, Fischer exact test) and high-teen IOP ($\leq$ 18 mmHg, complete and qualified success) were 83.1% in the iStent + PHACO group and 80.9% in the XEN45 + PHACO group ($P = 0.469$, Fischer exact test).

A Kaplan-Meier curve was employed to illustrate the relationship between the type of surgical intervention and the risk of failure. The analysis revealed no statistically significant difference between the two groups ($P = 0.126$) (Fig. 1). In the iStent + PHACO group, all cases of surgical failure were attributed to suboptimal IOP control. In contrast, among patients in the XEN45-PHACO group who experienced surgical failure, it was attributed either to suboptimal IOP control or the necessity for surgical reintervention.

Multivariable Cox regression analysis was employed to explore potential factors influencing the outcome, as summarized in Table 4. None of the examined variables demonstrated a statistically significant influence on the risk

Table 1 Baseline demographic and clinic characteristics of the study population according to the surgical procedure.

	iStent + PHACO ($n = 101$)	XEN45 + PHACO ($n = 66$)	P
Age, years			
Mean (SD)	71.67 (6.96)	71.92 (7.5)	
95% CI	70.30 to 73.05	70.07 to 73.78	0.770[a]
Median (IQR)	72 (8)	73 (11)	0.434[a]
Gender, *n* (%)			
Male	58 (57.4)	31 (47.0)	
Female	43 (42.6)	35 (53.0)	0.207[b]
Eye, *n* (%)			
Right	53 (52.5)	32 (48.5)	
Left	48 (47.5)	34 (51.5)	0.365[b]
Ethnic group, *n* (%)			
Spanish	98 (97)	58 (87.9)	
Latin American	3 (3)	4 (6.1)	
Russian	0 (0)	2 (3.0)	0.044[b]
English	0 (0)	2 (3.0)	
Diabetes mellitus, *n* (%)			
Yes	32 (31.7)	5 (7.6)	< 0.001[b]
No	69 (68.3)	61 (92.4)	
Anticoagulation/Antiaggregation, *n* (%)			
Acetylsalicylic acid	12 (11.9)	10 (15.2)	
Double antiaggregation	1 (1)	0 (1)	
Acenocoumarol	3 (3)	4 (6.1)	0.696[b]
DOACs	7 (6.9)	2 (3)	
Clopidogrel	2 (2)	2 (3)	
None	76 (75.2)	48 (72.7)	
Diagnosis, *n* (%)			
Primary open-angle glaucoma	65 (64.4)	42 (63.6)	
Pseudoexfoliative glaucoma	27 (26.7)	12 (18.2)	
Inflammatory glaucoma	0 (0)	1 (1.5)	0.345[b]
Pigmentary glaucoma	2 (2)	2 (3)	
Angle closure glaucoma	7 (6.9)	9 (13.6)	
Visual acuity, logMAR			
Mean (SD)	0.31 (0.32)	0.44 (0.53)	0.280[a]
95% CI	0.25 to 0.38	0.31 to 0.57	
Median (IQR)	0.22 (0.23)	0.26 (0.37)	0.780[a]
IOP, mmHg			
Mean (SD)	17.73 (3.63)	18.45 (5.73)	0.419[a]
95% CI	17.02 to 18.45	17.32 to 20.16	
Median (IQR)	17 (5)	18 (5)	0.242[a]
NOAM			
Mean (SD)	2.36 (0.820)	2 (0.928)	0.010[a]
95% CI	2.19 to 2.52	1.77 to 2.23	
Median (IQR)	2 (1)	2 (2)	0.206[a]
Oral carbonic anhydrase inhibitor, *n* (%)			
Yes	1 (1)	1 (1.5)	0.636[b]
No	100 (99)	65 (98.5)	

PHACO: phacoemulsification; n: number of eyes; SD: standard deviation; CI: confidence interval; NOAM: number of antiglaucoma medications; DOACs: direct oral anticoagulants; IQR: Interquartile range; IOP: intraocular pressure.
[a] Mann-Whitney test.
[b] Fischer exact test.

of failure at the twelfth month. There was a slightly elevated likelihood of surgical failure in eyes with higher preoperative NOAM (odds ratio [OR] 1.909; $P = 0.069$) and those with higher preoperative IOP (odds ratio [OR] 1.928; $P = 0.087$), although these findings did not reach statistical significance.

Regarding the safety profile, a comparison of the incidence of adverse events is presented in Tables 5 and 6. Overall, the iStent + PHACO group exhibited a lower incidence of intraoperative complications than the XEN45 + PHACO group (5 vs. 15.2%; $P = 0.029$). Within the XEN45 + PHACO

Table 2 Comparison of strict, complete and qualified success between iStent + PHACO and XEN45 + PHACO groups. The data are expressed as number of eyes (%).

	Strict success			Complete success			Qualified success		
	iStent + PHACO	XEN45 + PHACO	*P*[a]	iStent + PHACO	XEN45 + PHACO	*P*[a]	iStent + PHACO	XEN45 + PHACO	*P*[a]
Month 1	14/89 (15.7)	25/64 (39.1)	0.001	52/89 (58.4)	41/64 (64.1)	0.506	66/89 (74.2)	43/64 (67.2)	0.370
Month 3	9/48 (18.8)	20/62 (32.33)	0.042	29/48 (60.4)	41/62 (66.1)	0.555	39/48 (81.3)	47/62 (75.8)	0.642
Month 6	16/72 (22.2)	22/63 (34.9)	0.208	39/72 (54.2)	39/63 (61.9)	0.387	61/72 (84.7)	46/63 (73.0)	0.136
Month 12	16/73 (21.9)	13/56 (23.2)	0.473	35/73 (47.9)	27/56 (48.2)	1.000	59/73 (80.8)	38/56 (67.85)	0.103

PHACO: phacoemulsification.
[a] Fischer exact test.

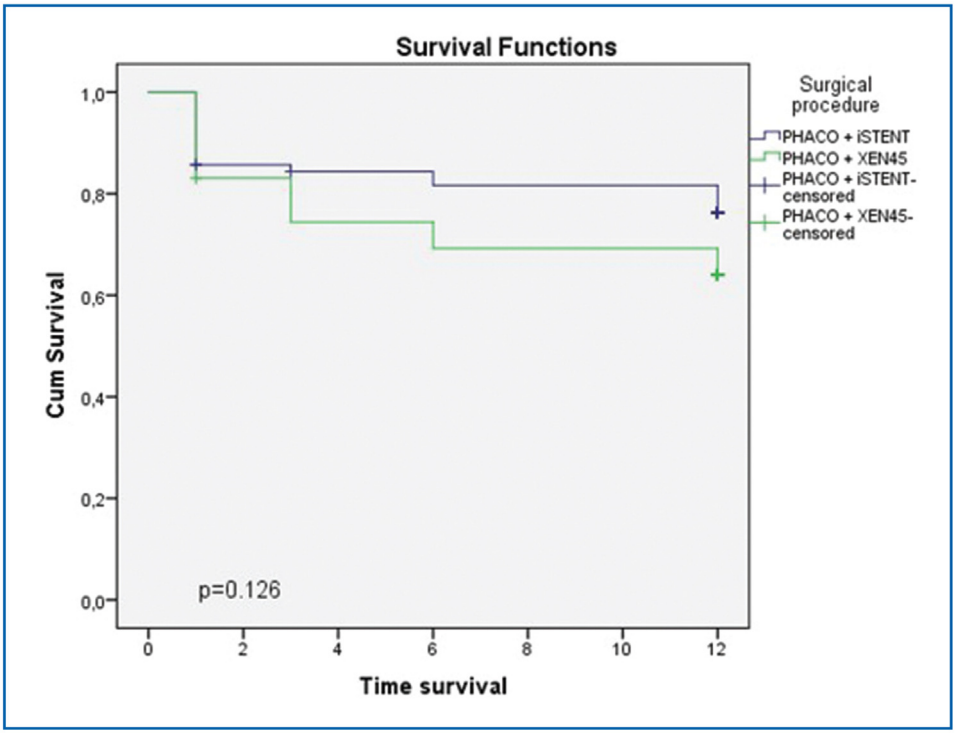

Figure 1. Kaplan-Meier event free survival.

group, the most prevalent intraoperative complication was iris prolapse, occurring in 4.5% of cases. Conversely, in the iStent + PHACO group, the primary complication involved issues associated with stent implantation, which included one instance of a lost implant and the requirement for an additional injector, collectively accounting for 4% of cases. The overall postoperative complication rate was also lower in the iStent + PHACO group compared to the XEN45 + PHACO group (1 vs. 46.2%). In the XEN45 + PHACO group, the majority of postoperative complications were related to bleb events. Conversely, the iStent + PHACO group experienced only one postoperative complication, which was cystoid macular edema (1%). Rates of reintervention (0 vs. 24.6%), the mean number of operating room visits (1 vs. 1.41), and the mean number of postoperative required visits (4.50 vs. 11.13) were all statistically significantly higher in the XEN45 + PHACO group ($P < 0.001$). Patient data were gathered at the specified postoperative time points, as previously indicated. Nevertheless, the requirement for postoperative visits was at the discretion of the attending surgeon.

In total, 38.84% of patients in XEN45 + PHACO group required needling, and among those individuals, 43.5% received 5-FU, while 12% received MMC (Table 6). The average time elapsed before the first needling procedure was 53.37 days, and the mean number of needling procedures per patient was 1.85. The XEN45 + PHACO group exhibited an average of

Table 3 Overview of the change in intraocular pressure (IOP) and number of antiglaucoma medications (NOAM) from baseline for eyes that underwent either iStent + PHACO or XEN45 + PHACO.

IOP	iStent + PHACO			XEN45 + PHACO			Difference between treatment groups	P^b
	Mean (95% CI) absolute difference from baseline	Mean (95% CI) percentage difference from baseline	P^a	Mean (95% CI) difference from baseline	Mean (95% CI) percentage difference from baseline	P^a	Mean difference (95% CI)	
Day 1	0.3465 (−1.29 to 1.98)	−4.23 (−5.02 to 13.47)	0.724	−5.95 (−7.7 to −4.10)	−30.04 (−38.70 to −21.38)	< 0.001	5.02 (2.78 to 7.63)	< 0.001
Month 1	−0.58 (−1.46 to 0.29)	−1.06 (−6.16 to 4.04)	0.055	−1.52 (−3.60 to 0.56)	−3.96 (−14.35 to 6.41)	0.009	0.147 (−1.85 to 2.14)	0.077
Month 3	−2.43 (−3.85 to −1.02)	−10.28 (−16.70 to −3.85)	0.001	−1.88 (−3.67 to −0.947)	−6.88 (−15.47 to −1.70)	0.005	−0.73 (−3.03 to 1.57)	0.725
Month 6	−2.39 (−3.4 to −1.38)	−10.84 (−15.65 to −6.02)	< 0.001	−3,23 (−4.84 to −1.63)	−14.27 (−21.57 to −6.98)	< 0.001	0.851 (0.59 to 2.30)	0.217
Month 12	−2.4 (−3.5 to −1.3)	−10.83 (−16.37 to −5.29)	< 0.001	−3.10 (−4.8 to −1.4)	−13.65 (−21.01 to −6.29)	< 0.001	0.74 (−1.63 to 1.299)	0.332

NOAM	Mean (95% CI) absolute difference from baseline	P^a	Mean (95% CI) absolute difference from baseline	P^a	Mean difference (95% CI)	P^b
Month 1	−1.89 (−2.09 to −1.69)	< 0.001	−1.82 (−2.07 to −1.58)	< 0.001	0.33 (−0.12 to 0.55)	0.496
Month 3	−1.92 (−2.17 to −1.66)	< 0.001	−1.64 (−1.92 to −1.36)	< 0.001	0.14 (−0.17 to 0.44)	0.177
Month 6	−1.82 (−2.02 to −1.61)	< 0.001	−1.65 (−1.91 to −1.39)	< 0.001	0.35 (0.09 to 0.615)	0.263
Month 12	−1.67 (−1.89 to −1.45)	< 0.001	−1.43 (−1.73 to −1.12)	< 0.001	0.17 (0.14 to 0.49)	0.102

PHACO: phacoemulsification; SD: standard deviation; CI: confidence interval; NOAM: number of antiglaucoma medications.
[a] Wilcoxon signed rank test.
[b] Mann-Whitney test.

1.13 reinterventions per patient, with the initial reintervention taking place at an average of 100.67 days post-surgery. Among the 16 patients (24.2%) requiring reintervention, 8 (12.1%) underwent bleb revision, 4 (6.1%) received a new XEN45 implant, 3 (4.5%) underwent trabeculectomy, and 1 (1.5%) underwent a non-penetrating deep sclerectomy (NPDS).

Discussion

This study suggests that both iStent + PHACO and XEN45 + PHACO procedures significantly reduce intraocular pressure (IOP) by month 12 postoperatively. In terms of strict success, the proportion between both groups became comparable after the sixth month. When analyzing the proportion of patients achieving complete success, no significant differences were observed between the two groups at any time point. Our complete success rate in the iStent + PHACO group is similar to the 50 and 54% observed by Arriola et al., Hengerer et al. and Neuhann et al. [9,21,22]. In contrast with our results, Ma et al. reported a significantly higher success rate of 83.3% in terms of complete success (defined with an upper limit IOP of 21 mmHg) in the XEN + Phaco group when compared to the iStent + Phaco group [19]. The complete success rate in the XEN45 + PHACO group was 48.2% and was consistent with findings from other studies (ranging from 15.5 to

Table 4 Multivariable Cox regression for surgical failure.

Variable	Hazard ratio	95%-confidence interval	*P* value
Surgical procedure			
PHACO + iStent	—	—	
PHACO + XEN45	1.817	0.884—3.735	0.104
Patient age (years)	1.001	0.958—1.047	0.960
Ethnic group			
Spanish	—	—	
Latin American	0	0.504—4.885	0.437
Northern European	1.569	0—0	0.977
Diabetes mellitus			
Yes	—	—	—
No	0.726	0.322—1.639	0.441
Gender			
Female	—	—	—
Male	0.973	0.491—1.928	0.938
Diagnosis			
Open-angle glaucoma	—	—	—
Angle closure glaucoma	0.685	0.197—2.382	0.552
Pre-OP IOP			
≤ 21	—	—	—
> 22	1.928	0.909—4.091	0.087
Pre-OP medication			
≤ 2	—	—	—
> 2	1.909	0.951—3.832	0.069

PHACO: phacoemulsification; Pre-OP: preoperative; IOP: intraocular pressure; —: reference variable.

66%). However, there is considerable heterogeneity in terms of the upper limit for IOP between these studies [14,15,18,23—29].

During the initial months, the XEN45 + PHACO group demonstrated a more pronounced reduction in IOP (on day 1 and at month 1). Subsequently, there was no discernible difference between both groups, possibly attributable to progressive fibrosis of the XEN45 implant post-surgery, resulting in a subsequent IOP increase in this cohort [18]. The higher IOP observed at day 1 in the iStent + PHACO group may be due to the amount of viscoelastic substance required during the stent injection procedure. Additionally, both groups experienced a hypertensive peak at month 1 when compared to other time points (day 1, month 3, month 6, and month 12), which is likely attributed to the use of corticosteroid eye drops.

Our 10.83% percentage reduction in IOP for the iStent + PHACO group is lower than the reported by Arriola et al. and Hengerer et al., but those eyes had higher preoperative IOP values than our study population [9,21]. They reported reductions ranging from 30 to 37% in IOP value. Clement et al. and Salimi et al. found a 16 and a 17.8% reduction in IOP, respectively, among patients who underwent phacoemulsification in combination with iStent inject in their real-world studies [30,31]. The percentage reduction in IOP reported by Neuhann et al. was 25.5% at the 12-month mark and 26.6% at the 24-month endpoint [22]. Our percentage reduction in IOP observed in the XEN45 + PHACO group, which amounted to a 13.65% IOP reduction at the 12-month mark, falls within the lower range compared to findings in other studies [14,15,28,29,32—36]. However, those studies included also the results of the standalone XEN45 implantion. Our results align closely with those reported by Kee et al. in Asian eyes, where they documented a mean 13.2% reduction in IOP at the 12-month follow-up for the XEN45 + PHACO procedure [18]. In their study comparing the XEN45 implant with iStent inject in Korean eyes over a 6-month period, Ma et al. found no statistically significant differences in the mean intraocular pressure (IOP) between the iStent inject + Phaco group (comprising 32 eyes) and the XEN + Phaco group (consisting of 12 eyes) [19]. Only during the first month was the mean IOP significantly lower in the XEN + Phaco group, however, the sample was small [19]. Non-Caucasian eyes have exhibited higher rates of fibrosis and surgical failures in the context of subconjunctival filtering surgery [14,15,18,32,36,37]. This trend could potentially account for the relatively modest reduction in intraocular pressure (IOP) observed in our study compared to the results documented in the published literature.

Both groups in our study exhibited a significant reduction in the number of antiglaucoma medications (NOAMs) when compared to their respective baseline measurements at each time point. This finding aligns with the results reported in other studies [8,10,19,30,31]. A trend of NOAMs gradually increasing over time in our study was noted.

We did not identify any associations between failure at the 12-month mark and variables such as gender, age, diabetes mellitus, preoperative intraocular pressure (IOP), and the number of preoperative antiglaucoma medications. This aligns with findings from other studies [18]. Some XEN45 studies have identified variables like a preoperative IOP < 15 mmHg, intraoperative temporal position of the

Table 5 Comparison of the incidence of intra- and postoperative complications between iStent + PHACO and XEN45 + PHACO groups. The data are expressed as number of eyes (%).

	iStent + PHACO ($n = 101$)	XEN45 + PHACO ($n = 66$)	*P* value
Intraoperative complications	5 (5)	10 (15.2)	0.029[a]
Types of intraoperative complications			
Zonulysis	0 (0)	1 (1.5)	0.395[a]
Iris prolapse	1 (1)	3 (4.5)	0.302[a]
Hyphema	0 (0)	1 (1.5)	0.395[a]
Posterior capsule rupture	0 (0)	2 (3)	0.155[a]
Intraocular lens defects	0 (0)	1 (1.5)	0.395[a]
Zonulysis	5 (5)	1 (1.5)	0.395[a]
Insufficient intraoperative dilation	0 (0)	1 (1.5)	0.395[a]
Anterior capsule rupture	1 (1)	0 (0)	1.000[a]
Technical problems with the implant/stent implantation	4 (4)	0 (0)	0.154[a]
Postoperative complication	1 (1)	30 (46.2)	< 0.001[a]
Types of postoperative complications			
Bleb-related			
Corneal dellen	0 (0)	1 (1.5)	
Implant rupture	0 (0)	5 (7.7)	
Bleb fibrosis	0 (0)	12 (18.5)	
Implant migration	0 (0)	9 (13.8)	
Seidel	0 (0.0)	0 (0.0)	1.000[a]
Not Bleb-related			
Cystoid macular edema	1 (1)	2 (3.1)	0.562[a]
Hyphema	0 (0)	3 (4.6)	0.058[a]
Aqueous misdirection	0 (0)	3 (4.6)	0.392[a]
Anterior uveitis	0 (0)	2 (3.1)	0.152[a]
AC flattening[c]	0 (0)	2 (3.1)	0.152[a]
Infection[d]	0 (0.0)	0 (0.0)	1.000[a]
Reoperation	0 (0)	16 (24.2)	< 0.001[a]
Mean number of operating room uses (SD) 95% CI	1	1.41 (0.859) 1.20—1.62	< 0.001[b]
Mean postoperative visits required in the first year (SD)95% CI	4.50 (1.30)4.16—4.84	11.13 (5.33)9.62—13.03	< 0.001[b]

P values were calculated comparing the number of adverse events occurring from day 1 to month 12. AC: anterior chamber; PHACO: phacoemulsification; n: number of eyes; SD: standard deviation; CI: confidence interval.
[a] Fischer exact test
[b] Mann-Whitney test.
[c] Required some intervention.
[d] Bleb-related infection or endophthalmitis.

surgeon, gender, diabetes mellitus as risk factors for failure [29,32,33,37]. Ma et al. identified preoperative IOP as a risk factor for failure of iStent inject and Xen surgery in their study [19]. Salimi et al. showed that greater baseline preoperative and thinner corneas were associated with a larger postoperative IOP reduction [31]. They did not find associations between age, sex, type, and severity of glaucoma and in prior history of glaucoma surgery and IOP reduction [31]. However, they did not analyze the correlation with surgical success [31].

The safety profiles during both the intra- and postoperative periods were more favorable for the iStent + PHACO group. In their study of the iStent inject, Arriola et al. and Clement et al. also reported that intraoperative complications were limited solely to issues with the implant [9]. Some studies did not report intraoperative complications related to the iStent inject [21,22,31]. The reintervention rate of the iStent inject combined with phacoemulsification varies between 0.6—3.82% over a two-year period [21,22,30]. We observed a 15.2% rate of intraoperative complications and a 46.2% rate of postoperative complications in the XEN45 + PHACO group, consistent with findings in other studies [27,29,32—34,36—38]. 24.4% of the eyes in the XEN45 + PHACO group required a reintervention. Other studies have reported a reintervention rate of 12.3—43.7% [28,32—34]. Our needling rate fit into the range encountered in other studies, which reported a needling rate of 2.4—55.4% after Xen implantation [12,25—29,32—36,38]. In their comparative study between the XEN45 implant and iStent inject, Ma et al. reported one case of gross hyphema and high intraocular pressure (IOP) as a postoperative complication in the iStent + Phaco group. In contrast, they observed no postoperative complications in the XEN + Phaco group [19].

This current study has several limitations. The considerable heterogeneity in the definitions of success and the

Table 6 Needling and reoperation details for the XEN45 + PHACO group.

	XEN45 + PHACO
Needling rate, *n* (%)	23 (34.84)
Antimetabolite needling	
5-FU	10 (43.5)
MMC	3 (13.0)
None	10 (43.5)
Mean time (days) to first needling (SD)	53.37 (53.43)
95% CI	30.26—76.48
Mean number of needlings per patient (SD)	1.85 (1.137)
95% CI	1.32—2.38
Mean number of reoperations per patient mean (SD)	1.13 (0.342)
95% CI	0.94—1.31
Mean time (days) to first reoperation (SD)	100.67 (85.027)
95% CI	53.58—147.75
Type of reoperation, *n* (%)	
Bleb revision	8 (12.1)
New XEN45 implant	4 (6.1)
Trabeculectomy	3 (4.5)
NPDS	1 (1.5)

PHACO: phacoemulsification; n: number of eyes; SD: standard deviation; CI: confidence interval; 5-FU: 5-Fluorouracil; MMC: Mitomycin C; NPDS: non-penetrating deep sclerectomy.

preoperative IOP values among various glaucoma studies makes it challenging to achieve a significant comparison. The retrospective design of the study carries a risk of selection bias, variability in treatment approaches, variability in the measurement IOP, variability in the number of subjects within each group and loss to follow-up. Additionally, there was no standardized protocol for procedures such as bleb manipulation, the administration of antiglaucoma medications, or postoperative interventions. These variations could contribute to the disparities observed in terms of qualified success and the rate of reintervention between the two study groups. The short follow-up period is not sufficient to correctly assess the long-term effect of both procedures. However, the advantage of the real-world nature is the opportunity to keep collecting follow-up data under typical population circumstances and to extend the analysis over longer follow-up periods in future studies.

Conclusion

Our findings suggest that both combined iStent -phacoemulsification and combined XEN45-phacoemulsification procedures lead to a similar reduction in IOP and the NOAM, particularly beyond the third month post-surgery. However, the intraoperative and postoperative safety profile of combined iStent-phacoemulsification is better. Additionally, the rate of reintervention is higher in the XEN45-phacoemulsification group, along with an increased need for postoperative follow-up visits. These factors, together with an adequate angle visualization, should be taken into consideration when deciding on a MIGS procedure to combine with phacoemulsification.

Disclaimer

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Disclosure of interest

Dr. Marcos has received a grant from Allergan in the past.

The co-authors declare that they have no competing interest.

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