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Complications and post-operative interventions in XEN45 gel stent implantation in the treatment of open angle glaucoma—a systematic review and meta-analysis

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BACKGROUND: The XEN45 Gel Stent is a subconjunctival filtering device that has demonstrated promising efficacy. This meta-analysis quantitatively evaluates reported complications and interventions after XEN45 implantation in the treatment of open angle glaucoma (OAG).

METHODS: Pilot, cohort, observational studies, and randomised controlled trials that included at least ten patients undergoing ab interno or externo XEN45 surgery, with or without phacoemulsification were deemed eligible for inclusion. A meta-analysis of proportions with random-effect models was performed using the meta routine in R version 3.2.1. Outcomes included the rate of complications and post-operative interventions.

RESULTS: One hundred and fifty-two studies were identified on initial literature search and 33 were included in final analysis. Numerical hypotony was the most common post-operative complication, involving 20% of patients (95% CI: 10–31%). Post-operative gross hyphema occurred in 14% (95% CI: 7–22%) and transient intra-ocular pressure (IOP) spikes (>30 mmHg) in 13% (95% CI: 4–27%). Stent exposure occurred in 1% (95% CI: 0–2%). Stent migration occurred in 1% (95% CI: 0–3%). XEN45 revision and/or a second XEN45 implantation was performed in 5% of patients (95% CI: 3–7%). Stent relocation was performed in 3% (95% CI: 1–7%). A second glaucoma procedure was performed in 11% (95% CI: 8–15%). 26% underwent one (95% CI: 17–36%), 13% underwent two (95% CI: 5–24%) while 4% underwent three (95% CI: 2–6%) bleb needling procedures. 35% of patients (95% CI: 29–40%) required at least one needling. The average rate of needling per patient was 0.38 (95% CI: 0.20–0.59). However, there is a lack of high-quality data, with 8 of the 33 studies assessed to have a moderate to high risk of bias.

CONCLUSIONS: While literature suggests that XEN45 Gel Stent implantation is safe in the treatment of OAG, the overall current level of evidence is low and further studies are needed. More than a third of patients require at least one post-operative bleb needling procedure.

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INTRODUCTION

Glaucoma is the most common cause of irreversible blindness worldwide [1]. Intra-ocular pressure (IOP) remains the primary modifiable risk factor, with effective IOP reduction being shown to prevent progressive optic nerve damage and visual field impairment [2]. While ocular hypotensive medications are used as first-line therapy, they are subject to patient adherence, ocular surface toxicity and other local and systemic side effects [3]. Surgical intervention in the form of glaucoma filtering procedures is indicated when maximal medical therapy fails to ensure adequate IOP reduction [4, 5].

Minimally Invasive Glaucoma Surgery (MIGS) techniques have emerged in the past decade, characterised by ab interno device implantation, little or no scleral dissection, minimal local trauma, high safety profile and rapid post-operative recovery [6, 7]. The XEN45 Gel Stent is a MIGS device that involves creation of a subconjunctival filtration bleb, as in traditional trabeculectomy. It is FDA-approved for use in refractory glaucoma with failed previous surgical treatment and in open-angle glaucoma unresponsive to maximum tolerated medical therapy [8].

MIGS techniques are often marketed as procedures with a higher safety profile than traditional subconjunctival filtration surgery [9–11]. However, XEN45 implantation is not without risks. In contrast to trabeculectomy, XEN45 is a device-based surgery that may have device-related complications, such as stent migration and extrusion, in addition to other complications such as hypotony, transient IOP spikes and endophthalmitis [12–14]. Secondary interventions may be necessary to address these complications, including anterior chamber reformation, implant relocation and bleb revision. Furthermore, post-operative bleb manipulation and needling procedures are employed to manage suboptimal IOPs due to encapsulation and bleb fibrosis. However,

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there is a paucity of quantitative information in current literature on the risk of these post-operative complications and incidence of secondary interventions [15, 16].

In a prior meta-analysis [17], our group compared surgical outcomes of standalone XEN45 implantation with combined XEN45-phacoemulsification surgery. However, we were unable to compare safety profiles then, as insufficient papers had reported surgical complications and post-operative interventions. The potential to analyse a larger data pool, from a greater number of studies of a wider context from those previously included in our earlier synthesis, justified a separate review.

This present systematic review and meta-analysis therefore aims to characterise the safety profile of XEN45 Gel Stent implantation by quantitatively evaluating the risk of surgical complications and incidence of post-operative interventions.

METHODS

Study selection

A comprehensive search of MEDLINE, EMBASE, Current Contents, Cochrane Central Register of Controlled Trials (CENTRAL) databases was performed. A combination of subject headings and text words were used as needed to define XEN45 surgery. We employed the terms 'Xen surgery' to ensure a comprehensive search, followed by selective vetting. The search workflow was in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [18].

Identified studies were assessed independently by two authors (SYL, BKB) to determine eligibility for inclusion in the analysis. Pilot, cohort, observational studies, and randomised controlled trials that included at least 10 patients undergoing XEN45 surgery, for the treatment of open angle glaucoma (OAG) were deemed to be eligible for inclusion. Case reports, review articles, studies involving less than 10 patients and duplicate data were excluded. Articles not written in English were also excluded from the study.

Primary outcomes included the rate of surgical complications and post-operative interventions. Outcomes were only analysed if they were reported by three or more papers.

The following information from each study was extracted manually from full text: first author, year of publication, study design, study period, country of origin, number of patients in study, mean age of patients, patient gender, type of intervention and complication rates. Where there was a difference in opinion, a senior author was consulted.

Where more information was required, corresponding authors of articles were contacted to the best of our ability.

Statistical analysis

A meta-analysis of proportions was performed (BKB, SYL) with data available on the complication and intervention rates using the *meta* routine [19] in R version 3.2.1 [20]. The Freeman-Tukey double arcsine transformation was implemented to calculate an overall proportion. To assess heterogeneity between the studies, I^2 was quantified, which estimates the percentage of variability between studies. An I^2 of >75% suggested considerable heterogeneity. Random-effect models were used in view of the heterogeneity of the studies. P values < 0.05 were considered statistically significant.

Risk of bias and quality assessment

Two authors (BKB, SYL) independently assessed the included studies for the risk of several biases, including selection, performance, detection, attrition, and selective reporting bias. We deemed there to be a high risk of attrition bias if the follow-up rate was <50%. Performance bias was determined to be low risk in publications where no subjective patient-reported outcomes were used even in the absence of participant blinding. Risk of Bias in Non-Randomised Studies—of Intervention (ROBINS-I) tool was used to evaluate the quality of evidence for each outcome measure (Supplementary Table 1).

RESULTS

One hundred and fifty-two studies were found on the initial literature search governed by PRISMA on 10th April 2020. After full text evaluation and a secondary search of the references of each paper, 33 studies were identified for inclusion [10, 12–14, 21–49]. Of these, ten papers [10, 21–29] performed standalone XEN45 surgery and combined XEN45 with phacoemulsification (XEN45-Phaco) with distinct reporting of outcomes; 17 papers performed standalone XEN45 surgery and XEN45-Phaco but reported the outcomes together; five papers performed standalone XEN45 surgery only; three papers performed XEN45-Phaco only.

We analysed the outcomes of XEN45 surgery in 3062 eyes, with representation across the Caucasian, African-American, Mexican, Latino and Asian populations. There were 15 prospective studies and 18 retrospective studies, with majority being of case series design. Maximum follow-up duration ranged from 6 months to 36 months with most studies ending follow-up at 12 months. Amongst the papers which reported age, the mean (SD) age of patients was 67.02 (11.93). A summary of each study design, study period, population, patient characteristics is shown in Table 1.

Across the studies, a variety of surgical techniques for XEN45 Gel Stent implantation were employed. However, the general steps of surgery were largely consistent and are as follows. The corneal main and side port incisions are created, followed by the instillation of the anterior chamber (AC) with viscoelastic. The needle tip of the preloaded injector is inserted through the main incision or a separate corneal incision and advanced across the AC towards the supero-nasal quadrant with advancement through the sclera. A second instrument at the side port is used to provide stabilisation and countertraction. The needle and needle tip bevels are then visualised in the subconjunctival space before stent deployment. The injector is then removed and the viscoelastic is aspirated. The AC is pressurised, and the formation of a subconjunctival bleb is checked. The implant is ideally placed through the scleral spur and tracked 3 mm posterior to the limbus, exiting through the sclera into the subconjunctival space. Approximately 1–2 mm of the implant is left in the AC to provide a passage from the AC into the subconjunctival space. Gonioscopic visualisation is used at the surgeon's discretion. Intraoperative adjunctive anti-fibrotic therapy in the form of Mitomycin C (MMC) was administered in all studies. Of note, the subconjunctival injection route of MMC administration was used for all studies except for Grover et al. [41] which employed sponge-application of the MMC instead. Across the studies, MMC was applied at varying volumes (0.05–0.2 ml) and concentrations (0.01–0.02%). IOP lowering medications were stopped one day prior with no medication wash out period implemented.

Incidence of complications after XEN45 implantation

Numerical hypotony was the most common complication involving 20% of patients (95% CI: 10–31%), defined as IOP < 6 mmHg and resolving without intervention (Fig. 1). This was followed by post-operative hyphema, occurring in 14% of patients (95% CI: 7–22%). Post-operative transient IOP spike with IOP ≥ 30 mmHg occurred in 13% of patients (95% CI: 4–27%). Stent exposure occurred in 1% (95% CI: 0–2%). Stent migration occurred in 1% (95% CI: 0–3%). Hypotonous maculopathy occurred in 1% (95% CI: 0–3%). Choroidal effusion occurred in 2% (95% CI: 1–3%) while choroidal detachment occurred in 4% (95% CI: 1–7%). Dysesthetic bleb occurred in 2% (95% CI: 1–3%). Endophthalmitis was reported in 1 patient in each of 4 papers. Malignant glaucoma occurred in 1% (95% CI: 0–2%).

Incidence of interventions after XEN45 implantation

2% of patients had a shallow anterior chamber (95% CI: 1–4%), while 1% had a shallow anterior chamber requiring reformation (95% CI: 0–3%) (Fig. 2). XEN45 revision or 2nd XEN45 implantation was performed in 5% of patients (95% CI: 3–7%). Stent relocation was performed in 3% (95% CI: 1–7%). A second glaucoma procedure was performed in 11% (95%CI: 8–15%). 26% of patients

Table 1. Summary of included studies.

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
Buffault et al. [30]	Retrospective case series	4	France	XEN45-77 XEN45 + Phaco-30	68.3 ± 10.8	6	20.4 ± 6.1	2.8 ± 1.0	Closed conjunctival Ab interno	After subconjunctival injection of 0.1 ml mitomycin C (MMC) diluted to 0.1 mg/ml in the supero-temporal quadrant, a 2.2 mm inferotemporal corneal incision was made.	A miotic (Miostat 100 ®, Carbachol 100 µg, Alcon, Rueil-Malmaison, France) was injected, then the AC filled with viscosurgical device. The preloaded 27-gauge injector was inserted through the incision, then directed to the opposite side of the AC, penetrating the iridocorneal angle, passing through the sclera and arriving in the subconjunctival space approximately 3 mm posterior to the limbus as previous marked, in the target supero-nasal quadrant. The XEN implant was then injected, when the injector retracted. The viscosurgical device (Provisc® OVD, 1% Sodium Hyaluronate, Alcon, Rueil-Malmaison, France) was then removed and the corneal incisions hydrated. At the end of the procedure, 0.1 ml cefuroxime was injected into the anterior chamber. When patients underwent concomitant cataract surgery, the implantation of the stent was performed after placement of the posterior chamber intra-ocular lens (PCIOL) and injection of the miotic. Post-operative treatment included a steroid and antibiotic drop instilled three times a day for 4 weeks (Tobradex®, Dexamethasone 0,1 g and Tobramycine 0,3 g per unit dose, Novartis Pharma, Rueil-Malmaison, France), an anti-inflammatory drop (Indocollyre 0,1% ®, Indometacin, Bausch & Lomb, Montpellier, France) instilled three times a day for 6 weeks and all glaucoma medications were discontinued on the day of surgery.
Cutolo et al. [31]	Prospective case series	4	Italy	XEN45-93 XEN45 + Phaco-30	74.5 ± 39.8	12	26.4 ± 8.2	2.9 ± 1.0	Closed conjunctival Ab interno	About 20 min before surgery, 0.12 ml of mitomycin C 0.2 mg/mL was injected subconjunctivally in the target area using a 30-gauge needle	In combined procedures, phacoemulsification and intra-ocular lens insertion were always performed before the XEN implantation. The conjunctival tissue of the target area was marked 3 mm from the limbus. After the anterior chamber was filled with viscoelastic, the XEN injector beveled needled tip was advanced through a clear corneal incision toward the opposite supero-nasal target quadrant. The use of intra-operative gonio-lens was at the discretion of the surgeon and was adopted only in a few cases. An adequately positioned device should be visible for approximately 1 mm in the anterior chamber and for 2 mm in the subconjunctival space, exiting the sclera 3 mm posteriorly to the limbus. In case of suboptimal stent position, the XEN was reinserted in the injector and the implantation repeated. Then, viscoelastic was carefully removed from the anterior chamber and intracameral cefuroxime was applied. The post-operative management included topical corticosteroids and antibiotics for one week followed by topical corticosteroids slowly tapered down over 4 to 6 months.
Dar et al. [32]	Retrospective case series	4	Israel	Non-PXFG XEN45-22 XEN45 + Phaco-2 PXFG XEN45-19 XEN45 + Phaco-15	Non-PXFG 74.0 ± 9.7 PXFG 74.2 ± 9.3	6	Non-PXFG 22.6 ± 7.9 PXFG 24.3 ± 9.1	Non-PXFG 3.6 ± 0.5 PXFG 3.6 ± 0.5	Closed conjunctival Ab interno	0.1 ml MMC (0.03 mg/ml) was injected under the superior-nasal conjunctiva 3 mm from the limbus and diverted to the presumed site of the future bleb	After temporal and nasal paracentesis, 1% lidocaine and high viscosity viscoelastic were injected into the anterior chamber. The apex of the injector was pushed through the trabecular meshwork and through the sclera, aiming at 3 mm distance from the limbus. Gonioscopy using an intra-operative gonio-lens was performed to confirm the position of the stent, and the viscoelastic substance was removed by irrigation with BSS. Combined procedures were carried out in the following manner. Principal corneal incision was made at its superior position and two paracentesis incisions were performed 1 mm from the limbus, in nasal and infero-temporal positions. At the end of the phacoemulsification procedure, the asphalt concrete viscoelastic was removed and additional temporal paracentesis incision was made. The XEN procedure was performed through the latter incision as previously described.
Fea et al. [34]	Prospective case series	4	Italy	XEN45-10 XEN45 + Phaco-2	71.3 ± 10.0	12	21.8 ± 2.8	2.9 ± 1.2	Closed conjunctival Ab interno	Thirty minutes before surgery, 0.02% mitomycin C (MMC) was injected into the subconjunctival space in the quadrant selected for implantation of the device.	A 1.5 mm inferotemporal corneal incision was made 1 mm anterior to the limbus. Following injection of cohesive ophthalmic viscosurgical device (OVD, Healon GV), a supero-nasal paracentesis was created. Using an ab interno approach, the preloaded inserter needle was directed across the anterior chamber and implanted in the target quadrant. If the implant procedure was combined with cataract surgery, successful and uncomplicated cataract surgery was performed prior to the AqueSys XEN implantation. Once the device had been implanted, the anterior chamber was flushed with balanced saline solution to remove viscoelastic fluid followed by hydro sealing of the corneal incision. If cataract surgery was performed, a 10–0 single stitch suture was used for phaco entry. Patients were instructed to refrain from rubbing their eyes for a few weeks following surgery. BAK-free fluoroquinolone was

Table 1. continued

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
											prescribed QID during the first week post-operative. Prednisolone acetate 1% or equivalent, or difluprednate 0.05% without BAK, was prescribed QID, 1–4 weeks postsurgery, TID, week 5 post-operative, BID, week 6 post-operative, and QD, 7–12 weeks postsurgery.
Fea et al. [25]	Prospective multi-centre clinical trial	4	Italy, France, Sweden	XEN45-115 XEN45 + Phaco-56	70.0 ± 13.3	12	25.0 ± 7.6	3.3 ± 1.0	Closed conjunctival Ab interno	Intra-operative 0.1 ml MMC 0.02% was injected subconjunctivally using a 30-gauge hypodermic needle under the tenon capsule and spread with a microsponge applied to the conjunctiva in the superior-nasal quadrant where the implant was to be inserted	Using an ab interno approach, the preloaded injector needle was inserted through a 1.8 mm corneal incision. The needle was then directed across the AC towards the supero-nasal quadrant. Intraoperatively, a gonio-lens could be used at the surgeon's discretion. Viscosurgical material was removed from the AC by irrigation/aspiration in the combo group or by washing with saline in the solo group.
Fernandez-Garcia et al. [35]	Retrospective case series	4	Spain	XEN45-12 XEN45 + Phaco-81	74.0 ± 8.0	36	18.2 ± 5	1.9 ± 0.9	Closed conjunctival Ab interno	Under topical anaesthesia, 0.1 ml of mitomycin C (0.02 mg/ml) was introduced 5 mm away from the limb—in the area where the XEN45 was to be implanted. It was spread toward the back, never toward the limb to avoid limbic toxicity.	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 anaesthetise 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. The corneal incision was hydrated and the patient received intracameral cefuroxime.
Galal et al. [36]	Prospective interventional study	4	Germany	XEN45-3 XEN45 + Phaco-10	73.1 ± 10.0		16 ± 4	1.9 ± 1.0	Closed conjunctival Ab interno	Intra-operative 0.1 ml MMC 0.01% was injected subconjunctivally using a 27 G hypodermic needle under tenon and spread with microsponge applied to conjunctiva in the superior-nasal quadrant where the implant would be inserted, and it remained for 10 min before the implant was injected or in case of cataract extraction before phacoemulsification starts. The MMC was not washed out.	Using an ab interno approach, the preloaded injector needle was inserted through a 1.2 mm corneal paracentesis incision opposite the site of desired implantation after the AC was filled with highly cohesive viscoelastic device. An intra-operative gonio-lens was used to verify placement through the angle to avoid iris and iris root trauma in all cases. The needle was then directed across the AC and implanted in the target quadrant (usually supero-nasal). The implant is ideally placed through the scleral spur and tracked 3.0mmposterior to the limbus exiting through the sclera into the subconjunctival space. Approximately, 2 mm of the implant is left in the AC to provide a connection from the AC to the subconjunctival space which was confirmed by the gonio-lens. Viscoelastic device was removed from the AC. No further sutures were applied, and at that point, the surgery is terminated. In cases where cataract extraction was indicated, a main incision was performed at the steepest corneal axis and the paracentesis incisions were performed one nasal and one temporal-inferior at 7 o'clock position and 5 o'clock position for the right and left eyes, respectively. The latest incision was done 2–3 mm central to the limbus and used for the insertion of the XEN45 into the superior-nasal area. After phacoemulsification was finished, no viscoelastic material was used to implant the intra-ocular lens (IOL) and was implanted only under BSS being our standard technique in phacoemulsification procedures. After the IOL was properly placed in the bag, the AC was filled with cohesive viscoelastic device and a corneal suture was used to secure the principle 2.4 mm incision. XEN implantation followed as previously indicated. Viscoelastic was promptly removed from AC to prevent XEN implant potential blockage or partial closure after surgery. Patients were prescribed Isoptomax (dexamethasone 0.1%, neomycin sulfate, and polymyxin B sulfate, Alcon USA) 4 times a day which was tapered by one drop each week, Predforte (prednisolone acetate 1%, Allergan USA) twice daily for 1 month then once for another month, and Ketovision (Ketolactrometamol Omnivision, Germany) 3 times a day for 3 weeks post-operatively.

Table 1. continued

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
Gillmann et al. [38]	Prospective interventional study	4	Switzerland	PEXG XEN45-13 XEN45 + Phaco-40 POAG XEN45-16 XEN45 + Phaco-41	PEXG 78.5 ± 8.5 POAG 71.3 ± 8.7	24	PEXG 19.8 ± 8.2 POAG 19.8 ± 5.8	PEXG 2.0 ± 1.3 POAG 2.0 ± 1.2	Closed conjunctival Ab interno	A dose of 0.1 mL mitomycin C (MMC) at a concentration of 0.02% was injected under Tenon's capsule using a 27-G needle immediately before surgery. The MMC was spread subconjunctivally across the superior-nasal quadrant where the implant would be inserted, using a microsponge or vitreous spatula. No washout was performed.	The AC was filled with a cohesive viscoelastic gel before the preloaded injector needle was inserted through a 1.2-mm inferotemporal corneal paracentesis incision. The needle was directed towards the supero-nasal quadrant and advanced into the sclera slightly anterior to the nonpigmented trabecular meshwork. The implant was tracked posteriorly through the sclera, 3 mm from the limbus, into the subconjunctival space. One millimetre of the XEN gel stent was left in the AC, to ensure visualisation of the opening remained possible under gonioscopy. When phacoemulsification was indicated, a principal corneal incision was made at its steepest axis, and 2 paracentesis incisions were performed 1 mm from the limbus, in nasal and inferotemporal positions. Phacoemulsification was performed in a standard manner until the end of the emulsification stage when AC viscoelastic was left in place, and the XEN procedure was performed through the paracentesis ports. Post-operatively, patients were treated with a topical combined therapy of tobramycin and dexamethasone (Tobradex, Alcon, TX), initially 4 times a day and then in reducing doses, tapered down by 1 drop a week over 4 weeks. In inflammationprone eyes and following combined procedures, topical nepafenac (Nevanac, Novartis, Basel, Switzerland) was added. All antiglaucoma medications were stopped on the day of surgery.
Gregorio et al. [39]	Prospective interventional study	4	Italy	XEN45 + Minimally Invasive Cataract Surgery-41	74.0 ± 7.1	12	22.5 ± 3.7	2.5 ± 0.9	Closed conjunctival Ab interno	0.1 ml of mitomycin C, 0.1 mg/ml (absolute dose of 10 lg) injected in the subconjunctival supero-temporal quadrant space in order to obtain a bubble that was gently rolled toward the supero-nasal quadrant	The anterior chamber (AC) was filled with standard cohesive OVD, and an infero-temporal 1.8-mm clear corneal incision was created through which the preloaded inserter needle (double bevelled 27-gauge) was directed across the AC in the opposite side to penetrate the angle. The needle passed through the sclera and arose in the subconjunctival space approximately 3.0 mm posterior to the limbus, as previous marked, in the target supero-nasal quadrant. Once the needle was visible in the subconjunctival space, it was rotated toward 12 o'clock and the stent was gently delivered advancing the sliderat. The needle housing the implant was retracted without drawing the implant back. During this step, to stabilise the eye, we used a straight micro-manipulator in the side port corneal incision in order to maintain the contact between the needle sleeve and the angle and a third hand pushed the sliderat to deliver the stent. The ideal stent placement should be 2.0 mm of exposed implant in the subconjunctival space, 1.0 mm in the AC and 3.0 mm tunnelled through sclera. A mirrored gonioscopic lens was used to verify the correct stent placement in the angle (Fig. 1). The OVD was then washed while the implant, if correctly positioned and patent, immediately begins shunting fluid from AC to the subconjunctival space with an initial extended bleb due to the gentle diffuse dispersion of AH into the nondissected conjunctiva. All corneal incisions were hydro-sutured. Post-operative treatments included a combination of dexamethasone and tobramycin (Tobradex; Alcon Laboratories, Inc., Fort Worth, TX, USA) given 4 times daily for 15 days and then slowly reducing during the following 3 weeks. All preoperative hypotensive
Grover et al. [41]	Prospective case series	4	USA	XEN45-65	70.0 ± 12.3	12	25.1 ± 3.7	3.5 ± 1.0	Open conjunctival Ab interno	Subconjunctival pre-treatment of target area with sponges saturated with mitomycin C 0.2 mg/ml for 2 min	Bevelled tip of injector advanced through a peripheral corneal incision (1–2 mm anterior to limbus) and across the anterior chamber towards the target quadrant using an ab interno approach. Needle tip was then aligned with the desired entry point of the trabecular meshwork (under gonioscopic guidance), Gelatin stent was released in the subconjunctival space and injector removed from the eye. Seidel testing was then performed to ensure there was no leakage of aqueous from anterior chamber or conjunctiva (as a result of post-surgical bleb formation).
Heidinger et al. [13]	Retrospective case series	4	Austria	XEN45-61 XEN45 + Phaco-138	74.8 ± 10.5	12	22.8 ± 6.9	2.9 ± 1.0	Closed conjunctival Ab interno	0.1 mL of mitomycin C 0.1 mg/mL was applied under the conjunctiva at the superior-nasal conjunctiva and was not washed out.	After the anterior chamber (AC) was filled with a cohesive viscoelastic device (Healon Ophthalmic Viscoelastic Device, Abbott Medical Optics, CA) the XEN preloaded injector was inserted and directed across the AC to penetrate the iridocorneal angle. Passing through the sclera the needle exited approximately 3 mm postlimbal into the subconjunctival space, where the implant was then released. After the injector was removed, the AC was cleared from the cohesive viscoelastic and cefuroxime was applied. No sutures were needed for the incision. At the end, a combination of

Table 1. continued

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
											dexamethasone and gentamicin sulfate eye ointment (Dexagenta, Ursapharma, Austria) were applied to the eye. The post-operative management included topical steroid and antibiotics for five weeks. In case the implantation was combined with a cataract surgery, phacoemulsification was done first.
Hengerer et al. [37]	Retrospective case series	4	Germany	XEN45-39 XEN45 + Phaco-203	67.6 ± 13.6	12	32.2 ± 9.1	3.13 ± 1.0	Closed conjunctival Ab interno	0.1 mL of MMC solution (0.01% mitomycin C, 10 µg) was injected subconjunctivally	After marking a limbal distance of 3 mm in the targeted area for the placement of the implant, an opposite clear cornea incision of 1.2 mm was performed using a metal keratome (1.2 mm angled slit knife, Alcon, Fort Worth, TX). A second side-port incision was made 90 degrees away from it at the limbus margin. The anterior chamber was gently filled with a medium viscous ocular viscoelastic device (OVD) (Healon, AMO, Santa Ana, CA) and the injector needle was introduced into the primary incision. Although the globe was stabilised using an iris spatula placed into the side-port incision, the injector tip was used to penetrate through the opposite chamber angle passing trabecular meshwork and the sclera at least 3 mm in length. Without perforating the overlying conjunctiva, the implant was released in the targeted place, facing the anterior chamber internally. The OVD was removed by irrigation/ aspiration using the Stellaris system (Bausch and Lomb, Aliso Viejo, CA). The anterior chamber was pressurised by gently injecting BSS through the side-port while hydrating both incisions.
Hu et al. [26]	Retrospective case series	4	Singapore	XEN45-19 XEN45 + Phaco-44	71.9 ± 7.1	6	24.2 ± 6.0	3.7 ± 0.7	Closed conjunctival Ab interno	0.1–0.2 ml (at the discretion of the attending surgeon) of 0.2 mg/ml Mitomycin-C (MMC) was injected in the supero-nasal conjunctiva quadrant and massaged over the area of anticipated XEN45 gel stent insertion.	After inserting the injector into the anterior chamber via the main phacoemulsification port or the custom-made injector port, the injector needle was directed towards the supero-nasal quadrant. Under gonioscopy guidance, a scleral tunnel was then made using the needle, advancing the needle above the pigmented trabecular meshwork to exit approximately 3 mm from the limbus in the subconjunctival space. A second instrument was used to provide countertraction. The injector was then withdrawn and viscoelastic removed.
Ibanez Munoz et al. [40]	Retrospective Case Series	4	Spain	XEN45-13 XEN45 + Phaco-8	80.9 ± 8.1	12	21.1 ± 3.8	3.0 ± 1.0	Closed conjunctival Ab interno	Intraoperatively, a 27-gauge hypodermic needle was used to inject 0.1 mL of mitomycin-C (MMC; 0.01%) subconjunctivally under the tenon capsule. A microsponge applied to conjunctiva was used to spread the MMC in the area where the implant would be inserted (superior-nasal quadrant). The MMC remained for 8–10 min before the implant was injected or, in case of combined surgery, before phacoemulsification starts.	The surgery was performed under gonioscopic control and a highly cohesive viscoelastic was used to stabilise the anterior chamber during surgery. The 27-gauge preloaded injector was inserted through a 1.2-mm corneal paracentesis incision at the inferotemporal quadrant. The implant is ideally placed, through the scleral spur, extending about 1.0–1.2 mm into the anterior chamber at its proximal end, 3.0 mm of the implant in the scleral tunnel, and 2.0 mm at the distal end of the implant lying flat in the subconjunctival space. The viscoelastic material was aspirated to reduce the risk for stent blockage and elevated post-operative IOP. Following this step, constant irrigation of balanced salt solution (BSS) into the anterior chamber was done to prime the implant and induce formation of a bleb. Finally, the clear corneal incisions were hydrated with BSS. In cases where cataract extraction was indicated, it was performed with a standard phacoemulsification technique and, after finished, XEN implantation followed as previously indicated. Patients were prescribed Tobradex (dexamethasone 0.1% and tobramycin 0.3%) four times a day which was tapered by one drop each week and dexamethasone 0.1% twice daily for 1 month then once for another month.
Ibanez Munoz et al. [42]	Retrospective Case Series	4	Spain	POAG XEN45-18 XEN45 + Phaco-18 SOAG XEN45-22 XEN45 + Phaco-15	POAG 79.4 ± 8.2 SOAG 79.9 ± 8.3	12	POAG 22.8 ± 5.7 SOAG 21.8 ± 5.7	POAG 3.6 ± 0.5 SOAG 3.1 ± 0.9	Closed conjunctival Ab interno	Intraoperatively, mitomycin C (0.1 mL, 0.01%) was injected under the tenon capsule	Viscoelastic was used for stabilising the anterior chamber during the surgery. XEN implant was placed, using an ab interno approach, in the superior-nasal quadrant. Afterward, the viscoelastic material was aspirated, and the implant permeability was checked.
Kalina et al. [21]	Prospective interventional	4	USA		78.2 ± 8.6	12	24.2 ± 8.2	Not Reported		Using a 30 G needle, 0.1 ml of MMC (0.2	Main and side port incisions were created. The angle was inspected before XEN45 stent insertion with a disposable

Table 1. continued

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
	study, non-comparative			XEN45-20 XEN45 + Phaco-27					Closed conjunctival Ab interno	mg/ml) was injected posteriorly into Tenon's capsule. Using cellulose sponges, the MMC was massaged over the area of anticipated stent placement, with efforts to keep it away from the limbus.	gonioprism. The inserter was introduced into the eye through the main incision and the needle was directed across the anterior chamber towards 12 OC. Countertraction was supplied by using a Vera hook in the side port. XEN45 stent was released into the subconjunctival space. Viscoelastic was removed via automated irrigation/aspiration. The presence of a bleb superiorly was confirmed.
Karimi et al. [22]	Retrospective case series	4	UK	XEN45-187 XEN45 + Phaco-72	74.8 ± 11.4	18	19.6 ± 5.9	Not Reported	Closed conjunctival Ab interno	0.1 ml of MMC at 0.2 mg/ml was injected into the subconjunctival/sub-tenon's space and massaged into the supero-nasal quadrant.	Using the preloaded injector, the XEN45 implant was inserted anterior to the trabecular meshwork, following which viscoelastic was aspirated. Intra-operative gonioscopy was performed to ensure correct insertion, position of the implant and subsequent bleb formation. All patients received standardised post-operative antibiotic and steroid medications: guttae chloramphenicol 4×/day for 2 weeks and guttae dexamethasone 0.1% or prednisolone 1% 2 h for 2 weeks, tapering down depending on post-operative progress.
Laroche et al. [43]	Retrospective Case Series	4	USA	20 eyes total Out of 12 eyes which were successful at 1 year: XEN45-3 XEN45 + Phaco-9	Not reported	12	15.3 ± 6.2	3.58 ± 0.7	Closed conjunctival Ab interno	After implantation, 20 µg (0.02 mg/ml) of Mitomycin C was given subconjunctivally in the quadrant using a 27 G hypodermic needle under tenon's capsule and spread under the conjunctiva in the superior-nasal quadrant.	Using an ab interno approach, the preloaded injector needle was inserted through a 1.2-mm corneal paracentesis incision opposite the site of the desired implantation after the AC was filled with the highly cohesive viscoelastic device. The needle tip was then aligned with the desired entry point of the trabecular meshwork and advanced anterior to the trabecular meshwork (under gonioscopic guidance) and sclera, while the eye was stabilised to provide counterforce to the implanting needle. If the stent was properly positioned, approximately 2 mm and 1 mm of its length were visible in the subconjunctival space and AC, respectively. In cases where cataract extraction was indicated, the main incision was performed at the steepest corneal axis and the paracentesis incisions were performed nasally and infratemporally at 7 o'clock position and 5 o'clock positions for the right and left eyes, respectively. The latest incision was done 2- 3 mm central to the limbus and used for the insertion of the XEN45 into the superior-nasal area. After phacoemulsification was finished, viscoelastic material was used to implant the intra-ocular lens (IOL). After the IOL was properly placed in the bag, the AC was filled with the cohesive viscoelastic device, and a corneal suture was used to secure the principle 2.4 mm incision. XEN implantation followed as previously indicated. Viscoelastic was promptly removed from AC to prevent XEN implant potential blockage or partial closure after surgery.
Lenzhofer et al. [56]	Prospective Case Series	4	Austria	XEN45-32 XEN45 + Phaco-34	72.2 ± 12.5	12	23.5 ± 5.6	3.3 ± 0.6	Closed conjunctival Ab interno	Twenty minutes prior to implantation, a balanced salt solution (BSS) plus mitomycin C (MMC) was injected subtenon using a 30-gauge needle (0.05–0.1 ml, 4–8 lg MMC total). The concentration was determined by the surgeon.	The route of implantation starts through a clear corneal incision, follows the opposite angle in the anterior chamber, through the sclera, and ends in the subconjunctival space. The outer lumen of the stent is situated approximately 5 mm posterior to the limbus suprascleral.
Mansouri et al. [23]	Prospective interventional study	4	Austria, Canada and Germany	XEN45-40 XEN45 + Phaco-109	74.7 ± 11.4	24	20.0 ± 2.2	2.5 ± 1.1	Closed conjunctival Ab interno	0.1 ml MMC 0.02% was injected subconjunctivally using a 27 G hypodermic needle under Tenon's capsule and spread with a microsponge applied to conjunctiva in the superior-nasal	Using an ab interno approach, the preloaded injector needle was inserted through a 1.2 mm corneal paracentesis incision opposite the site of desired implantation after the AC was filled with highly cohesive viscoelastic device. An intra-operative gonio-lens was occasionally used. The needle was then directed across the AC and implanted in the supero-nasal quadrant. Viscoelastic was removed from the AC by irrigation/aspiration. Post-operatively, patients were prescribed combined tobramycin and dexamethasone ophthalmic suspension 4×/day, tapered by 1 drop each week over 4 weeks.

Table 1. continued

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
										quadrant where the implant would be inserted.	
Marcos Parra et al. [10]	Retrospective Case Series	4	Spain	XEN45-17 XEN45 + Phaco-48	71.2 ± 11.7	12	22.2 ± 6.8	2.5 ± 0.8	Closed conjunctival Ab interno	27 G hypodermic needle was used to inject 0.1 ml of MMC 0.01% subconjunctivally under the Tenon capsule. MMC was subsequently displaced and distributed with a surgical sponge to the superior-nasal sector and remained for 8–10 min before the implant was injected.	AC was filled with a highly cohesive viscoelastic. Gonioscopic visualisation was performed. The 27 G preloaded injector was inserted through a 1.2 mm corneal paracentesis incision in the inferotemporal quadrant. The needle was then directed across the anterior chamber and the XEN45 implant was placed at the supero-nasal part of the anterior chamber angle under gonioscopic view. The viscoelastic was withdrawn and BSS constant irrigation was used to check implant function and bleb formation. Post-operatively, antibiotic prophylaxis 4×/day for 2 weeks and dexamethasone 0.1% 2×/day for 1 month then 1×/day for another month was prescribed.
Olate-Perez et al. [44]	Prospective Case Series	4	Spain	XEN45 + Phaco-30	76 ± 5.9	12	21.2 ± 3.4	3.1 ± 0.7	Closed conjunctival Ab interno	Fifteen minutes prior to surgery, 1 ml 0.01% mitomycin C was injected subconjunctivally at 12 o'clock and 5 mm from the limbus, which was subsequently displaced and distributed with a surgical sponge to the superior-nasal sector.	After completing cataract surgery that included standard phacoemulsification and placement of acrylic intra-ocular lens in the capsular sac, 1% acetylcholine was injected in theanterior chamber to contract the pupil, followed by viscoelastic to increase angle opening. The XEN 45 injector needle was introduced in the anterior chamber through an inferior-temporal incision previously made for cataract surgery in order to subsequently introduce the needle in the opposite (supe-rior nasal) chamber angle up to subconjunctival visualization3 mm from the limbus, proceeding to the release of the XEN device from the injector. After hydrating the incisions, 0.1 ml of 1% cefuroxime was injected in the anterior chamber and betamethasone acetate subtenon.
Olgun et al. [24]	Retrospective Case Series	4	Turkey	XEN45-51 XEN45 + Phaco-45	60.3 ± 10.8	24	24.4 ± 4.3	3.4 ± 0.5	Closed conjunctival Ab interno	Adjunctive anti-fibrotic therapy was administered pre/perioperatively via subconjunctival injection at the surgeon's discretion	Creating a temporal clear corneal main and side port incisions, filling the AC with cohesive viscoelastic, inserting the needle tip of the injector through the main incision and advancing across the AC (towards the supero-nasal quadrant) with needle entry at the desired angle position and advancement through the sclera using a second instrument at the side port to provide stabilisation and counterforce, visualising the needle and needle tip bevel in the subconjunctival space, deploying the stent, removing the injector and viscoelastic, pressurising the AC and creating a subconjunctival bleb with BSS.
Ozal et al. [27]	Retrospective Case Series	4	Turkey	XEN45-9 XEN45 + Phaco-6	63.6 ± 13.3	12	36.1 ± 3.6	3.6 ± 0.5	Closed conjunctival Ab interno	Anti-fibrotic was not injected into the conjunctiva at any stage of the surgery	Surgery performed under peribulbar anaesthesia with 5 mL of prilocaine and 5 mL of bupivacaine. Clear corneal incisions (main and side-port) were created in the inferotemporal and supero-temporal quadrants. A highly cohesive viscoelastic was used to stabilise the anterior chamber during surgery. A 27-gauge preloaded injector was placed into the eye through the main clear corneal incision at the inferotemporal quadrant. One hand was used to manipulate the injector, and the other was used to fix and rotate the eye. A 6-mm-long implant was positioned 2 mm into the subconjunctival space, 3 mm into the sclera, and 1 mm into the anterior chamber. The viscoelastic material was aspirated, and then 0.1 mL of 1% cefuroxime was injected into the anterior chamber. Finally, the clear corneal incisions were hydrated with balanced salt solution.
Perez-Torregrosa et al. [45]	Prospective Case Series	4	Spain	XEN45 + Phaco-30	76.0 ± 5.9	12	21.2 ± 3.4	3.1 ± 0.7	Closed conjunctival Ab interno	Fifteen minutes before the surgical procedure, 1 mL of 0.01% mitomycin C was injected with a gauge 13 needle SC at 5 mm of the limbus at 12 o'clock, subsequently displaced and distributed with a	After implanting an acrylic intra-ocular lens, 1% acetylcholine was injected. The XEN45 injector needle was introduced into the AC through the inferior-temporal incision. At the same time, in order to fix the eye and exert counterpressure, a Vera hook was introduced through the superiortemporal incision. The injector penetrated through the opposite side to the implantation site. The needle was introduced and fixed in the angle to carry out a 3 mm intra-scleral pathway. The SC needle was withdrawn. When the entire bezel is seen, it is rotated 90o. After moving down the implantation sleeve, the implant is released. Subsequently the needle is withdrawn. The SC pathway of the XEN device is verified.

Table 1. continued

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
										surgical sponge to the superior-nasal sector	Viscoelastic is aspired and, by means of gonioscopy, the adequate implementation of the device in the angle is verified. The incisions are hydrated and bleb formation (caused by filtration of the serum toward the SC space) is also verified. Finally, 0.1 mL of 1% cefuroxime is injected in AC and betamethasone acetateinferior subconjunctival (Celestone Cronodose®, MSD, Madrid, Spain).
Post et al. [46]	Prospective interventional study	4	Poland	XEN45-20	69.85 ± 4.59	12	21.6 ± 2.3	3.2 ± 0.8	Closed conjunctival Ab interno	0.1 ml of 0.02% MMC was injected within the superior-nasal conjunctival quadrant 2× 2 cm from limbus.	Needle of XEN45 injector was advanced through the clear corneal incision via an ab interno approach. Stent was implanted into the previously marked subconjunctival space. 0.1 ml of cefuroxime administered into the anterior chamber after. Postop: all patients were administered dexamethasone 5×/week for a total of 5 weeks with a reduction of 1 drop per week and floxacillin 4×/day for 1 week.
Qureshi et al. [47]	Retrospective Case Series	4	UK	XEN45-37	45.97 ± 15.24	12	36.1 ± 9.6	3.7 ± 0.5	Closed conjunctival Ab interno	MMC 0.02 mg in 0.1 ml was injected into the subconjunctival space at the 12OC position 4–5 mm behind the limbus.	Preloaded injector was placed through the corneal incision and directed across the AC to the supero-nasal quadrant to deliver the XEN45 implant anterior to the pigmented trabecular meshwork, via a scleral tunnel into the subconjunctival space. All patients received intracameral antibiotic and subconjunctival steroid injection. Postop: Topical chloramphenicol 2×/day and atropine 1% once daily. Topical prednisolone acetate 1% was given 2 h and tapered according to conjunctival injection and degree of AC inflammation.
Reitsamer et al. [28]	Prospective case series	4	Austria, Belgium, England, Germany, Italy, Poland, Spain, and Switzerland	XEN45-114 XEN45 + Phaco-88	68.3 ± 11.7	24	21.7 ± 3.8	2.7 ± 0.9	Closed conjunctival Ab interno	Adjunctive anti-fibrotic therapy was administered pre/perioperatively via subconjunctival injection at the surgeon's discretion.	Creating a temporal clear corneal main and side port incisions, filling the AC with cohesive viscoelastic, inserting the needle tip of the injector through the main incision and advancing across the AC (towards the supero-nasal quadrant) with needle entry at the desired angle position and advancement through the sclera using a second instrument at the side port to provide stabilisation and counterforce, visualising the needle and needle tip bevel in the subconjunctival space, deploying the stent, removing the injector and viscoelastic, pressurising the AC and creating a subconjunctival bleb with BSS.
Schlenker et al. [14]	Retrospective interventional cohort study	4	Canada, Germany, Austria and Belgium	XEN45-185	65.0 ± 7.37	30	Not Reported	Not Reported	Closed conjunctival Ab interno	0.05–0.2 ml MMC mg/ml injected in the supero-nasal quadrant or supero-temporal quadrant and massaged over the area of anticipated microstent insertion.	Injector was placed in the main incision and the needle was directed across the anterior chamber towards the supero-nasal quadrant. A needle was used to tunnel through sclera coming out subconjunctivally 3.0 mm from the limbus, using a second instrument to provide countertraction. The injector then was withdrawn, subconjunctival and anterior chamber microstent placement was confirmed. Bevacizumab and steroids were also injected at the Belgium site.
Smith et al. [29]	Retrospective Case Series	4	UK	XEN45-58 XEN45 + Phaco-10	76.0 ± 10.0	12	21.9 ± 5.9	2.79 ± 0.8	Closed conjunctival Ab interno	0.2 mls of 0.02% Mitomycin-C was injected into the subconjunctival/subtenon space in the supranasal quadrant at the start of surgery.	A clear corneal incision was made in the inferotemporal quadrant and the anterior chamber filled with viscoelastic. Using the preloaded injector the Xen 45 device was implanted via an ab interno approach in the supero-nasal quadrant. The viscoelastic was then removed and intracameral antibiotics given.
Sng et al. [48]	Prospective Case Series	4	Singapore	XEN45-22 XEN45 + Phaco-2	45.3 ± 18.1	12	30.7 ± 3.6	3.1 ± 0.9	Closed conjunctival Ab interno	0.1 ml of 0.2 mg/mL mitomycin C was injected subconjunctivally in the superior-nasal quadrant of the eye 5–10 min prior to implantation of the XEN-45 implant	A 1.1-mm corneal incision was made in the inferior-temporal cornea with a 20 gauge MVR knife (Bausch & Lomb, Tampa, FL, USA), approximately 1 mm anterior to the limbus, at approximately the 4 o'clock position for the left eye and 10 o'clock position for the right eye. The anterior chamber was filled with viscoelastic (Healon GV; Abbott Medical Optics, Abbott Park, IL, USA). The preloaded inserter needle was introduced through the corneal incision and directed across the anterior chamber to the superior-nasal quadrant of the angle, inserted through the angle and the sclera, and exiting the sclera approximately 3 mm posterior to the limbus. After implantation, the viscoelastic was evacuated completely using irrigation and aspiration at the end of the surgery and the cornea incision was hydrated. A subconjunctival bleb was noted around the implant in all patients at the end of surgery. Contact with the iris, lens and the corneal endothelium was avoided during the implantation procedure. After surgery, all glaucoma medications were discontinued, and all patients were prescribed topical antibiotics for 2 weeks and topical

Table 1. continued

Author, ref.	Study design	Level of evidence[a]	Country	No. of eyes at baseline	Age, mean ± SD	Follow-up (months)	Baseline IOP, mean ± SD	Baseline Mmeds, mean ± SD	Approach	Anti-fibrotic use and application	Surgery remarks
											dexamethasone 0.1% for at least 3 months. The frequency of topical steroid therapy was initially 2 h and tapered according to the extent of conjunctival injection
Tan et al. [49]	Retrospective Case Series	4	UK	XEN45-43	70.1 ± 13.8	12	24.9 ± 7.8	3 ± Not reported	Closed conjunctival Ab interno	0.2 mg/ml of MMC was injected into the subconjunctival/sub-tenon space at 12OC 4–5 mm behind the surgical limbus.	The XEN45 was implanted ab-inernally using a preloaded injector, superior to the trabecular meshwork via a scleral tunnel into the subconjunctival/sub-tenon space. Viscoelastic was then aspirated. Attention was paid to ensure the implant was inserted correctly, with subsequent bleb formation noted at the end of surgery. All patients received intracameral antibiotics and subconjunctival steroid injections. Patients were given chloramphenicol drops QDS, atropine 1% OD and prednisolone 1% 6x/day. The prednisolone 1% was tapered gradually over 3 months according to the amount of conjunctival injection post-operatively.
Widder et al. [12]	Retrospective Case Series	4	Germany	XEN45-184 XEN45 + Phaco-49	73.0 ± 11.0	18	24.3 ± 6.6	2.6 ± 1.1	Closed conjunctival Ab interno	0.1 ml mitomycin C (0.1 mg/ml) was injected under the conjunctiva, 6 mm from the limbus.	The apex of the injector was pushed through the trabecular meshwork and through the sclera, aiming a 3 mm distance from the limbus. Then the stent was injected under the conjunctiva and the injector removed from the anterior chamber. The position of the stent was confirmed by gonioscopy, and the viscoelastic substance was removed by irrigation. Performing combined XEN Gel Stent and cataract surgery, a 2.8 mm temporal corneal incision was made after mitomycin C was injected under the conjunctiva. Two paracenteses were positioned at 12 and 6 o'clock. After standard phacoemulsification and lens implantation, the procedure was performed as described above.

[a]Based on the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence.

underwent one bleb needling procedure (95% CI: 17–36%), 13% underwent two needling procedures (95% CI: 5–24%) while 4% underwent three needling procedures (95% CI: 2–6%). 35% of patients (95% CI: 29–40%) required at least 1 needling procedure over the entire follow-up period. The average rate of needling procedures per patient was 0.38 (95%CI: 0.20–0.59).

DISCUSSION

In this meta-analysis evaluating the safety profile of XEN45 implantation, we found that the incidence of post-operative complications was low, as well as often transient and self-resolving in nature. However, post-operative intervention rates were relatively high.

Complications after XEN45 implantation

Most reported cases of hypotony were that of numerical hypotony, which resolved without intervention and were not clinically significant. This may have been attributable to early persistent leak and the effect of medications that had not yet completely washed out during this early post-operative period. Some rare complications of hypotony were reported—hypotonous maculopathy was described in 5 patients by Karimi et al. [22] in 1 patient by Mansouri et al. [23] and in 2 patients by Schlenker et al. [14]. The low incidence of clinically significant hypotony is unsurprising, given the design of the XEN45 stent, which has been modelled on the Hagen-Poiseuille equation [50, 51]. Prior flow testing demonstrated the implant's ability to maintain a steady-state pressure above numerical hypotony levels [51].

While our study did not aim to compare complication rates between XEN45 implantation and trabeculectomy, we highlight some observations from some comparative studies included in our analysis. Schlenker et al. [14] demonstrated that trabeculectomy eyes experienced more transient complications than XEN45 surgery, which were mostly contributed by bleb leaks and dehiscence. They reported 2 cases and 1 case of hypotonous maculopathy in the XEN45 and trabeculectomy groups respectively. These cases subsequently resolved, though no details were given. In another comparative study, Marcos Parra et al. [10] noted that the incidence of hyphema and anterior chamber flattening was significantly greater in the trabeculectomy group than in the XEN45 group.

Transient post-operative IOP spikes (IOP ≥ 30 mmHg) occurred in 13% of patients, all of whom required no intervention. Post-operative hyphema (occurring in 14% of patients in our analysis) and retained viscoelastic may have contributed to this early, transient elevation of IOP. Stent exposure was uncommon, but still occurred in 1% of patients and presents a risk of endophthalmitis. Of note, stent exposure and erosion has been shown to occur despite the ability of the XEN45 stent to conform to tissue after swelling upon contact with water [52]. Other case reports have described implant dislocation [53] which at times may necessitate implant removal and re-implantation. Choroidal effusion occurred in 2% of patients. Most studies did not describe any further association with concurrent hypotony, the type of effusion (serous or haemorrhagic), the absence or presence of accompanying symptoms and visual outcomes. Most resolved with conservative management. Grover et al. [41] reported 2 cases unrelated to hypotony which extended posterior to the equator without haemorrhage. Karimi et al. [22] reported 4 cases which lasted more than 1 month and extended posterior to the equator. Smith et al. [29] reported 2 cases, both of which were associated with hypotony. One case developed in the early post-operative period requiring revision surgery, while the other developed in the late post-operative period with severe choroidal effusions following tube revision, necessitating further revision with a pericardial patch graft. Dysesthetic blebs occurred in 2% of patients. Karimi et al. [22] reported 6 cases of large, overhanging dysesthetic blebs

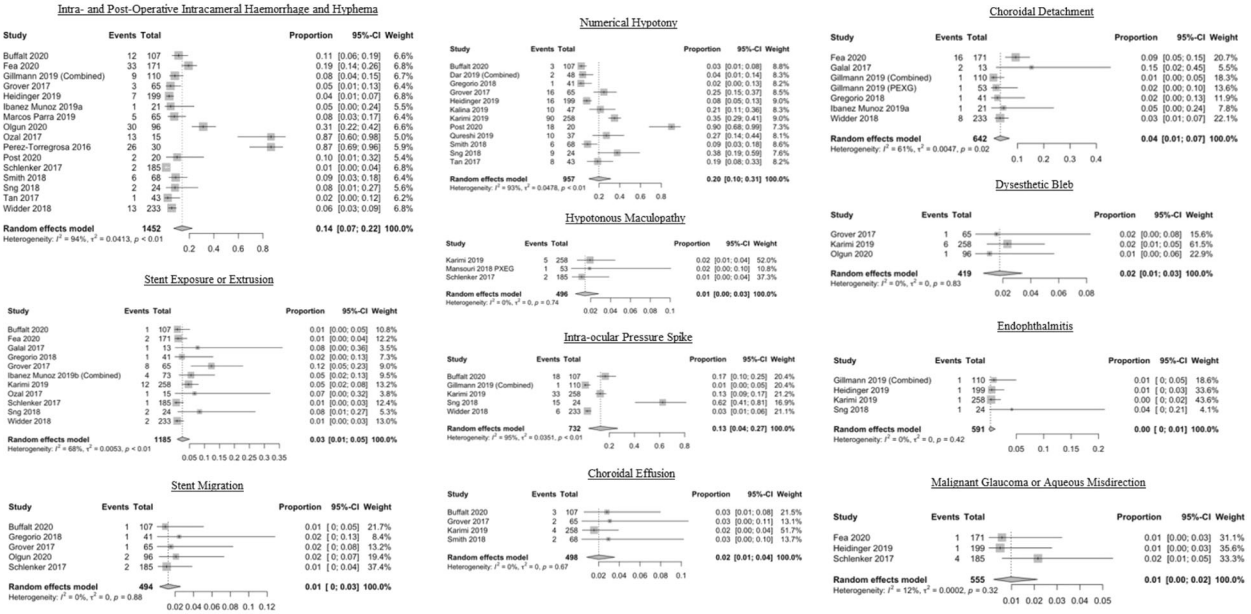

Fig. 1 Complications after XEN45 implantation (with or without concurrent phacoemulsification surgery). Complications after XEN45 implantation include (from top to bottom, left to right) – Intra- and post-operative intracameral haemorrhage and hyphema; stent exposure or extrusion; stent migration; numerical hypotony; hypotonous maculopathy; transient intra-ocular pressure spike; choroidal effusion; choroidal detachment; dysesthetic bleb; endophthalmitis; malignant glaucoma or aqueous misdirection. CI confidence interval.

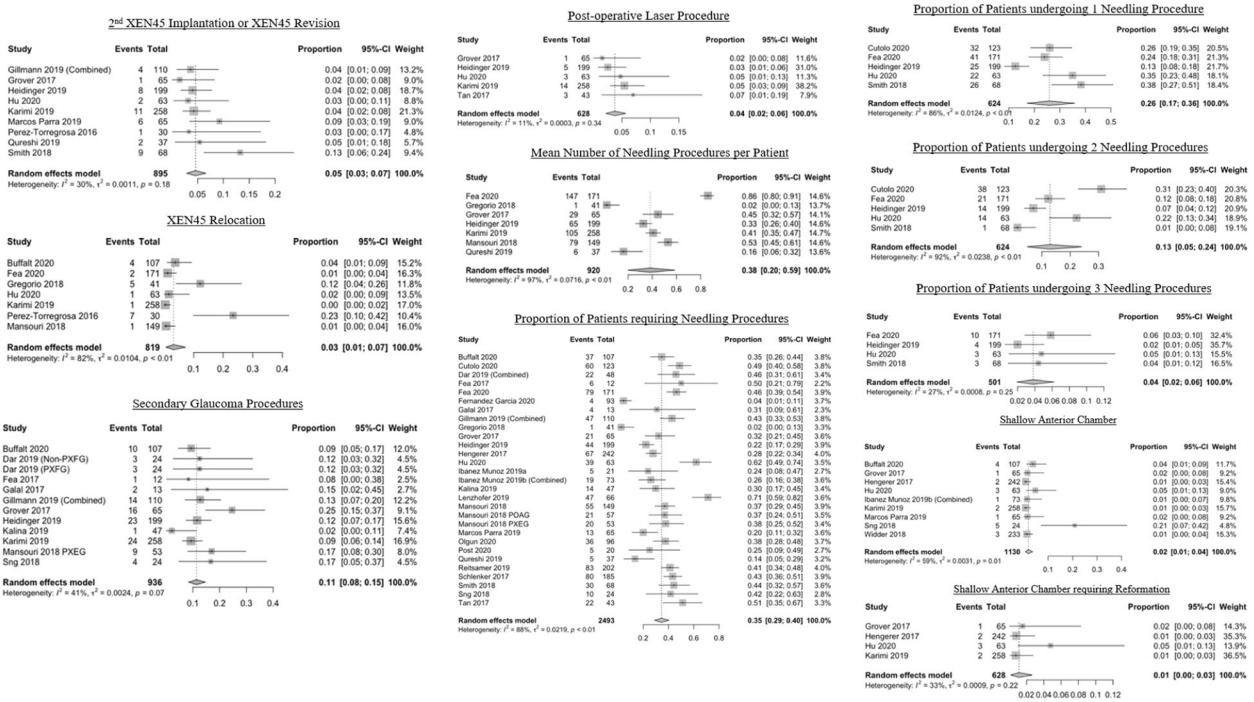

Fig. 2 Interventions after XEN45 implantation regardless of phacoemulsification (with or without concurrent phacoemulsification surgery). Interventions after XEN45 implantation include (from top to bottom, left to right) – 2nd XEN45 implantation or XEN45 revision; XEN45 relocation; secondary glaucoma procedures; post-operative laser procedure; mean number of needling procedures per patient; proportion of patients requiring needling procedures; proportion of patients undergoing 1 needling procedure; proportion of patients undergoing 2 needling procedures; proportion of patients undergoing 3 needling procedures; shallow anterior chamber; shallow anterior chamber requiring reformation. CI confidence interval.

which required post-operative lancing, application of a bandage contact lens, cryotherapy to the conjunctiva or subsequent bleb revisions. Olgun et al. [24] and Grover et al. [41] reported one case of a hypertrophic and a dysesthetic bleb respectively, but did not specify symptoms or the need for further management.

Major complications were rare and there was a very low incidence of severe, sight-threatening complications. 4 cases of malignant glaucoma were reported in Schlenker et al. [14]. 1 case of malignant glaucoma was reported in Fea et al. [25] which subsequently underwent vitrectomy with irido-zonular-

hyaloidectomy. 1 case of malignant glaucoma was reported in Heidinger et al. [13] which necessitated vitrectomy. 1 case of endophthalmitis was reported each in Reitsamer et al. [28], Gillman et al. [38], Heidinger et al. [13], Karimi et al. [22] and Sng et al. [48].

Interventions after XEN45 implantation

Bleb needling has been established as an effective [54, 55] post-operative procedure that aims to re-establish aqueous outflow through the disruption of fibrosis after bleb-forming, subconjunctival drainage surgeries. A sizable proportion of patients in our analysis (35%) required at least 1 needling procedure post-operatively, with an average rate of 0.38 needlings per patient. Most required only one needling (26%) while a minority required three needlings (4%). In terms of mean number of days to first needling, Gillmann et al. [38], Lenzhofer et al. [56], Mansouri et al. [23] reported a mean of 143.8, 137 and 136 days respectively. Reitsamer et al. [28] reported a mean (SD) time to first needling of 152 (160) with a median of 90 days. Heidinger et al. [13] reported a range of 6 to 582 days for time of needling, with a median of 59.5 days while Hengerer et al. [37] did not specify but reported all needling procedures taking place between POW1 to POM3. In terms of the number of needling procedures conducted as a proportion of eyes included in the study, needling was performed in 39.1% (n = 975/2493) of eyes, in studies which reported needling rates. The needling rate was markedly higher in Fea et al. [25] ($n = 147/171$, 85.9%) and lower in De Gregorio et al. [39] ($n = 1/41$, 2.4%). Most needling procedures were performed at the slit lamp. Fea et al. [34] performed needling at the slit lamp or in the operating room, according to surgeon preference. Kalina et al. [21] performed all needlings under microscopic guidance in a procedure room while Gillmann et al. [38] and Mansouri et al. [23] performed all needlings under surgical microscope in the operating theatre.

There is likely to be significant variability in the indication, threshold and method of post-operative bleb needling across studies. The decision for needling is left to the surgeon's discretion, with consideration of patient preference. Other factors affecting the decision to needle may include the target IOP, the risk of recurrence of fibrosis, whether the needling is performed at the slit lamp or in the operating theatre, and bleb morphology, which has been correlated with the performance of a filtering bleb [34, 57, 58]). Higher needling rates may reflect a more proactive approach to needling, while lower needling rates may conversely reflect a more conservative approach. Explicit indications for needling were not detailed by the studies. In our review, most papers did not report the timepoints at which needling was carried out, or criterion for needling, making meaningful comparison difficult. However, Grover et al. [41] did define the criteria for needling as a flat bleb with absence of microcysts, fibrotic or blocked bleb filtration area and high risk of bleb failure based on investigator assessment. Of note, the last criteria was still open to surgeon discretion. Sng et al. [48] reported a criterion of an absence of a subconjunctival filtering bleb and IOP ≥ 21 mmHg. Furthermore, in recent times, modifications to XEN45 implantation surgery have been made in an attempt to reduce post-operative bleb fibrosis and needling rates, including increasing the dose and concentration of intra-operative MMC, performing needling at the time of primary surgery, as well as performing open conjunctival surgery to ensure a sub-tenon's placement of the stent. Most studies did not provide these details. Nonetheless, overall in comparison to trabeculectomy surgery, it may appear that higher rates of needling can be expected after XEN45 implantation surgery [10, 14].

A second glaucoma procedure was performed in 11% (95%CI: 8–15%) of patients. Of the studies that reported rates of second glaucoma procedure, many did not describe the specifics of the second procedure (Supplementary Table 2). However, we note that a majority of second glaucoma procedures, where described, were trabeculectomies.

Risk of bias

All 33 manuscripts included in this meta-analysis were assessed for sources of bias using the ROBINS-I Tool (Supplementary Table 1). A low to moderate risk of bias across all domains was determined in 28 studies. Five papers were deemed to have serious risk of bias [13, 22, 29, 32, 35].

Karimi et al. [22] and Heidinger et al. [13] reported a 73 and 56% loss to follow-up at the 12-month mark respectively. Fernandez-Garcia et al. [35], Dar et al. [32] and Smith et al. [29] excluded otherwise eligible patients that did not attend follow-up, subjecting data to selection bias.

Limitations and further considerations

First, studies included in this review only reported outcomes up till the end of their follow-up period, which ranged from 6 to 36 months (most commonly 12 months). Longer-term safety profiles beyond this timepoint could not be analysed. Second, most included studies were retrospective in nature. Selection and observation biases, as well as confounding factors, are inherent limitations of retrospective studies. This reduces the level of evidence of a systematic review. Third, this review was not prospectively registered and could be subject to reporting bias. While we adhered to our pre-planned protocol, knowledge of potential includable reports could influence key components of the review process such as criteria for study selection, target population and outcomes to be assessed. Fourth, the specific timepoints at which various complications and interventions occurred were not reported. Knowledge of these timepoints would have allowed survival analysis and may have enabled postulation of underlying causes of these complications, as well as better anticipation of post-operative interventions. Fifth, XEN45 implantation is performed as either a standalone procedure or in combination with phacoemulsification surgery. Because most included papers did not report results from these groups separately, we were unable to analyse these outcomes separately. The difference in outcomes between standalone trabeculectomy surgery and combined phacoemulsification-trabeculectomy surgery is well understood. Differences in complication and post-operative intervention rates between standalone XEN45 and combined XEN45-phacoemulsification surgery may similarly be expected [59]. Sixth, post-operative complications and intervention rates may be related to patient and ocular factors, including age, scleral thickness, and diabetic status. However, data on these factors was largely not available for analysis. Seventh, ethnicity has been shown to impact trabeculectomy outcomes [60, 61], hypothesised to be due to differing rates of healing and fibrosis [62]. It is reasonable to assume similar ethnic differences in fibrosis after XEN45 Gel Stent implantation, also a subconjunctival bleb-forming surgery. However, differences in outcome between ethnicities could not be further explored as most studies included a mix of ethnicities. Eighth, initial surgical learning curves in XEN45 Gel Stent implantation are likely to affect outcomes and incidence of complications and interventions. This has been acknowledged in some papers [33, 46, 63]. Ninth, heterogeneity levels across included studies were high, reaching I^2 values of >90% in several of our models. While excessive clinical diversity in our included studies restricted our ability to derive overall effect estimates, this was expected due to variations in glaucoma sub-type, population size, baseline IOP, number of IOP lowering medications and follow-up durations.

CONCLUSIONS

XEN45 Gel Stent implantation is an effective surgical modality in the treatment OAG, with a low incidence of complications but a relatively high incidence of post-operative interventions. There is currently a lack of high-quality evidence available regarding

the safety of XEN45 implantation for OAG. Properly designed randomised controlled trials (RCTs) which compare the medium- and long-term safety of the XEN45 Gel Stent compared to conventional medical, laser and surgical treatments for OAG may be useful. It was observed that there was significant heterogeneity of data reporting across studies. The World Glaucoma Association Guidelines on Design & Reporting Glaucoma Trials [64] provide a clear, standardised guide for reporting of complications specific to glaucoma drainage device surgery. Detailed reporting of event timepoints will also be useful in facilitating survival analysis.

SUMMARY

What was known before

- The XEN45 Gel Stent is a subconjunctival bleb-forming MIGS device used in the treatment of OAG.
- Known post-operative complications include hyphema, transient numerical hypotony, intra-ocular pressure spikes, stent migration and extrusion, as well as endophthalmitis.
- Secondary bleb interventions, including needling, may be required after surgery.

What this study adds

- Review and meta-analysis of current literature suggests a low incidence of complications and secondary glaucoma procedures after XEN45 Gel Stent implantation.
- However, there is a relatively high incidence of post-operative bleb needling.
- Overall, there remains a lack of high-quality, longer-term evidence regarding the safety of XEN45 Gel Stent implantation in the treatment of OAG.

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COMPETING INTERESTS

BKB and SYL declare no competing interests. BAL has previously received speaker's honorarium from Allergan plc. VCHY has previously received funds for travel from Allergan plc. BCHA has previously received funds for travel and research, as well as speaker's honorarium from Allergan plc.

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