Safety and Efficacy of iStent Inject® Trabecular Micro-Bypass Stents in Combination with Phacoemulsification for Chronic Open Angle Glaucoma Associated with Cataract

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Research Article

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Abstract

Background

The goal of this study was to assess the efficacy and safety of phacoemulsification combined with iStent Inject® implantation for the treatment of chronic open-angle glaucoma controlled on topical anti-glaucoma medications and associated with cataract.

Methods

This study was a retrospective analysis of patients who underwent phacoemulsification and implantation of an iStent Inject® for chronic open-angle glaucoma associated with cataract. For all patients, pre- and postoperative characteristics, including number of glaucoma medications and intraocular pressure (IOP), were compared using repeated measures ANOVA. Postoperative visits were scheduled at 7 days and 1, 3, 6, and 12 months after surgery.

Results

Forty-nine eyes of 39 patients were included in the study. Mean preoperative IOP at baseline was 16.3 ± 4.3 mmHg (range, 10–29 mmHg) with a mean of 2.2 ± 1.0 mmHg antiglaucoma medications. At 1 month, the mean IOP reduction was 16% ($p < 0.05$) along with an 18.7% reduction in the mean number of medications. At 6 months, the mean IOP was 12.8 ± 2.6, with a mean of 1.1 ± 0.9 antiglaucoma medications. The mean IOP reduction at 6 months was 22% ($p < 0.05$) along with a 49% reduction in the mean number of medications. At 12 months, the mean IOP was 13.8 ± 2.5 with a mean of 1.1 ± 1.2 medications. The mean IOP reduction at 12 months was 15% ($p < 0.05$) along with a 47% reduction in the mean number of medications. No severe device-related side effects were observed.

Conclusions

iStent Inject® implantation combined with phacoemulsification resulted in effective IOP reduction and medication burden in patients with mild to advanced chronic open-angle glaucoma and preoperative IOP well controlled with topical hypotensive medications.

Background

Glaucoma is the leading cause of irreversible blindness. The main risk factor is chronic elevation of intraocular pressure (IOP). Most of patients with mild to moderate primary open angle glaucoma (POAG) are well controlled on topical medical treatment with hypotensive eye drops. However, several topical medications may be necessary to control IOP, which can lead to frequent side effects on the ocular

surface (1) (2) (3). In case of intolerance to topical treatment or uncontrolled glaucoma, trabeculectomy is the standard surgical treatment for reducing IOP, despite potentially severe side effects (4) (5).

If there is a clinically significant cataract, depending on the severity of glaucoma and the target IOP, phacoemulsification alone or in combination with glaucoma surgery may be performed. Several studies have shown an IOP decrease after phacoemulsification alone in eyes with open-angle glaucoma (6) (7), with a mean IOP decrease of 1.5 mmHg observed 2 years after surgery. This effect was increased when preoperative IOP was higher (8) (9). Nevertheless, previous studies did not observed any significant effect of cataract surgery alone on reducing the number of hypotensive eye drops (10) (11), and this modest IOP reduction was only transient, with a gradual loss of the initial effect after 2 years. Thus, the combination of trabeculectomy and phacoemulsification remains the gold standard surgical treatment for uncontrolled glaucoma associated with clinically significant cataract. However, this combined surgery may lead to more frequent complications and much more complicated postoperative follow-up than cataract extraction alone (12).

Minimally Invasive Glaucoma Surgery (MIGS) devices, implanted alone or in combination with cataract surgery, are usually used in patients requiring IOP reduction to a lesser extent than trabeculectomy, but with a lower risk of complications, a faster visual recovery and a much simpler postoperative course. Among them, the iStent Trabecular Micro-Bypass (Glaukos Corp., Laguna Hills, California, United States) has been proven safe and effective to lower IOP and number of hypotensive eye drops in glaucoma patients when implanted alone or in combination with phacoemulsification (13–19). The goal of these devices is to increase aqueous humor outflow into Schlemm's canal, bypassing the trabecular meshwork, so as to decrease IOP (15).

The first generation iStent® contained a single stent in the inserter, and the second generation, the iStent Inject®, contains two. Previous studies have demonstrated the efficacy and safety of phacoemulsification combined with iStent® or iStent inject® implantation, with significant, lasting and safe reductions in IOP and topical medications (13–18). The indication for their implantation in combination with cataract surgery is in patients with poorly controlled mild to moderate open-angle glaucoma or in case of intolerance to topical hypotensive medications. However, a study by Buffet *et al.* (14) reported significant IOP and topical medication reduction, 10% and 40% respectively, 24 months after implantation of two iStents® combined with cataract surgery in patients whose IOP had been well controlled by topical medications.

A prospective, randomized study showed that iStent inject® implantation combined with cataract surgery was more effective than cataract surgery alone (15). Hengerer *et al.* (16) reported a 37% reduction in IOP and a 68% reduction in the number of hypotensive medications three years after combined surgery with implantation of two iStent Injects®. These previous results concerned eyes with uncontrolled preoperative IOP. Few studies have shown, thus far, the efficacy of iStent inject® implantation combined with cataract surgery in patients with medically well-controlled IOP, defined as IOP < 21mmHg under medical treatment. Indeed, a large proportion of glaucoma patients who require cataract surgery have IOP

well controlled on ≥ 1 topical medication. Furthermore, Manning *et al.* (17) reported that iStent Inject® implantation was more effective than that of iStent® in reducing IOP and topical medications.

The purpose of this study was therefore to assess the efficacy and safety of iStent Inject® implantation combined with standard phacoemulsification cataract surgery in patients with mild to advanced open-angle glaucoma with well controlled IOP under hypotensive topical medications.

Methods

We conducted a retrospective case series of consecutive patients with chronic open angle glaucoma who had undergone phacoemulsification in combination with iStent Inject® implantation in the department of Ophthalmology at Quinze Vingts National Ophthalmology Hospital, Paris, France, from October 2018 to February 2019. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles. Inclusion criteria, based on ICD-10 glaucoma staging, were eyes with mild to advanced chronic open angle glaucoma treated and controlled with topical hypotensive eye drops associated with a visually significant cataract requiring surgical treatment. All patients underwent phacoemulsification combined with iStent Inject® implantation between October 2018 and February 2019 and were treated by 4 surgeons experienced in the surgical technique. The second generation iStent Inject® device consists of a single-use stainless steel inserter, preloaded with two titanium micro-stents coated with heparin. These two stents are each 360 µm in length and 230 µm in width and contain four outlet lumens to facilitate aqueous humor outflow. They are both introduced *ab interno*, one after the other, through the phacoemulsification incision under cohesive viscoelastic after intraocular lens implantation. The insertion of the stent into the trabecular meshwork is performed under high magnification gonioscopy, pressing the button of the inserter to precisely release the devices into Schlemm's canal with the snorkel remaining in the anterior chamber.

All eyes had undergone standard uncomplicated phacoemulsification combined with *ab interno* implantation of both iStent Inject® stents into the inferior trabecular meshwork through the superotemporal or superonasal corneal incision used for phacoemulsification. Patients were checked the day after surgery and were asked to continue their topical antiglaucoma medications postoperatively the same as preoperatively. The following pre- and postoperative characteristics were evaluated : best corrected visual acuity (BCVA), gonioscopy, pachymetry, number of antiglaucoma medications, IOP, visual field mean deviation (MD), and vertical cup/disc ratio measured by optical coherence tomography or clinically evaluated by a glaucoma specialist. We analyzed the postoperative IOP and number of medications at 7 days and 1, 3, 6 and 12 months after surgery. Mean ± SD are provided.

Using definitions that aligned with World Glaucoma Association (WGA) guidelines (18), and other studies (5) (19), the failure of the surgery was defined as postoperative IOP > 21 mm Hg or less than 20% IOP reduction from baseline or reoperation for glaucoma.

We used descriptive statistics such as the mean and standard deviation to summarize the pre- and postoperative data for continuous variables. Pre- and post-operative mean values of IOP and number of

medications were analyzed and compared using repeated measures ANOVA and Sidak's multiple comparison tests. Failure rates over time were analyzed using the Kaplan–Meier method.

Statistical tests were performed using GraphPad Prism® software. A *p*-value of 0.05 or less was considered statistically significant.

Results

Patient characteristics

A total of 49 eyes of 39 patients, 22 women (56.4%) and 17 men (43.6%), were included in the study, and the mean age was 73.9 ± 8.9 years. Most patients (84.6%) had POAG. A minority of patients had pseudoexfoliative glaucoma (n = 4; 10.2%), pigmentary glaucoma (n = 1; 2.0%), and normal tension glaucoma (n = 1; 2.0%). Mean preoperative IOP was 16.3 ± 4.3 with a mean of 2.2 ± 1.0 antiglaucoma medications. Mean cup/disc ratio was 0.73 ± 0.2, and visual field mean deviation was − 8.8 ± 7.3. 6 eyes (12.2%) underwent prior glaucoma surgery, and 13 eyes (26.5%) have had prior laser trabeculoplasty. Table 1 summarizes the main preoperative characteristics.

Table 1
Preoperative characteristics

No. Eyes/patients	**49/39**
Sex (eyes/patients) [N/n (%)]	63
Male	22/17 (44.9/43.6)
Female	27/22 (55.1/56.4)
Age (mean ± SD) (y)	73.9 ± 8.9
Follow-up (mean ± SD) (mo)	8.9 ± 4.4
Side [N (%)]	
Right eye	26 (53)
Left eye	23 (47)
Best-corrected visual acuity (mean ± SD)	0.5 ± 0.2
(logMAR)	
Type of glaucoma [n (%)]	
POAG	33 (84.6)
Pseudoexfoliative glaucoma	4 (10.2)
Pigmentary glaucoma	1 (2.0)
Normal tension glaucoma	1 (2.0)
Preoperative IOP (mean ± SD) (mm Hg)	16.3 ± 4.3
Preoperative medications (mean ± SD)	2.2 ± 1.0
Preoperative vertical cup/disc ratio (mean ± SD)	0.73 ± 0,2
Preoperative MD (visual field) (mean ± SD)	-8.8 ± 7.3
Pachymetry (mean ± SD) (µm)	527 .7 ± 30.5
Prior glaucoma surgery [N (%)]	6 (12.2)
Prior trabeculoplasty SLT/ALT [N (%)]	13 (26.5)
ALT: argon laser trabeculoplasty; MD: mean deviation; POAG: primary open-angle glaucoma; SLT: selective laser trabeculoplasty.	

IOP and number of medications

Preoperative mean IOP was 16.3 ± 4.3 mmHg (range, 10 to 29 mmHg) (n = 49) with a mean of 2.2 ± 1.0 antiglaucoma medications (n = 49). Seven days postoperatively, the mean IOP was 15.4 ± 3.0 mmHg (n = 47) with 1.7 ± 1.0 medications (n = 42). At 1 month, the mean IOP was 13.7 ± 3.3 mmHg (n = 38) with a mean of 1.8 ± 1.1 medications (n = 39). At 6 months, the mean IOP was 12.8 ± 2.6 mmHg (n = 25) with a mean of 1.1 ± 0.9 medications (n = 24); at 12 months, the mean IOP was 13.8 ± 2.5 mmHg (n = 31) with a mean of 1.1 ± 1.2 medications (n = 31) (Fig. 1 and Table 2). These mean IOP reductions represent a 16% decrease at 1 month (p = 0.001), 22% at 6 months (p = 0.0118) and 15% at 1 year (p = 0.0016), along with a significant reduction in the mean number of medications by 18.7% (p = 0.02) at 1 month, 49% (p = 0.0001) at 6 months, and 47% (p < 0.0001) at 1 year, respectively.

Table 2
Mean IOP and Medications: All Patients

Visit	N	Mean IOP (mmHg) and % Change	Eyes on medications (n)	Mean medications and % Change
Preoperative	49	16.3 ± 4.3 mmHg	49	2.2 ± 1.0
Day 7	47	15.4 ± 3.0 mmHg; (− 6) *P* = 0.5663*	42	1.7 ± 1.0; (-21) *P* = 0.1054*
Month 1	38	13.7 ± 3.3 mmHg; (-16) *P* = 0.0001*	39	1.8 ± 1.1; (-18.7) *P* = 0.02*
Month 3	27	13.4 ± 3.2 mmHg; (-18) *P* = 0.043*	26	1.2 ± 1.0; (-46) *P* = 0.0018*
Month 6	25	12.8 ± 2.6 mmHg; (-22) *P* = 0.0118*	24	1.1 ± 0.9; (-49) *P* = 0.0001*
Month 12	31	13.8 ± 2.5 mmHg; (-15) *P* = 0.0016*	31	1.1 ± 1.2; (-47) *P* < 0.0001*
*Statistically significant difference.				
IOP indicates intraocular pressure.				

In a Kaplan–Meier survival analysis, the failure rate of the procedure, defined as IOP > 21 mm Hg or less than 20% reduction from baseline or reoperation for glaucoma, was 20.3% at 1 month, 39.3% at 3 months, 58.8% at 6 months, and 86.3% at 12 months (Fig. 2).

We noticed a more significant postoperative IOP decrease of 38.5% between 1 and 12 months in the 6 cases having IOP higher than 21 mmHg before surgery. At 12 months, 10 of 31 eyes (32%) were no longer receiving hypotensive eye drops, compared to 3 of 49 eyes (6.1%) at baseline, and 18 of 31 eyes (58%) experienced an IOP reduction with at least 1 fewer topical medication than before surgery. For the 7 patients who had an increase in IOP, 5 of them were on fewer medications, and 2 of them were on the same number of medications as preoperatively. Mean best-corrected visual acuity (logMAR) improved

after surgery for all patients, going from an average of 0.5 ± 0.2 preoperatively to 0.9 ± 0.2 postoperatively.

Safety

An overall high safety profile was observed, no significant intraoperative or postoperative complications were noted. Three eyes (6.1%) developed postoperative IOP spikes between D1 and D3, which resolved quickly prior to D7 with medical management. One of these eyes also developed a minimal hyphema prior to D3, which also resolved in less than one week. Only one patient (2.0%) underwent incisional surgery after 1.5 months, with placement of a XEN gel® implant (Allergan, Irvine, USA) (Table 3).

Table 3
Postoperative Adverse Events

Postoperative Adverse Events	**n (%)**
Endophthalmitis	0
Early transitory postoperative elevated IOP (> 25mmHg)	3 (6)
Persistantly high IOP (≥ 1 mo) *	3 (6%)
Hyphema	1 (2%)
Pseudophakic bullous keratopathy	0
Retinal detachment	0
*Persistently high IOP defined as requiring ≥ 4 topical hypotensive medications, or IOP > 21, or requiring ≥ 1 topical hypotensive medications than at the preoperative visit. IOP indicates intraocular pressure.	

Discussion

In this retrospective study conducted over 12 months, we showed the real-life efficacy and safety of iStent Inject® implantation combined with phacoemulsification in patients with controlled IOP on medical treatment, with a 15% IOP decrease after surgery. A greater reduction in postoperative IOP in eyes with higher IOP at baseline had been previously demonstrated (20), but our population was defined as having medically controlled IOP. With a mean preoperative IOP of 16.29 mmHg, we observed a 15% IOP decrease at one year. Previous studies have established that every 1 mmHg IOP reduction produces a 10% or 19% lower risk of glaucoma progression (21) (22), thus highlighting the clinical relevance of these results. Similarly, 12 months after surgery, we observed a 47% decrease in topical hypotensive medications, or a decrease of approximately 1 medication. The majority of eyes (58%) had a reduction in their medication regimen compared to baseline. Thus, the main result of this combined surgery in most of our patients was to achieve an even lower IOP while reducing the number of medications (23). Furthermore, the mean IOP decreased by more than 2.5 mmHg at 1 year, 1 mmHg more than the reduction expected from phacoemulsification alone, which is on average 1.5 mmHg in both healthy and glaucomatous eyes (24)

(25). This result confirms the benefit of stent implantation in addition to cataract surgery in patients with POAG.

These outcomes are consistent with previous studies (16) (20) (26). A large multicenter retrospective Australian study reported a significant decrease in mean IOP and topical medications of 23.2% and 71.5% respectively 1 year after combined surgery with implantation of iStent Inject® in patients with various types of glaucoma. These patients also had a low mean preoperative IOP of 18.27 ± 5.41 mmHg (24). A Brazilian case series (20) with a mean IOP of 16.2 ± 3.1 mmHg at baseline also showed a 19.1% IOP reduction and 94.1% medication reduction 12 months after surgery. On the other hand, in a 3-year prospective case series of patients who underwent iStent Inject® implantation with phacoemulsification, Hengerer *et al.* (16) demonstrated a 37% reduction in IOP and a 68% reduction in the number of antiglaucoma medications. This greater mean IOP and topical medication reduction compared to our results could be explained by the higher mean preoperative IOP (22.6 ± 3.2 mmHg) and number of medications at baseline. In our study, we noticed a more significant postoperative IOP decrease in the 6 cases having IOP higher than 21 mmHg before surgery. These data suggest that implantation of iStent Inject® may be a viable treatment option even in eyes with higher IOP.

The second generation iStent Inject® device, marketed since 2019, contains 2 stents in the same injector, while the first generation iStent® contains one. The iStent® device has also demonstrated substantial, durable, and safe reductions in IOP and number of medications (27) (28). The greater efficacy of the iStent Inject® device compared to the iStent®, especially since the former contains two stents, has been reported in some previous studies. Manning *et al*. (17) showed better results with implantation of the iStent Inject® compared to that of iStent® on IOP and topical medication reduction after combined surgery. Indeed, 68.6% vs. 62.7% of cases respectively had an IOP decrease ≥ 20%, and 92.9% vs. 76.1% were no longer on topical medication at 12 months. Likewise, Paletta-Guedes *et al.* (29) found a significantly greater IOP reduction of 19.1% after combined surgery with iStent Inject® implantation, compared to 4.3% with iStent®. The increased effect of multiple stents was also confirmed by preclinical studies. Bahler *et al.* (30) (31) have demonstrated further increased outflow facility and IOP decrease after implantation of more than one stent in a human anterior segment model. Similarly, clinical studies have shown that while the first stent is responsible for the majority of IOP decrease, further reduction is achieved after implantation of additional stents (20) (32). At 18 months postoperatively, Katz *et al.* (32) observed that the mean IOP decrease was significantly greater with the implantation of additional stents as a standalone procedure, with a mean 1.84 mmHg difference in IOP reduction in favor of the 3-stent group compared with the 2-stent group, and a 1.73 mmHg greater IOP decrease in favor of the 2-stent group compared with the 1-stent group. Indeed, three main characteristics differentiate these two devices and promote efficacy of the iStent Inject®, as highlighted in a comparative study by Paletta Guedes *et al*. (20). First, the iStent Inject® injector contains two preloaded stents rather than one, which are inserted into two distinct regions of the trabecular meshwork, each designed to allow 2.5 µL/min flow of aqueous humor, thus allowing for a more rapid evacuation. Second, each of the two iStent Inject® stents contains four outlet lumens (instead of one for the iStent®), allowing for multidirectional flow and maximizing the

number of accessible collector channels. Finally, these stents are smaller and easier to implant, improving procedural efficiency and reducing the risk of complications.

The safety profile of iStent Inject® was very favorable in this study, and we did not report any severe adverse events. Three eyes (6.1%) experienced IOP peaks prior to 7 days postoperatively, which resolved quickly with medical management. These IOP peaks might be due to the fact that patients did not instill their antiglaucoma medications after surgery or to possible transient postoperative inflammation. Moreover, other studies have demonstrated that 13–46% of glaucoma patients experience IOP spikes after phacoemulsification (33). Only one patient (2.0%) underwent incisional surgery after 1.5 months, with placement of a XEN implant, because of persistent high IOP, defined as requiring ≥ 4 topical hypotensive medications, or IOP > 21, or requiring ≥ 1 topical hypotensive medication more than preoperatively. Some possible late complications of MIGS device, not observed in our study, include dislocation or extrusion in the introduction section (34). Mean visual acuity improved after surgery for all patients.

Our study has some limitations. First, our sample is relatively small but rather homogeneous, as the majority of patients had well-controlled preoperative IOP. The absence of a control group introduced the confounding factor of the effects of cataract surgery alone on IOP. As in almost all real-life studies, there was no washout period before or after surgery. Finally, some patients were lost to follow-up because they were returned from our center to their referring ophthalmologists. We did not evaluate postoperatively the progression rate of glaucoma damage based on perimetric data, due to missing data related to patients lost to follow-up. As only the numbers of medications were recorded in the present study, the influence of the type of antiglaucoma medication on postoperative outcomes was not evaluated. Similarly, the influence of prior filtering surgery was not analyzed, as this subgroup of patients was too limited (4 of 49 eyes) to allow a precise evaluation.

Conclusions

This study reports that cataract surgery combined with implantation of the iStent® Inject® appears to be safe and effective in reducing IOP and medication burden in patients with open angle glaucoma and preoperative IOP well controlled with topical medication, allowing an IOP lowering effect beyond that of cataract surgery alone, with fewer medications and better long-term tolerance. While the IOP decrease is more modest than that seen after incisional surgery, these MIGS are less traumatic, have an excellent safety profile and might delay or avoid more invasive surgeries. In case of the need for further filtering surgery, reducing medication-induced ocular surface damage is of particularly high interest. These results should be re-explored through larger controlled studies, but they suggest a relevant indication for the implantation of iStent Inject® devices in patients with well controlled mild to advanced glaucoma.

Abbreviations

IOP

intraocular pressure
POAG
primary open angle glaucoma
MIGS
minimally invasive glaucoma surgery (MIGS)
BCVA
best corrected visual acuity
HFA
Humphrey Field Analyser
MD
Mean deviation
ALT
argon laser trabeculoplasty
SLT
selective laser trabeculoplasty

Declarations

Ethics approval and consent to participate

This study adhered to the tenets of the Declaration of Helsinki.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable resquest.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

D.C.: acquisition of data, analysis and interpretation of data, drafting the article. A.L: performing surgical procedures, provided the conception and design of the study, supplied the acquisition of data, revised the article critically for important intellectual content, and final approval of the version to be submitted; E.B

and P.H and C.B : performing surgical procedures, supplied the acquisition of data, revised the article critically for important intellectual content, and final approval of the version to be submitted.

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Figures

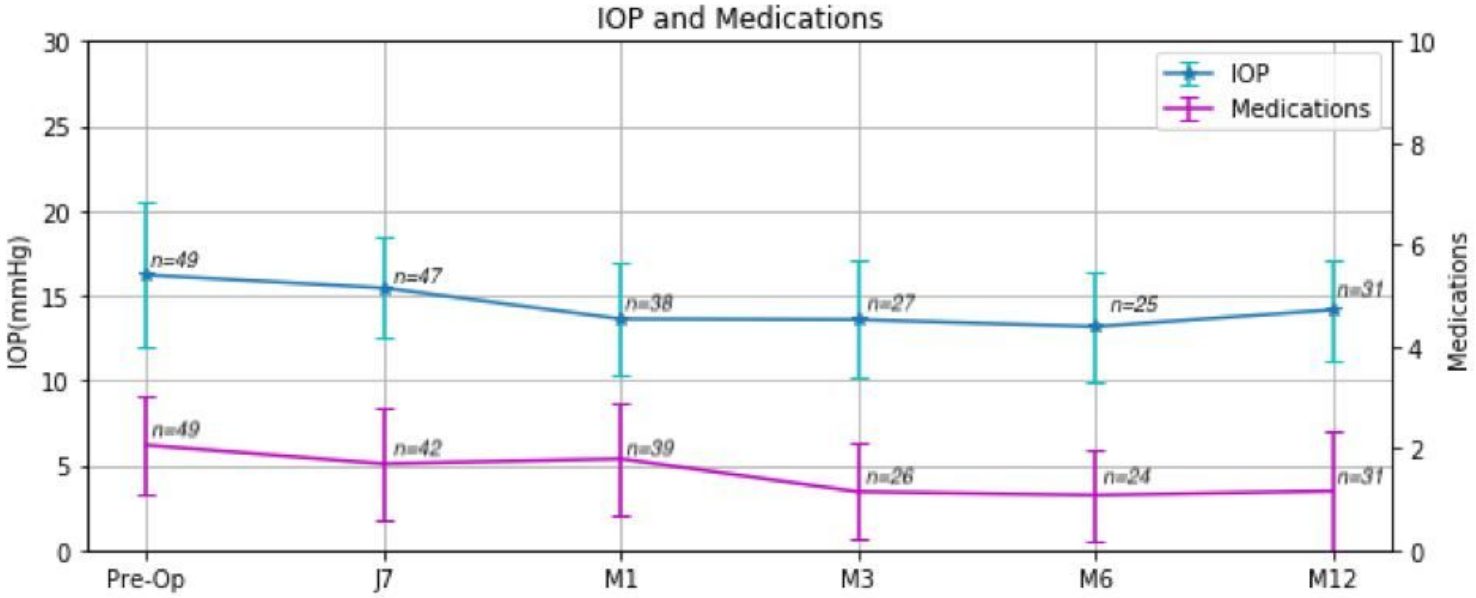

Figure 1

Mean IOP and medications. IOP: intraocular pressure.

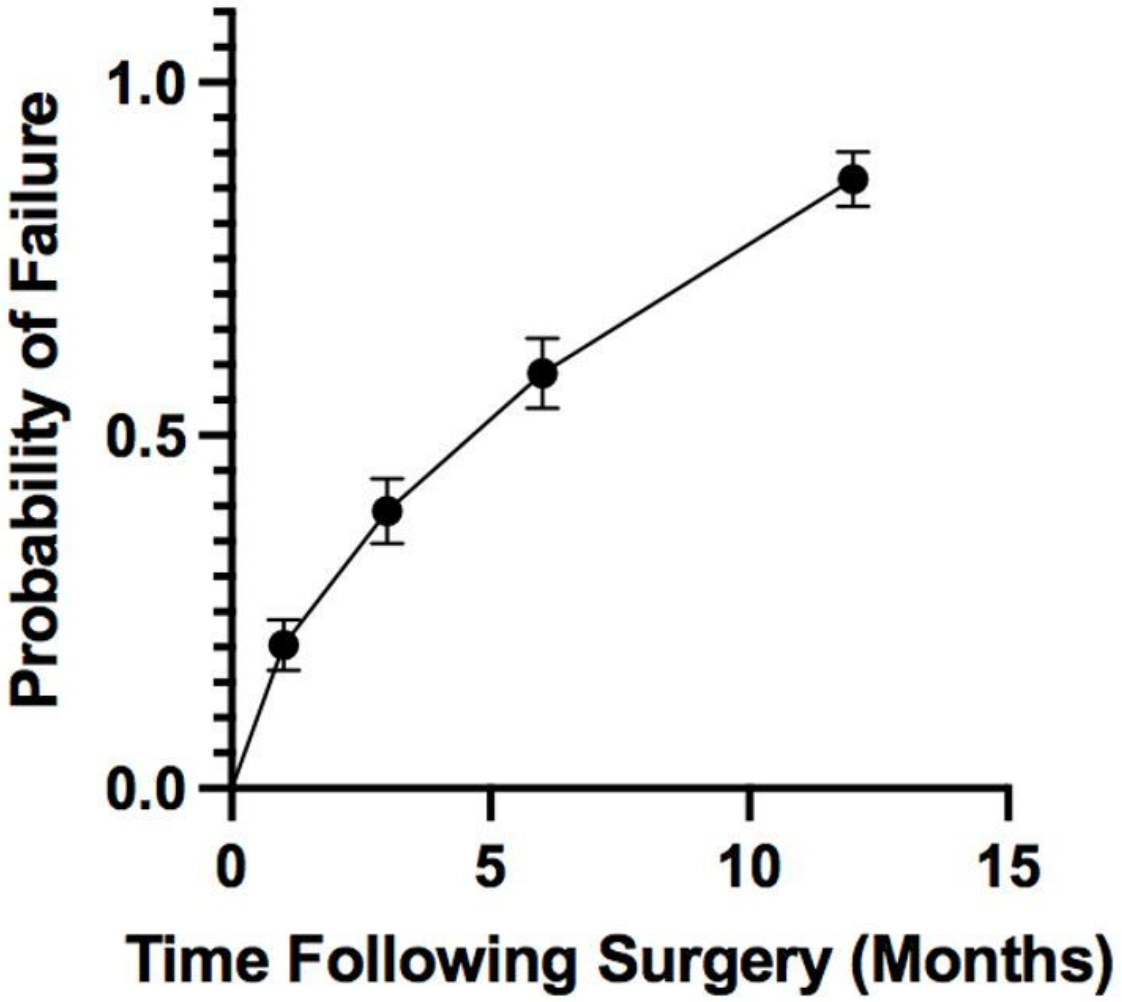

Figure 2

Kaplan–Meier survival analysis showing the cumulative probability of failure up to year 1.