TITLE: Minimally Invasive Glaucoma Surgery: Comparison of iStent with iStent *inject* in Primary Open Angle Glaucoma.

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ABSTRACT

Importance: Minimally Invasive Glaucoma Surgery has gained significant traction in recent years. This study evaluates the first and second-generation trabecular micro-bypass stents 'iStent' and 'iStent *inject*'.

Background: To evaluate and compare the effect of a single iStent and double iStent *inject* in Primary Open Angle Glaucoma.

Design: Prospective comparative case series.

Participants: Primary Open Angle Glaucoma patients undergoing trabecular micro-bypass stent insertion combined with cataract surgery.

Methods: Baseline demographic information, pre-operative, intra-operative and post-operative outcomes including intraocular pressure (IOP), visual acuity, reliance on glaucoma medication and complications were collected and analysed.

Main Outcome Measures: Primary, secondary and tertiary outcome measures were consecutively defined as an IOP of ≤ 18mmHg with zero medications, an IOP of ≤ 18mmHg with reduced medications or a 20% reduction in IOP with or without medication.

Results: The study comprised 145 eyes in the iStent and 100 eyes in the iStent *inject* group. At 12 months, 56.0% of the iStent and 51.3% of the iStent *inject* eyes had achieved primary

success and 63.1% and 57.7% secondary success. The mean post-operative IOP was 16.6mmHg in iStent and 16.9mmHg in iStent *inject.* Survival analysis demonstrated a greater incidence of failure in the iStent *inject* beyond 5 months.

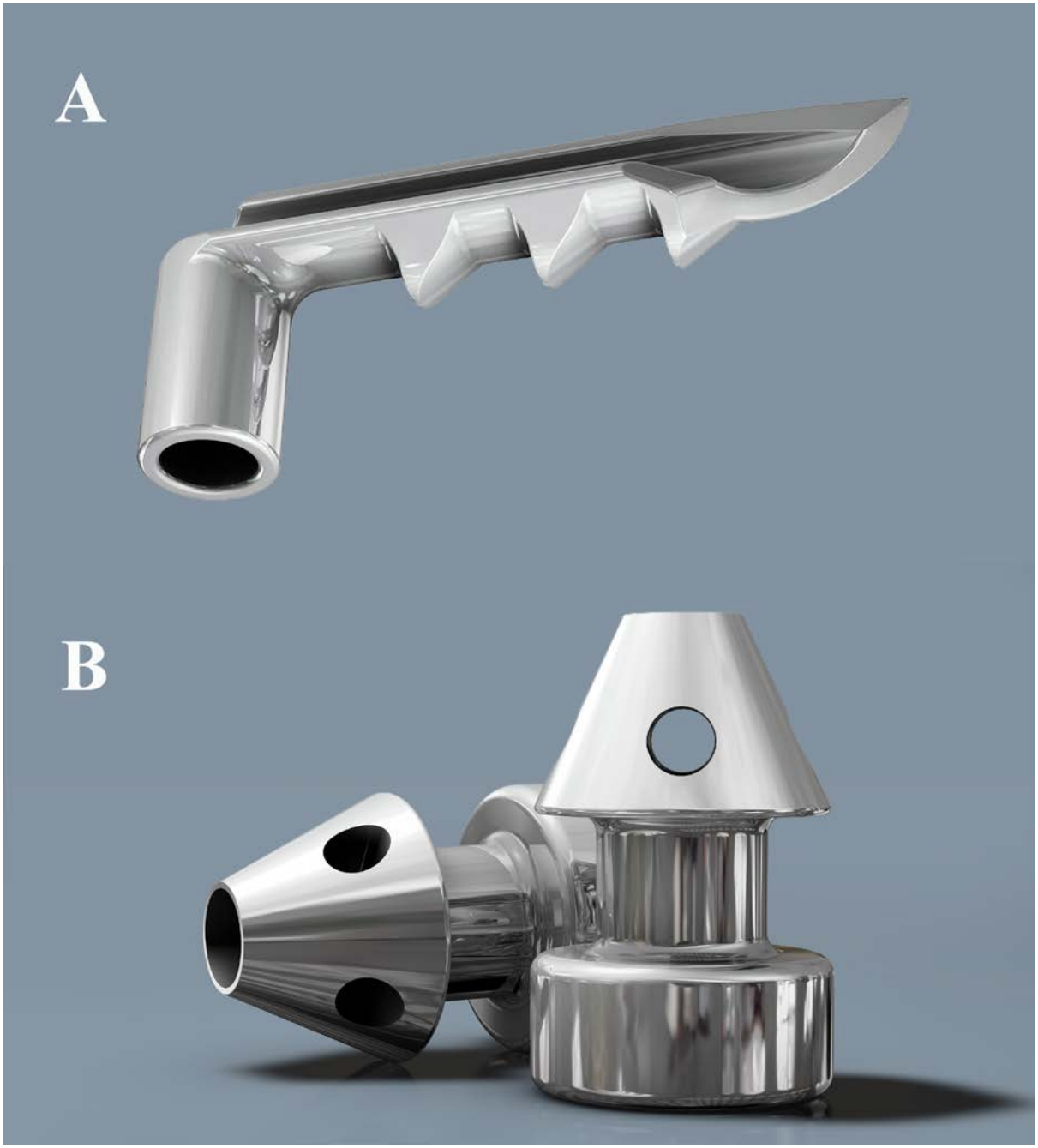
Conclusions: Both trabecular micro-bypass stents in this study were effective in reducing IOP and the burden of medication when combined with cataract surgery. There was no statistically significant difference between the two groups across our outcome measures although the iStent *inject* required earlier recommencement of medications for optimal IOP control.

Introduction

Minimally Invasive Glaucoma Surgery (MIGS) has gained significant traction over the past few years. New devices and procedures are constantly being developed in an effort to lower intraocular pressure (IOP) in a less invasive and purportedly safe manner. In Australia, there has been a marked increase in MIGS uptake with Medicare data indicating an exponential increase in use over the last few years.[1, 2] Although MIGS is currently seen primarily as adjunct to cataract surgery, it is increasingly being considered as a viable initial treatment option.[3]

The objective of this study was to evaluate and compare the first and second-generation trabecular micro-bypass stents, 'iStent' and 'iStent *inject*' (Glaukos Corporation, CA, USA). Trabecular stent bypass microsurgery aims to reduce intraocular pressure by creating a bypass channel between the anterior chamber and Schlemm's canal to improve the drainage of aqueous humour. iStent was the first ab-interno micro-bypass device of its kind based on this principal. The 1mm long, L-shaped titanium device is implanted via a preloaded injector through the trabecular meshwork under gonioscopic guidance. Once inside the trabecular meshwork, a well placed stent provides aqueous outflow directly into collector channels.

Figure 1 A. First generation trabecular micro-bypass stent (iStent). B. Second generation trabecular micro-bypass stent, (iStent *inject*). Image supplied.



Although successful in reducing the IOP, the iStent was superseded by iStent *inject*, a much smaller second generation trabecular micro-bypass stent. The iStent *inject* is a 0.4mm long, 0.3mm wide plug shaped implant with a central opening that is injected into the trabecular meshwork under gonioscopic guidance. The stent was redesigned for easier insertion and its

injector is pre-loaded with two stents inserted approximately 2 to 3 clock hours away from each other. (Figure 1)

A number of studies have demonstrated the effectiveness of iStent and iStent *inject*. In a systematic review and meta-analysis of 2,143 patients from 32 studies, comparing stent insertion combined with phacoemulsification against phacoemulsification alone in patients with glaucoma and cataract, there was a statistically significant decrease in IOP from baseline in the combined group compared with the phacoemulsification only group at a follow up of 12- 58 months.[4] The meta-analysis also demonstrated a significant reduction in the number of glaucoma medications used after the procedure in the combined group compared with the phacoemulsification only group (weighted mean reduction of 1.33 from baseline compared with 1.01).[4] Significant reduction in IOP from baseline has also been demonstrated in patients with mild to moderate glaucoma treated with stent insertion alone at follow up of 6-18 months.[5]

Although each trabecular micro-bypass device has proven to be efficacious, the two devices have not been previously compared in performance and efficacy.

Methods

Study design

We conducted a prospective comparative case series on patients with mild to moderate primary open angle glaucoma (POAG) and cataracts. Patients undergoing cataract surgery combined with stent insertion were consecutively recruited from two centres across Launceston, Tasmania, Australia. Mild to moderate POAG was defined as having a vertical cup to disc ration of 0.8 or less with stable serial IOPs and visual field assessments. All patients were seen and operated on by a single senior glaucoma specialist with extensive

experience in trabecular stent micro-bypass surgery. iStent was considered well placed when only the "snorkel" component was visible with the rest of the implant inside the Schlemm's canal. iStent *inject* was considered well placed when the level of the "collar" was flush with the trabecular meshwork. The study was conducted in accordance with the tenets of the Declaration of Helsinki; ethics approval was obtained from the University of Tasmania Human Research Ethics Committee (H0014226).

Baseline demographic information as well as data on IOP, visual acuity and reliance on the number of glaucoma medications were recorded pre and post operatively. Intraoperative observations on device performance and complications were made. Patients were seen at day 1 and week 3-4 post operative at which point all glaucoma medications were ceased. The post-operative steroid regime was kept identical between the two groups. Follow up occurred every 3 months or as otherwise clinically indicated. Patients were recommenced on monotherapy if IOP was greater than 18mmHg in any follow up visit; an IOP of 18mmHg was chosen as it has been shown to reduce the long term progression of visual field defects.[6] Further agents were added one at a time at each follow up if clinically indicated. A cut off of 18 months was chosen as very few patients had passed this milestone in the second generation device, iStent *inject*, group.

Outcome measures

- Primary success was defined as an IOP of 18mmHg or less with zero number of topical glaucoma medications.
- Secondary outcome was defined as an IOP of 18mmHg or less with reduced number of topical glaucoma medications.
- Tertiary outcome was defined as a 20% reduction in IOP with or without topical glaucoma therapy.

Statistical analysis

Patient data entered into Excel (Microsoft Inc, WA, USA) were extracted and imported into Stata 15 (StataCorp LLC, TX, USA) for analysis. Numbers of eyes and percentages are reported for categorical data and means with standard deviations for continuous data. Cross-tabulations were produced to compare categorical data in the iStent and iStent *inject* groups, with chi-square tests used to evaluate statistically significant differences. Independent t-tests were used to investigate mean IOP, number of glaucoma medications and visual acuity (logMAR) comparison in the iStent and iStent *inject* groups. A Kaplan-Meier survival curve was plotted for time to glaucoma medication re-initiation after surgery within 18 months of follow-up and median time to drop re-initiation was calculated.

Results

The study comprised 245 eyes from 148 patients, aged 53-89 years at the time of the operation (Mean 71, SD 7.1). There were 145 eyes in the iStent and 100 eyes in iStent *inject* groups. All patients had a confirmed diagnosis of POAG. The mean pre-operative IOP was identical in both groups (18.9mmHg). The mean pre-operative number of topical agents was 1.7 in the iStent and 1.6 in the iStent *inject* group. Patient demographics and baseline characteristics are shown in table 1.

Table 1. Patient demographics and baseline characteristics

	Mean (SD) or n (%)			
Variable	**Both**	**iStent**	**iStent inject**	***P* value**
Eyes (n)	245	145	100	-
Right (n)	120 (49.0)	73 (50.3)	47 (47.0)	0.61
Age (years)	71 (7.1)	70.2	70.9	0.40
Gender (female)	135 (55.3)	87 (60.4)	48 (48.0)	0.06
Pre-operative IOP (mmHg)	18.9 (5.2)	18.9 (4.7)	18.9 (5.9)	0.93
Pre-operative agents (n)	1.6 (0.1)	1.7 (0.1)	1.6 (0.1)	0.64
Pre-operative visual acuity (logMAR)	0.2 (0.1)	0.2 (0.1)	0.1 (0.1)	0.28

(Snellen equivalent)	9.5	9.5	7.5	-

IOP = intraocular pressure

Outcome measures

At 12 months, 56.0% of the iStent and 51.3% of the iStent *inject* eyes had achieved primary success and 63.1% and 57.7% secondary success. Tertiary success was achieved in 34.8% in the iStent and 29.5% in the iStent *inject* eyes. Forty-three eyes reached 18 months of follow up in the iStent *inject* group due to later introduction of the device. The main outcome measures achieved at different time points across the study are outlined in table 2.

Table 2. Primary, Secondary and Tertiary outcome comparison

Time (Months)	Both	iStent	iStent inject	*P* value
	Primary Success n (%)			
3	158 (67.8)	93 (67.4)	65 (68.4)	0.87
6	148 (63.2)	94 (65.3)	54 (60.0)	0.42
12	119 (54.3)	79 (56.0)	40 (51.3)	0.50
18	84 (47.5)	65 (48.5)	19 (44.2)	0.62
	Secondary Success n (%)			
3	164 (70.4)	98 (71.0)	66 (69.5)	0.80
6	161 (68.8)	105 (72.9)	56 (62.2)	0.09
12	134 (61.2)	89 (63.1)	45 (57.7)	0.43
18	102 (57.6)	81 (60.4)	21 (48.8)	0.18
	Tertiary Success n (%)			
3	88 (37.8)	51 (37.0)	37 (38.9)	0.76
6	67 (28.6)	42 (29.2)	25 (27.8)	0.82
12	72 (32.9)	49 (34.8)	23 (29.5)	0.43
18	67 (37.9)	51 (38.1)	16 (37.2)	0.92

N = number; % = percentage; Total number of eyes for both groups n = 233 at 3 months, 234 at 6 months, 219 at 12 months and 177 at 18 months. There were 43 eyes that reached 18 months follow up in the iStent inject group.

Intraocular pressure

Figure 2 depicts the mean IOP for the iStent and iStent *inject* groups pre-operatively and at each follow-up timepoint. For each timepoint, there was no significant difference in mean IOP between the groups. The mean IOP was generally reduced over the study period however an uptrend was noted in the iStent *inject* eyes from 6 months following surgery. Raw IOP data pre-operatively compared with 12 months post-operative are shown in Figure 3.

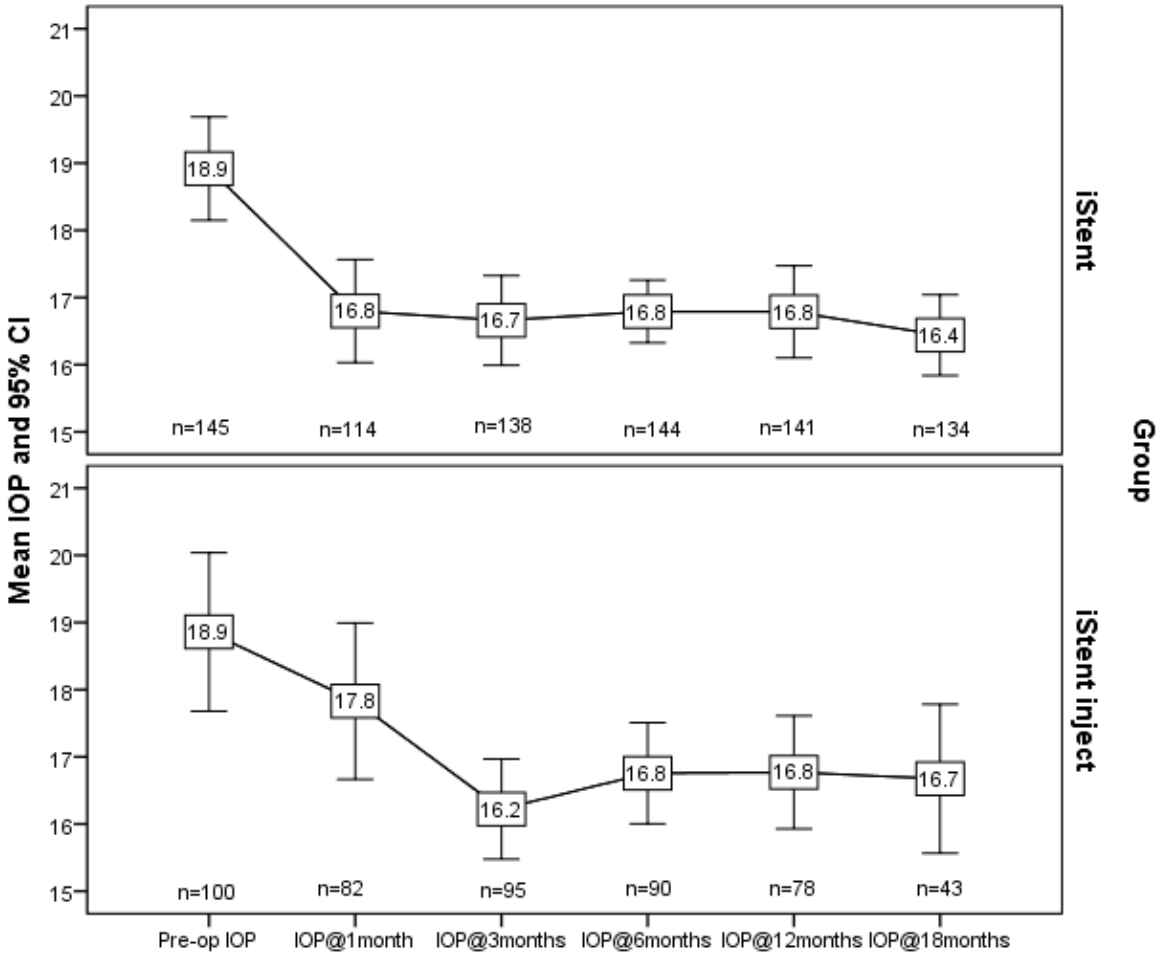


Figure 2. Error bar graphs demonstrating the mean IOP trend in iStent (top) and iStent *inject* (bottom).

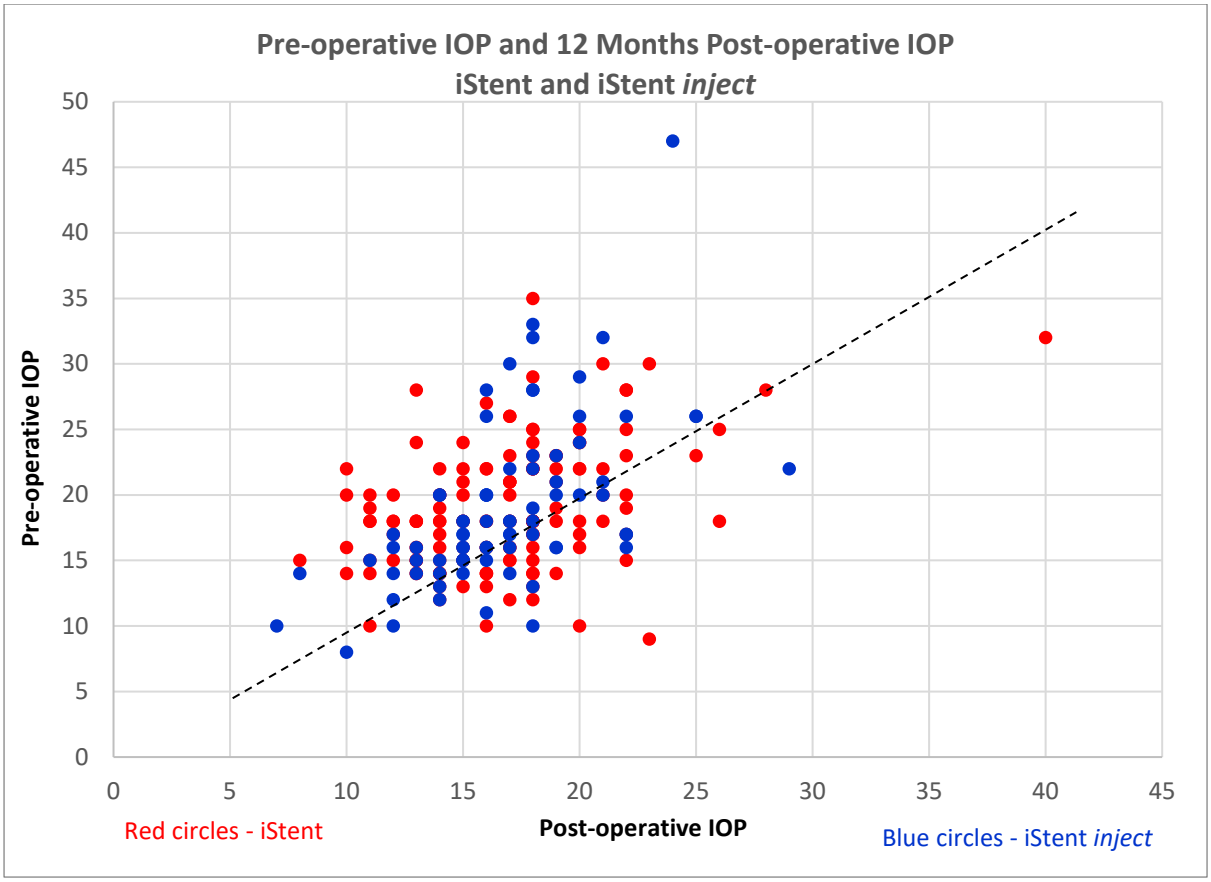


Figure 3. Scatter plot graph of the raw IOP data pre-operatively compared with 12 months post-operative for iStent and iStent *inject* eyes. Data points above the line indicate a reduction in IOP, those on the line indicate no change with those below the line indicating an increase in post-operative IOP.

Glaucoma medication

The mean number of glaucoma medications used reduced from 1.7 to 0.6 in the iStent group and 1.6 to 0.7 in iStent *inject* eyes. An overview of the reduction in the mean number of the glaucoma medications used is demonstrated in Figure 4. The number of eyes and the distribution of the number of glaucoma agents required in the pre-operative compared with the post-operative period is demonstrated in Figure 5.

By 12 months, 90 of the 141 (63.8%) iStent and 52 of the 79 (66.7%) iStent *inject* eyes had recommenced topical glaucoma therapy. Of those who required recommencement of topical therapy, the mean time to drop initiation was 12 months for iStent and 7 months for iStent *inject*. Overall, 49% of the eyes did not require topical therapy during the follow up period.

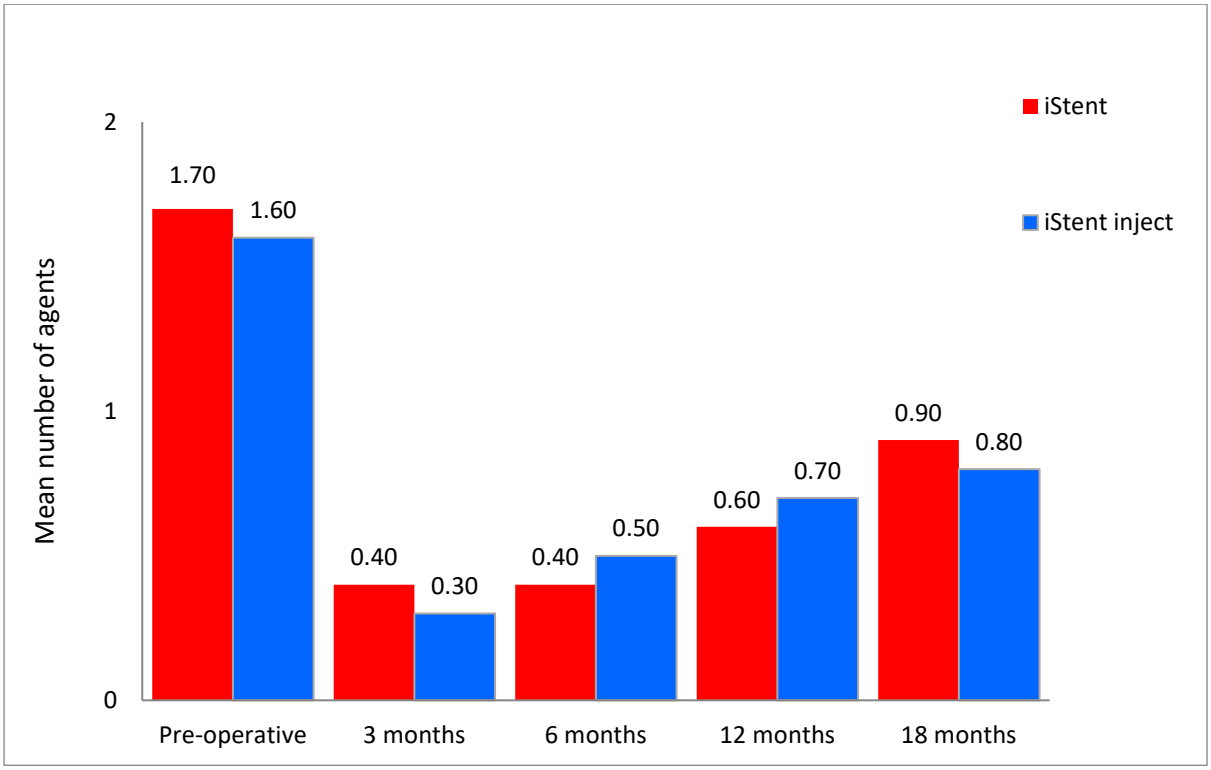


Figure 4. Mean number of glaucoma agents used over 18 months.

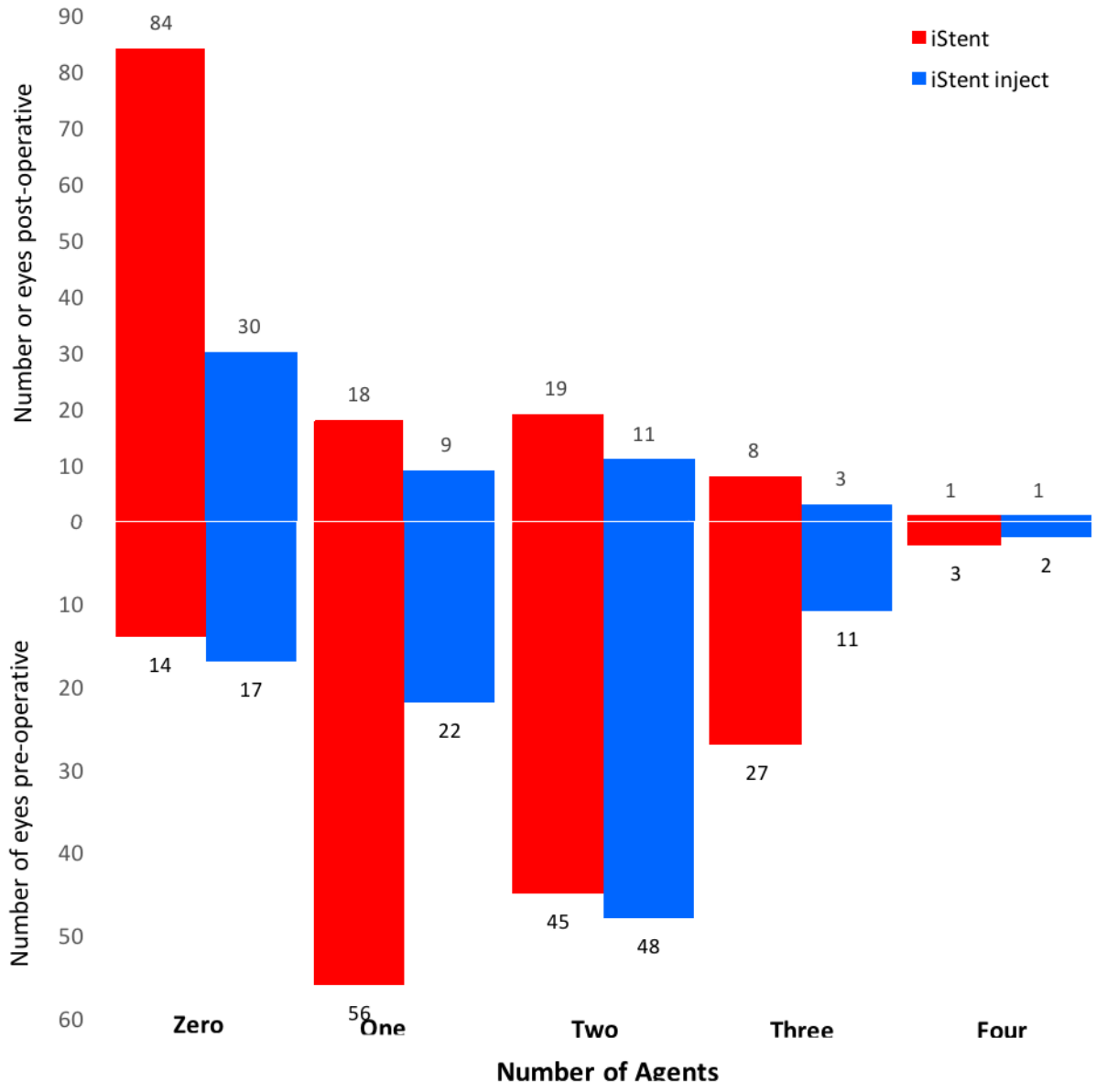


Figure 5. Number of eyes (y axis) and the distribution of the number of glaucoma agents (x axis) required in the pre-operative (bottom) compared with the post-operative (top) period.

A very similar survival experience (estimated time to topical therapy initiation post surgery) was demonstrated in both groups for up to 5 months post-operative utilising the Kaplan – Meier survival estimator. From 5 months on, the survival curves begin to diverge, with the

greater incidence of failure (defined as the initiation of eye drops) in the iStent *inject* eyes (Figure 6).

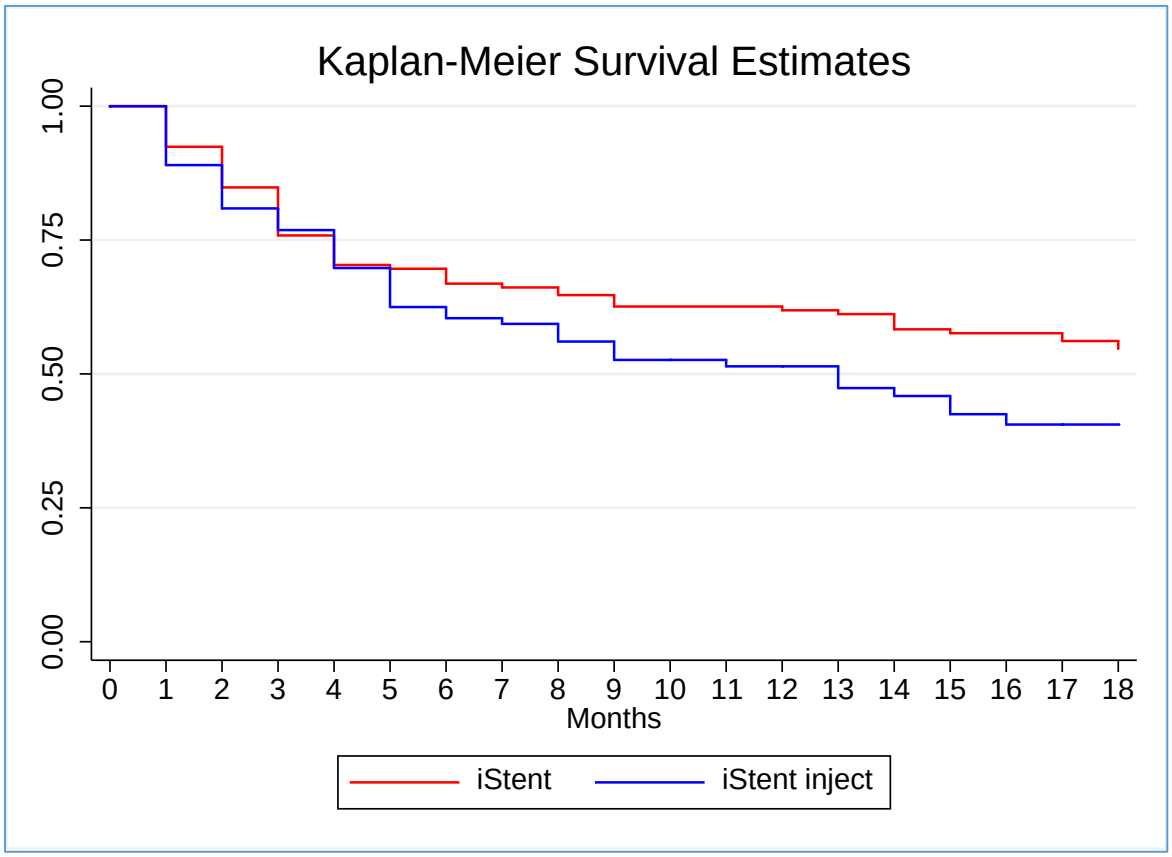


Figure 6. Kaplan-Meier survival analysis demonstrating time to post-operative initiation of glaucoma medications.

Visual acuity

The mean best corrected visual acuity at 12 months was 0.09 logMAR (SD 0.11) or 6/7.5 Snellen equivalent, with no significant difference between the two groups ($t_{(188)} = -0.8$, $p = 0.41$).

Complications

Hyphaema was the most common complication observed with higher incidence in the iStent eyes. These were conservatively managed with no further complications. Corneal abrasions, corneal oedema, implant failure and stent malposition made up the remainder of the small number of complications observed (Table 3.) Only 1 patient implanted with iStent *inject*, presented with a delayed spontaneous non-traumatic macro-hyphaema 4 months post implant insertion. This was conservatively managed and resolved without further complications.

Table 3. Complications

	Complication	iStent [n = 145]	iStent inject [n = 100]	*P* value
Intra - operative	Bleeding in AC	13 (8.9%)	4 (4.0%)	0.13
	Corneal abrasion	3 (2.1%)	0	0.27
	Failure to implant	1 (0.7%)	0	1.00
	Failure to implant 2 stents	N/A	2 (2.0%)	N/A
	Stent malposition	3 (2.1%)	1 (1.0%)	0.65
Early Post operative	Hyphaema	14 (9.7%)	6 (6.0%)	0.35
	Corneal oedema	3 (2.1%)	1 (1.0%)	0.65
	Corneal abrasion	1 (0.7%)	1 (1.0%)	1.00

AC = anterior chamber; NA = not applicable

Discussion

The first and the second generation trabecular micro-bypass stents are both proven to be efficacious in reducing IOP and reliance on glaucoma medications in mild to moderate glaucoma. Despite the relative ease in intraoperative insertion of these implants under gonioscopic guidance, these ab-interno micro-stents are subject to intraoperative malpositionning which can result in failure of implantation or luminal obstruction and decreased efficacy.[7, 8] The 1mm long, L shaped first generation device, iStent, is slightly more difficult to implant owing to its size and shape. Higher incidence of intraoperative hyphaema is also reported with occasional recurrence and lumen blockage requiring implant

removal.[9-11] The second generation device, iStent *inject*, is a much smaller implant at 0.4mm long and was specifically designed for ease of insertion. The iStent *inject*'s pre-loaded injector is also equipped with 2 implants usually utilised at the same time, thereby reducing the impact of single implant blockage.

Our results confirm the efficacy of each stent consistent with other published literature to date. In a randomised controlled clinical evaluation of the trabecular micro-bypass stent (iStent) with phacoemulsification in patients with glaucoma and cataract 72% achieved primary outcome success.[12] The nominated IOP to recommence treatment in this study was however set higher at 21mmHg. We elected for a more conservative approach and chose to recommence treatment at 18mmHg based on evidence from the Advanced Glaucoma Intervention Study (AGIS).[6] Interestingly 50% of the control eyes in the randomised controlled trial achieved an IOP of less than 21mmHg following cataract surgery alone.[12]

Our study found 56.0% primary success at 12 months in the iStent group and 51.3% in the iStent *inject* group. Given the small difference between the groups, a post-hoc power calculation found more than 1500 patients would need to be recruited to each group to detect a significant difference at 80% power and $\alpha = 0.05$. This suggests a true null difference between the groups in the proportion of eyes achieving primary success at 12 months.

We compared the effects of both stents in a prospective study of POAG patients with very similar if not identical demographics and baseline characteristics. Although there were no statistically significant differences between the two groups across our outcome measures, we noted iStent *inject* patients require earlier recommencement of topical glaucoma therapy for optimal IOP control. We postulate this to be due to the dynamics of fluid flow through the stent lumen with the iStent having a larger drainage pathway than that of the iStent *inject*.

The higher incidence of complications associated with iStent observed in our cohort are statistically not significant and had no bearing on our patients' final visual outcomes.

Conclusion

Both trabecular micro-bypass stents in this study reduced IOP by a mean of 2.0 – 2.3mmHg and reduced the mean number of medications by 0.8 to 1.0 . There was no statistically significant difference between the two groups across our outcome measures. Both devices appear to be safe with no significant visual or IOP related complications.

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