ORIGINAL ARTICLE

The Short-Term Efficacy and Safety of iStent Implantation Combined With Cataract Extraction on Lowering The Intraocular Pressure in Patients with Glaucoma: A Pilot Study in Indonesia

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ABSTRACT

Introduction: Minimally invasive glaucoma surgery (MIGS) is continuously being improved after it was first initiated in the early 2000s. This promising method is hoped to fill the gap between medication and traditional surgeries in management of glaucoma.
Objective: To evaluate the efficacy and safety of iStents implantation combined with cataract extraction in managing intraocular pressure in glaucoma patients.
Methods: We collected data from 6 eyes of 5 patients with POAG and cataract pre-operatively. The extraction of cataract was then performed, combined with second generation iStents implantation. The follow up procedure included the change of intra ocular pressure (IOP), Visual acuity, and the need for IOP lowering Medication at 1 week and 1 month post-operatively.
Results: There was a reduction of mean IOP from the baseline, which was 21.33 ± 6.15 to 18.0 ± 6.0 and 18.11 ± 5.57 at 1-week and 1-month following the surgery. The reduction of IOP was also followed by the reduction of medications needed for the patients. The mean visual acuity following the surgery was also increased from the baseline 0.53 ± 0.41 to 0.85 ± 0.17 at 1 – week and 0.91 ± 0.16 at 1 – month. For safety outcomes, there were no major adverse effect nor complication from the procedures after 1 month of follow up.
Conclusion: The iStents implantation helped lowering the IOP of patients with glaucoma. It also reduced the need for further IOP lowering medication following the procedure.

Keywords: MIGS, Glaucoma, iStent, cataract.

Minimally invasive or also known as micro incision glaucoma surgery (MIGS) was initiated in the early 2000s and continuously being developed and expanded until recently [1]. MIGS provides safer, less invasive method of reducing intra ocular pressure (IOP) than the traditional surgeries and also aims to reduce the dependency on topical glaucoma medications [2]. MIGS is hoped to fill the gap that has existed in the treatment algorithm for glaucoma between medical therapies and laser at one side, and traditional glaucoma surgeries at the other side. Patients who had failed laser therapy and was not adequately controlled on medications, are then referred to undergo traditional glaucoma surgery [1].

Given the complications of traditional surgeries that can occur intra or post operatively such as hypotony, hyphema, infection of the bleb, and endophtalmitis which also reportedly found in 35% of the procedures, MIGS can provide an alternative for these patients. Especially, when the IOP reduction goal is modest, the glaucoma is newly diagnosed, and the optic nerve damage is only mild to moderate [1][3]. The other purpose of MIGS is to reduce the dependency on lifelong glaucoma medications. One of the most currently known techniques of MIGS is istent implantation. This technique could benefit from others by being easier to perform and causing less complications. This newly developed technique could be a solution to serve as an effective and safe therapy between medications and conventional glaucoma surgery for mild to moderate glaucoma cases. [3,13]

Glaucoma has been one of the major burdens for health economics in decades with its direct or indirect cost. It is reported that the cost for glaucoma for 2 million US citizens is estimated to reach $2.9 billion and it can be increased as the severity of disease advances. This already complicated problem is then compromised by the adherence of patients which can be different from one to another. There are many factors that play a big role in the patients' compliance on taking the medications such as the side effects which are almost impossible to prevent [4][5]. Several publications are available regarding the efficacy and safety of iStent as a management of high IOP but they dominantly based in the U.S and Europe. This case series will serve as the first publication related to the efficacy and safety of the second generation of iStent device in Indonesia.

METHODS

Design

This was a 1 – month clinical evaluation of the efficacy and safety served as interventional case series of the iStent by Glaukos corp in 6 patients with mild to moderate open angle glaucoma and cataracts who underwent the phacoemulsification plus the insertion of IOL surgery, and implantation of iStent whose IOP was insufficiently controlled by the current medication(s).

Patients

The inclusion criteria included the patients with mild to moderate primary open angle glaucoma with cataracts who has never been performed any eye surgery prior to the evaluation and whose IOP is insufficiently managed by medications and with the intention of reducing the number of medications. The exclusion criteria included the patients with closed angle and insufficient visualization of trabeculum with gonioscope. Informed consent was obtained from all the subjects after a thoroughly explanation regarding the procedures, benefits, risks and complications.

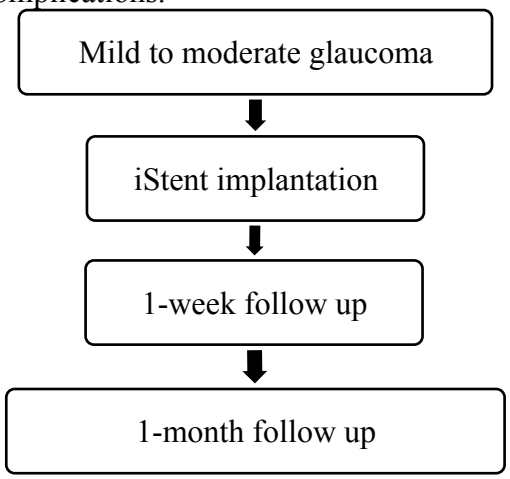

Figure 1. Flowchart of the study

Devices

The device used in this study is iStent Inject® manufactured by *Glaukos*. This device has been approved by United States food and drug administration (U.S. FDA) on 2018.

Procedures

All the surgeries were performed in the same center divided into two different locations which were JEC Menteng and

JEC Kedoya by the same surgeon (R.S.). All the surgeries took place in 2018 and performed after the approval of iStent by the FDA. The surgeries that were performed included phacoemulsification and intra ocular lens (IOL) insertion combined with iStent inject implantation. The cataract surgeries were performed using the routine procedures. The iStent is then placed at 10/8 o'clock for the right eye and 4/2 o'clock for the left eye using a small incision to insert the injector and trocar. The procedures were done using gonioscopy lens to make sure the adequacy of the implantation. The placement of iStent was then evaluated again post-operatively.

Follow up and Evaluations

All the subjects underwent routine eye examination preoperatively including the visual acuity, IOP, and corneal pachymetry. All the IOP lowering medications were also documented. All the IOP lowering medications were all stopped after the surgery, only antibiotics and anti-inflammatory medications were administered post-operatively. The subjects were then evaluated on postoperative day one, after 1 week and after 1 month. The assessment included visual acuity evaluation (BCVA), applanation tonometry measurement, and the necessity for further administration of IOP lowering medications. IOP was measured using applanation technique, and BCVA was measured using a standard Snellen chart and also LogMAR chart. The proper positioning of the iStents was also verified by gonioscopy examination. The safety outcomes were evaluated and documented at all clinical examinations throughout the follow up.

RESULTS

Demographics and Baseline Characteristics of the Patients

Six eyes from 5 patients are were included in this study. The mean ± standard deviation age was 63 ± 9.46 years and ranging from 54 to 76 years old. The majority of the patients were male (66.67%). The laterality is spread equally for both right and left eye (50% each) and one patient listed as Subject 2 and subject 5, underwent the surgeries for both eyes. All the patients are diagnosed with mild to moderate stage glaucoma which shares the same proportion (50% each). No patients with severe or advanced glaucoma was included in this study. All the patients have all diagnosed with cataracts in the different stages.

Table 1. Characteristics of the Patients

Variable	Value (N = %)	Mean ± SD (min – max)
Age (years)		63 ± 9.46 (54-76)
Gender		
Male (%)	4 (66.67%)	
Female (%)	2 (33.33%)	
Laterality		
Right Eye (%)	3 (50%)	
Left Eye (%)	3 (50%)	
Diagnosis of Glaucoma		
Mild (%)	3 (50%)	
Moderate (%)	3 (50%)	
Degree of Cataract		
Grade I - II (%)	4 (66.7%)	
Grade III - IV (%)	2 (33.3%)	
Baseline Visual Acuity with Best Correction (BCVA) Snellen chart		0.53 ± 0.41
Baseline Visual Acuity with LogMAR chart		0.75 ± 0.49
IOP (mmHg)		21.33 ± 6.15 (11 – 27) mmHg
Corneal Pachymetry (mm)[a]		569.16 ± 48.35 (491 – 618) µm

Intra Ocular Pressure

The Mean IOP of the patients was reduced by 3.33 mmHg from 21.33 ± 6.15 mmHg to 18 ± 6.0 mmHg at 1 week after the surgery was performed. After 1 – month of follow up the mean IOP was reduced by 3.22 mmHg from the baseline and was measured at 18.11 ± 5.57 mmHg.

Table 2. Efficacy outcomes

Time Point	IOP[a]	Visual Acuity (Snellen)[a]	Visual Acuity (logMAR)[a]	Number(s) of mean IOP lowering Medication(s)
Baseline	21.33 ± 6.15 (11 – 27) mmHg	0.53±0.41	0.75±0.49	3.0
1-Week After Surgery	18 ± 6.0 (13 – 26) mmHg	0.85±0.17	0.08±0.09	1.5
1-Month After Surgery	18.11 ± 5.57 (10 – 26) mmHg	0.91±0.16	0.05±0.08	0.66

[a]presented as mean ± standard deviation (min – max)

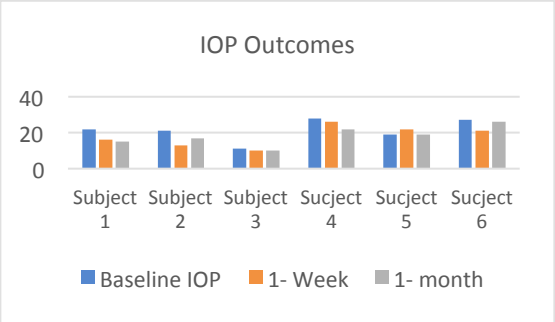

Figure 2. The IOP outcomes of the patients after surgery

Visual Acuity

There was a distinguishable improvement in visual acuity of the patients following the surgery. The mean logMAR best corrected visual acuity was decreased from 0.75 ± 0.49 to 0.08 ± 0.09 at 1 month follow up. Figure 1 shows the change of visual acuity from each patients following the surgery. After 1 month of follow up, 5 eyes out of 6 experienced the improvement of visual acuity. One subject (number 5) experienced a decrease of visual acuity this is arguably due to the dry eye and irregular astigmatism which the patient has and it has been previously examined for macular thickness using optical coherence tomography (OCT). One subject (number 6) had best corrected visual acuity (BCVA) at 1.0 prior to the surgery but then improved to 1.0 for uncorrected visual acuity (UCVA).

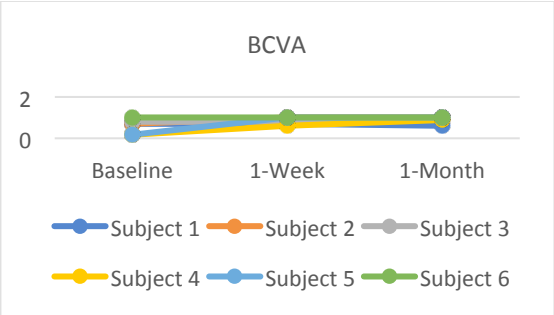

Figure 3. Visual Acuities from the Subjects using Snellen Chart

Medications

In eyes implanted with iStent device the number of medications is reduced after 1 month of follow up. Table 4 shows each patient's reduction of the number of medications needed to maintain the preferred ocular pressure. One subject (number 5) was also taking one oral IOP lowering glaucoma medication in addition to two topical eye drops before istent implantation. After 1 month of follow up, this subject no longer requires any IOP lowering medication.

Although three subjects (number 4,5, and 6) have considerably high IOP (>18 mmHg), the reductions from the baseline were achieved with less or no medications required. For these subjects, we then continued our follow ups to 6-month after istent implantation and the IOP of all three patients were reduced to the normal limit (<18 mmHg).

Table 3. The number of medication compared to the IOP

	Baseline	1-Week	1-Month
Subject 1	3	2	0
Subject 2	2	2	0
Subject 3	3	2	1
Subject 4	3	2	2
Subject 5	3	2	0
Subject 6	3	1	1

Safety

There are minimal complications of the procedure such as minimal hyphaema and subconjunctival hemorrhage. These complications lasted less than 24 hours after the surgery. The complications occurred on only one subject (number 5) which were were minimal hyphaema and subconjunctival hemorrhage. There was no other adverse event related to the procedure or the medications.

DISCUSSION

There are several available devices that are used in MIGS. Among all of these devices, trabecular bypass stents (iStent) provide the least invasive technique and less complications compared to the others due to the location of the devices' placement. Istent allows aqueous humor to directly drain from the anterior chamber into the Schlemm's canal by bypassing the trabecular meshwork thus enhance the natural outflow. There are two generations of iStent, the first one was approved in 2012 and the second one was approved in 2018 by the FDA and serves as the smallest device ever planted in the human body. The second generation of iStents benefit from the first one due to the fact that it requires a shorter and relatively easier surgical procedure for implantation. Therefore, the second generation of iStent, provides a smaller and faster learning curve for the surgeons with the same outcomes compared to the first one.[1,7]

Of all the currently available therapies for glaucoma, traditional surgeries remain superior in terms of the efficacy for achieving lower IOP and preventing progressive vision loss [9][10]. However, traditional surgeries are still highly associated with unwanted complications that may occur early or delayed. More importantly, the procedure doesn't always produce successful outcomes due to the occurrence of post – operative scarring.[11]

In this study, the procedure of iStent implantation was combined with phacoemulsification for cataracts. There are several available comparison studies regarding IOP after iStent implantation with or without cataract extraction. It has been known that the improvement of visual acuity, is mainly due to the successful process of cataract extraction. On the other hand, in terms of lowering the IOP, even without the cataract extraction, some studies reported bigger reduction of IOP compared to the combined procedure. After a 12 and 24 - month follow up, the implantation of iStent without cataract extraction can lower the mean IOP up to 7.45 ± 0.49 and 8.18 ± 1.18 respectively ($p < 0.0001$). This reduction is bigger than the study which combined iStent implantation and cataract extraction (3.89 ± 0.73 mmHg) ($p< 0.001$). For cataract surgery alone, it has been reported that the phacoemulsification procedure can reduce the IOP up to 1.9 ± 3.9 mmHg after 12-month follow up (13). Other study reported A 4% IOP reduction (IOPR%) from baseline was achieved following phacoemulsification as a solo procedure compared to 9% following an iStent implant combined with phacoemulsification, and 27% following 2 iStents implants combined with phacoemulsification. IStent with phacoemulsification resulted in significant reduction in the post-operative IOP (IOPR%) (SMD = -0.46, 95% CI: [-0.87, -0.06]) compared with phacoemulsification as the solo procedure. This meta-analysis included several studies with the average baseline IOP of 23.33 ± 1.33 reduced to 16.1 ± 4.4; 23.2 ± 0.9 to 13.7 ± 2.5; 23.2 ± 2.4 to 13.6 ± 2.1. All the studies included in the meta-analysis shows a reduction between the average baseline IOP with the

outcomes IOP after the procedures. A weighted mean reduction in the number of glaucoma medications per patient was 1.01 following phacoemulsification alone compared to 1.33 after one iStent implant with phacoemulsification, and 1.1 after 2 iStent implants with phacoemulsification. Compared to cataract extraction alone, iStent with cataract extraction showed a significant decrease in the number of glaucoma medications (SMD = -0.65, 95% CI: [-1.18, -0.12]). This also concludes that reduction of the mean IOP in patients with POAG was mostly associated with iStent implantation rather than the phacoemulsification (ranging from 9% for iStent as solo procedure, and 26% to 31% for combination between iStent and phacoemulsification). [12,13,14] These studies mostly utilized the first generation of istent. To the best of our knowledge and literature researches, there weren't many studies which include the second generation of istents (istent inject) as used in this study.

The best IOP reduction was achieved by subject 1 which is 7 mmHg (from 22 to 15 mmHg) after 1-month follow up, this subject can also stop the medications that he had prior to the surgery. The same expected outcome was also achieved by subject number 3. After 1 month follow up, the IOP has been decreased from 22 to 16.7 mmHg and the subject can also stop his medication. But it still requires further follow up as the IOP of this subject was increased at 1-month follow up compared to 1-week follow up. In this study, after 1-month follow up, one eye (Subject no.4) maintain a high ocular pressure which was 22 mmHg. This is presumably due to the fact that the subject also has a thick cornea which was measured by corneal pachymetry (618 micrometers). The central corneal thickness (CCT) has been reported to have a correlation with IOP. A Thicker cornea (> 550 nm) is associated with high IOP although the correlation is not significant. Other Study also mentioned that there is a 0.38 mmHg IOP difference per 0.1 mm cornea thickness that can contribute to the measurement assuming the normal thickness of cornea is 520 µm [15][16]. For this subject, we then decided to observe for longer period of time. Although the IOP still remains unchanged (22 mmHg), this was achieved by reducing the number of medications needed for the patient from three to two medications only. Aligned with subject number 4, reduction of the number of medications was achieved from all the subjects. Although the IOP of three subjects remained high (>18 mmHg) all of those three subjects can stop or reduce the topical or systemic IOP lowering medications with careful follow up and routine eye examination. All the IOP lowering medications were stopped after 1-week following istent implantation to assess the efficacy of istent. All the subjects were carefully and routinely examined and when the IOP rises, the ophthalmologist will then decide to add more IOP lowering medication. After 6 months of follow up, all these three subjects' IOP were able to be reduced to lower than 18 mmHg. The subjects now require less medications to maintain the IOP to its safe point. Other studies also reported the correlation of iStent implantation with reduction of IOP lowering medications. A study reported that the mean number of IOP lowering medications after iStent implantation after 12-month follow up was 1.0 (p = 0.005).[1] Our approach regarding IOP management of the patients was to assess the IOP regularly and determine the best medication to control the IOP. If the IOP was raised, then the patient may need to take more medications to control the IOP. Reducing the number of medications was only done when the IOP was controlled as we try to determine the efficacy of istents implantation.

The efficacy of istents may depend heavily on the implantation procedures. The IOP of post-operative implantation may raise due to the mispositioning of

istents. The istents must be placed correctly at the trabecular meshwork in order to work perfectly. It is difficult to determine which are the best positions to insert the devices. The devices must be placed at the healthiest trabecular meshwork possible in order to enhance the outflow. Impairment of trabecular meshwork occurs in glaucoma patients which causes the resistance resulting in the impaired outflow. Therefore, we may conclude that the flow of every trabecular meshwork in 360-degree circle may not be uniform.[18] According to this condition, placing the istents at the healthiest trabecular meshwork possible is relatively difficult as we have to determine the position first. This also concludes that not every istents device should be located at the same place.

Additional to the efficacy, short-term safety point of view has also been assessed. The most common post-operative complications reported in the other studies were related to the iStents malpositioning. Aligned with this study, one Subject (number 3), experienced minor complications from the procedure which was subconjunctival hemorrhage. The other complication happened intra – operatively such as hyphaema which lasted less than 24 hours after the surgery. All the iStents position were re-assessed on the follow up and no patient required iStent reposition or replacement. Malpositioning of the iStent can result in the obstruction of humor aqueous flow and may require repositioning, replacement or laser iridoplasty for management. The incidence of these complications has been reported at less than 5% by several previous studies. (7) Some of these subjects are continuously being followed up, not only for the visual acuity and IOP but also for the safety and complications of iStents. The longest period of time for these subjects was 6 months of follow up and no complication was found after iStent implantation.

Concordance to the safety, in terms of the economy, a study by Iordanous and colleagues reported a comparison regarding the cost effectiveness of iStent and the IOP lowering medications. The cost of 2 iStent implants for both eyes is considerably expensive but compared to 6 years of medication iStent costs only $20.77 more than the cost of monotherapy but cheaper by $1272.55 compared to dual therapy of IOP lowering medications. The study indicated that the cost of iStent implants may be expensive, but for the long-term cost effectiveness, it could contribute to lower the burden of Glaucoma in Health economics. [17] Further study regarding the cost benefit of iStent is required in order to decide which modalities will serve to be more effective and more cost-effective for glaucoma patients.

The limitations of this study are the sample size that needs to be more expanded in order to statistically significate the results. Longer period of follow ups is also necessary regarding the fluctuation of the efficacy outcomes and to adequately observe the safety of the procedure.

CONCLUSION

To conclude, MIGS was not established to replace trabeculectomy but more to present as the other option for the patients with mild to moderate glaucoma. IStent serves an alternative option for patients with glaucoma and has established itself as a promising modality in-between the medications and traditional surgeries. This pilot study showed that iStent is considered to be a safe, minimally invasive therapy and also have less complications compared to the other glaucoma surgeries. Further study with longer period of follow up and more subjects is needed to investigate more about the efficacy and safety of iStent as part of MIGS for glaucoma treatments.

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