



Effect of iStent Trabecular Micro-Bypass device on outflow system morphology

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Abstract

Purpose: Rigorous clinical testing has established that Schlemm's canal cross-sectional area (SC-CSA) is reduced in glaucomatous eyes. However, to date, it is unclear whether trabecular bypass procedures impact the morphology of the proximal aqueous outflow tract, or if the introduction of a local region of low outflow resistance

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adversely affects SC-CSA elsewhere, specifically presenting as SC diminution. This study quantifies changes in the morphology of the distal outflow pathway after iStent Trabecular Micro-Bypass stent (Glaukos Corp, Laguna Hills, CA, USA) implantation in living eyes by anterior segment optical coherence tomography (OCT).

Design: This was a prospective observational study.

Subjects: This study included six patients (eight eyes) with primary-open angle glaucoma.

Methods: Patients underwent iStent placement in the nasal anterior chamber angle quadrant. OCT imaging was obtained of both nasal and temporal eye quadrants before and after surgery. For each SC parameter, an average of ten consecutive, evenly spaced measurements were manually obtained over a 1 mm segment of SC on FIJI ImageJ. Linear mixed effects modeling quantified the effect of the iStent on these parameters.

Main outcome measures: Main outcome measures were changes in SC-CSA, inner-to-outer wall distance (IOD), and trabecular meshwork (TM) thickness following iStent placement.

Results: Following iStent placement, total SC-CSA increased an average of 1,039.12 μm^2 ($P = 0.05$). Individually, there were no significant changes in SC-CSA in the nasal or temporal quadrants. Total SC-IOD and nasal SC-IOD increased an average of 2.35 μm ($P = 0.01$) and 2.96 μm ($P = 0.04$), respectively. There were no significant changes in temporal quadrant SC-IOD. There were no significant changes in TM thickness in either quadrant.

Conclusions: Implantation of the iStent Trabecular Micro-Bypass stent significantly increases SC-IOD in the nasal quadrant at the location of implant, with no evidence of SC diminution in the temporal quadrant. It remains unclear how these observations relate to the surgical efficacy of trabecular bypass procedures.

Keywords: glaucoma, iStent, outflow, Schlemm's canal, trabecular meshwork

1. Introduction

Glaucoma is the second leading cause of irreversible blindness in the world.¹ While elevated intraocular pressure (IOP) is a known risk factor for the development and progression of this disease,²⁻⁷ changes in eye morphology have also been observed. IOP is maintained through a tightly regulated equilibrium of aqueous humor formation and elimination.⁸ Aqueous humor is eliminated from the anterior chamber of the eye through an outflow system consisting of the trabecular meshwork (TM), Schlemm's canal (SC), and aqueous vasculature (veins and collector channels), and lastly, scleral veins connecting to the venous circulation.⁹ In the presence of glaucoma, critical outflow structures appear to narrow,¹⁰ which may alter the eye's ability for aqueous humor elimination.

In normal eyes, the location of greatest resistance to outflow is the juxtacanalicular tissue and inner wall of SC, the interface between SC and the TM.^{11,12} In recent years, surgically-inserted micro-bypass devices such as the iStent (Glaukos Corp, Laguna Hills, CA, USA) have been shown to effectively lower IOP.¹³⁻¹⁸ This L-shaped device, typically inserted in the nasal quadrant, transverses the juxtacanalicular tissue and TM and is believed to create a low-resistance channel between the anterior chamber and SC. This low-resistance channel increases aqueous humor outflow, and decreases IOP as a result. While it is likely that insertion of the iStent will alter the morphology of SC at the site of implantation, introduction of a localized low-resistance outflow pathway may alter the morphology of the SC elsewhere in the eye as the pattern of outflow is altered.

Previously, we have been able to image the primary aqueous humor outflow system in living human eyes, and observe decreased SC cross-sectional area (SC-CSA) in response to acutely elevated IOP.¹⁹⁻²¹ Furthermore, the SC-CSA is known to decrease in patients with primary open-angle glaucoma.^{10,22,23} It is not known if iStent insertion relieves SC-CSA diminution at the site or implant, or, exacerbates it elsewhere. The purpose of this study was to investigate the effects of iStent insertion on outflow system morphology using spectral domain optical coherence tomography (SD-OCT Bioptigen, Research Triangle Park, NC, USA), both at the site of implantation within the nasal quadrant, and in the opposing temporal quadrant.

2. Methods

All subjects were recruited in accordance with the tenets of the Declaration of Helsinki and the United States Health Insurance Portability and Accountability Act. This study was approved by the institutional review board of the University of Colorado (CO, USA), and all subjects provided written informed consent prior to participation.

2.1 Subjects

Subjects were enrolled at the University of Colorado Eye Center. Patients undergoing placement of iStent Trabecular Micro-Bypass device for primary open-angle glaucoma were recruited for this study. Subjects were imaged by SD-OCT before and after iStent. Images were obtained from both the nasal quadrant adjacent to iStent insertion, and also the temporal quadrant 180° from the insertion site. With the exception of one patient, all postoperative images were obtained within the one-month postoperative period.

2.2. iStent placement

All iStent insertions in this series were performed by glaucoma surgeons on the faculty of The Rocky Mountain Lions Eye Institute, University of Colorado Health

Sciences Center. Phacoemulsification with intraocular lens implantation was performed through a temporal corneal incision, with subsequent implantation of the iStent device in the nasal quadrant. The device was introduced through the temporal corneal incision and inserted through the TM and into SC via *ab interno* gonioscopy guidance. iStent was placed in the nasal quadrant in each eye; at the 3-4 o'clock position in right eyes and at 8-9 o'clock in left eyes.

2.3. Measurement of SC parameters

To ensure image consistency, all SD-OCT images were obtained in an office setting within the University of Colorado Eye Center and using the same scanner. Nasal and temporal quadrants were both imaged before and after iStent placement. Images were subsequently processed using 3D neighborhood averaging and contrast limited adaptive histogram equalization to improve discriminative resolution of SC and other outflow structures.²⁴ To account for variability of SC and outflow structure morphology, each measured parameter was obtained by taking an average of 10 consecutive, evenly spaced, measurements over a 1 mm segment of each 4 mm scan. Parameters were measured using FIJI (ImageJ, <http://imagej.nih.gov/ij>) image-processing software.

To measure TM thickness, we employed a previously described technique of fitting three perpendicular measurements from the anterior, middle, and posterior aspects of SC to the anterior chamber.²⁵ These three measurements were averaged, producing one measurement of TM thickness. SC-CSA was measured via manual segmentation,²⁰ and SC length was measured via a single linear measurement of the SC anterior-posterior axis (Fig. 1). Lastly, SC inner-to-outer wall distance (SC-IOD)

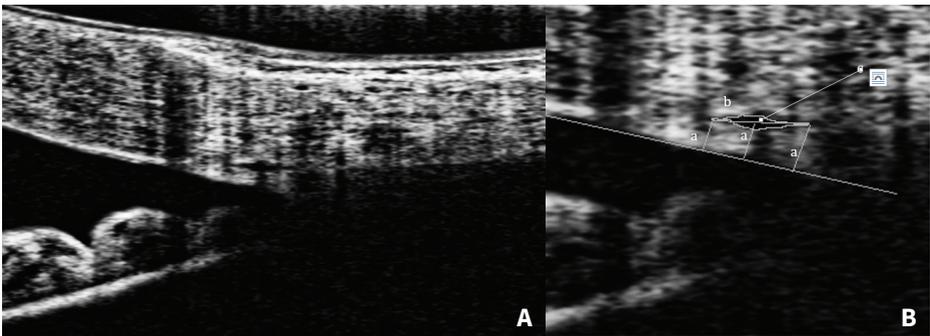


Fig. 1. (A) SD-OCT image of a living human eye. (B) Measurement of SC parameters: (a) three perpendicular measurements of TM thickness from anterior, middle, and posterior of SC to the anterior chamber; (b) SC-CSA; and (c) SC length measured via linear measurement of SC anterior-posterior axis.

was calculated by dividing SC-CSA by SC length. Complete blinding of the measuring process was not possible, as the iStent device was visible in postoperative scans of the nasal quadrant.

2.4. Statistical analysis

Statistical analysis was performed using the R Language and Environment for Statistical Computing software (version 3.2.2). Preoperative and postoperative SC and TM parameters were compared using a linear mixed-effects model. Separate comparisons were made for both the nasal and temporal quadrants. To compare an average outflow response across the limbus, a total value of each preoperative and postoperative parameter was also calculated. Continuous variables were compared using paired t-test. Statistical significance was defined as $P < 0.05$.

3. Results

Eight eyes from six patients with primary open-angle glaucoma were included in the analysis, four female and two male. Mean patient age was 75.5 years (range: 65 to 90 years). Patients underwent iStent placement between October 2012 and August 2014. Preoperative imaging was obtained a median of 7 days prior to surgery (range: 0 days to 31 days), and postoperative imaging was obtained a median of 8 days after surgery (range: 1 to 50 days).

3.1. IOP and medications

Median IOP and number of ocular anti-hypertensive medications did not vary considerably throughout the study period (Table 1). One patient (1 eye) failed to return for IOP measurements at months 3, 6, and 12.

3.2. TM thickness

There was no consistent change in TM thickness following iStent insertion. No significant change in TM thickness was observed in either the nasal or temporal quadrant, and likewise there was no significant change in overall total TM thickness (Table 2).

Table 1. Patient response to iStent insertion over one year

	Pre-iStent n = 6 (8 eyes)	1 Week n = 6 (8 eyes)	3 Months n = 5 (7 eyes)	6 Months n = 5 (7 eyes)	1 Year n = 5 (7 eyes)
IOP, median (range)	12 (11-15)	13.5 (11-22)	11 (8-14)	13 (8-22)	13 (9-14)
Medications, median (range)	2 (1-3)	--	1 (0-3)	1 (0-3)	1 (0-3)

IOP: intraocular pressure

Table 2. Changes in SC and TM morphology following iStent placement

	Pre-iStent	Post-iStent	Mean difference
SC-CSA, mean (SD), μ^2			
Total	3,321.08 (1,464.66)	4,570.92 (1,212.91)	1,039.12 [#]
Nasal	3,398.39 (1,136.91)	4,743.45 (1,323.24)	1,345.06
Temporal	3,242.76 (1,847.33)	4,312.14 (1,160.34)	580.22
SC length, mean (SD), μ			
Total	226.68 (51.80)	264.30 (54.17)	29.20
Nasal	248.79 (27.04)	285.03 (53.00)	36.24
Temporal	204.57 (63.23)	233.20 (44.41)	18.63
TM thickness, mean (SD), μ			
Total	187.51 (69.46)	222.29 (119.20)	24.41
Nasal	180.83 (52.73)	247.29 (142.66)	66.46
Temporal	194.20 (87.90)	184.78 (74.72)	-38.68
SC-IOD, mean (SD), μ			
Total	14.37 (3.63)	17.18 (2.51)	2.35 [*]
Nasal	13.47 (3.23)	16.43 (2.67)	2.96 [†]
Temporal	15.26 (4.08)	18.32 (2.05)	1.45

CSA: cross-sectional area; IOD: inner-to-outer wall distance; SC: Schlemm's canal; SD: standard deviation; TM: trabecular meshwork

* indicates $P = 0.01$; † indicates $P = 0.04$; # indicates $P = 0.05$

3.3. SC parameters

Overall total SC-CSA increased following iStent insertion ($P = 0.05$). When examining each quadrant individually, an increasing, but not statistically significant, trend in SC-CSA was observed in both the nasal and temporal quadrants ($P = 0.10$ and $P = 0.45$). There were no significant changes in SC length overall ($P = 0.18$). Furthermore, no significant changes were observed in either the nasal or temporal quadrant individually ($P = 0.22$ and $P = 0.64$, respectively) (Table 2).

An overall trend of increasing SC-IOD was observed after iStent insertion. Total SC-IOD and nasal quadrant SC-IOD increased significantly (2.35 micrometers; $P = 0.01$ and 2.96 micrometers; $P = 0.04$). There were no significant changes in temporal quadrant SC-IOD following iStent insertion (1.45 micrometers; $P = 0.24$) (Table 2).

4. Discussion

We found that insertion of the iStent micro-bypass device significantly increased the width of SC, as measured by the SC-IOD parameter, in the nasal quadrant adjacent to the point of insertion. Additionally, a non-significant trend of increasing SC-CSA was observed within the nasal quadrant. There were no significant changes to SC parameters in the temporal quadrant observed. This may suggest that introduction of a local region of reduced outflow resistance within the nasal quadrant does not alter outflow structures elsewhere in SC.

Bahler *et al.* have shown that insertion of a single iStent device increases ocular outflow facility of normal enucleated eyes by 84%.²⁶ Similarly, Fernandez-Barrientos *et al.* demonstrated an increase in outflow facility by 157% in living human eyes following insertion of 2 iStent devices.²⁷ Yuan and colleagues have mathematically modeled outflow facility following iStent insertion, and predicted that TM bypass may result in increased SC pressure, reflecting that of the IOP. This increased pressure may then cause dilation of SC and higher flow rates within the SC and downstream collector channels, resulting in the observed increased outflow facility.²⁸ The present study suggests that bypass of the TM may in fact dilate the SC locally, perhaps due to increased pressures from aqueous humor inflow. As previously demonstrated, the SC is a dynamic structure, collapsing in response to glaucoma and acutely elevated IOP.^{10,19,22,23} As these conditions promote collapse of SC structures, increasing inflow and pressure within the SC may promote local dilatory effects.

The dilatory effect of iStent implantation has been noted in a published case study. Gillmann *et al.* found a SC diameter of 390 micrometers after implantation of two devices in a 74-year-old female patient.²⁹ The authors compared their finding to the observed average SC diameter of 122 μm , suggesting a device effect and not an idiopathic finding. While the effect of implantation appears to be large, note that the SC diameter was compared to a normative average SC diameter of 122 micrometers, and not a pre- vs post-surgery comparison. Also, the authors used two devices, as compared to the single device implantation employed in the present study. Nevertheless, the observation of larger-than-expected SC diameter supports the hypothesis that iStent implantation has a favorable impact on outflow structure morphology.

We consider an alteration of outflow morphology to be favorable if it is associated with increased aqueous humor outflow facility. In a recent study of distal outflow structure filling before and after iStent implantation, Huang *et al.* observed subjective improvements in the filling of outflow structures by angiographic methods.³⁰ Using indocyanine green (ICG) to establish baseline flow patterns, and fluorescein to describe post-implant filling patterns, the authors found improved filling patterns regions characterized by poor filling at baseline, as well as those characterized by faster baseline filling. This suggested that iStent

implantation had a favorable effect on outflow whether implanted in regions of low or high baseline.³⁰ Taking these findings and those of the present study together, there appears to be structure/function agreement between alterations in outflow morphology within SC, and outflow as represented by angiography immediately after device implantation. However, these findings are unable to predict if this synergistic structure/function relationship persists long-term.

An interesting finding from this study was the trend of increasing temporal SC parameters following iStent insertion. As previously mentioned, we hypothesized that iStent may result in SC dilation in regions adjacent to the nasal insertion site. As aqueous humor outflow facility increases in this region, we predicted a collapse in outflow morphology in more distant regions. This prediction was based on the assumption that aqueous humor would drain predominantly from the dilated regions closest to the iStent device and with the highest outflow facility. As a result, we predicted that distant SC regions may experience lower pressures and ultimately collapse. This, however, was not observed. It is possible that SC patency is either maintained or increased circumferentially across the entirety of the ocular limbus. Previous work has described the presence of myofibroblast-like cells and direct insertions of the ciliary muscle within the TM.^{31,32} Both relaxation of these myofibroblast-like cells and contraction of the ciliary muscle can reduce outflow resistance, and it may be possible that these structures play a role in maintaining the patency of the distal outflow structures relative to the point of iStent insertion.

This study had several limitations. First, this study included a small patient sample from a single institution, which may affect the generalizability of its findings. Additionally, our protocol did not dictate a specific time window for which patients were required to obtain postoperative imaging. In order to maximize recruitment, all available post-implant visits were used. Despite these limitations, a statistically significant difference in SC-IOD was detected in the nasal quadrant, suggesting that iStent opens the SC adjacent to its point of insertion. Another potential limitation of this study is the ability of current SD-OCT to discriminate the smallest structures of SC with adequate resolution. Attempts to improve this discriminative ability and resolution of commercially available SD-OCT were made through the technique of averaging, as has been demonstrated in previous studies.^{19,24} Despite potential error in estimation of true SC parameters such as SC-CSA, SC length, and ultimately, the calculation of SC-IOD, the limited resolution of commercial SD-OCT capabilities were able to detect a significant increase in SC-IOD in the nasal quadrant following iStent insertion. This study serves as a starting point for understanding the important morphological effects surgically implanted devices such as iStent have on the living human eye. Lastly, our study was limited by the natural variability of SC across its circumferential course around the eye. Because the SC is not uniform circumferentially around the eye, changes in SC parameters, both nasally and temporally, may vary

individually with the location of iStent placement. Furthermore, measurement of SC parameters at one location may considerably differ from other measurements taken nearby. To minimize this potential error, we employed an average of consecutive, equally spaced, measurements across a 1 mm sample in order to obtain each SC parameter, an important technique we have previously demonstrated.^{19,33} Thus, each measurement was not a random sample of each parameter, but an average of these parameters across a 1 mm section. Ideally, in order to fully ascertain the mean response of SC parameters following iStent, a 360° scan of the entire limbus and SC would need to be developed.

5. Conclusion

iStent implantation significantly increases SC-IOD in the nasal quadrant, while leaving structures in the temporal quadrant unaffected. These results could influence the surgical decision of implantation in more than one quadrant, as previously suggested. Indeed, multiple devices may be able to increase dramatically the IOD in other parts of the TM circumference and thus facilitate aqueous humor outflow. Looking at the collector channel location and adjusting implantation to the individual SC's and distal outflow structure morphology might be a valuable approach for future studies and clinical outcomes.

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