Glaucoma

A Multi-Lumen Glaucoma Stent With Titratable Pressure-Lowering Effect: A Proof of Concept Study

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Purpose: To explore the feasibility of a glaucoma stent with a titratable pressure-lowering effect.

Methods: This was an in vitro study. We created a resin stent with a micro-precision three-dimensional printer. It represented a cylinder with one primary and two secondary lumina. The inner opening of each secondary lumen was sealed with a membrane. We used a surgical eye model to simulate implantation of the stent and a laser procedure analogous to argon laser trabeculoplasty (ALT) to ablate each membrane. To study the fluid dynamics, we used a high-precision syringe pump and measured the steady-state pressure for one, two, and three lumina in parallel at flow rates of 2.5, 5.0, and 10.0 µL/min.

Results: The stent could be implanted into the eye model and visualized in the anterior chamber angle. Coloring the membrane facilitated laser membranotomy, and a 0.1-second laser pulse with 250-mW power was enough to ablate one membrane. The steady-state pressure for one lumen increased linearly with increasing flow rate, in accordance with the Hagen–Poiseuille equation. Two and three lumina in parallel decreased the pressure by factors of 2.1 and 3.2, respectively, in accordance with the electronic–hydraulic analogy and Ohm's law applied to parallel resistors.

Conclusions: The study presents proof of concept for a glaucoma stent with multiple lumina, which can be separately opened with an ALT-like procedure to induce a predictable, stepwise increase in pressure-lowering effect.

Translational Relevance: The glaucoma stent in this experimental study can be reproduced in a biocompatible material and further studied in vivo.

Introduction

Drainage of aqueous fluid is the cornerstone of glaucoma surgery. Trabeculectomy has been the gold standard for decades, but there is a trend toward replacing this invasive surgical procedure with stents, so-called micro-invasive glaucoma surgery (MIGS), particularly to treat patients in the gap between early and advanced glaucoma.

When draining fluid from the anterior chamber to a second reservoir, the anterior chamber pressure is regulated by the combined outflow resistance through the stent and out of the second reservoir. A healthy conjunctiva provides minimal outflow resistance, and for subconjunctival draining devices the stent configuration itself must balance the full pressure-lowering potential with the risk of ocular hypotony.[1] Currently, two MIGS devices target the subconjunctival space: the XEN Gel Stent (Allergan, Dublin, Ireland) and the PreserFlo MicroShunt (Santen, Osaka, Japan). Because both are single-lumen tubes, the Hagen–Poiseuille equation is used to determine dimensions that ensure a steady-state pressure above hypotony levels at physiological flow rate.[2] Still, their fixed designs only provide one shot at the target intraocular pressure (IOP), and, although glaucoma patients generally achieve a reduction in IOP and medication burden through MIGS surgery, only some can discontinue topical treatment altogether.[3,4] A titratable MIGS
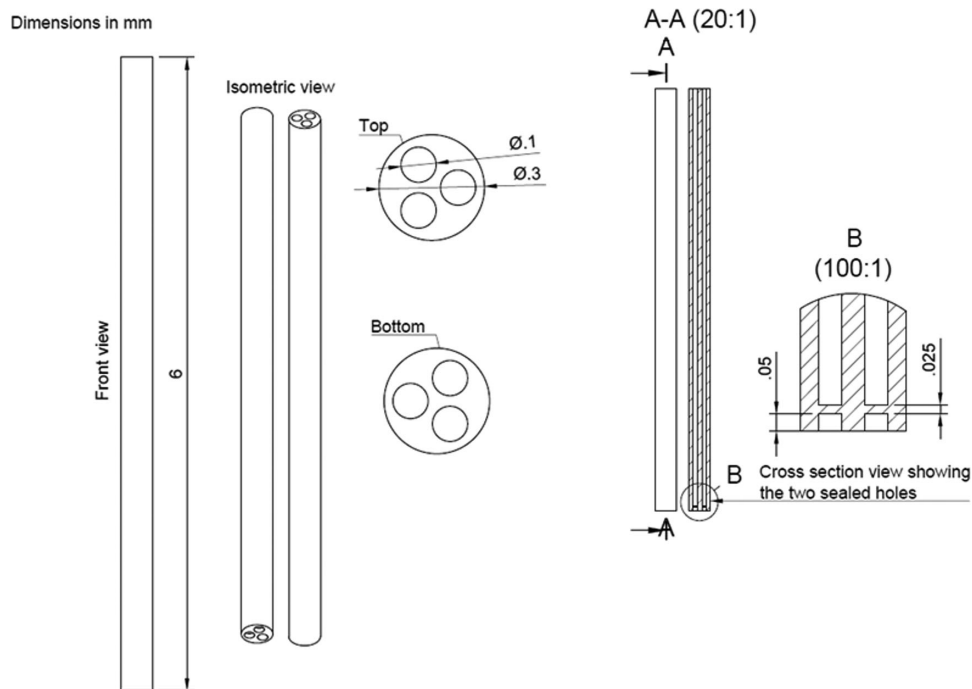
Figure 1. Technical drawing of the glaucoma stent. The stent represents a cylinder with a length of 6 mm and an outer diameter of 300 μm. The cylinder has one primary and two secondary lumina, each with a diameter of 100 μm. The inner opening of each secondary lumen is sealed with a 25-μm thin membrane.

device would be appealing in this regard; adjusting the pressure-lowering effect according to need could optimize the balance between benefit and risk and increase the likelihood of safely achieving long-term IOP control through MIGS alone.

The purpose of this in vitro study was to explore the feasibility of a MIGS stent with multiple lumina, which could be separately opened by laser to induce a stepwise decrease in net resistance.

Methods

Stent Design

We created the MIGS stent with an industrial micro-precision three-dimensional (3D) printer (Boston Micro Fabrication, Maynard, MA). The printer utilized projection micro stereolithography technology and photosensitive resin, which allowed for ultra-high 2-μm printing resolution and ≥10-μm dimensional tolerance. The resin had a transparent yellow color. The MIGS stent represented a cylinder with a length of 6 mm and an outer diameter of 300 μm. The cylinder had one primary and two secondary lumina arranged in parallel. Each lumen had a diameter of 100 μm. The primary lumen was open, whereas the inner opening

(i.e., to be placed in the anterior chamber of the eye) of each secondary lumen was sealed with a 25-μm thin membrane (Fig. 1).

Eye Model

To simulate implantation of the MIGS stent into the eye, we used a XEN ophthalmic surgical training model (SimulEYE, Westlake Village, CA). This eye model is developed specifically for training with the XEN Gel Stent and reproduces the conjunctiva and anterior segment, including the anterior chamber angle, which can be visualized with a goniolens.

Laser Membranotomy

To ablate the membrane sealing the inner opening of each secondary lumen, we used a slit lamp–mounted multicolor laser system (MC-500 Vixi; NIDEK, Gamagori, Japan). The spot size was set to 50 μm. As the two resin membranes had a transparent yellow color, we colored them with a fineliner pen to improve absorption of laser energy. The procedure was analogous to argon laser trabeculoplasty (ALT), but, instead of aiming the laser at the junction between the pigmented and nonpigmented trabecular meshwork, we aimed at the membrane.
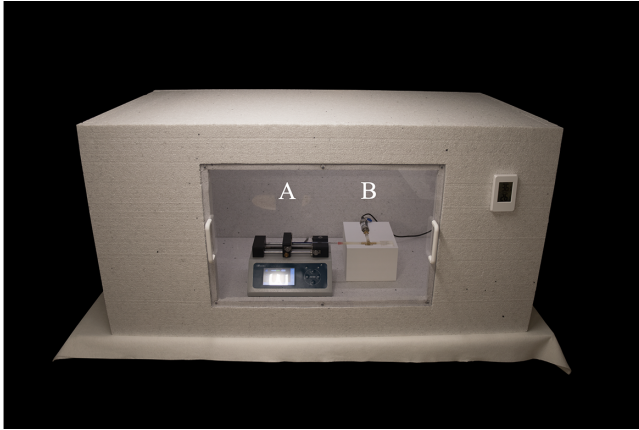
Figure 2. Setup for the fluid dynamics experiments. A high-precision syringe pump (A) houses a syringe filled with distilled water. The syringe is attached to a tube plugged with a rubber stopper. The stents are placed through the stopper, and the pressure is measured upstream with a dynamic pressure transducer (B). As the viscosity of water is temperature dependent, the experiments are performed in a polystyrene container heated to 37°C.

Fluid Dynamics

Originally, we wanted to use the 3D-printed MIGS stent to study the fluid dynamics of a triple-lumen system. However, as the dimensional tolerance of the 3D printing technology was $\geq 10\,\mu m$, we were unable to print the stent with entirely accurate inner dimensions. Keeping in mind that even small dimensional deviations will affect the resistance (according to the Hagen–Poiseuille equation, the resistance is inversely proportional to the fourth power of the radius), we instead acquired XEN Gel Stents as surrogates for the MIGS stent in the fluid dynamics experiments.

Apart from slight modifications, our setup for studying the fluid dynamics resembled previously described experiments (Fig. 2).[2,5] We used a high-precision ZA100 syringe pump (Baoding Chuang Rui Precision Pump Co., Ltd., Baoding, China) housing a syringe

filled with distilled water. We attached the syringe to a tube plugged with a rubber stopper. The stents were placed through the stopper and the pressure measured upstream with a GD4200 dynamic pressure transducer (ESI Technology Ltd., Wrexham, UK). As the viscosity of water is temperature dependent, we heated the equipment in a polystyrene container and made sure the water held a temperature of 37°C throughout the experiments. The equipment could be monitored through a transparent front door.

We first confirmed that the setup was resistance free without a rubber stopper attached; that is, the pressure was 0 mmHg at maximum flow rate of 10.0 µL/min. We then measured the pressure at steady state for one lumen (stent A, B, or C), two lumina in parallel (stent A + B, A + C, or B + C), and three lumina in parallel (stent A + B + C) at flow rates of 2.5 µL/min (physiologic flow rate), 5.0 µL/min, and 10.0 µL/min. We repeated the experiment three times for each flow rate.

Statistical Analyses

We determined the mean and standard deviation of the steady-state pressure for each flow rate. As the Hagen–Poiseuille equation states that the relationship between flow and pressure is linear, we used linear regression of the observed data to model the relationship between pressure and flow for a system with one, two, and three lumina in parallel.

Results

Stent Implantation Into the Eye Model

By visual inspection, the 3D-printed MIGS stent appeared satisfactory, with two of three lumina sealed with membranes, which were slightly depressed from the surface of the inner end (Fig. 3A).
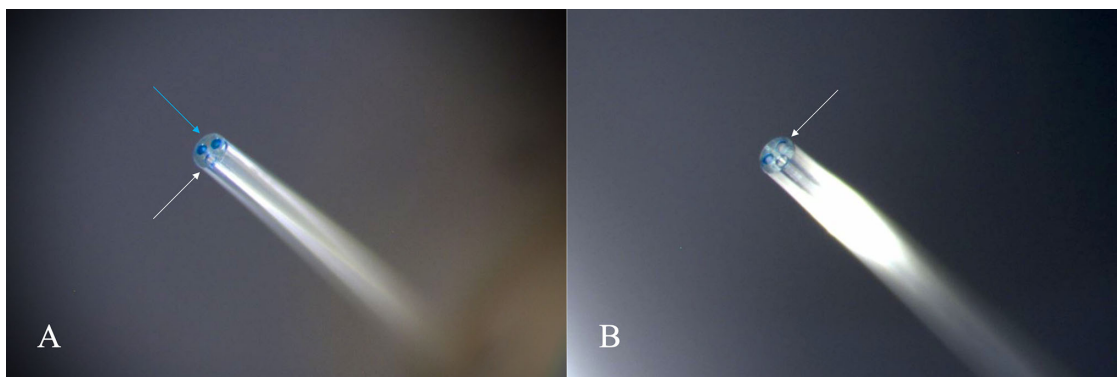

Figure 3. Slit lamp photography of the glaucoma stent. (A) The primary lumen is open (*white arrow*). The inner opening of each secondary lumen is sealed with a thin membrane, which is colored to improve absorption of laser energy (*blue arrow*). (B) A single laser pulse has ablated one membrane and opened one of the two secondary lumina (*white arrow*).
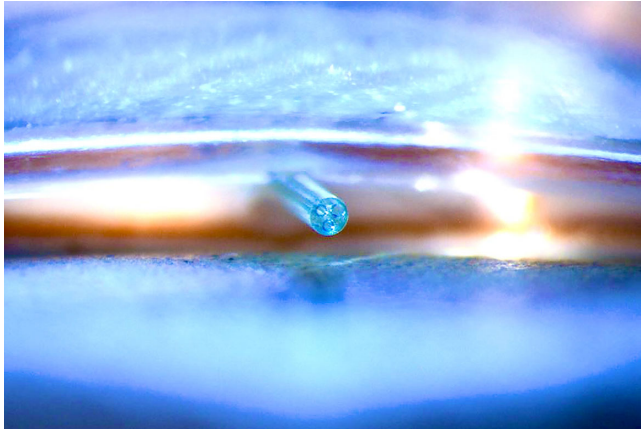
Figure 4. Slit lamp photography of the glaucoma stent placed in the anterior chamber angle of the surgical eye model.

The MIGS stent could be implanted into the eye model both ab externo and ab interno by means of a needle. We also tried to use the XEN Gel Stent injector, but because the MIGS stent had an outer diameter of 300 μm it was slightly too large for the injector (the XEN Gel Stent has an outer diameter of 150 μm). After implantation, the inner opening of the MIGS stent could be visualized in the artificial anterior chamber angle (Fig. 4).

Laser Membranotomy

We used 40× slit lamp magnification to focus the 50-μm-diameter laser spot onto the membrane. As could be expected, we were unsuccessful in our attempts to ablate the original resin membrane, which was almost transparent and absorbed laser energy poorly. However, coloring the membrane facilitated the procedure, and for subtractive colors (e.g., green laser and magenta membrane) a single 0.1-s laser pulse with 250-mW power was enough to ablate one membrane (Fig. 3B). Carefully coloring the membrane but not its surroundings also prevented the transparent stent walls from absorbing too much laser energy and being visibly damaged.

Fluid Dynamics

The steady-state pressure for one lumen increased linearly with increasing flow rate. The pressure increase was slightly steeper than in the study by Sheybani et al.,[2] with some measurement variation, particularly at a flow rate of 10.0 μL/min. Two lumina in parallel decreased the steady-state pressure at a given flow rate by a factor of 2.1, whereas three lumina in parallel decreased the steady-state pressure at a given flow rate by a factor of 3.2. Figure 5 shows the results of the fluid dynamics experiments.

Discussion

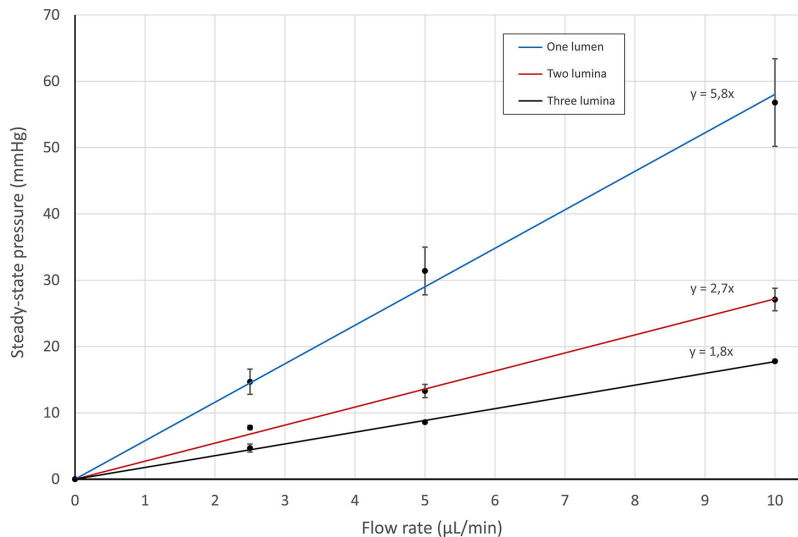It is a well-established practice in the medical treatment of glaucoma to adjust the medication

Figure 5. Fluid dynamics of a triple-lumen system. The figure shows steady-state pressure for one, two, and three identical lumina at flow rates of 2.5 μL/min (physiologic flow rate), 5.0 μL/min, and 10.0 μL/min. The *error bars* represent the standard deviation. The steady-state pressure for one lumen increases linearly with increasing flow rate, in accordance with the Hagen–Poiseuille equation. Two and three lumina in parallel decrease the pressure at a given flow rate by a factor of approximately two and three, in accordance with the electronic–hydraulic analogy and Ohm's law applied to parallel resistors.

according to need. The initial management is commonly monotherapy, and a second drug (preferably a fixed combination) is added if the target IOP is not reached.[6] Likewise, an individualized approach to glaucoma surgery is emphasized, and advances in the trabeculectomy procedure allow for some adjustment of the IOP in the early postoperative phase.[7,8] MIGS devices targeting the subconjunctival space have gained increasing popularity in the treatment of glaucoma but still lack a similar titrating ability. In this in vitro study, we used an advanced 3D printer to create a MIGS stent with one primary and two secondary lumina; a thin membrane sealed the inner opening of each secondary lumen. We implanted the stent into a model eye and showed that the secondary lumina could be opened individually with an ALT-like procedure. We also explored the fluid dynamics of a triple-lumen system and demonstrated that each secondary lumen contributed to a stepwise decrease in net resistance. The experimentally determined IOP could be theoretically predicted, as we will explain below. Accordingly, the study presents proof of concept for a multi-lumen glaucoma stent with modifiable pressure-lowering effect.

As we discussed in the introduction, the Hagen–Poiseuille equation serves to determine dimensions for a single-lumen stent that ensure adequate IOP at physiological flow rate. Clearly, the same degree of predictability is necessary for a multi-lumen MIGS stent. Our fluid dynamics experiments demonstrated that the introduction of a second lumen into the system approximately halved the pressure at a given flow rate, whereas a third lumen decreased the pressure to about one third. The explanation for these observations can be found in the electronic–hydraulic analogy; the three lumina behaved like parallel resistors in an electric circuit, for which Ohm's law states that the reciprocal of the total resistance (R_t) is equal to the sum of the reciprocals of each resistance (R_1–R_3):

$$\frac{1}{R_t} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}$$

Notably, we explored the fluid dynamics of a MIGS stent with three identical lumina, but the combination of the Hagen–Poiseuille equation and Ohm's law can also be used to design devices that induce other stepwise decreases in IOP. For example, choosing larger dimensions for the primary lumen than the secondary lumina would provide a MIGS stent for which the secondary lumina contribute relatively less to the net resistance, mainly allowing for fine-tuning of the IOP.

We used an ALT-like procedure to open each of the two secondary lumina. In this way, the pressure-lowering effect of the MIGS stent could be adjusted with a familiar technique and standard equipment. The smaller the diameter of the membrane, the more difficult it will be to hit with a laser. We therefore created a 100-µm-diameter membrane, which facilitated aiming a smaller 50-µm-diameter laser spot. However, unless it is impractically long, a tube with a diameter of 100 µm cannot establish a sufficient IOP at physiological flow rate, and in practice it is necessary to balance the need for a larger membrane diameter with the need for a smaller lumen diameter. One solution to this issue is to choose dimensions similar to the PreserFlo MicroShunt, which has an inner diameter of 70 µm. If sealed with a membrane, this diameter could be sufficient for aiming a 50-µm-diameter laser spot. Another solution is to keep the 100-µm-diameter membrane but let it cover a lumen of smaller diameter.

This study has several limitations. First and foremost, all experiments were conducted in vitro, and we created the MIGS stent without regard to biocompatibility, a key issue for glaucoma implants. Some biocompatible materials are available for 3D printing.[9] An even tighter dimensional tolerance is also necessary if 3D printing technology is chosen to create the MIGS stent in future in vivo studies. Moreover, like any other subconjunctival draining device, a multi-lumen glaucoma stent targeting the subconjunctival space will be susceptible to bleb failure in vivo, necessitating modulation of the conjunctival wound healing process. Additionally, it should be noted that the fluid dynamics experiments displayed measurement variation. Each stent was placed through a rubber stopper, and it is possible that the stopper exerted compressive force on the relatively soft stent, which influenced its resistance. An implant fixation block of metal, such as used in the study by Sheybani et al.,[2] could have been better.

In conclusion, this in vitro study presents proof of concept for a multi-lumen glaucoma stent that can be titrated with an ALT-like procedure. The combination of the Hagen–Poiseuille equation and Ohm's law determines its stepwise pressure-lowering effect. It is necessary to accurately reproduce the stent in a biocompatible material to study it in vivo.

Acknowledgments

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