A Newly Designed Glaucoma Drainage Implant Made of Poly(styrene-b-isobutylene-b-styrene)

Biocompatibility and Function in Normal Rabbit Eyes

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Objective: To report clinical evaluation, flow patency, and histopathological findings of a novel glaucoma drainage implant (GDI) made of poly(styrene-b-isobutylene-b-styrene) (SIBS) in rabbits.

Methods: In 16 normal eyes, the proximal end of the SIBS GDI was inserted into the anterior chamber while the distal end was placed in the subconjunctival space. A control group underwent implantation of a similarly designed silicone GDI. Slitlamp follow-up and intraocular pressure measurements were recorded. Flow patency was evaluated by injecting 0.01% fluorescein into the anterior chamber. Immunostaining against collagen IV, macrophages, and smooth muscle actin was performed.

Results: Slitlamp examination suggested adequate biocompatibility. A low and diffuse bleb was observed in the SIBS group. All SIBS tubes were patent 6 months after insertion. Immunostaining demonstrated noncontinuous collagen deposition. No macrophages or myofibroblasts were visible around the SIBS tubes. In contrast, silicone induced collagen deposition and myofibroblast differentiation.

Conclusion: This new GDI is clinically biocompatible in the rabbit and maintained 100% patency at 6 months. A remarkable difference was the absence of myofibroblasts in the surrounding tissue in the SIBS group.

Clinical Relevance: This novel GDI made of SIBS would prevent the feared complication of hypotony and will decrease the amount of subconjunctival fibrosis.

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DRAINAGE SURGERY TO CONTROL INTRAOCULAR PRESSURE (IOP) with different devices has limited success because of a buildup of extracellular matrix. The initial devices used to drain aqueous were horsehair threads. Other materials including glass rods, gold, silk, and even artificial trabecular meshworks were tried without success because of subconjunctival scarring. New devices including the EXPRESS glaucoma implant and Wilcox shunt are described in the literature; however, long-term effectiveness data are not available.

Modern glaucoma drainage surgery began with the pioneer work of Molteno in rabbits and humans, where the aqueous humor was drained from the anterior chamber to a plate adjacent to the limbus. He later increased the silicone tube length to allow the drainage of aqueous into a more posterior area. Another modification in glaucoma drainage implants (GDIs) was the introduction of unidirectional valve systems to avoid postoperative hypotony. Krupin et al reported their results with a valved system in 1976, followed by Coleman et al with the Ahmed implant. Subsequent design changes by Molteno and Baerveldt were aimed at increasing the plate area.

It is believed that the fibrotic and inflammatory reactions induced by biomaterials are a major determinant of success. Other factors such as shape, flexibility, modulus, and texture could also be associated with erosion, extrusion, inflammation, and scarring. Hypothetically, selecting a biomaterial and a design that produces minimal inflammation and fibrosis is a means to increase success.

Poly(styrene-b-isobutylene-b-styrene) (SIBS), a novel synthetic polymer consisting of a triblock of polystyrene-polyisobutylene-polystyrene, has been studied in different medical fields. Multiple investigators observed that SIBS has excellent biostability. The lack of biodegradation byproducts is believed to be a major factor enhancing its biocompatibility. In addition, SIBS can be loaded with different pharmaceutical agents. These unique ma-
terial properties of SIBS are crucial for the fabrication of life-lasting implants, as demonstrated by the TAXUS coronary stent (Boston Scientific, Natick, Mass). The TAXUS stent uses SIBS as a carrier for the antiproliferative agent paclitaxel, which is released into the vessel wall to prevent the proliferation of smooth muscle cells.26,27

In this article, we report the preliminary results of biocompatibility, flow patency, and histopathology of a novel GDI made of SIBS, where the new features include a new biostable elastomeric polymer, a small and flexible design, and a valveless tube with an inner diameter of 65 µm.

METHODS

ANIMALS AND MATERIALS

The animals used in the study were 25 normal female New Zealand white rabbits from Harlan Laboratories (Indianapolis, Ind), weighing 2.5 to 3.0 kg. All animals were treated in accordance to the Association for Research in Vision and Ophthalmology statement for the use of animals in ophthalmic research. The Committee and Review Board for Animal Research of the University of Miami (Miami, Fla) approved all animal studies. Prior to surgery, all animals were examined to exclude ocular diseases. A Perkins tonometer (Clement Clarke, London, England) and a pneumotonometer (Mentor Inc, Norwell, Mass) were calibrated. Evaluation of the central corneal thickness was performed using an ultrasonic pachymeter (DGH 500 Pachette; DGH Technology, Frazer, Pa). The newly designed GDIs were made of SIBS, with 24 mol% styrene (InnFocus LLC, Miami, Fla).

The polydimethylsiloxane tubes, known as silicone, were purchased (Silastic; Dow Corning, Midland, Mich). The lumens of the SIBS tubes were coated with glycerol to avoid sticking during manipulation. The initial design of the SIBS tube had a mean inner diameter of 65 ± 10 µm, and a mean outer diameter of 250 ± 10 µm (Figure 1A). The silicone rubber tubes had a mean inner diameter of 300 ± 10 µm and a mean outer diameter of 640 ± 15 µm (Figure 1C). This design was later modified by attaching a tab composed of the same materials to the wall in the middle region of the tube in both the SIBS and silicone tubes (Figures 1B and 1D, respectively). A disposable inserter device with a grip, a 27-gauge slotted needle, and a deployment slide were developed to facilitate insertion.

SURGICAL PROCEDURE

The right or left eye of 25 rabbits was randomly assigned for surgery; the other eye was used as a control. Animals were given an intramuscular injection of a ketamine-xylazine-acepromazine mixture (35 mg/kg, 5 mg/kg, and 0.75 mg/kg, respectively). All surgeries were performed by the same surgeon (A.C.A.). The surgical area was exposed with a corneal traction suture. A 90° fornix-based conjunctival peritomy was made in the supertemporal quadrant and the subconjunctival space was dissected posteriorly 10 to 14 mm using Westcott scissors. A 27-gauge needle was inserted 2 mm posterior to the limbus and directed to the anterior chamber. The SIBS GDI was preloaded into the inserter. The preloaded inserter entered the sclera following the needle scleral tract. Once the GDI was 3 mm into the anterior chamber, the GDI was released by retracting the thumb slide. Flow through the tube was confirmed by gently pressing the cornea until aqueous came out of the distal end. The distal end was then positioned under the conjunctiva. The conjunctiva was sutured with 7-0 Vicryl (Ethicon, Somerville, NJ). The silicone GDI was inserted in a similar manner, except that a 23-gauge needle was used for the scleral tract. The animals were treated with a subcutaneous injection of 0.03 mg/kg of buprenorphine after surgery and bacitracin-neomycin-polymyxin ointment and prednisolone acetate 1% (Allergan Inc, Irvine, Calif) twice a day for 3 days.

SLITLAMP BIOMICROSCOPY, IOP MEASUREMENTS, AND CORNEAL PACHYMETRY

Slitlamp follow-up was performed weekly. After topical anesthesia, IOP was measured with the Perkins tonometer and pneumotonometer in both operated and nonoperated eyes at 0, 1, 3, 14, 21, 60, 120, and 150 days after surgery. Animals were examined under general anesthesia at days 7, 28, 90, and 180 after surgery.

FLUORESCEIN PATENCY TEST

To evaluate the patency of the GDI and the passage of aqueous humor from the anterior chamber to the subconjunctival space, a solution of 0.01% sodium fluorescein (AK-Fluor; Akorn, Decatur, Ill) in a balanced salt solution was injected into the anterior chamber of 16 eyes in the SIBS group and 6 eyes in the silicone group. These experiments were performed at 90 and 180 days postoperatively. Briefly, the anterior chamber was entered with a 30-gauge needle, and the aqueous humor was allowed to drain out from the anterior chamber to avoid excessive IOP. A second 30-gauge needle was introduced into the anterior chamber and approximately 0.5 mL of fluorescein was injected for 20 minutes. Intraocular pressure was monitored during the procedure and did not exceed 25 mm Hg. Photographic documentation was acquired using an illuminator paraxial to the operation microscope (OMS-300; Topcon USA, Paramatta, NJ) and blue dichroic excitation and yellow barrier filters (V54-653 and NT47-247; Edmond Industrial Optics, Barrington, NJ).

LIGHT MICROSCOPY AND IMMUNOFluoresCENT STAINING

Animals were euthanized with 390 mg/ml Euthanasol (Delmarva Laboratories Inc, Midlothian, Va). The GDI and the surrounding tissue were dissected, immersed in optimal cutting temperature component (Tissue-Tek; Sakura, Torrance, Calif), and snap-frozen in liquid nitrogen. Frozen sections, 5-µm thick, were cut and fixated in acetone for 10 minutes at −20°C.
and blocked with 1% goat serum for 30 minutes. Sections were incubated overnight with the following antibodies: α-smooth muscle actin (α-SMA) (monoclonal, 1:100 dilution; DAKO, Carpintera, Calif), macrophages (monoclonal, 1:50 dilution), and collagen IV (polyclonal that cross-reacts with collagens I, II, and III, 1:100 dilution; Southern Biotechnical, Birmingham, Ala). Rhodamine-B-isothiocyanate–antigoat and fluorescein-3-isothiocyanate–antimouse secondary antibodies (Sigma-Aldrich, St Louis, Mo) were used at 1:100 dilution. The 4',6-diamidino-2-phenylindole mounting media Vectashield was from Vector laboratories (Burlingame, Calif). Some frozen sections were stained with hematoxylin-eosin. Photographs were taken using a confocal laser scanning microscope (LSM-510; Carl Zeiss, Oberkochen, Germany).

RESULTS

**SIBS GDIs AND POSTOPERATIVE HYPTONICITY**

Surgical time varied between 11 and 18 minutes in both groups. The immediate postoperative period was unremarkable in the SIBS group. In contrast, all rabbits in the silicone group had flat or shallow anterior chambers for 2 to 3 days. Hyphema formed in all rabbits in the silicone group during the surgical procedure. One rabbit in this group had blood and fibrin inside the tube and did not form a bleb. Immediate postoperative IOP readings were taken only with the Perkins tonometer to avoid the pressure exerted by the pneumotonometer in a shallow chamber. In the SIBS group, the mean IOP taken immediately after tube insertion and still under the effect of general anesthesia was 5.6±2.1 mm Hg. The lowest IOP recorded was 3.5 mm Hg. One day postoperatively, the mean IOP was 7.9±1.8 mm Hg in all eyes with SIBS implants. In contrast, all controls in the silicone group had flat or shallow anterior chambers for 2 to 3 days. Hyphema formed in all rabbits in the silicone group (Figure 3B) and the SIBS group (Figure 3C). Without directly contacting them, SIBS tubes were parallel to the iris or the cornea (Figure 3E). With this group during the immediate postoperative period (not shown). At the end of follow-up, all animals in the silicone group (Figure 3B) and the SIBS group (Figure 3E) had deep and quiet anterior chambers. Gonioscopy demonstrated the silicone tubes in a close position to the iris (Figure 3C). Without directly contacting them, SIBS tubes were parallel to the iris or the cornea (Figure 3F). Small blebs were a typical finding during the first 3 postoperative days in the SIBS group (Figure 4A), compared with very large blebs that slowly flattened in the silicone group (Figure 4B). One week after surgery, only loose subconjunctival space was noticed at the end of the tube, suggesting the presence of a diffuse bleb in both SIBS and silicone groups. In the SIBS group, the bleb was diffuse and vascularized; however, encapsulation and neovascularization were never observed around the tube for the duration of the study (Figure 4C). Fibrous encapsulation and neovascularization around the tube were clearly observed at 1 month (Figure 4D) in eyes that underwent silicone tubes implantation. Two animals in the silicone group were euthanized because of tube extrusion at the limbus area 45 and 109 days postoperatively (Figures 4E and 4F).

**CLINICAL BIOCOMPATIBILITY OF SIBS GDIs**

Tubes without a tab (the initial design in both materials) migrated into the anterior chamber. Silicone tubes migrated almost entirely within 2 days (Figure 3A), while SIBS tubes migrated within 2 weeks (Figure 3D). No changes in central corneal thickness were recorded in any group after surgery or during the 6-month follow-up. The mean central corneal thickness was 360±8 µm. No tube migration was observed once a silicone or SIBS tab was attached to the silicone or SIBS tubes, respectively. No other complications were observed in any of the SIBS tubes with an attached tab. In contrast, all silicone tubes produced flat anterior chambers and hyphema during the immediate postoperative period (not shown). At the end of follow-up, all animals in the silicone group (Figure 3B) and the SIBS group (Figure 3E) had deep and quiet anterior chambers. Gonioscopy demonstrated the silicone tubes in a close position or in contact with the iris (Figure 3C). Without directly contacting them, SIBS tubes were parallel to the iris or the cornea (Figure 3F). Small blebs were a typical finding during the first 3 postoperative days in the SIBS group (Figure 4A), compared with very large blebs that slowly flattened in the silicone group (Figure 4B). One week after surgery, only loose subconjunctival space was noticed at the end of the tube, suggesting the presence of a diffuse bleb in both SIBS and silicone groups. In the SIBS group, the bleb was diffuse and vascularized; however, encapsulation and neovascularization were never observed around the tube for the duration of the study (Figure 4C). Fibrous encapsulation and neovascularization around the tube were clearly observed at 1 month (Figure 4D) in eyes that underwent silicone tubes implantation. Two animals in the silicone group were euthanized because of tube extrusion at the limbus area 45 and 109 days postoperatively (Figures 4E and 4F).

**SIBS GLAUCOMA DRAINAGE IMPLANTS AFTER 6 MONTHS**

Although we observed a low bleb surrounding the tube during slitlamp examination and confirmed it with an-
Ciliary imaging (Figure 5), fluorescein flow and tube patency was clearly observed through all tubes in 16 eyes of 16 rabbits evaluated in the SIBS group. Ten of these animals had a follow-up of 6 months at the time of the fluorescein assay (Table). After injection of fluorescein into the chamber, fluorescein began to fill the perilimbal region and the tube lumen within seconds. Fluorescein exited from the distal tip of the tube into the subconjunctival space (Figure 6B) and slowly diffused around (Figure 6C). Fluorescein continued to diffuse through the tube into the subconjunctival space to define a 90° to 120° bleb (Figure 6D). In contrast, only 2 of 6 silicone tubes were patent at 3 months. The blebs were limited to the area adjacent to the silicone tube and did not diffuse to the surrounding subconjunctival space after 30 minutes of injection (not shown).
FIBROTIC RESPONSES OF SIBS GDIs

Sections were obtained at different locations along the tube track in the SIBS group at 3 and 6 months and at 3 months in the silicone group. Hematoxylin-eosin staining in the SIBS group showed no excessive collagen deposition, lymphocytes, or inflammatory cell infiltration (Figure 7A), even in the area where the tab was located (not shown). Collagen IV deposition was weak around the tube and did not surround the entire tube circumference (Figure 7B). α-SMA Smooth muscle actin did not stain the cells surrounding the tube (Figure 7C). No staining against macrophages was observed (not shown). Similarly, sparse collagen IV deposition was observed around the tab with the absence of a continuous capsule (not shown). No reactivity against α-SMA was observed around the tab (not shown). At 6 months, hematoxylin-eosin staining of the SIBS tubes did not show collagen deposition or cell infiltration around the tube. Interlaminar spaces were clearly observed in the subconjunctival space suggesting the presence of interstitial aqueous humor (Figure 8A). A light deposition of collagen IV completely surrounded the tube (Figure 8B), which was clearly evident at higher magnifications (Figure 8C). No smooth muscle actin or macrophages reactivity were observed in any of the SIBS tubes (Figure 8D) in any time frame.

Drainage implants are valuable in the management of neovascular and juvenile glaucoma, as well as glaucoma associated with uveitis, penetrating keratoplasty, aphakia, and failed filtering surgery. Despite different modifications to the material, surgical technique, and

Table. Summary of Different Variables Studied During the Experiments

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Abbreviations: H-E, hematoxylin-eosin; NA, not applicable; POD, postoperative day; SIBS, poly(styrene-b-isobutylene-b-styrene).
size and design of implants, the most important cause of failure continues to be the excessive scarring that impedes the exit of aqueous.39

Although the biocompatibility of any device is mainly related to the material, other issues, such as design and flexibility, are critical. This new SIBS GDI is made of an inert, soft, and flexible thermoformable material more conforming to the eye curvature in contrast to silicone controls. The thermoset nature of silicone rubber provides a memory to the tubes, which remain in their original shape. This straightening may be responsible for the 2 extrusions described. The combination of flexibility and conformability, the ability of SIBS to take on a new relaxed shape, the overall design, the chemical inertness, and the lack of molecules that elute from the material all contribute to the reduction in microtrauma and inflammation, therefore decreasing scarring.

The excellent biocompatibility observed clinically with the SIBS implants was confirmed by histological evaluation that showed reduced collagen deposition around the SIBS tubes at 3 and 6 months. Immunofluorescence demonstrated a modest and discontinuous collagen deposition in the SIBS group, whereas a complete circular collagen deposition was observed around the silicone tubes. To further study the amount of reaction induced by the implants, the cellular components responsible for scarring were characterized. Surprisingly, myofibroblasts in the tissue surrounding the SIBS devices—either in areas where SIBS was in contact with the iris, in the area where the tab was located, or in the subconjunctival space where the bleb was formed—were never observed. In contrast, the silicone drainage device always induced the expression of α-SMA. This expression was more evident in the area where the silicone tab was located. These histological results support the concept that SIBS is indeed a material that reduces the capsule formation by decreasing the amount of collagen deposition and the differentiation of myofibroblasts. This lack of scarring allows the outflow of aqueous humor into the subconjunctival space.

It was a challenge to confirm that there was indeed flow in the aqueous shunts in the long-term in the absence of a discernable bleb and without the ability to visualize direct flow in the healthy rabbit model. For this reason, we chose to inject fluorescein into the anterior chamber at 3 and 6 months after surgery. Immediate flow of aqueous was observed with the fluid dispersing into the subconjunctival space within seconds, with subsequent enlargement into a diffuse bleb 20 to 30 minutes later. This experiment confirmed that the tubes that showed fluorescein flow were patent. As reported, all (16 of 16) SIBS tubes (100%) were patent in the fluorescein study, in contrast to the 2 of 6 (33%) silicone tubes.
The SIBS GDI did not demonstrate postoperative hypotony, in contrast to the silicone rubber tubes, which did. The reason for this disparity is that the lumen of the SIBS tube was significantly smaller than the silicone tube. The SIBS lumen was designed to be approximately 60 µm with an 11-mm length, as suggested by the Hagen-Poiseuille equation, given a flow rate of approximately 2.5 µL/min and a desired resultant inflow pressure of 5 to 10 mm Hg in the absence of a distal resistance to outflow. However, the effects of a continuous force on the eye or Valsalva maneuvers on eye pressure are unknown because there is no capsule at the distal end that limits the outflow. The 300-µm lumen of the silicone tube extrapolates to negligible pressure by the Hagen-Poiseuille equation at a similar flow rate, as was confirmed by the hypotony observed in vivo.

Although the argument can be made that the hypotony, capsule formation, and other factors relating to the poor performance of the silicone tubes were inherent to their design and size, and were perhaps a result of immediate hypotony and the spewing of inflammatory cytokines into the subconjunctival space, we are convinced that this is not entirely the case, albeit large amounts of cytokines in the subconjunctival space would not be desirable nor would hypotony, and the SIBS GDIs were designed appropriately smaller for this reason. In a previous pilot study, 0.3-mm-thick discs with a 3-mm diameter made of SIBS showed minimal inflammation without cellular infiltration, neovascularization, infection, or toxic reaction when compared with identically sized cross-linked poly(dimethylsiloxane) discs that demonstrated marked neovascularization and fibrotic reaction. These materials were implanted both in the corneal stroma and sub–Tenon space of healthy rabbits. It is noteworthy that in these cases there was no aqueous humor or other active source of cytokines in contact with the biomaterials, clearly indicating a local response to the material as opposed to the geometry.

Using normal rabbits without established high IOP may explain the similarities in the IOP between the silicone and the SIBS tubes and between operated and nonoperated eyes. Although the SIBS GDIs were patent and formed a flat and extended bleb, no statistically significant difference in IOP between the SIBS and silicone groups was found after 7 days. We hypothesize that the pressure similarities between the SIBS and silicone groups relate to the remaining normal drainage system parallel to the shunt. Finally, a major advantage of SIBS is the possibility of loading the distal end of the GDIs with antiproliferative or anti-inflammatory agents.

Long-term studies in humans will determine whether these small GDIs made of SIBS are clinically useful in long-term IOP reduction. Hopefully, this novel GDI, with its simple and quick method of implantation, will avoid and prevent some of the complications observed with the implantation of current GDIs. The small size of the SIBS GDI, as well as ease of removal, if necessary, may provide a valuable tool to treat patients suffering from glaucoma.

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