Biocompatibility of a Novel Microfistula Implant in Nonprimate Mammals for the Surgical Treatment of Glaucoma

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Purpose. The purpose of this study was to evaluate the ocular safety of a novel microfistula implant and its composite materials in an animal model.

Methods. The anterior chambers of 12 rabbit eyes were injected with either glutaraldehyde cross-linked porcine gelatin extract or balanced salt solution and were followed by serial slit lamp examinations over 3 days. The eyes of 18 canines underwent microfistula implantation or a sham procedure. The animals were monitored over the subsequent 12 months, using serial slit lamp examinations, indirect ophthalmoscopy, tonometry, specular microscopy, and high-resolution ultrasonography. Ocular tissues were examined histopathologically on postoperative days 7, 30, 90, 180, and 365.

Results. Glutaraldehyde cross-linked porcine gelatin did not induce significant intraocular inflammation in the rabbit model. The microfistula implant was well tolerated and did not stimulate significant tissue response in the canine eye. The microfistula tube did not undergo structural change or degradation over the course of the study.

Conclusions. In nonprimate mammals, the material composing the microfistula implant and the implant itself do not induce significant inflammation or tissue reaction.

Keywords: biocompatibility, drainage device, glaucoma, microfistula, microinvasive glaucoma surgery

Glaucoma is the leading cause of irreversible blindness worldwide, affecting more than 64 million people. By 2040, the number of individuals with glaucoma is expected to eclipse 110 million.[1] Treatment for glaucoma carries a significant economic burden, with annual expenditures estimated to be US $2.86 billion in the United States[2] and CAD $300 million in Canada.[3] Lowering IOP by medications, lasers, and incisional surgery remain the only interventions successful at decreasing the risk of vision loss from glaucoma. The most commonly performed glaucoma surgeries, trabeculectomy and tube shunt procedures, aim to lower IOP by diverting aqueous humor (AH) into the subconjuctival space. Early hypotony resulting from these procedures has been associated with complications that could result in vision loss in at least 20% of patients.[4]

Attempts to develop a successful glaucoma drainage device have been published since 1907.[5] Ideally, the device would be composed of inert materials to avoid an inflammatory response. Long-term success of currently available glaucoma drainage devices may be limited by the composition of the devices themselves. Most devices use silicone or polypropylene components, both of which have been shown to incite inflammation in ocular tissues.[6,7] The resultant fibroproliferation can lead to progressive inhibition of aqueous flow and bleb failure. Although antifibrotics such as 5-fluorouracil or mitomycin C have increased the success rate of trabeculectomy, their intraoperative use for glaucoma drainage device surgery is not as beneficial.[8,9] Novel devices made from more biocompatible materials are needed to reduce the fibroproliferative response after placement.

As previously described, a novel microfistula implant (XEN model 45; AqueSys, Aliso Viejo, CA, USA) provides outflow resistance that should protect against hypotony at physiologic flow rates without the need for complex valve systems and intraoperative manipulations.[10] The device is a glutaraldehyde (GA) cross-linked porcine gelatin tube. It is placed by ab interno surgical technique through the trabecular meshwork, using an insertion device under direct gonioscopic visualization. It traverses the sclera and terminates in the subconjunctival space. Here, we describe the biocompatibility of the composite

materials and the microfistula implant itself in two animal models.

Materials and Methods

Animal studies were completed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The rabbit study was performed under Good Laboratory Practice regulations (title 21, part 58; Code of Federal Regulations; North American Science Associates Laboratories, Northwood, OH, USA). The canine study was designed as a non-Good Laboratory Practice, protocol-controlled preclinical safety study and carried out by the University of Georgia College of Veterinary Medicine.

Device Composition

The implant is a small hydrophilic tube composed of porcine gelatin cross-linked with GA. The most recently developed device (XEN 45) was designed using principles of fluid dynamics to avoid early postoperative hypotony. The device has been previously described in detail, including its biomechanical properties, histopathology, and fluid dynamics.[10,11]

Rabbit

From one eye of each of six rabbits, 150 μL of AH was removed from the anterior chamber (AC) and replaced with 150 μL of GA cross-linked porcine gelatin extract. The contralateral eye was injected with balanced salt solution (BSS) to serve as a control. Eyes were examined using slit lamp biomicroscopy at the end of day 0 and on days 1, 2, and 3 after the procedure. Ocular changes were scored in accordance with the McDonald-Shadduck score system, modified to exclude fluorescein and lens examination.

Canine

Eighteen beagles between 6 and 9 years old underwent implantation of the device in one eye and a sham procedure in the contralateral eye, using surgical techniques designed to emulate those used in humans as closely as the model would allow. Animals were separated into six groups of three, and the procedure was performed on a designated day. Two devices were implanted in each experimental eye in order to increase antigenic exposure. The anterior segment was examined by slit lamp biomicroscopy, and the posterior segment was examined using indirect ophthalmoscopy preoperatively and at 1, 3, 7, 30, 90, 180, and 365 days postoperatively. Spectral microscopy was performed (model 2000; Topcon, Tokyo, Japan) before and after implantation to evaluate endothelial cell count and morphology. Tonometry (TonoPen; Reichert Inc., Buffalo, NY, USA) and 80-MHz ultrasound biomicroscopy were performed preoperatively and on postoperative days (POD) 7, 30, 90, 180, and 365. Animals were sacrificed, and ocular tissues were harvested for histopathologic examination on postimplant days 7 (group 5), 30 (group 6), 90 (group 4), 180 (group 3), and 365 (groups 1 and 2).

Surgical Procedure

Rabbit. Following induction of general anesthesia, proparacaine hydrochloride was instilled on each eye, and the animal was positioned under the operating microscope. A lid speculum was placed, and forceps were used to stabilize the eye.

The syringe and needle containing test extract was introduced into the AC through the cornea above and parallel to the iris plane. Similarly, an evacuator needle was introduced at a remote location in the cornea. Approximately 150 μL of AH was aspirated from the AC while 150 μL of the test extract was injected intracamerally. A similar procedure was performed in the contralateral eye by using BSS in place of test extract. After the procedure, the animals were returned to their individual cages and monitored during recovery from anesthesia.

Canine. After induction of general anesthesia, a lid speculum was placed. A lateral canthotomy was performed to improve exposure. A 2.2-mm keratotomy was made at approximately the 12-o'clock position. Viscoelastic fluid was injected into the anterior chamber. The implanter needle was inserted through the keratotomy and advanced across the AC to engage the iridocorneal angle in the opposite quadrant. A custom-made three-mirror Goldman goniolens was used to visualize the path of the needle tip and engage the trabecular meshwork. The needle tip was advanced across the trabecular meshwork and sclera until visualized within the subconjunctival space. Advancement continued until approximately half of the needle tip bevel was visible. The surgeon then actuated the automated device to deliver the microfistula tube. Upon implantation, the delivery device was removed from the eye. The position and integrity of the tube, as well as the presence or absence of a conjunctival bleb were noted. A second tube was implanted in a similar manner in the same eye. In cases during which the tube was damaged or retracted with the implant guidewire, tube fragments were left in the AC to ensure that each eye was exposed to two tubes. A sham procedure, which included all procedural steps except tube deployment, was performed on the contralateral eye. In instances where there was significant hyphema, the AC was irrigated either manually or with an automated irrigation/aspiration (IA) device to remove excess blood. Care was taken to leave free-floating tube segments within the AC during IA. At the end of each procedure, the keratotomy was closed with a single interrupted 9-0 polyglactin suture (Vicryl; Ethicon, Cincinnati, OH, USA). Animals were allowed to recover from anesthesia on a heated pad and were returned to their housings once ambulatory.

Postoperative Medication

Commercially available triple-antibiotic ointment (neomycin, polymyxin, and bacitracin) and prednisolone 1% drops were administered upon completion of the surgery and three times daily during the subsequent follow-up period.

Canine Postmortem Assessment

After clinical data were collected, animals were euthanized by injection. The eyes were placed in Davidson fixative and allowed to fix before additional tissue trimming and sectioning. In addition, representative visceral organ samples were harvested and fixed in formalin. After fixation, the eyes were dissected to separate the quadrant of the eye that contained the implanted devices or the sham treatment sites. The quadrant of tissue was trimmed to provide bread-loaf sections transverse to the orientation of the implant or sham needle tract. This provided sections of cornea and iris in the anterior chamber as close to the trabecular meshwork as possible, as well as 2-mm tissue sections through the sclera and conjunctiva. Sections were processed using standard histology methods and slides prepared with hematoxylin-eosin (H&E) staining. Sections of optic nerve and posterior segment tissues were also harvested, sectioned, and stained with H&E. Samples of preserved visceral organs were not

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Table 1. Slit Lamp Findings in the Rabbit Model

	Conjunctival Congestion						Peripheral Anterior Synechiae					
	POD1		POD2		POD3		POD1		POD2		POD3	
Rabbit	Exp	Sham	Exp	Sham	Exp	Sham	Exp	Sham	Exp	Sham	Exp	Sham
1	1	1	1	0	0	0	0	2	0	0	0	0
2	1	1	1	0	0	0	2	2	2	2	2	1
3	0	1	1	1	1	1	1	1	1	0	1	0
4	1	0	1	0	0	0	1	0	1	0	1	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	1	0	1	0	0	0	1	0	1	0	1
Mean	0.5	0.67	0.67	0.33	0.17	0.17	0.67	1	0.67	0.5	0.67	0.33
±SD	0.55	0.52	0.52	0.52	0.41	0.41	0.82	0.89	0.82	0.84	0.82	0.52
P value		0.6		0.29		1		0.52		0.73		0.42

For conjunctival congestion: 0 = normal, 1 = reddish color predominantly confined to palpebral conjunctiva with slight perilimbal injection; 2 = bright red palpebral conjunctiva with perilimbal injection at 9-o'clock position; 3 = dark red color with congestion of bulbar and palpebral conjunctiva with pronounced perilimbal injection and petechiae. For peripheral anterior synechiae: 0 = none; 1 = 1 site; 2 = 2 sites. Exp, experimental (eye); POD, postoperative day.

histologically prepared or evaluated because no signs of device-related systemic adverse effects were observed over the course of the study.

Results

Intraocular Irritation in the Rabbit Model

Experimental and sham eyes showed mild injection at the end of the work day on POD 0 and on POD 1. Macroscopic findings were considered acceptable for the procedure. Slit lamp findings in experimental eyes were were similar to those in sham eyes, with neither exhibiting signs of significant inflammation or irritation over the 3-day period of study. Peripheral anterior synechiae (iris to injection site) were noted in both groups (Table 1).

Table 2. Conjunctival Chemosis and AC Fibrin in Experimental and Sham Eyes

	Conjunctival Chemosis				AC Fibrin			
	POD1		POD3		POD1		POD7	
Canine	Exp	Sham	Exp	Sham	Exp	Sham	Exp	Sham
1	0	0	0	0	1	1	0	0
2	1	0	0	0	2	0	1	0
3	0	0	0	0	1	1	1	1
4	1	1	0	0	1	1	1	0
5	1	1	0	0	1	1	1	1
6	2	1	0	0	1	1	1	1
7	0	0	1	1	2	0	1	1
8	0	0	0	0	1	0	1	0
9	2	1	1	1	3	2	0	0
10	2	1	0	0	2	0	3	0
11	1	1	0	0	1	1	0	1
12	1	1	0	0	1	1	1	0
Mean	0.92	0.58	0.17	0.17	1.42	0.75	0.92	0.42
±SD	0.79	0.51	0.39	0.39	0.67	0.62	0.79	0.51
P value		0.23		1		0.02		0.08

Values are 0 = none; 1 = mild; 2 = moderate; 3 = severe. AC, anterior chamber; Exp, experimental (eye); POD, postoperative day.

Intraoperative Observations in the Canine Model

A conjunctival bleb was observed at the time of retraction of the implant needle. The conjunctiva was breached by the guidewire in only one case. The site was sealed with cauterization, and the tube was deployed in this eye without need for further treatment.

The tube was damaged in 11 eyes and was retracted with the implant guidewire in 2 eyes. All tube fragments were left in the AC.

All treated and sham animals developed hyphema. At the conclusion of the procedure, excess blood was irrigated from the eyes by using either the automated IA device of a phacoemulsification machine or by manual irrigation with a syringe on a blunt cannula with BSS. Care was taken to retain any free-floating tube segments within the eye.

Clinical Observations

All animals exhibited mild to moderate conjunctival hyperemia and chemosis in the acute postoperative phase in both implanted and sham eyes. One implanted animal demonstrated severe erythema and edema of the eyelids and bulbar conjunctiva. A slightly higher severity of reaction was noted in the implanted eyes at days 1 and 3 post procedure. All changes resolved rapidly, and by day 7, there were no differences between implanted and sham eyes. By day 30, no adverse effects from the procedure were apparent.

Mild to moderate chemosis was observed in animals on days 1 and 3 after implantation. Chemosis was graded as slightly more severe in the implanted eyes than in sham eyes during the acute postoperative period, but this difference was not significant. (Table 2) The conjunctival blebs observed in sham and implanted eyes during surgery had resolved in all but one eye by POD 1. An aqueous leak was observed in one animal at the keratotomy suture site on POD 1. An additional suture was placed, and the leak resolved without negative sequelae. Any conjunctival changes associated with the surgical procedure were acute in nature and had resolved by 1 week post surgery.

Corneal edema, increased corneal vascularity, epithelial erosion, or pigmentation were not observed at any time point in implanted or sham eyes.

Mild to moderate fibrin was noted in many animals on days 3 and 7. Beyond day 7, some eyes had localized areas of fibrin clots, but there was no evidence of generalized fibrin in the AC. One animal showed synechiae oriented toward the keratotomy

Table 3. Mean Endothelial Cell Densities in the Canine Model

	Endothelial Cell Densities (Cells/mm²)									
	Pre-Op		POD7		POM1		POM3		POM6	
Canine	Exp	Sham	Exp	Sham	Exp	Sham	Exp	Sham	Exp	Sham
1	2212	2519	2353	2427	2481	2632	2532	2331		
2	2227	2208	2128	2309	2232	2193				
3	2364	2283	2326	2336	2381	2463	2358	2247		
4	2247	2217	2217	2188	2475	2551	2169	2160		
5	2278	2169	2242	2119	2041	2033				
6	2618	2463	2584	2525						
7	2242	2364	2203	2132						
8	2545	2427	2375	2410						
9	2375	2525	2331	2532	2212	2315	2309	2309	2198	2364
10	2020	2041	2041	2114	2070	2049				
11	2268	2070	2283	2370	2083	2070	1866	2123	2151	2037
12	2353	2299	2342	2336	2315	2433		2252	2294	2381
Mean	2312	2299	2285	2316	2254	2304	2247	2237	2214	2261
±SD	156	165	137	149	170	228	249	82	73	243
P value		0.84		0.60		0.61		0.93		0.72
		% Diff	−1.17	0.77	−2.51	0.24	−2.84	−2.69	−4.24	−1.66

Diff, difference; Exp, experimental (eye); Pre-op, preoperative measurement; POD, postoperative day; POM, postoperative month.

site. No significant incidence of tube-related synechiae was observed. Animals implanted with the device demonstrated slightly higher severity of fibrin in the AC than sham-treated animals (Table 2). Few animals exhibited mild to moderate flare at 1 to 3 days, but this quickly resolved. Any observable differences in the severity or incidence of changes between the implant- and the sham-treated eyes had resolved by POD 7.

No significant treatment-related changes were observed in any posterior segment tissues.

Implant Disposition

There was no evidence of changes in the physical shape of the tubes implanted in the trabecular meshwork. Free-floating tube segments became adhered to AC tissues without significant adverse changes and remained stable over the 12-month course of the study. There were no signs of tube degradation.

There was no evidence of late stage changes associated with the implanted devices. No toxicity to the cornea, lens, iris, or conjunctival tissues was observed over the 12-month duration of study.

Ultrasonography demonstrated that tubes could be visualized within the scleral channel without evidence of peri-implant tissue reaction. There were no subjective changes observed in tube dimensions over the course of the study, and patency was evident when the tube orientation allowed for visualization of the tube lumen.

Intraocular Pressure

All IOP measurements were within normal limits for the animal. No significant differences between IOP in implanted and in sham eyes were observed.

Specular Microscopy

On POD 7, the mean endothelial cell density (ECD) for the implanted eye decreased 1.17% from baseline, whereas the sham-treated eye increased slightly (0.77%). After 30 days, the mean ECD for the implanted eye decreased 2.51%, while the sham eye remained constant at +0.24%. At 90 days, the implanted eye ECD decreased 4.24%, while the sham eye ECD decreased 1.66% (Table 3).

At 7 days in both the implanted and the sham eyes, there were changes in the coefficient of variation of cell size and percent of hexagonal cells. These changes resolved over a similar time period (within 30 days) in both groups.

Histopathology

No evidence of toxic changes was observed in any sections examined, including sclera, cornea, conjunctiva, anterior uvea and trabecular meshwork, lens, choroid, retina, or optic nerve head. Additionally, there was no late stage increase in implant site cellular response that might be indicative of stimulation from device degradation products (Fig. 1).

Blebs containing proteinaceous fluid were seen in Descemet's membrane in both implant- and sham-treated eyes.

Rupture of Descemet's membrane was present in implant- and sham-treated eyes and was most likely due to the introduction of the needle. In all cases, the ruptured edges showed minimal to mild fibrosis, consistent with healing over the first 180 days. With a single exception, no 365-day-treatment eye showed evidence of rupture of Descemet's membrane.

Mild cataract formation was seen in the 7-day and 30-day eyes in both the sham and treatment groups. One sham-treated eye demonstrated cataract associated with fibrin adherence to the lens capsule. The mild cataractous changes seen in sham and treatment eyes were not observed in the 90-day eyes. There was mild to moderate focal cataractous change in two of the 180-day treatment eyes but none of the 180-day sham eyes. Mild sclerotic changes were also noted in five of the 365-day treatment eyes and three of the 365-day sham eyes.

Mild, localized neutrophilic inflammation was seen in the 7- and 30-day treatment eyes. It was not present in the 90-, 180-, or 365-day eyes.

Thin preiridial fibrovascular membrane and fibrin adhered to the anterior face of the iris in a single 7-day treatment eye but was not noted in any of the sham eyes or later in any other implanted eyes.

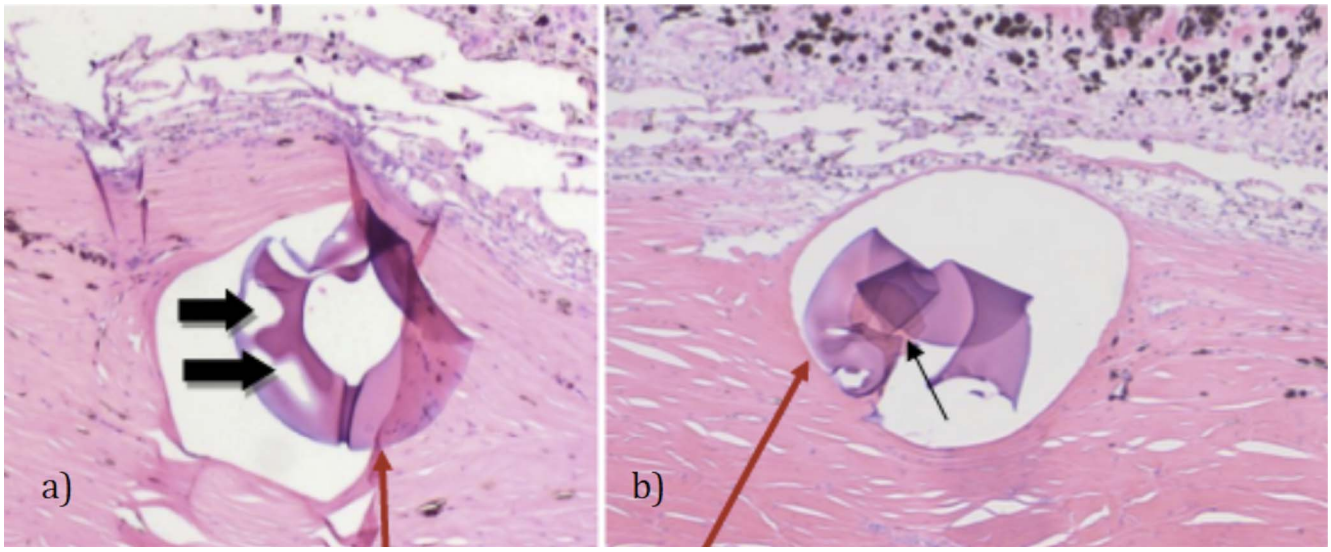

Figure 1. Twelve months post implantation. (**a**) Implant in sclera with slight displacement of scleral collagen toward trabecular meshwork (*black arrows* indicate sectioning artifact; *red arrow* denotes scleral channel). (**b**) Implant in sclera with focal nodular fibrosis (*black arrow*) within scleral canal (*red arrow*).

Hemosiderin-laden macrophages were observed in one of the 30-day implant eyes, indicating a prior hemorrhagic event. Low numbers of plasma cells were noted in the same area (Fig. 2).

Two sections of implant were absent in two of the 180-day treatment eyes, most likely due to implant dropout during sectioning or slide preparation. All visible implants were patent and positioned in the anterior chamber and sclera. Two 365-day treatment eyes showed evidence of intraluminal implant fibrosis which resulted in less than 20% occlusion (Fig. 3). In all treatment cases at all time points the implant was intact with little to no tissue reaction present. The implant itself showed no histological differences between the appearance in the 7-day eyes and any of the other time periods examined.

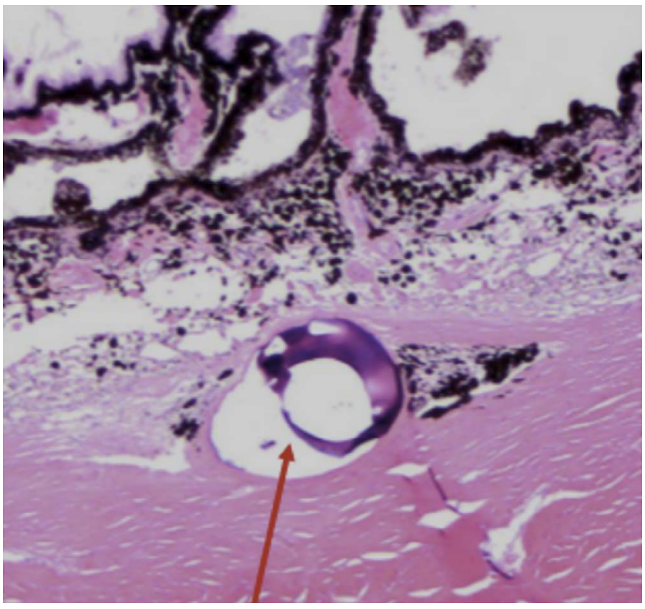

Figure 2. Implant in sclera with mild surrounding fibrosis and wedge-shaped accumulation of melanophages. *Red arrow* represents sectioning artifact.

Discussion

Rabbit Study

No significant differences were observed between rabbit eyes injected with GA cross-linked porcine gelatin extract and those injected with BSS. All changes observed were judged to be related to surgical trauma and were considered acceptable following this type of procedure. Simultaneous injection of solution and aspiration of AH was necessary to maintain AC volume and avoid proinflammatory events such as lens-cornea touch or increased intraocular pressure. Although it is likely that a small volume of the injected solution was removed with

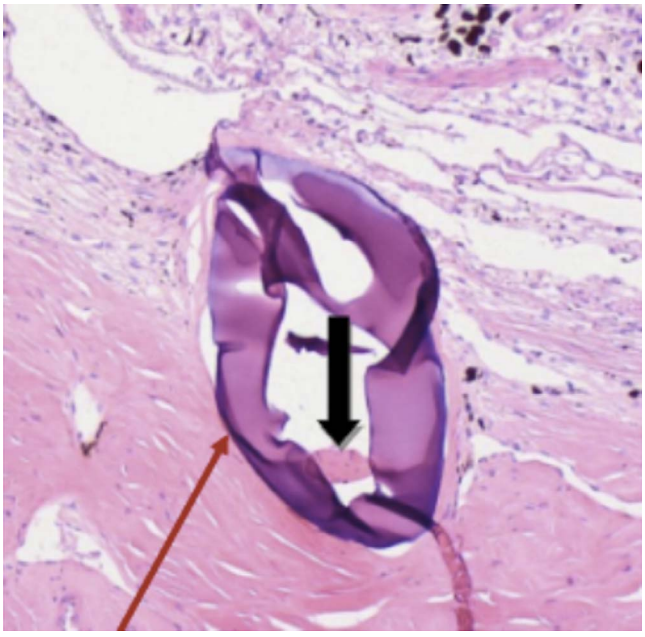

Figure 3. Implant in scleral channel (*red arrow*) with very small intraluminal fibrotic nodule (*black arrow*) at 12 months post implantation.

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aspiration of AH, technique standardization ensured all eyes were exposed to similar concentrations of extract or BSS.

Canine Study

Clinical observations suggest the presence of mild to moderate intraocular inflammation in the acute postsurgical phase, consistent with a procedure of this type. The changes observed in the anterior segment were exclusively acute in nature and resolved in the early postoperative period. As there were no significant differences between experimental and sham-treated eyes, any postsurgical changes can be attributed to the procedure itself rather than to the presence of the implanted device. The minimal increases in severity of conjunctival and AC findings in the experimental eyes were likely due to the increased manipulation and surgical duration required for implant placement versus sham treatment. No significant long-term effects related to the device were observed over the 1-year period of evaluation.

The histopathology results indicated mild acute effects consistent with the clinical observations at the 7- and 30-day time points. The significance of blebs in Descemet's membrane in both the sham and the treatment eyes is uncertain, but it is not considered a toxic change and is most probably artifact. In the single 365-day treatment eye that showed evidence of Descemet's rupture, the implant was positioned in close proximity to the cornea. This poorly placed implant may have continued to traumatize the endothelium over the course of the study. Even in this case, fibrosis was mild and not likely to be clinically significant.

Given the difficulties in accurate placement of the implants in canine eyes, an uncertainty existed in the number of properly positioned tubes. Without adequate positioning, the microfistula implant cannot function properly, and a decrease in IOP should not be expected. Studies to assess the IOP-lowering effect of the microfistula implant are ongoing.

The mild cataracts noted suggest interanimal variability in the development and resolution of lenticular changes. Given their presence in both treatment and sham groups, none of the observed changes were attributed to the implant.

Mild neutrophilic infiltration in the acute postoperative period was interpreted to be a slight reaction to the procedure itself rather than to the presence of the implant. One animal had developed a conjunctival hematoma following the procedure and was found to have localized hemosiderin-laden macrophages at the 30-day time point. Low numbers of plasma cells noted in the same area suggested a resolving immune response probably triggered by the localized bleeding as a result of the procedure.

The lack of significant fibrosis in all sections of both sham and treatment eyes was especially remarkable. Although there was a very slight increase in reaction between the 7- and 30-day eyes, this increase was not seen in the later groups. This indicates that the procedure, as well as the implant itself, induces very little tissue response.

The implant sites showed minimal device-related changes that stabilized by 30 days and were essentially unchanged for the remainder of the study. No adverse effects on the posterior segment tissues were observed.

The use of a specular microscope designed for humans introduced variability in the cell density measurements at each time point in the study. The inability of the anesthetized animal to fixate on the fixation light minimized the ability to obtain images from the same central area. This undoubtedly played a role in the fluctuating cell densities noted in individual corneas over the course of the study. Considering the wide variability observed during baseline and postoperative measurements, it is reasonable to conclude that decreases in average ECD at each time point do not represent a significant effect associated with implantation of the device. The initial changes in the coefficient of variation and percentage of hexagonal cell in the implanted group is indicative of surgical stress. Reversal of these changes within 30 days suggests that the corneal endothelium recovered nicely after surgery and remained stable thereafter.

Prior studies have demonstrated that ECD loss occurs after trabeculectomy and following implantation of glaucoma drainage devices.[12–15] Trabeculectomy with or without mitomycin C is associated with a 10% decrease in ECD over 1 year. Similarly, Ahmed valve placement has been found to decrease ECD by 12.6% over 12 months and by 15.4% over 16 months. In this study, no statistically significant differences in ECD were observed between experimental and sham eyes (Table 3). The lack of significant ECD loss after microfistula implantation suggests that the microfistula tube is well tolerated by the corneal endothelium over 1 year.

The results of this study support the intraocular biocompatibility of the implanted microfistula device. Histologically, the device did not show signs of degradation or change, indicating that the materials have long-term durability in the implant site.

It is well known that GA fixation decreases the antigenicity of similar biomaterials. The results of these studies are consistent with prior published data demonstrating that the porcine gelatin does not elicit a significant inflammatory response.[16] The microfistula tube itself demonstrated excellent intraocular durability over the 12-month period of study.

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