Comparison of Different Biomaterials for Glaucoma Drainage Devices

Part 2

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Background: Inflammation associated with biomaterials may contribute to the failure of glaucoma drainage devices.

Objective: To compare the inflammatory reaction associated with the insertion of Krupin silicone, Molteno polypropylene, and Acrosof end plates in the subconjunctival space of rabbits.

Methods: Similar-sized glaucoma end plates made of 3 different biomaterials were sutured to the sclera in the superotemporal quadrant of the rabbit eye. Thirty eyes of 15 albino New Zealand rabbits were randomly assigned to the 3 groups. Conjunctival vascular hyperemia was graded in a masked fashion among the 3 groups. At the end of 3 weeks, the enucleated eyes were examined histologically and by scanning electron microscopy.

Results: Molteno polypropylene was associated with more inflammation both in clinical observations and based on histological grading. Silicone and Acrosof were associated with less intense inflammation. One polypropylene end plate was extruded on day 21.

Conclusions: Polypropylene appears to be more inflammatory than silicone. Flexible biomaterials appear to be less inflammatory than rigid ones.

Clinical Relevance: Bleb failure following glaucoma drainage device implantation could be related to the biomaterial-associated inflammation. Choosing a biomaterial with the least inflammatory potential might enhance the success rate of the glaucoma drainage device.


LABORATORY SCIENCES

From the Departments of Ophthalmology, Tulane University Medical Center, School of Medicine, New Orleans, La, and Medical Center of Louisiana at New Orleans (Dr Ayyala); Departments of Ophthalmology (Drs Michelini-Norris and Flores) and Pathology (Dr Haller), University of South Florida, Tampa, and Department of Ophthalmology, Watson Clinic, Lakeland, Fla (Dr Margo).

Bleb failure secondary to scar formation is the main reason for failure of glaucoma drainage devices. Part of the bleb-related inflammation may be due to the biomaterial used as the end plate. One way of minimizing the inflammatory response in the bleb is to use a biomaterial that has the least inflammatory response. The end plates in the Ahmed glaucoma valve and the double-plate Molteno are made of polypropylene, whereas the Baerveldt and the Krupin disc implants are made of silicone. The polypropylene in the Molteno implant may not be the same medical grade as that of the Ahmed glaucoma valve (the texture, flexibility, and finish are different). Similarly, even though the Baerveldt and Krupin disc implants are made of medical grade silicone, they differ in their texture, flexibility, and consistency. Our laboratory studies have demonstrated that the Ahmed glaucoma valve polypropylene is more inflammatory than the Baerveldt silicone in the rabbit subconjunctival space. This response was confirmed both clinically and histologically and may account for the high incidence of hypertensive phase demonstrated with certain glaucoma valve implants. The double-plate Molteno end plate and Krupin disc implant end plate were not tested in the previous study. We performed a similar study to compare the inflammatory response of Molteno polypropylene and Krupin silicone end plates in the subconjunctival space of the rabbit. Acrosf is a new acrylic (polymethylmethacrylate), foldable intraocular lens implant that appears to have excellent biocompatibility properties in the human eye. We included Acrosf as part of the present experiments to study its suitability as potential end plate material.

RESULTS

There was no occurrence of anterior chamber reaction, corneal epithelial defects or ulcers, or endophthalmitis. One rabbit (No. 11) died on day 14. Postmortem examination revealed an enlarged liver that probably existed before the experiments. Red reflex remained good in all animals. Mild
MATERIALS AND METHODS

The inflammatory response associated with 3 different biomaterials using a rabbit model was studied. Polypropylene end plates of the Molteno glaucoma implant (IOP Inc, Costa Mesa, Calif) were compared with the silicone end plates of the Krupin eye valve with disk (EY-6003; Hood Laboratories, Pembroke, Mass) and Acrosil intraocular lens (MA60BM; Alcon Laboratories Inc, Fort Worth, Tex). The Institutional Animal Care and Use Committee approved the study protocol at the University of South Florida, Tampa. Institutional guidelines regarding animal experimentation were followed.

Blocks of sterilized Krupin silicone and Molteno polypropylene measuring 8 × 8 × 2 mm were used in the experiment to simulate the end plate of the existing glaucoma drainage devices. The Molteno end plate that was used was the end plate of the pediatric-size implant. An 8-mm trephine was used to obtain a circular disc of silicone with smooth edges from the Krupin end plate. The haptics of 6-mm Acrosil intraocular lenses were cut flush with the optical zone before insertion. Care was taken to ensure that the edges of all the blocks were smooth and the samples were of uniform size and shape. Fifteen healthy albino New Zealand rabbits with no preexisting ocular inflammation were used in the present experiment. Both eyes of the 15 rabbits were used for a total of 30 eyes. Five rabbits were randomly assigned to 3 groups. The test material was sutured to the sclera, 8 to 9 mm from the limbus in the superotemporal quadrant of either the right or left eye.

SURGICAL PROCEDURE

The surgical procedure was described previously. Briefly, after adequate general anesthesia (ketamine hydrochloride, 35 mg/kg, and xylazine hydrochloride, 3 mg/kg, administered intramuscularly), the rabbit eyes were prepared and draped with sterile towels and the lids secured with a lid speculum. Topical 0.5% tetracaine hydrochloride was instilled to prevent any discomfort. Westcott scissors were used to perform a superior limbal peritomy from the 11-o'clock to 2-o'clock meridian. The conjunctival dissection was performed posteriorly in the subconjunctival plane to expose the sclera in the superotemporal quadrant. Hemostasis was achieved with the help of a handheld cautery. A block of the test material was placed on the sclera, 8 to 9 mm from the limbus, and sutured to the sclera with 2 interrupted 9-0 nylon sutures. The conjunctiva was sutured to the limbus with a running 9-0 nylon suture.

POSTOPERATIVE CARE

Postoperative care included application of tobramycin-dexamethasone ointment (Tobradex) twice daily for 1 week. The animal’s general health, presence or absence of conjunctival hyperemia, subconjunctival hemorrhage, biomaterial extrusion, suture exposure, discharge, infection, corneal edema, corneal epithelial defects, anterior chamber reaction, quality of red reflex, and any complications were assessed and recorded on postoperative days 1, 3, 7, 14, and 21. Slitlamp biomicroscopy was performed on postoperative days 3, 7, and 21. Conjunctival vascular hyperemia was rated by both intensity and location in each of the eyes. The examination and grading of the conjunctival vascular hyperemia was performed by one of us (R.S.A.) in a masked fashion. The grading was performed as follows: grade 0, no hyperemia; grade 1, mild hyperemia; grade 2, moderate hyperemia; and grade 3, severe hyperemia. The animals were humanely killed at the end of 3 weeks (sedation with ketamine followed by a lethal dose [100 mg/kg] of intracardiac pentobarbital sodium). The eyes were enucleated, taking care not to disturb the conjunctiva in the quadrant containing the implant.

SCANNING ELECTRON MICROSCOPY

We performed scanning electron microscopy on 12 eyes (4 specimens of each test material) to look for inflammatory cells attached to the material surface. The specimens were submitted in isotonic sodium chloride solution. Before fixation, the implants and encasing capsules were carefully dissected from the enucleated eyes. The implants were removed from the fibrous capsules surrounding them and dipped in isotonic sodium chloride solution to remove adherent blood from the surface of the implants and capsules. The implants and fibrous capsules were placed in 2% buffered paraformaldehyde for 24 hours at 40°C. Following fixation, the implants and capsules were rinsed for 1 hour in physiological saline solution at 40°C then in distilled water for 30 minutes to ensure removal of erythrocytes from the implants and luminal surfaces of the fibrous capsules that had accumulated in the capsules as a result of manipulation during surgical removal of the eyes from the rabbits. Following water rinse of the capsule tissue and implants, all samples were dehydrated through a graded series of ethyl alcohol, which was replaced with hexamethyldisilazane, a drying and hardening agent. The samples were air dried at 70°C overnight after removal from the hexamethyldisilazane. Following drying, the samples were mounted on conductive carbon tape in a manner that portions of both sides of the implant and portions of both halves of the fibrous capsule’s inner surface could be evaluated.

This generated 4 surfaces to be evaluated per sample. Following mounting, the samples were coated with metal in a sputter coater (Hummer VI sputter coater; Anatech Ltd, Alexandria, Va) and subsequently examined with a scanning electron microscope (Philips 515 S.E.M; Philips Electronic Instruments, Eindhoven, the Netherlands) at an accelerating voltage of 10 kV.

LIGHT MICROSCOPY

Eighteen of the enucleated eyes (6 specimens of each test material) were fixed immediately in 10% buffered formalin. Semithin sections were cut and stained with hematoxylin-eosin. Light microscopic analysis of the specimens was performed in a masked fashion without knowledge of the biomaterial implant by one of us (C.E.M.). Attention was directed toward the degree of fibrosis and inflammatory response in the immediate vicinity of the explant material. The relative density of the inflammatory cells (macrophages, lymphocytes, plasma cells, and mast cells) and the amount of fibrosis in the conjunctival substantia propria were graded from 0 to 4, with grade 4 being the most severe.
mucoid discharge occurred in association with suture exposure and extrusion, but no cases of infection occurred.

**Table 1** shows the degree of conjunctival hyperemia on postoperative days 1, 3, 7, 14, and 21. The degree of conjunctival vascular hyperemia was more pronounced for the polypropylene implants throughout the postoperative period.

Light microscopy revealed mild-to-moderate fibrosis with the silicone and Acrosoft implants and moderate fibrosis with polypropylene. The inflammatory reaction was often mixed, consisting of polymorphonuclear leukocytes most often followed by macrophages, lymphocytes, and giant cells. The mean ± SD grade of inflammation (on a scale of 0 to 4) averaged 2.0 ± 1.6 with Krupin silicone implants, 2.8 ± 1.8 with Acrosoft, and 3.7 ± 1.2 with Molteno polypropylene. The mean ± SD grade of fibrosis (on a scale of 0 to 4) averaged 2.6 ± 0.9 with silicone implants, 2.6 ± 1.5 with Acrosoft, and 3.5 ± 1.8 with polypropylene.

Extrusion of the material occurred in 1 eye with polypropylene implants (postoperative day 21). None of the silicone and Acrosoft implants were extruded. Since the extrusion was noticed on the last day of the experiments, the eye in question was included in the study. The rabbit that died on day 14 was excluded from the study. Histological examination of these 2 eyes revealed 2+ inflammation and 2+ fibrosis for the Krupin silicone and 3+ inflammation and 3+ fibrosis for the Acrosoft implant.

Scanning electron microscopy demonstrated a fibrous capsule formation around all 3 biomaterials. Inflammatory cells were found in the fibrous capsule in all 3 groups. Both Molteno and Krupin implants appeared to have acted as a scaffold, allowing cells to grow on the surface of the implants, Krupin more than the Molteno. This finding appears to be related to the shape of the Molteno end plate, which is like an inverted cup and thus prevented the fibrous capsule from adhering to the implant surface, except along the edges and side walls (Figure, A and B). The Acrosoft surface appears to have attracted sheets of cells on its surface, with the fibrous capsule tenaciously attached to the implants (Figure, C).

**COMMENT**

The present experiments demonstrate that polypropylene is more inflammatory than silicone in the rabbit subconjunctival space. This confirms the findings of previous studies. When compared with the results from previous experiments (Table 2), the Molteno polypropylene end plate appears to be less inflammatory than the Ahmed valve end plate and also did not promote extensive cellular adhesions on its surface, as was seen with the Ahmed valve end plate. This may be related to the difference in the shape, surface, and flexibility of the implant end plates. As was noted previously, the Molteno end plate is shaped like an inverted cup and is much more flexible than the Ahmed valve end plate, which is extremely rigid. Also, because of its shape, less of the Molteno end plate is in contact with the scleral and conjunctival tissues when compared with the Ahmed end plate. Because of its rigidity and shape, the Ahmed end plate is also more likely to shift position (so-called micromotion) and promote more inflammation.

The Krupin silicone end plate, even though less inflammatory than both the polypropylene end plates, ap-

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**Table 1. Conjunctival Vascular Hyperemia Among the 3 Biomaterials on Various Postoperative Days**

<table>
<thead>
<tr>
<th>Postoperative Day</th>
<th>Acrosoft</th>
<th>Silicone (Krupin)</th>
<th>Polypropylene (Molteno)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.6 ± 0.5</td>
<td>2.0 ± 1.1</td>
<td>2.3 ± 1.0</td>
</tr>
<tr>
<td>3</td>
<td>1.0 ± 0.4</td>
<td>1.2 ± 0.6</td>
<td>1.75 ± 0.8</td>
</tr>
<tr>
<td>7</td>
<td>0.7 ± 0.4</td>
<td>0.8 ± 0.3</td>
<td>1.0 ± 0.6</td>
</tr>
<tr>
<td>14</td>
<td>0.5 ± 0.4</td>
<td>0.4 ± 0.3</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>21</td>
<td>0.05 ± 0.2</td>
<td>0.05 ± 0.2</td>
<td>0.8 ± 1.2</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD.

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pears to be more inflammatory than the Baerveldt silicone end plate (Table 2). Also, the Krupin end plate promoted cell adhesion on its surface, which was not the case with the Baerveldt implant. Again, this may be related to the increased rigidity of the Krupin end plate when compared with the Baerveldt end plate.

End plate inflammation appears to be influenced not only by the biomaterial used but also by other physical properties, such as size, shape, and flexibility. Inflammation around the end plate, resulting in scar formation, is the leading cause of glaucoma drainage device failure. The overall success of the currently available glaucoma drainage devices is 78% at 1 year. This success rate may be improved with modified end plates made of the least inflammatory biomaterial.

This study has some limitations. The experiments were performed on rabbits, and so the results may not be directly generalized to humans. We do not know if the presence of aqueous humor would have altered the results. The Acrosol intraocular lens used in the present experiment appears to be associated with extensive cellular adhesions and hence may not be suitable in its intraocular lens design as a glaucoma drainage device end plate. However, modifications of the biomaterial to make it more flexible and porous could enhance its success.

In summary, we demonstrated that polypropylene end plates are more inflammatory than silicone. The inflammation appears to be related not only to the biomaterial but also to the rigidity, flexibility, and shape of the end plate. Inflammation caused by biomaterials may contribute to the glaucoma drainage device failure and transient periods of elevated intraocular pressure. The ideal glaucoma drainage device should be made of a completely inert biomaterial.

Accepted for publication January 13, 2000.

This study was supported in part by the Dorothy Benjamin Ophthalmology Research Endowment and Research to Prevent Blindness, New York, NY.

We thank IOP Inc, Costa Mesa, Calif, and Hood Laboratories, Pembroke, Mass, for providing the biomaterials that were used in the laboratory studies and the Pathology Core Facility at the University of South Florida and the H. Lee Moffitt Cancer Research Institute, Tampa.

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Table 2. Comparison of Histologic Findings Among the 4 Commonly Used Glaucoma Drainage Devices (GDDs)*

<table>
<thead>
<tr>
<th>GDD</th>
<th>Biomaterial</th>
<th>Fibrosis</th>
<th>Inflammation</th>
<th>Scaffolding Ability†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baerveldt</td>
<td>Silicone</td>
<td>Mild to moderate</td>
<td>1.6 ± 0.4</td>
<td>None</td>
</tr>
<tr>
<td>Krupin</td>
<td>Silicone</td>
<td>Mild to moderate</td>
<td>2.0 ± 1.6</td>
<td>+</td>
</tr>
<tr>
<td>Ahmed</td>
<td>Polypropylene</td>
<td>Marked</td>
<td>2.2 ± 0.7</td>
<td>++</td>
</tr>
<tr>
<td>Molteno</td>
<td>Polypropylene</td>
<td>Marked</td>
<td>3.7 ± 1.2</td>
<td>+</td>
</tr>
</tbody>
</table>

* Fibrosis was graded as mild, moderate, and marked. Inflammation was graded on a scale of 0 to 4. Scaffolding ability is the tendency of the end plate to allow cells to adhere and grow on the surface.
† Based on a scale of 0 to 4+.