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Histological Biocompatibility of a Stainless Steel Miniature Glaucoma Drainage Device in Humans: A Case Report

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ABSTRACT

The purpose of this study was to evaluate the histological biocompatibility of a stainless steel miniature glaucoma drainage device. Twenty-four months before death due to heart failure, this seventy-three-year-old female patient underwent filtration surgery for primary open-angle glaucoma uncontrolled in the right eye. The device was implanted at the limbus under a scleral flap. For histopathological evaluation, two corneoscleral specimens were embedded in methacrylate blocks sectioned to a thickness of 50 microns, polished and stained with periodic acid schiff. Some sections included a longitudinal cross-section of the implant. At the interface between the spur and the flange of the device and the cornea, there was a small shoulder of fibrous tissue. A thin, fibrous capsule covered the remainder of the body of the device up to the distal tip. No inflammatory cells occurred within the fibrous capsule. No material or blockage was noted within the lumen. Our results support the biological inertness of the device.

Keywords: stainless steel implant; glaucoma filtering surgery; intraocular pressure (IOP); biocompatibility.

INTRODUCTION

Glaucoma filtering surgery is indicated when the level of intraocular pressure (IOP) obtained with pharmacological and/or laser treatment proves inadequate (European Glaucoma Society 2008). Trabeculectomy, the most widely used form of filtering surgical treatment for primary open-angle glaucoma, has variable success rates (30-90%) and a number of complications such as cataract induction, hypotony, bleb infections (Watson et al. 1990). The Ex-PRESSTM (Optonol Ltd., Neve Ilan, Israel) is a miniature stainless steel glaucoma shunt developed as an alternative to trabeculectomy surgery for glaucoma (Mermoud 2005). Theoretically, this procedure should be more reproducible and less traumatic to the ocular tissue, allowing the avoidance of both the excision of the corneoscleral tissue block and the iridectomy. The implant is inserted at the limbus

under a scleral flap (Dahan and Carmichael 2005) and diverts the aqueous humor from the anterior chamber to the episcleral space yielding a conjunctival filtration bleb, similar to that formed in trabeculectomy. The implantation can be performed on its own or in combination with phacoemulsification cataract extraction. The histological biocompatibility of the Ex-PRESS device was previously tested in rabbit eyes (Nyska et al. 2003) and found to be inert. We report the first histopathologic findings from a human corneoscleral specimen containing this stainless steel implant.

MATERIAL AND METHOD

All procedures were approved by the Institutional Ethics Committee, which is the "Comitato Etico dell'Azienda Ospedaliera Universitaria San Martino di Genova." Consent from the relatives was obtained for the tissue donation. The implant was evident on gross examination (Figure 1B).

Patient

Twenty-four months before death due to heart failure, this seventy-three-year-old female patient underwent filtration surgery for primary open-angle glaucoma (POAG) uncontrolled in the right eye at Clinica Oculistica, Di.N.O.G., University of Genova, Italy.

The patient was implanted in November 2004. The procedure was combined with phacoemulsification cataract extraction and posterior chamber intraocular lens insertion.

There are no competing interests for any of the authors. The Di.N.O.G., University of Genova, has received research funds from Optonol but not specifically for this research. This study conforms to the applicable laws regarding human participants in a research protocols and to the Eye Banking EU directives. Local Ethics Committee "Comitato Etico dell'Azienda Ospedaliera Universitaria San Martino di Genova" approval no. 15490.

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Abbreviations: APL, Goldmann Applanation Tonometry; CFR, Code of Federal Regulations; FDA, Food and Drug Administration; IOP, intraocular pressure; MMA, methyl methacrylate; PAI, Pathology Associates International Charles River Laboratories; PAS, periodic acid Schiff; POAG, primary open-angle glaucoma; SOPs, standard operating procedures.

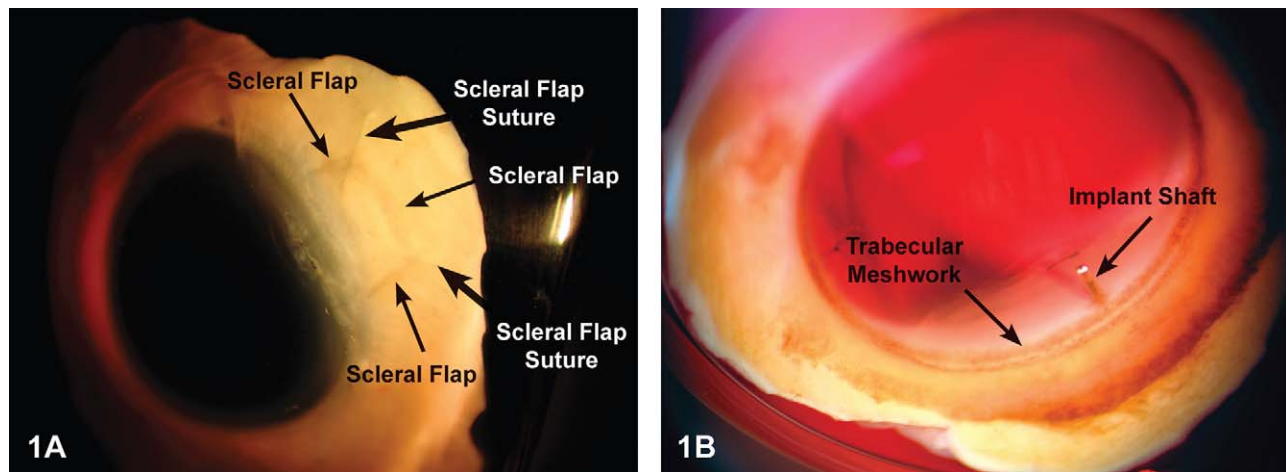


FIGURE 1.—(A) Corneoscleral donor tissue, conjunctival side; diffuse conjunctival filtration bleb is evident as well as the outline of the rectangular scleral flap (full arrows), hinged at the limbus, with two 10-0 nylon sutures at each cornea visible transconjunctivally (empty arrows). (B) Corneoscleral donor tissue, endothelial side; shaft of the device is clearly visible anterior to the trabecular meshwork (full arrows).

The preoperative intraocular pressure (IOP) was 34 mmHg APL (Goldmann Applanation Tonometry; normal value in a Caucasian population is 17 (2.5) mmHg APL), with three topical medications, while the IOP at last follow-up was 13 mmHg, which was maintained during the two years after implantation. APL without medical therapy (reduction: 61.8%, success defined as IOP < 18 mmHg). A diffuse conjunctival filtration bleb was evident (Figure 1A).

The Ex-PRESS drainage device is made of medical-grade stainless steel, has an external plate, and an inner penetrating tip with three holes, one distal and two on its side. The length is 2.42 mm, and the lumen is 200 μ m. The external plate diameter is 1 mm, and plate-to-spur distance is 1.2 mm. The surgical technique is described elsewhere (Dahan and Carmichael 2005).

Corneal Endothelial Staining

The routine Eye Banking procedures were followed (http://www.europeaneyebanks.org/public/_cfm/page/page_871.cfm). Endothelial staining was obtained using trypan blue 0.1% and alyzarine red. Cell counts were performed using a microscope-mounted micrometric grid.

Histological Evaluation

Embedding and specimen preparation were performed by Charles River Laboratories, Pathology Associates, conducted in accordance with Pathology Associates' Standard Operating Procedures (SOPs) and according to U.S. FDA Good Laboratory Practices (21 CFR Part 58).

Two corneoscleral specimens were embedded whole in methyl methacrylate (MMA) blocks. Each block was sectioned once using a diamond-coated band saw, ground to a thickness of approximately 50 microns using the Exakt system (Cano-Sánchez et al. 2005.), polished, and stained with periodic acid schiff (PAS). The section from the specimen containing the

device was prepared to obtain a longitudinal cross-section of the implanted device.

RESULTS

Figure 2A shows a low-magnification image of the histologic section containing the device. In the space between the spur and the flange of the device, a small shoulder of fibrous tissue is visible. A thin, fibrous capsule covered the remainder of the body of the device up to the distal tip, as shown in Figure 2B. No obvious inflammatory cells appeared within the fibrous capsule.

There was no histologic evidence of inflammation or active irritation in either specimen. The iris was absent from both sections. Immediately adjacent to the external flange opening of the device, a clear (drainage) pocket contained an ovoid, moderately dense, acellular, and granular to waxy castlike structure. The structure, primarily PAS-positive, contained numerous punctate black particles. The structure was similar in shape to the clear pocket and had comparable staining to the adjacent connective tissue, which was slightly compressed. There was no tissue reaction adjacent to the structure (Figure 3). While the identity and composition of the structure was unknown, its location and shape were consistent with an accumulation of material associated with the aqueous humor outflow. The PAS-staining characteristics of the material are suggestive of a carbohydrate-rich material. In addition to the granular structure, mild in-growth of fibrous tissue occurred at the anterior pole of the clear pocket. An optical artifact associated with the embedding plastic was observed adjacent to the interior aspect of the flange. No material or blockage occurred within the visible lumen of the device. As expected, no histopathologic abnormalities could be seen in the contralateral cornea.

The corneal endothelium of the two specimens was rated stained with Trypan Blue and Alyzarine red staining to better define cell margins and allow for precise cell count (Figures 1A, 1B, 4A, and 4B). Prior to embedding, the

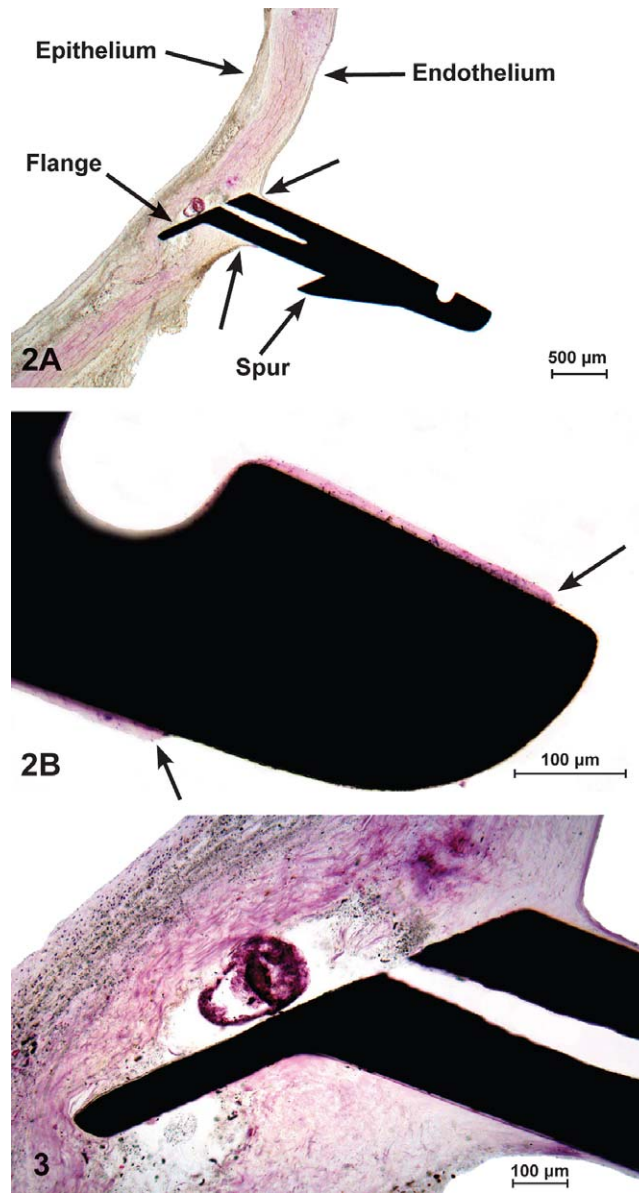


FIGURE 2.—(A) Low-magnification image of cornea with implanted device showing fibrous shoulder (arrows) (PAS). (B) Section showing the distal tip illustrating the end of fine fibrous capsule (arrows) (PAS).

FIGURE 3.—Section showing the flange region with granular structure (with measurements) and fibrous in-growth into clear pocket (PAS).

endothelial-cell count was 2500 cell/mm^2 in the implanted eye and 2600 cell/mm^2 in the nonimplanted eye. This difference was not significant.

DISCUSSION

This is the first report of the histological features of the Ex-PRESS shunt in a human.

The biocompatibility of this device was already tested on rabbit eyes when it was implanted at the corneoscleral junction in eight white New Zealand rabbits (Nyska et al. 2003); the contralateral eye served as control. Three and six months after implantation, the rabbits were killed, and their eyes were

enucleated and processed histologically. Three and six months postoperatively, the local tissue reaction typically consisted of a thin, fibrotic capsule (thickness $< 0.04 \text{ mm}$), devoid of inflammatory cells. This capsule surrounded approximately 25% of the implant surface area present in the sections. The luminae of the devices were devoid of inflammatory exudates or other obstructions in all specimen examined. No differences in the nature and thickness of the capsule three and six months after implantation suggested that the remodelling of the capsular reactive layer into a thin fibrous-tissue capsule occurred in less than three months. Frequently used for glaucoma filtration surgery research (Ayyala et al. 2000; Lloyd et al. 1996), the rabbit is a popular model for analyzing the effects of an

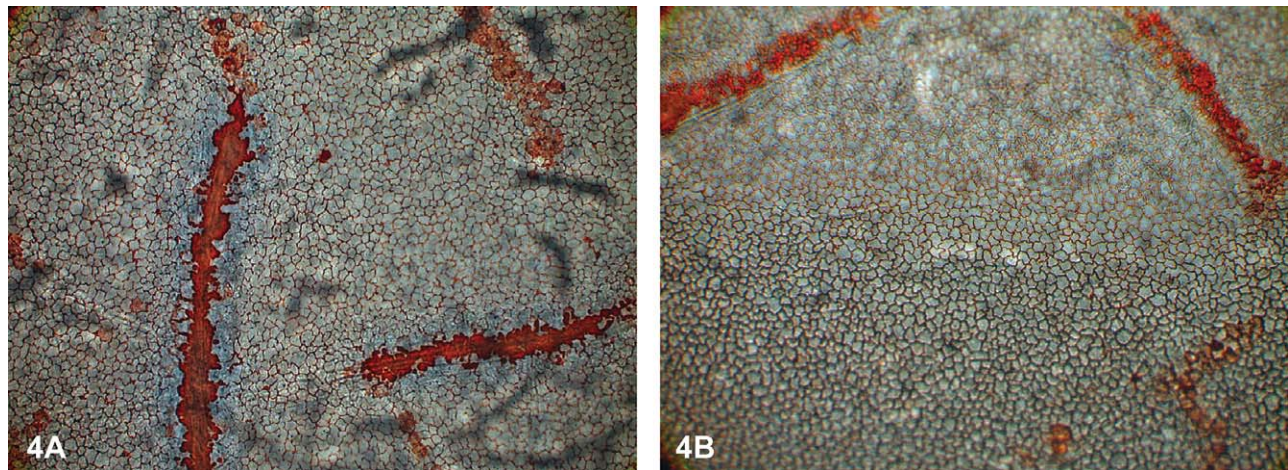


FIGURE 4.—Histologic section of corneal endothelium stained with trypan blue and alyzarin red. The red/brownish striae show areas of cell death due to artifactual tissue folds. (A) Implanted eye, cell count is 2500 cell/mm². (B) Fellow eye, cell count is 2600 cell/mm². These cell counts are equivalent.

implanted device on the scarring reaction due to its tendency to respond with rapid and intense cellular proliferation and fibrin formation.

The results from our study demonstrate a healing response in humans that is very similar to that observed rabbits (Nyska et al. 2003). In both species, the response is characterized by the formation of a thin, fibrous capsule around the majority of the device, lack of scar formation, absence of inflammation, and lack of luminal obstruction. The presence of an unknown, castlike minute structure at the aqueous outflow in the human was the only notable difference. This material did not appear to induce any reaction in the adjacent tissue or have any clinical effects on maintaining IOP in the patient.

Other glaucoma drainage devices are known to cause intensive tissue reaction. A histological study of the Baerveldt implant revealed an outer layer of the capsule composed of fibrous tissue with fibroblasts, macrophages, and inflammatory cells. This could reflect variations in tissue reactions to various foreign substances or a distinct healing response to different implant materials (Lloyd et al. 1996).

The main reason for failure of glaucoma surgery is an insufficient drainage of aqueous, secondary to scar formation. Numerous studies have evaluated the presence of different scar reactions to different devices in the rabbit eye, comparing the Molteno polypropylene device to the Baerveldt and to the Krupin silicon-disc implant (Ayyala et al. 2000) and the polypropylene Ahmed glaucoma valve to the silicone Baerveldt shunt (Ayyala et al. 1999).

The Ex-PRESS is made of medical-grade stainless steel. The oxide layer of 316L stainless steel has conductive electrochemical properties. The conductivity of the oxide and the corresponding electric field that develops adjacent the implant could be determinants of its biologic response (Healy and Ducheyne 1992); the presence of this material has a persistent inhibitory effect on the inflammatory process (Shannon, Thull, and Von Recum 1997).

The corneal endothelium is a nonmitotic monolayer of cells. If damaged, the cell density can be reduced below a critical level (usually 500 cells/mm²) resulting in corneal decompensation occurs (Mian and Sugar 2005). Both specimens in our study show normal endothelium with equivalent cell counts.

The clinical efficacy and safety of the Ex-PRESS have been reported (Traverso et al. 2005; Coupin, Li, and Riss 2007; Maris, Ishida, and Netland 2007).

Our results support that this stainless steel glaucoma drainage device is safe and effective.

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