Journal of Glaucoma 12:275–280

Biocompatibility of the Ex-PRESS Miniature Glaucoma Drainage Implant

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Purpose: Based on lessons learned from earlier attempts, a novel miniature glaucoma implant, Ex-PRESS, was developed in 1998. The current study summarizes the histopathologic evaluation of this device implanted in the eyes of rabbits.

Methods: The device was implanted into the anterior chamber at the corneoscleral junction in 1 eye each of 8 white New Zealand rabbits, while the contralateral eye served as control. Three and 6 months after implantation, the rabbits were killed and their eyes were enucleated and processed histologically, leaving the device in situ when sectioning.

Results: Three and 6 months postoperatively, the local tissue reaction typically consisted of an enveloping, thin, mature, fibrotic capsule (thickness <0.04 mm), devoid of inflammatory cells. This capsule surrounded approximately 25% of the implant surface area present in the sections. The lumina of the devices were devoid of inflammatory exudates or other obstructions in all specimens examined, suggesting free flow of fluid.

Conclusions: The implantation of the Ex-PRESS miniature glaucoma shunt resulted in minimal capsular reaction. Considering the high reactivity of the rabbit eye, it is possible that this implant will induce a smaller cellular inflammatory reaction in the human eye.

Key Words: Aqueous shunts—Biocompatibility—Drainage device—Glaucoma.

Glaucoma drainage devices, first introduced almost a century ago, were designed to control aqueous humor flow with the intention of eliminating hypotony. Much experience has been gained with the use of some of these devices, which has led to many modifications in design, construction, and implantation technique.[1] Nevertheless, the relatively high postoperative complication rates and the relatively difficult, traumatic implantation procedure limit the use of glaucoma drainage devices only to complicated cases after other modes of treatment, both surgical and nonsurgical, have failed.[2]

Following the lead of pioneers in the design and manufacture of glaucoma drainage devices[3–6] and using present-day manufacturing technologies, we developed the Ex-PRESS (Optonol, Neve Ilan, Israel), a miniature unvalved glaucoma implant for draining the anterior chamber into a subconjunctival space. A combination of design and biomaterial improvements coupled with an easier, more rapid, and less traumatic implantation technique will enable a filtering surgery with success rates comparable to those of conventional trabeculectomy without resorting to the use of antiproliferative agents.

Received August 22, 2002; sent for revision December 2, 2002; accepted March 10, 2003.

This study was supported by Optonol Ltd. (Neve Ilan, Israel), the manufacturer of the Ex-PRESS Miniature Glaucoma Drainage Implant.

Dr. Belkin and Dr. Glovinski have proprietary interests in Optonol Ltd., and Dr. Epstein is a consultant to the company.

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Indeed, the short-term efficacy of the Ex-PRESS was demonstrated in a preliminary clinical study.[7]

Inflammation and scarring in the eye, which are due in part to implant bioincompatibility and the degree of trauma sustained by the eye during implantation, can be assessed by histologic and clinical parameters. In the current study, we focused on histopathologic evaluations of the eyes of rabbits implanted with the Ex-PRESS. The efficacy of the device in reducing intraocular pressure and its complications are the subject of another report.

MATERIALS AND METHODS

The Device

The Ex-PRESS, a miniature glaucoma drainage device, is a 3-mm-long tube, 2.5 mm of which is intraocular, with a 400-μ (27-gauge) external diameter and 50-μ inner diameter (Fig. 1). It is made of implantable stainless steel (316L) approved for medical and ophthalmic applications. The device has an outer flange to prevent implantation that is too deep and a spurlike inner projection to prevent extrusion. The flange and spur are designed and angled to conform to the anatomy of the relevant part of the sclera, and the distance between them corresponds to the length of the scleral track made by the device. Thus, movement of the implant in relation to the ocular wall is prevented. The device has 3 side holes near its distal tip to ensure aqueous humor flow if the iris should block the main orifice.

Study Protocol

Eight white New Zealand rabbits (1.8–3.0 kg), housed in the appropriate animal housing, underwent Ex-PRESS implantation with an intramuscular injection of general anesthesia (50 mg/kg ketamine and 10 mg/kg xylazine) given prior to surgery. Topical anesthesia with 0.4% benoxinate was used as needed. Only 1 eye of each rabbit was implanted, while the unimplanted eye served for as a control.

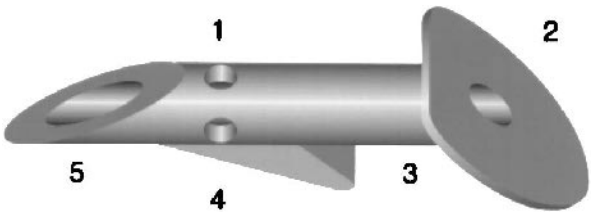

FIG. 1. A diagram of the Ex-PRESS miniature implant (3 mm long, 400-micron outer diameter). 1—Three orifices at the distal end, constituting an alternative conduit for aqueous humor drainage in case of occlusion of the primary (axial) opening by the iris. 2—Very thin (75μ) external flange assures a pre-determined implantation depth. 3—The distance between the flange and the spur precisely corresponds to the scleral thickness. 4—Spur for preventing extrusion of device from the eye. 5—Lumen for draining aqueous humor from the anterior chamber to the subconjunctival space.

In order to study the long-term biocompatibility of the device, 3 animals were killed 3 months after implantation and 5 animals were killed 6 months after implantation by an intracardiac injection of sodium pentobarbital (50 mg/kg). Eyes were enucleated immediately after death.

All procedures, care, and treatment of rabbits were in accordance with the principles of humane treatment outlined by the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health) and the guidelines set by the Association for Research in Vision and Ophthalmology for the use of animals in ophthalmic and vision research.[8] The study was conducted after approval by the local Committee for Ethical Conduct in the Care and Use of Laboratory Animals and in compliance with the rules and regulations set forth.

Implantation Procedure

The implantation procedure required 2 to 5 minutes and consisted of 3 steps. First, a small snip-incision was made in the conjunctiva 10 to 15 mm from the limbus. The device mounted on its introducer was then inserted through the conjunctival incision and slid, under direct visualization, between the conjunctiva and the sclera (under Tenon's capsule) toward the limbus. It was positioned parallel to the iris and pushed into the anterior chamber at the corneoscleral junction, at the 10-o'clock position. Counterpressure was applied to the opposite side of the eye when the device penetrated the anterior chamber. Finally, the introducer was withdrawn after the proper location of the device in the eye was ascertained. The conjunctiva was not sutured, and no postoperative medications were administered.

Histological Evaluation

The enucleated eyes were fixed in Davidson solution for 72 hours and stored in 70% ethanol. Eyes were processed histologically, leaving the device in situ when sectioning. Tissues were trimmed, embedded in methylmethacrylate, and routinely processed for light microscopy. Sections were stained using the PAS reaction. One histologic section was generated per eye. The sections were obtained from a standard location within the eye to reduce potential variability between the eyes. A board-certified toxicological pathologist (AN) performed the histopathologic evaluation.

Each sample was evaluated and graded for histopathologic changes. The reactive and inflammatory changes were assigned severity grades of 0 to 4 representing unremarkable, minimal, mild, moderate, and marked changes, respectively. Evaluated parameters included presence of the capsule and histologic components of the capsule (i.e., inflammatory cells including giant cells, fibroblasts, and mature collagen). The percentage and location of the device's surface area that was encapsulated was assessed. The thickest part of the capsule at all locations along the device, designated as proximal (external/subconjunctival), middle, and distal (intracameral) areas, was measured with a calibrated lens micrometer. The results were compared with the histologic picture of the contralateral side of the unimplanted eye.

RESULTS

Results of the histopathologic evaluation are summarized in Table 1. No differences in the inflammatory reaction and capsule thickness or composition were noted when samples from the 3- and 6-months implant periods were compared. A photographic representation of the tissue reaction noted in an exemplary case 3 months after implantation (case # OS-1), with comparison to the contralateral side of the unimplanted eye, is shown in FIG. 2.9. At 3 and 6 months postoperatively, the local tissue reaction typically consisted of an enveloping, thin, mature, fibrotic capsule (thickness <0.04 mm) with modest number of fibroblastic nuclei devoid of inflammatory cells. The fibrotic capsule surrounded approximately 25% of the implant outer surface area. In most cases, this fibrotic capsule enveloped the external surface of the flange (mean thickness 0.04 mm) and covered a portion of the proximal and distal regions of the device (mean thickness <0.01 mm). The lumen was free of obstruction in all specimens.

TABLE 1. *Detailed histological evaluation of eyes of rabbits implanted for 3 and 6 months with Ex-PRESS miniature glaucoma drainage device*

Case #	Duration (mo)	Fibrotic capsule*	
		Thickness (mm)	Location
1/OS	3	0.03–0.04	Proximal
2/OD	3	0.01	Distal and middle
		0.04	Flange
3/OS	3	0.04	Distal
		0.01	Spur
		0.02–0.04	Proximal and flange
4/OS	6	0.01	Proximal
		0.04	Flange
5/OD	6	0.01	Proximal and middle
6/OD	6	0.02	Distal
		0.01–0.02	Middle and proximal
		0.08	Flange
7/OS	6	<0.01	Distal
8/OS	6	No capsule	

* No evidence of active inflammatory reaction was noted in any of the samples examined. No pathological changes were present in any ocular tissue proximal to or distant from the device.

OS, left eye; OD, right eye.

No pathologic reaction was noted at 3 or 6 months postimplantation in any other ocular tissue (e.g., cornea, limbus, sclera, iris, lens, vitreous body) located in the proximity of the implanted device. Also, no pathologic changes were present in any ocular tissue distant from the device (e.g., retina and choroid). In all specimens examined, the lumina of the devices were patent and unobstructed by inflammatory exudates.

DISCUSSION

Histopathologic evaluation of the eyes implanted with the Ex-PRESS miniature glaucoma implant, performed 3 or 6 months after implantation, revealed no evidence of any active inflammatory reaction or tissue irritation. The only reaction noted consisted of the development of a relatively thin mature capsule, enveloping up to 25% of the implant outer surface area; there was no evidence of obstruction of the lumen of the device. Similar investigations of other glaucoma drainage devices revealed more intensive tissue reactions. Inflammatory cells as well as blood vessels were found in the outer layers of the capsular tissue surrounding the Molteno implant in primates at postimplantation times similar to ours.[9] A histologic study of the Molteno implant in human eye, performed 8 months after implantation, revealed that the outer wall of the capsule was composed of fibrous tissue with fibroblasts, inflammatory cells, and macrophages.[10] That these inner linings of the capsule reflect variations in tissue reactions to foreign substances by diverse species or a distinct healing response to different implant materials was suggested.[11]

Bleb failure secondary to scar formation, a complication that may be related to biomaterial-associated inflammation, is the main reason for failure of glaucoma drainage devices. A study that examined the inflammation associated with the Molteno polypropylene device versus the Baerveldt and Krupin silicon-disc implant emphasized this point.[12] Likewise, another study demonstrated that, in the rabbit subconjunctival space, the polypropylene Ahmed glaucoma valve is more inflammatory than the silicone Baerveldt shunt.[13]

The Ex-PRESS implant biocompatibility was demonstrated by the formation of only a very thin fibrotic capsule with a thickness equal to or less than 0.04 mm. No pathologic reaction was noted in the ocular tissue within

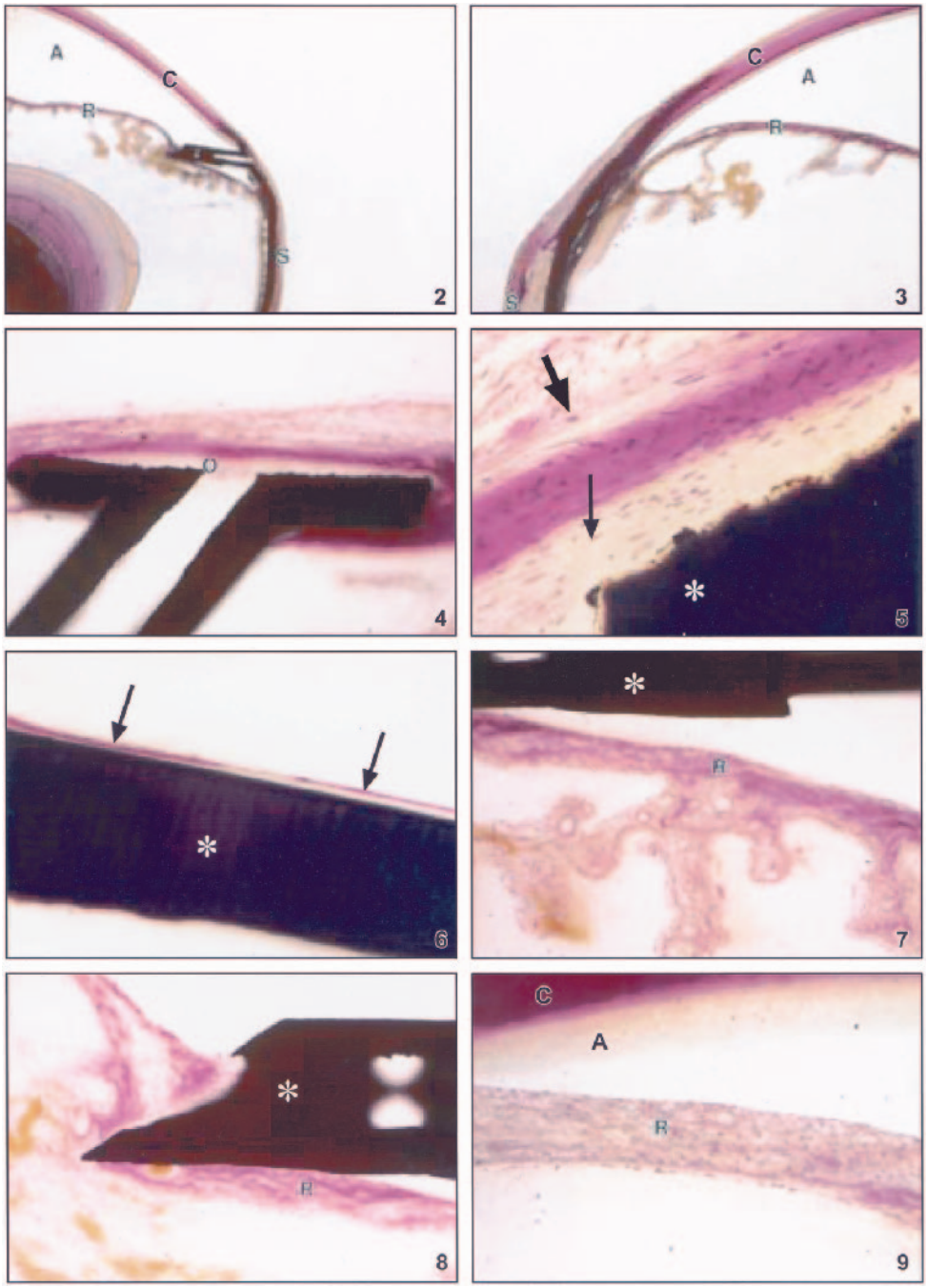

FIG. 2. Photographic presentation of histologic sections of the eyes of animal # OS-1, killed 3 months after implantation. Figures 2.2 and 2.4–2.8 are from an Ex-PRESS–implanted eye; Figures 2.3 and 2.9 are from contralateral side of an unimplanted eye. The eyes were embedded in methylmethacrylate, then routinely processed for light microscopy, and stained with PAS reaction. Figures 2.2 (X20) and 2.3 (X40) show low and intermediate magnifications of the site of implantation and localization of the device (A, anterior chamber; C, cornea; R, iris; S, sclera). Figures 2.4 (X100) and 2.5 (X200) depict the fibrotic capsule surrounding the external surface of the disc (mean thickness 0.04 mm). Figure 2.4 shows the unblocked external opening (O) of the device; Figure 2.5 shows the fibrotic capsule with modest amount of fibroblastic nuclei (arrows), devoid of inflammatory cells, lying over the middle aspect of the external opening (asterisk indicates the medial aspect of the device). The capsule consists of acidophilic (thick arrow) and paler (thin arrow) layers. The reason for changes in staining characteristics is unknown; they may be related to more mature collagen present in the acidophilic layer. Figure 2.6 (X200) reveals the very thin (<0.01 mm) fibrotic capsule covering the proximal part of the device (asterisk) located close to the disc. Figure 2.7 (X200) shows the approximately middle part of the device, surface close to the iris (R). Note the absence of any tissue reaction. Fig 2.8 (X200) shows the patent side holes of the device and demonstrates that the distal tip of the device is in close contact with the iris. Comparison with the contralateral side of the unimplanted eye (Fig. 2.9) and particularly the lack of any indication of tissue reaction suggest that the close contact of the device with the iris surface (R) is artifactual, having occurred during tissue processing.

the proximity of the implant device or any other ocular tissue distant from the device. The finding that there were no differences in the nature and thickness of the capsule 3 and 6 months after implantation suggests that the remodeling of the capsular reactive layer into a thin fibrous-tissue capsule occurred less than 3 months from implantation. No evidence for implant corrosion (e.g., granulomatous foreign-body reaction) was noted, suggesting stability, with no leaching of metallic components from the device embedded within the ocular tissue up to 6 months.

Several factors including material composition, implant design, physicochemical surface properties, condition of the host bed, surgical technique, and mechanical properties have been suggested to influence the inflammatory response to the devices and their outcome.[14,15] The Ex-PRESS, which is made of stainless steel, offers better biocompatibility characteristics than polymers. 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 have been proposed as possible determinants of the biologic response to the presence of such an implant.[16] Unlike normal healing, the presence of this material has a persistent inhibitory effect on the inflammatory process.[17,18] When a chronic inflammatory response or the development of fibrous granulation tissue follows implantation, collagen synthesis increases as the fibers become oriented parallel to the concentric layers of the surface-forming capsule around the implant. This process is minimized with a stainless steel implant.

The results presented in this report were obtained in a rabbit's eye, and may not be directly applicable to humans; however, the rabbit is the common model for glaucoma filtration surgery as well as implantation of drainage devices.[12] Furthermore, the much more rapid and intense fibrin formation and cellular proliferation in rabbit render the rabbit eye a preferable model for studying the effects of an implanted device on the scarring reaction. The low-grade inflammatory and scarring reactions that have been observed in the rabbit eye are encouraging when application of the device to the human eye is contemplated.

Failure in filtering surgeries often occurs because of early fibroblastic proliferation of episcleral cells in the subconjunctival space[19] and emphasizes the importance of a surgical procedure that is minimally irritating. Indeed, the conjunctival opening and consequent suturing 10 to 15 mm away from the limbal penetration site, the short implantation procedure duration of less than 5 minutes with minimal tissue manipulation; no extensive trauma to the conjunctiva, Tenon capsule, sclera, or limbus; no usage of cautery; and no performance of iridectomy contributed to the minimal inflammatory and fibrotic reactions, even without the use of antiproliferative agents.

The major determinant of long-term intraocular pressure levels after glaucoma filtering surgery is the healing response. Therefore, antiproliferative agents such as fluorouracil and Mitomycin C are often used to improve the prognosis of filtration surgery.[20–22] The use of antiproliferative agents raises the associated question of risk versus benefit. Although population surveys show a higher success rate after filtering surgery when antiproliferative agents are used, the risk of complications becomes higher. Therefore, a technique that does not require the use of antiproliferative agents offers, from a safety perspective, an advantage over other techniques in which these agents are used.

In summary, implantation of the Ex-PRESS miniature glaucoma shunt resulted in minimal inflammatory and scarring reactions in rabbit eyes. These results are encouraging because fibrin formation and cellular proliferation are much more rapid and intense in rabbits than in humans; therefore, it is possible that in the human eye the tissue response will be less extensive.

Acknowledgment: The authors thank Ms. JoAnne Johnson (NIEHS) for her critical review of the manuscript.

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