

Investigation of Surgical Techniques for Optimization of Long-Term Outcomes of LCP-Based Retinal Prosthesis Implantation

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Purpose: To investigate reproducible surgical techniques to optimize the long-term safety of liquid crystal polymer (LCP)-based retinal prosthesis implantation.

Methods: An LCP-based retinal prosthesis is fabricated monolithically on a single-body LCP substrate with all components, including the package and electrode array. We implanted the electrode array into the suprachoroidal space and anchored the package and transition part to the sclera in rabbits ($n = 11$). The safety profile was assessed upon the completion of the surgery and postoperatively.

Results: The surgical procedures for implantation of the entire system were easily performed in nine eyes (81.8%) without any intraoperative complications. In the other two eyes (18.2%), surgical complications related to electrode insertion, including optic nerve damage and retinal tear, arose. In 10 eyes (90.9%), the devices were well tolerated for at least 3 months. However, in most eyes (nine; 81.8%), two complications began to appear after 3 months, postoperatively, including conjunctival erosion or dehiscence over the package or transition part. The electrode arrays were maintained safely in the suprachoroidal space after surgery without any complications, regardless of the status of the extraocular components in all cases except two intraoperative complications.

Conclusions: We established safe and reproducible surgical techniques for implantation of our LCP-based retinal prosthesis into the suprachoroidal space. Although issues related to surgical technique or device configuration were identified, further technical solutions would improve the long-term safety of device implantation.

Translational Relevance: This study presents successful implantation of LCP-based retinal prosthesis. The technical solutions will permit an optimization of surgical techniques.

Introduction

Restoration of vision by retinal prosthesis implantation for electrical stimulation of the residual retinal neurons in blind patients suffering from retinal degenerative diseases such as retinitis pigmentosa or age-related macular degeneration is both promising

and challenging. Retinal prosthesis design, in general, is based on a hybrid combination of a polymer-based electrode array and a hermetic package formed by metal or ceramic. The electrode array is implanted into the eyeball to stimulate residual retinal neurons at different levels, including epiretinal,¹ subretinal,^{2,3} and suprachoroidal sites.^{4,5} Retinal prosthesis im-

plantation surgery, intraocular placement of the electrode array especially, requires high-level surgical skills to avoid damage to the diseased retina and achieve stabilization of the implanted device components. The extraocular components of the retinal prosthesis comprise a connecting cable and a hermetic package that contains electronics, including a receiver coil that couples with an external coil for power supply and signal transmission through wireless electromagnetic transfer. Most hermetic packages currently are made of metal or ceramic for good mechanical stabilization and biocompatibility with the human body. However, their bulky and heavy properties might compromise the long-term safety of prosthetic devices. Conjunctival erosion and dehiscence have frequently appeared over packages or connecting cables in worldwide trials.^{6,7}

Our group has developed and manufactured a seamless liquid crystal polymer (LCP)-based monolithic retinal prosthesis by integrating its components (i.e., inductive coil, circuit, electrode array) on an LCP substrate.⁸ The thin and light prosthetic device fits the curved surface of the human eyeball.^{9,10} We have already demonstrated in a preclinical study that the LCP-based retinal prosthesis can be successfully implanted in its entirety into the suprachoroidal space and on the sclera.⁸ We had focused on the development of basic implantation procedures and assessment of long-term biostability of the device itself in the previous report.⁸ However, establishment of reliable and reproducible surgical procedures ensuring the long-term safety of the prosthesis remains a challenge. The purpose of the present study was to investigate reproducible surgical techniques for optimization of the long-term safety of the overall LCP-based retinal prosthesis system.

Methods

All of the procedures in this study were approved by the Animal Care and Use Committee of Seoul National University Hospital and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research as well as the policies in the *Guide to the Care and Use of Laboratory Animals* issued by the US National Institutes of Health.

LCP-Based Retinal Prosthesis

The implanted components of the LCP-based retinal prosthesis consist of a circular package, an

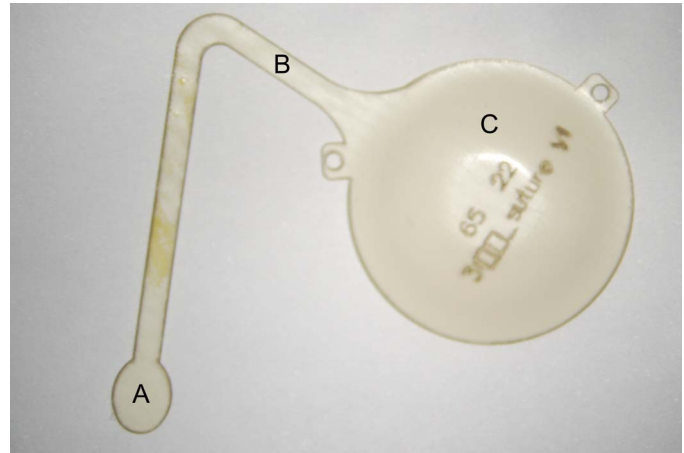


Figure 1. Overall configuration of dummy retinal prosthesis monolithically fabricated on LCP. The dummy device specifications were varied per device including suturing hole location, transition part angle, electrode array length. (A) Electrode array. (B) Transition part. (C) Package.

electrode array, and a transition part between the package and the array (Fig. 1). The device with all of its components is fabricated monolithically on a single-body LCP substrate.^{9,11,12} The device's overall design is streamlined for attachment to the curved eyeball surface. Full details on the device have been described in a previous report.¹¹ The circular package, an eye-conformable structure resulting in a crescent-shaped cross-section as shown in Jeong et al.,¹¹ has a maximum thickness of 1.3 mm and a diameter of 14 mm.¹¹ The electrode array, as formed by a laser-thinning process, has a thickness of 30 μm .^{11,13} The maximal width of electrode array was 3 mm. The transition part is deflected to connect the array with the package. The complete unit of the device encases the planar receiving coils and current stimulator with electronic circuits. However, in this study, we used dummy devices that are physically identical to the complete unit, but lack any embedded components. The specifications of the dummy devices varied as follows: electrode array length ranging from 16 to 22 mm, transition part angle ranging from 60° to 70°, and suturing holes along the anterior or posterior margin of package or transition part.

Surgical Procedures for Implantation of Retinal Prosthesis

Healthy adult New Zealand white rabbits aged 8 weeks were used in this study. They were anesthetized by intramuscular injection of tiletamine/zolazepam (Zoletil; Virbac, Carros, France) and xylazine (Rom-

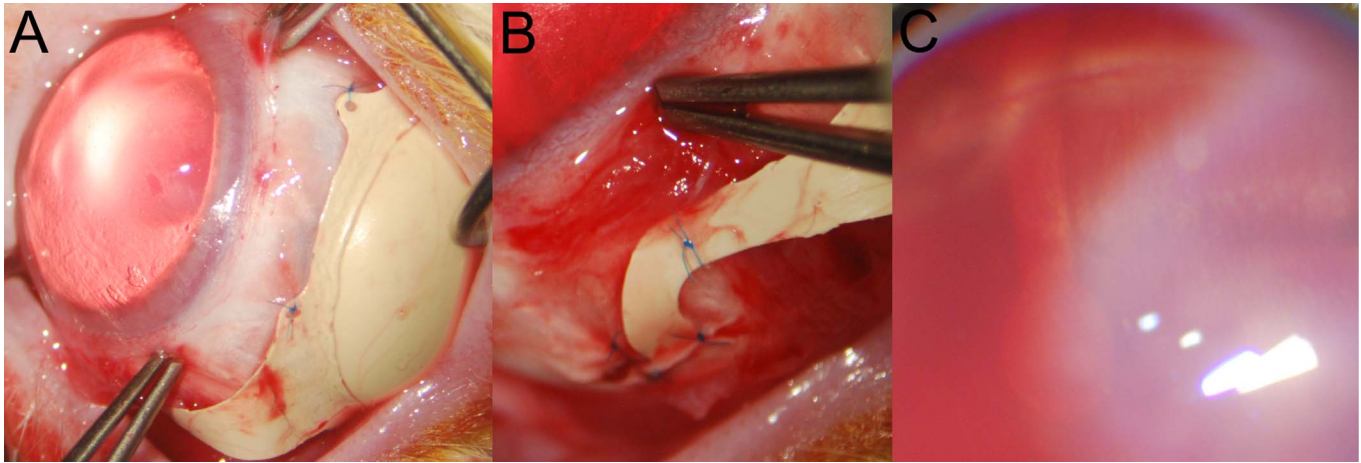


Figure 2. Surgical procedures for suprachoroidal implantation of retinal prosthesis in rabbits. (A) The package is attached to the scleral surface by fixation sutures. (B) The electrode array is inserted into the suprachoroidal space through the scleral incision, and the transition part is anchored to the sclera by fixation sutures. (C) The electrode array is successfully implanted into the suprachoroidal space without any complications such as suprachoroidal or subretinal hemorrhage.

pun; Bayer AG, Leverkusen, Germany) in a 1:1 mixture at a dose of 0.6 mL/kg. Before surgery, the eyelids and ocular surfaces were prepared with povidone-iodine solution, and the overall system was soaked in 70% ethanol and rinsed with sterile saline.

A total of 11 eyes of 11 rabbits were operated on for implantation of the LCP-based retinal prosthesis. The surgical procedures were performed by one vitreoretinal surgeon (SHB). After induction of anesthesia, fornix-based superior conjunctival peritomy was performed. In each experiment, the surgeon simulated where to fix the package and where to make an incision to access the suprachoroidal space. Fornix-based scleral tunneling (4×2 mm) was performed at least 3 mm from the corneal limbus posteriorly in the superonasal quadrant using a crescent knife (Sharptome 74-1010; Surgical Specialties Co., Reading, PA). At the base of the scleral tunnel, a scleral incision was made to approach the suprachoroidal space. The configuration of the scleral incision is straight and parallel to the limbus and of a length of at least 4 mm. Prior to electrode array insertion, the sclerotomy entrance was lubricated, and each electrode was coated with a viscoelastic substance such as Healon (Abbott Medical Optics, Santa Ana, CA) or Viscoat (Alcon Laboratories, Fort Worth, TX). The electrode array was inserted into the suprachoroidal space without the aid of any guide foil. The advancement of the electrode array was carefully monitored under fundus examination with a wide-field lens (Quad Pediatric; Volk Optical Inc.,

Mentor, OH). The surgeon modified the path of the electrode array in order to position the forepart under the visual streak near the papilla. If the path of the electrode array was inadequate, the array was retracted and reinserted in the correct direction. The scleral incision was sealed with interrupted sutures, if needed. The package was placed deeply into the subconjunctival pocket in the superotemporal quadrant. It was anchored onto the sclera by interrupted sutures along its margin. The transition part between the package and the electrode array was attached to the sclera over the superior retractor bulbi muscle by several interrupted sutures in all cases except one. In one case (case 5), the transition part was passed under the superior retractor bulbi muscle after retraction of muscle. The conjunctiva was repaired with interrupted 8-0 polyglycolic acid sutures (Vicryl; Ethicon Inc., Somerville, NJ). Subconjunctival injections of gentamicin were administered upon completion of the surgery. Topical antibiotics (moxifloxacin 0.5%) and corticosteroid (prednisolone acetate 1%) were applied to the operated eye postoperatively for 1 to 2 weeks. A representative case of implantation surgery (case 8) is shown in [Figure 2](#).

Assessment of Safety During and After Surgery

The feasibility of each of the surgical steps was evaluated at the discretion of the surgeon. Additionally, the safety profile was assessed upon completion of the surgery and postoperatively. The fundus was carefully examined under a wide-field lens to confirm

the presence of any intraocular hemorrhage, retinal tear or detachment, optic nerve damage, or endophthalmitis. The anterior segment of the eyeball was inspected under an operating microscope to detect any signs of infection, conjunctival erosion or dehiscence, or cataract progression. Photographic images of the fundus and anterior segment of the eyeball were obtained regularly during the follow-up periods in order to evaluate any displacement of the device relative to certain ocular landmarks. Optical coherence tomography (OCT) (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) was obtained across the tip of electrode implanted suprachoroidally.

Results

The surgical outcome of each case is summarized in the [Table](#).

Implantation Surgery

The surgical procedures for implantation of the prosthetic system were easily performed in 9 of 11 cases. With the exception of two cases (cases 5 and 10), there were no major intraoperative complications such as massive choroidal or subretinal hemorrhage, vitreous hemorrhage, or retinal detachment. The distance between the limbus and scleral incision ranged from 3 to 7 mm: 3 to 4 mm in seven eyes (63.6%), 4 to 6 mm in one eye (9.1%), and over 6 mm in three eyes (27.3%). The sclerotomy sites were well-preserved without any significant bleeding during the scleral incision or insertion of the electrode array. The fundus examination under a wide-field lens clearly visualized the advancement of the electrode without any need of assistance by guiding foil. The tips of the electrode arrays were properly located under the visual streak near the papilla in six eyes (54.5%; [Fig. 3](#)). In addition, the positions of the tips were acceptable in three eyes (27.3%); did not reach the visual streak, only the medullary ray, in one eye (9.1%, case 3) due to the short length (16 mm) of the electrode array; and passed through the visual streak by 1 to 3 disc diameters in two eyes (18.2%; cases 8, 9). The remaining two eyes showed inadequate electrode placement with surgical complications related to electrode insertion: optic nerve damage in one eye (case 5) and retinal tear in one eye (case 10). In case 5, the optic nerve was penetrated by the electrode array due to the surgeon having misjudged the course of insertion and the position of the package. In case 10,

the retinal tear developed near the visual streak due to the excessive force exerted for advancement of the electrode array. In both of those cases, the scleral incision was made more than 6 mm from the limbus. In all cases, the packages and transition parts were successfully anchored onto the scleral surface. The distance between the limbus and the anterior margin of the package ranged from 2.5 to 4 mm.

Postoperative Assessments

In all cases except one, the devices were safely implanted in the eyeball for at least 3 months. In that one exceptional case (case 9), the surgeon found extreme redundancy of transition part due to malposition of device during surgery. The surgeon had tried to attach the transition part to the scleral surface by anchoring sutures to minimize the bulging of that part, but failed. The protruded portion of the transition part eventually resulted in conjunctival dehiscence and displacement of the package by 1 month postoperatively. Over the 3-month period, in most cases, there appeared to be two crucial complications related to the extraocular components of the devices: exposure of the package or of the transition part. Conjunctival erosion or dehiscence over the transition parts was detected in four cases postoperatively: two cases at 4 months (cases 2 and 7) and two cases at 10 months (cases 3, 11; [Fig. 4](#)). Conjunctival dehiscence over the package was shown in five cases: four cases at 6 months (cases 1, 4, 8, 10) and one case at 8 months (case 6). The packages began to be pushed forward and rotated gradually, followed by detachment of the fixation sutures. This resulted in excessive tension of the overlying conjunctiva along the anterior margin of the package, which in turn induced the conjunctival dehiscence and displacement of the package. In those cases, the transition part passed over the superior retractor bulbi muscle and directly contacted the overlying conjunctiva. However, in one case (case 5), the transition part was attached to the sclera under the retractor bulbi muscle and was maintained without any conjunctival erosion or dehiscence over the course of 1 year. No signs of infection related to the device were detected prior to the development of conjunctival erosion or dehiscence over the external components of the prosthesis.

The fundus examinations revealed that, in general, the electrode arrays in the suprachoroidal space were well tolerated without any significant postoperative complications such as intraocular inflammation, hemorrhage, or array drift, regardless of the postop-

Table. Summary of Surgical Outcomes for Suprachoroidally Implanted LCP-Based Retinal Prosthesis

Rabbit No.	Scleral Incision Position From the Limbus, mm	Position of Electrode Array Tip	Intraoperative Complication	Postoperative Complication Related to External Component of Device		Postoperative Complication Related to Intraocular Component of Device	
				Onset	Type	Onset	Type
1	3	Under visual streak	None	6 mo	Conjunctival erosion/dehiscence over package		None
2	3	Under visual streak	None	4 mo	Conjunctival erosion/dehiscence over transition part		None
3	3.5	Acceptable ^a	None	10 mo	Conjunctival erosion/dehiscence over transition part		None
4	3.5	Under visual streak	None	6 mo	Conjunctival erosion/dehiscence over package		None
5	6.5	Inadequate ^b	Optic nerve damage during electrode array insertion	12 mo	None	3 mo	Displaced electrode array into vitreous cavity
6	3.5	Under visual streak	None	8 mo	Conjunctival erosion/dehiscence over package		None
7	3.5	Under visual streak	None	4 mo	Conjunctival erosion/dehiscence over transition part		None
8	5	Acceptable	None	6 mo	Conjunctival erosion/dehiscence over package		None
9	6.5	Acceptable	None	1 mo	Conjunctival dehiscence over transition part		None
10	6.5	Inadequate	Retinal tear during electrode array insertion	6 mo	Conjunctival erosion/dehiscence over package	4 mo	Chorioretinal atrophy along the path of the electrode array
11	3.5	Under visual streak	None	10 mo	Conjunctival erosion/dehiscence over transition part		None

mo, months.

^a The tips of the electrode arrays were located within 3 disc diameters of the visual streak.

^b The tips of the electrode arrays were located over 3 disc diameters of the visual streak.

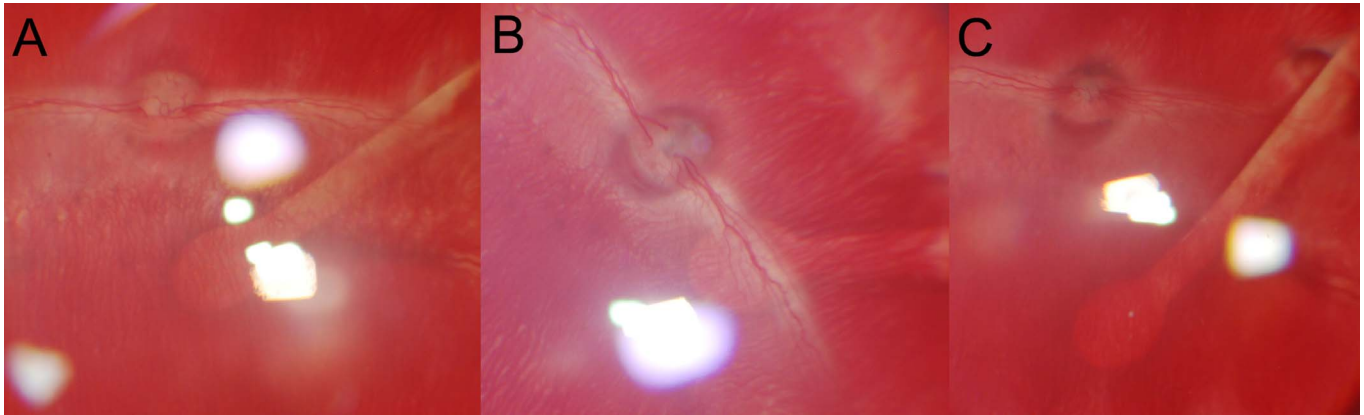


Figure 3. Position of suprachoroidally implanted electrode array. (A) The electrode tip is properly located under the visual streak. (B) The electrode tip is placed under the medullary ray due to the short length of the electrode array. (C) The electrode array passes through the visual streak due to the improper position of the scleral incision.

erative status of the extraocularly implanted components. The OCT images confirmed the proper positioning of the implanted electrode arrays in the suprachoroidal space. The representative case with postoperative OCT image is shown in [Figure 5](#). However, optic nerve or retinal damage continued to progress in the two aforementioned cases of intraoperative electrode-related complications: in one eye (case 5), the electrode array was displaced into the vitreous cavity as the result of optic nerve penetration, and in the other eye (case 10), chorioretinal atrophy along the path of the electrode was gradually extended as the result of retinal tear, but without development of retinal detachment.

Discussion

The surgical techniques for implantation of the LCP-based retinal prosthesis were relatively safe and reproducible in this study. However, we experienced two cases of complications resulting from inappropriate advancement of the electrode array into the suprachoroidal space. In one case, the surgeon selected an improper position of scleral incision, which was located too far posteriorly, resulting in failure to refine the electrode array insertion adequately and, thus, optic nerve damage. In another case, a retinal tear developed as a result of the application of excessive force to push the electrode

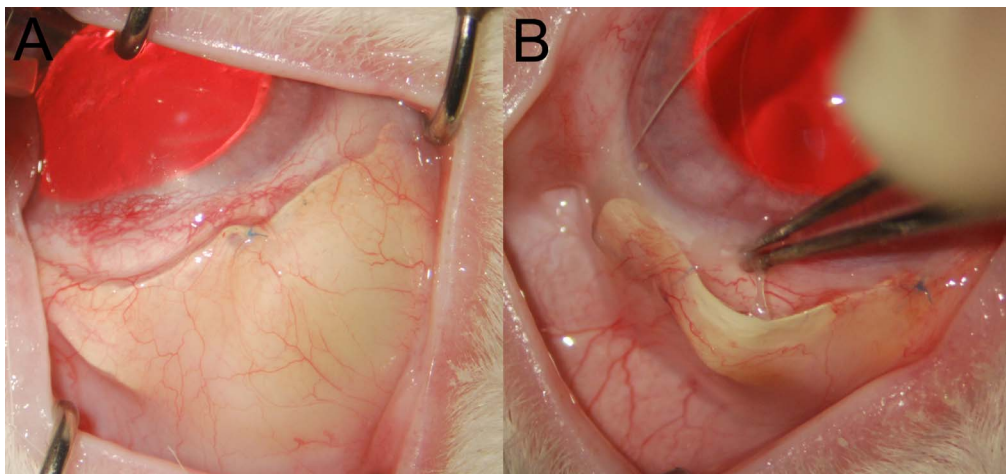


Figure 4. Anterior photographs of implanted retinal prosthesis package. (A) Implanted package on sclera with intact overlying conjunctiva 2 months after surgery. (B) Conjunctival dehiscence over transition part of implant 4 months after surgery.

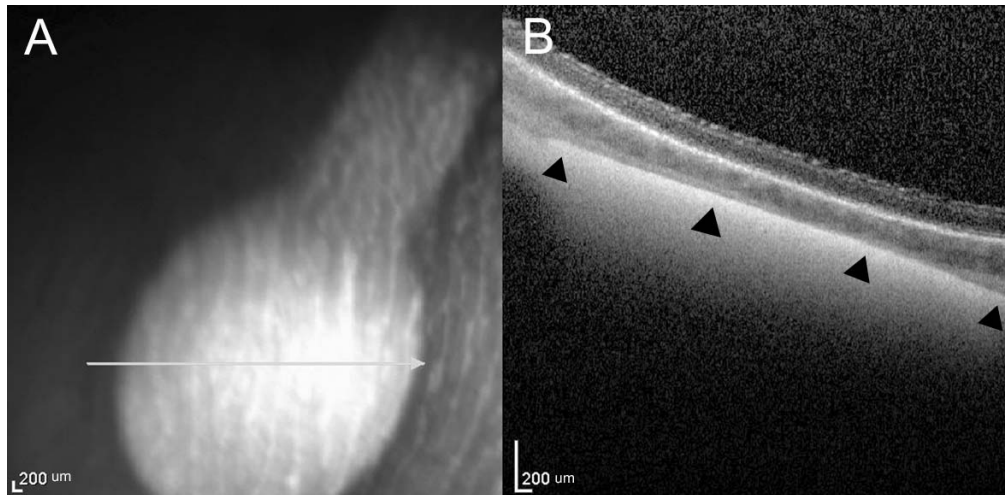


Figure 5. Representative OCT image of electrode array at 6 months after implantation surgery. (A) Infrared fundus image shows the location of electrode array. (B) Cross-sectional image through the *white arrow* in (A) shows the normal retinal structure overlying the implanted electrode array. *Black arrowheads* indicate the suprachoroidally implanted electrode array.

array into the suprachoroidal space. The monolithic fabrication process of LCP-based prosthesis includes the thermal bonding of LCP layers using a heating press.¹¹ A few LCP-based electrode arrays became slightly inflexible after the thermal bonding process. Such an unexpected fabrication result might have contributed to the development of the retinal tear in case 10. Correct positioning of each component of the retinal prosthesis is critical to its successful implantation. A scleral incision approximately 3 to 5 mm from the limbus was suitable for sufficient modification of the directionality of the electrode array. The proper orientation of the electrode array for arrival at the predetermined site should be planned preoperatively based on dimensional information on both the specific eyeball and the device. If the implantation surgery is performed on 8-week-old rabbits, the following conditions would be suitable for an electrode array to arrive properly under the visual streak: an LCP-based retinal prosthesis of 20- to 22-mm length and 65° to 70° angle between the electrode array and the transition part; a scleral incision 3 to 4 mm from the limbus and medial margin of the superior retractor bulbi muscle in the superonasal quadrant; complete insertion of the electrode array at the scleral incision to meet the transition part. Additionally, gentle manipulation with vigilant attention is needed to accomplish safe implantation of the retinal prosthesis without damage to the retina or device.

The implanted LCP-based retinal prosthesis was well tolerated for 3 months postoperatively. However,

subsequently, a critical complication related to the extraocular components of the device began to manifest: conjunctival erosion or dehiscence over the package or transition part. Conjunctival erosion or dehiscence, followed by device exposure, has been a persistent complication related to extraocularly implanted devices such as glaucoma drainage devices and retinal prostheses. As previously reported, our LCP-based retinal prosthesis (dimensions: 16 × 13 × 2.1 mm) is geometrically comparable to the Ahmed Glaucoma Valve (Model FP7; New World Medical, Inc., Rancho Cucamonga, CA).¹¹ Reported incidences of conjunctival erosion over a glaucoma drainage device have been as high as 30%.¹⁴ Rates of device exposure have been reduced by the introduction of patch grafts such as those based on the human sclera¹⁵ and human pericardium.¹⁶ Despite such technical improvements, however, exposure of the device remains one of the most common complications after implantation surgery of a glaucoma drainage device. Similar to the case of glaucoma drainage device, conjunctival erosion or dehiscence over a retinal prosthetic device has been the most prevalent adverse event in most clinical trials, with reported rates of 23.3% (7 of 30 subjects) for Argus II (Second Sight, Sylmar, CA)⁶ and 55.6% (five of nine subjects) among a Tübingen patient group for Retinal Implant Alpha IMS (Retinal Implant AG, Reutlingen, Germany).⁷

Several mechanisms for conjunctival erosion or dehiscence can be postulated, including mechanical friction of the eyelid and the tension of device to the

conjunctiva, particularly in cases of exposure of the transition part. In the present study, the surgeon attempted to anchor the transition part completely to the sclera with additional fixation sutures, but bulging of the transition part lead to excessive tension to the overlying conjunctiva. Such bulging can be ameliorated by covering the transition part by the superior retractor bulbi muscle or patch graft using donor sclera or by utilization of a modified design for complete attachment to the sclera. In one case (case 5), the transition part of the device was passed under the retractor bulbi muscle, resulting in excellent long-term safety of the device without any conjunctival erosion or dehiscence. However, this procedure might lead to inadvertent damage to the device. Thus, in the future, we will detach the retractor bulbi muscle before anchoring the device onto the sclera, followed by reattachment of muscle to minimize the damage to the device. However, in the present study, the mechanism of conjunctival dehiscence over the package was presumed to be different. The rabbit, compared with humans, has compressed dimensions in its anteroposterior axis, with a shorter axial length of 16 to 19 mm and a larger and steeper cornea,¹⁷ whereas the dummy devices used in our study had been manufactured to fit conformably to the human eyeball. The fixation sutures along the margin of the package became detached. Then, the displacement of the package began to progress, leading to the development of conjunctival dehiscence. In summary, the dummy device was pushed forward, followed by its detachment due to the configuration mismatch between it and the rabbit's eyeball. This problem is resolvable by revision of the device configuration for conformal attachment to the rabbit eyeball.

Many technical challenges remain for the improved long-term safety of implantation surgery and the biostability of prosthetic devices. Device miniaturization is one of the key priorities. The initial version of the epiretinal prosthesis, Argus I, is interfaced with a 16-platinum-electrode array embedded in a silicone rubber platform.¹⁸ Its intraocular components include an electrode array less than 1-mm thick and, extending from it, a 600- μ m diameter cable that might be too bulky for intraocular implantation.¹⁹ Meanwhile, the initial subretinal prosthesis version, Alpha IMS, consisted of a silicon-based microphotodiode array chip embedded between polyimide layers of approximately 70- μ m thickness. The current version of the epiretinal implant, Argus II, with its flexible polyimide-based microelectrode array,²⁰ is thinner than the previous version. Presently, a parylene-based electrode

array for better hermetic sealing is under investigation.²¹ Traditionally, hermetic enclosures packaging electronics are formed of titanium (Argus II) or ceramic (Argus I and Alpha IMS) and are joined to a feedthrough to deliver electrical signals to the electrode array.²² Feedthrough technologies, however, with their increasing number of stimulation channels, hinder the device miniaturization that is essential to the development of high-density electrode arrays. Our group offers outstanding prosthetic device miniaturization relative to the leading groups. We successfully manufactured a monolithically encapsulated LCP-based retinal prosthesis that does not require any feedthrough and that, accordingly, allows for further miniaturization comparable to the Ahmed Glaucoma Valve. Additionally, we realized a further reduction of electrode array thickness, to 30 μ m, by means of an advanced fabrication process such as laser-machining.¹³ Furthermore, the long-term reliability of our device, achieved through adequate hermetic sealing, has already been established in a previous report.⁸

In conclusion, in the present preclinical study, we investigated safe and reproducible surgical techniques for implantation of our LCP-based retinal prosthesis into the suprachoroidal space. Issues related to surgical technique or device configuration were identified, including intraocular trauma related to electrode array insertion and conjunctival erosion/dehiscence over the extraocular components of the device, respectively. However, we expect that the technical solutions suggested herein, along with the superiority of our miniaturized device, will improve the long-term safety of its implantation.

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