One-Year Outcome of 49-Channel Suprachoroidal–Transretinal Stimulation Prosthesis in Patients With Advanced Retinitis Pigmentosa

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PURPOSE. To determine the feasibility of a 49-channel suprachoroidal-transretinal stimulation (STS) retinal prosthesis that was implanted for 1 year.

METHODS. Three patients with advanced retinitis pigmentosa (RP) and with less than or equal to hand motion (HM) vision were studied. A 49-channel STS system was implanted in a scleral pocket, and the stability of the prosthesis, adverse events, and its efficacy were investigated.

RESULTS. The electrode array was implanted in a scleral pocket located under the parafoveal area through a scleral incision at 14 mm in patient (Pt) 1, 16 mm in Pt 2, and 18 mm in Pt 3 from the sclerocorneal limbus. No complications occurred during surgery in all cases. During the follow-up period, iridocyclitis developed in Pt 2 and Pt 3, which was successfully treated with topical medications. The implanted devices continued functioning and elicited phosphenes in all cases. The results of localization tests (P < 0.05) and table tests (P < 0.05) were significantly better with the prosthesis turned on than turned off in Pt 3. The deviations of the walking tests were smaller with the prosthesis turned on than off in Pt 2 and Pt 3 at multiple times after the implantation.

CONCLUSIONS. The 49-channel STS retinal prosthesis was able to elicit phosphens in all patients with advanced RP for the entire 1-year experimental period without major complications. Better results on visual tasks were found in the eyes in which the electrode array was implanted closer to the fovea centralis.

Keywords: retinal prosthesis, retinitis pigmentosa, phosphene, suprachoroidal-transretinal stimulation, retinal implant, clinical trial

A retinal prosthesis is a device designed to restore vision in near-blind patients by eliciting phosphens by electrical stimulation of the residual functioning retinal neurons.1–5 The targeted disease is mainly advanced retinitis pigmentosa (RP) in which almost all of the photoreceptors are degenerated but the inner retinal neurons are functioning to some degree.6 The visual acuity of patients who are candidates for a retinal prosthesis is currently set at bare light perception or less in most cases, but an English group recently implanted an epiretinal prosthesis in patients with dry age-related macular degeneration (AMD) in which residual vision was present (Stanga P, et al. IOVS 2016;57:ARVO E-Abstract 3753).

There are three types of retinal prosthesis. The first is the epiretinal type, in which the electrode array is implanted on the retinal surface;1–3 the second is the subretinal type, in which the electrode array is implanted between the retina and choroid;4,7; and the third is the suprachoroidal type, in which the electrode array is implanted between the choroid and sclera5,9 or in a scleral pocket.5 The Argus II epiretinal prosthesis, which was developed by Second Sight Medical Products, Inc. (Sylmar, CA, USA), has been approved for use in humans by the Food and Drug Administration (FDA) in the United States, and its long-term safety and benefits for patients blinded by RP have been reported.10 The Alpha IMS subretinal prosthesis was developed by Retina Implant, AG (Reutlingen, Germany), and has been approved in Europe. The provisional results of a clinical trial on 29 patients showed a restoration of low vision in blind patients with end-stage hereditary retinal degenerations.11

The suprachoroidal type of retinal prosthesis was developed by our group5,12 and by an Australian group.9,13 In the suprachoroidal type, the electrode array is inserted into a scleral pocket by our group and in the suprachoroidal space by the Australian group.

The potential advantages of the suprachoroidal prosthesis are that (1) it is safer because the electrode array does not touch the retina;2 (2) it has greater stability because the array is firmly fixed in the scleral pocket12; (3) it can have neuro-enhancement effects by electrical stimulation to the retina14,15 because the electrode array does not hinder choroidal circulation (Kanda H, et al. IOVS 2013;54:ARVO E-Abstract 1046) or block incoming light; and (4) it is clinically adaptable.
because pluripotent stem (IPS) cells or embryonic stem (ES) cells can still be injected into the subretinal space even after the implantation of the electrode array. The presumed disadvantages of the suprachoroidal prosthesis are that (1) the image resolution may be lower than that by epi- or subretinal prosthesis because the electrode-to-retina distance is longer, and (2) higher currents are needed to stimulate the retina.

We have shown that the suprachoroidal–transretinal stimulation (STS) type of retinal prosthesis using an array of nine channels enabled patients with advanced RP to reach and touch large targets when the system was turned on. The Australian group also reported on the feasibility of suprachoroidal prosthesis using a 20-electrode array prosthesis.

One of the limitations of the STS prosthesis has been the flexibility of the connecting cable because of the larger number of wires required for the multiple electrodes, which prevented the wires from encircling the eyeball.

To counter these limitations, we have made several alterations to improve our prosthesis. We have developed a multiplexer integrated circuit (IC) to deliver pulses to individual electrodes with a lower number of leads. A second development was the use of a connector between the decoder and lead wire, which facilitated the surgical procedures. A third development was a modification in the fabrication of the platinum electrodes, which increased the charge-injection capacity of each electrode.

The purpose of this study was to determine the safety and effectiveness of the improved 49-channel STS system in patients with advanced RP. To accomplish this, we implanted this 49-channel STS system into three patients with advanced RP, and we assessed its properties over a 1-year period.

METHODS

Study Design

This was a single-arm, prospective, unmasked pilot clinical trial. Three patients with advanced RP who were being followed at the Osaka University Hospital were studied. The patients served as their own controls, that is, tested with the prosthesis turned on or turned off.

The procedures used in this study adhered to the Declaration of Helsinki and were approved by the Ethics Committee of Osaka University Hospital. A full explanation of the purpose of this study and the procedures to be used was presented to each patient, and each signed an informed consent form. Patients were also instructed that they were free to withdraw at any time. The project was posted on University Hospital Medical Information Network (UMIN), and the registration number was UMIN 000012754 (2014.1.4).

Patients

Inclusion and Exclusion Criteria. Patients were enrolled if they had been clinically diagnosed with RP by fundus examinations and electroretinography (ERG). Functional inner retinal neurons were confirmed to be present by the presence of phosphenes elicited by transcorneal electrical stimulation (TES) with a pulse duration of 10 ms and a current of \( \leq 1.5 \) mA. The visual acuity of the three patients was \( \leq \) hand motion (HM) in both eyes, and their ages were 40, 64, and 75 years. An exclusion criterion was the presence of diseases that can affect the retinal or optic nerve function other than RP or the presence of manifest nystagmus.

Profile of Patients. Patient 1 (Pt 1) was a 64-year-old woman who had been blind since the age of 57 years. She had bare light perception (LP) in both eyes at the time of the surgery (Table). The TES elicited phosphenes that were perceived in the central visual field with a threshold current of 1.0 mA in the right eye and 1.2 mA in the left eye. Patient 2 was a 61-year-old man who had been night blind since the age of 20 years, and his visual acuity decreased to HM in both eyes at age 56 years. Transcorneal electrical stimulation elicited phosphenes that were perceived in the central visual field with a threshold current of 0.7 mA in the right eye and 0.8 mA in the left eye. Patient 3 was a 42-year-old man who had had night blindness since the age of 20 years. He was diagnosed and followed as a central type RP but was diagnosed later with Stargardt disease by genetic analysis. His visual acuity decreased to HM in his right eye at the age of 38 years and in the left eye at the age of 41 years. His visual acuity was bare LP in right eye and HM in left eye at the time of the surgery. Transcorneal electrical stimulation elicited phosphenes that were perceived in the central visual field with a threshold current of 0.65 mA in the right eye and 0.75 mA in the left eye. Fundus photographs and optical coherence tomography (OCT) images of the implanted eyes of each patient are shown in Figure 1.

All patients were free to use the device at home and have self-training such as watching a white bar against a black background with device on for up to 8 hours/day.

Prosthesis

Second-Generation STS Prosthesis. The second-generation implanted STS prosthesis was similar to the first-generation STS prosthesis, but the number of active electrodes was increased from 9 to 49 (Fig. 2). This prosthesis consisted of a secondary coil that received signals from the external coil and a decoder that generated biphasic pulses to deliver to the individual electrodes sequentially. The electrode array was 5.8 × 6.3 mm (Nidek Co., Gamabori, Japan) and contained 49 electrodes set in a 7 × 7 grid pattern. The electrodes were made of 0.5-mm-diameter bullet-type platinum, and the center-to-center separation of a pair of electrode was 0.7 mm, with the surface fabricated by a femtosecond laser (Fig. 2B). Each electrode protruded from the silicon base by 0.3 mm. The return electrode was a 0.5-mm-diameter, 6-mm-long platinum wire that was insulated except for 3 mm of the tip. A multiplexer IC was attached to the electrode array and distributed electric pulses to the individual electrodes. Cathodic-first biphasic pulses of 0.4-ms duration were delivered to the individual electrodes sequentially. The period of

<table>
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<th>Patient</th>
<th>Age, Years</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Visual Acuity, R/L</th>
<th>Phosphate Threshold R/L, mA</th>
<th>Years With Lowest Visual Acuity</th>
</tr>
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<tr>
<td>1</td>
<td>64</td>
<td>F</td>
<td>Retinitis pigmentosa</td>
<td>LP/LP</td>
<td>1.0/1.2</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>Retinitis pigmentosa</td>
<td>HM/HM</td>
<td>0.8/0.8</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>Stargardt disease</td>
<td>LP/HM</td>
<td>0.65/0.75</td>
<td>4</td>
</tr>
</tbody>
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F, female; M, male; R/L, right eye/left eye.
shorting a charge was 3.0 ms, which was added after 49 consecutive stimulations. The sampling rate was 20 Hz.

**External Device.** The external part of the STS system consisted of a spectacle-mounted video camera, a video processing unit, and a battery. Patients performed visual tasks using a complementary metal oxide semiconductor (CMOS) camera attached to the spectacles to detect the objects (Nidek Co.). The horizontal field of view of the camera was 15.1° of visual angle, and the implant covered the same visual angle. The camera was mounted at the center of one lens of the spectacles in Pt 1 and 2 and at the right side of spectacles in Pt 3. The angle of the camera was not adjusted in Pt 1 and 2 and was adjusted downward in Pt 3.

The objects viewed by the camera were converted to a 7 × 7 square, and if the light level was above the configurable threshold, the square was expressed as white (on); if the light level was below this threshold, the square was expressed as black (off) in the binary mode. In the grayscale mode, the square could be expressed as gray depending on the light level. The information of the square was converted to an electronic signal and sent to the secondary coil through the external coil. The electrodes in the array emitted pulses corresponding to

**Figure 1.** Fundus photographs (A–C) and optical coherence tomographic (OCT) images (D–F) of Patients 1, 2, and 3 before the implantation of the 49-channel eye prosthesis.

**Figure 2.** Photographs of the internal parts of the 49-channel STS system (A), magnified photograph of 49-channel stimulating electrode (B), and lateral view of the skull X-ray projection of Patient 1 after the implantation surgery (C).
the signals transmitted to the secondary coil, which stimulated the residual retinal neurons to elicit phosphenes. In the manual mode, patients were able to move a knob on the battery box to optimize the threshold light level.

**Surgical Procedures**

The visual acuity was not significantly different between right and left eyes in Pt 1 and Pt 2. The right eye was selected for the implantation in these patients because the threshold current to elicit phosphenes by TES was lower in the right eye than in the left eye. In Pt 3, the right eye was selected for implantation because the visual acuity was worse (Table).

Under local anesthesia, the lateral rectus muscle was dissected at its insertion, and tranasceral monopolar stimuli were given to determine the scleral area that consistently evoked low-threshold phosphenes. After identifying and marking the low-threshold area, the patient was placed under general anesthesia. The skin over the left temporal bone was incised to insert the electronic devices. A second skin incision was made over the left zygomatic bone to fix the cable. The electrode array and the return electrode were protected with a silicone cover and passed under the fascia of the temporal muscle from the first incision to the second incision through a trocar catheter (Medikit, Tokyo, Japan).

The bone of the lateral orbital wall was drilled and the electrode array, return electrode, and cable were passed into the periocular space using the trocar catheter. The cable with its protective cover was fixed by a titanium plate below the second incision. The electrode array and cable were circled around the equator passing under the four rectus muscles.

A 7 × 6-mm scleral pocket was made at the temporal to lower temporal area where the low-threshold phosphenes were elicited. The 49-electrode array was placed in the scleral pocket, and the multiplexer IC, which was connected to the electrode array, was sutured and fixed on the sclera (Fig. 3). The return electrode was inserted into the vitreous cavity through the upper nasal pars plana area.

After suturing the conjuntival incision, the electronic device was fixed to the temporal bone and the skin was sutured. At the end of the implantation procedure, the system was tested to be certain that all electrodes were functioning. Twelve months after the implantation, the device and wire were surgically removed and tested.

**Functional Testing of Electrodes**

Beginning 1 week after the implantation, the wireless system was tested twice a week for 2 weeks. An electronic stimulator was designed to deliver charge-balanced biphasic pulses to individual electrodes sequentially. Cathodic-first biphasic pulses (duration, 0.4 ms; frequency, 20 Hz; interpulse delay, 0.02 ms; and 20 pulses) were delivered through the selected channel. The current was applied for 0.5 second after a conditioning buzzer signal. The threshold current that elicited a phosphene was determined by increasing the current intensity from 0.1 mA in 0.1-mA steps until the patient was able to perceive a localized phosphene in more than 50% of the trials. For safety, the maximum current was set as 1.0 mA (Kanda H, et al. IOVS 2013;54:ARVO E-Abstract 1046).

Electrodes that elicited somatosensory (tingling) sensation were also used. The 49-electrode array was placed in the scleral area around the equator passing under the four rectus muscles.

A white square target (visual angle, 10° × 10°; target brightness, 252.0 cd/m²; background brightness, 5.3 cd/m²) was displayed on a 19-inch computer monitor at 16 random positions (4×4, uniform distribution) determined by a computer. The illuminance of the laboratory was 200 to 300 lux (LM331; AS ONE, Osaka, Japan). The subjects wore a mask over both eyes and viewed the screen at a distance of 40 cm. The center of the screen was aligned to the midpoint between the right and left eyes. The subjects were instructed to touch the center of the target with the index finger of either hand. The trial was repeated 20 times. The patients were permitted to move their head and eyes during the pointing task while keeping the distance between the head and the screen at 40 cm. They were also permitted to touch the frame of the screen before pointing to the target. The point where the subjects touched was automatically recorded, and the average distance from the center of a target to the touched point was calculated by the computer. Paired t-tests were used to determine the significance of the differences in

**Assessment of Safety**

All adverse events were logged and classified by their relatedness, that is, device related, surgery related, or subject related. Serious adverse events were defined as those requiring surgical intervention or hospitalization.

**Assessment of Device Reliability**

The function of the internal device was checked once per month using the self-inspection system of the device. This system can detect failure of the multiplexer IC and disconnections in the lead wires from the main device to the multiplexer or from the return electrode. This system can also detect a saturation of the power supply in each stimulating electrode that is caused by disconnection of the lead wires to the electrode or by high electrode impedance.

**Assessment of Visual Function**

The ability to locate and touch an object was assessed by the square localization test, and the ability to walk along a straight line was tested by a mobility test. The ability to perform under real-world conditions was assessed by a table test to discriminate a rice bowl and a pair of chopsticks.

**Square Localization Test.** A white square target (visual angle, 10° × 10°; target brightness, 252.0 cd/m²; background brightness, 5.3 cd/m²) was displayed on a 19-inch computer monitor at 16 random positions (4×4, uniform distribution) determined by a computer. The illuminance of the laboratory was 200 to 300 lux (LM331; AS ONE, Osaka, Japan). The subjects wore a mask over both eyes and viewed the screen at a distance of 40 cm. The center of the screen was aligned to the midpoint between the right and left eyes. The subjects were instructed to touch the center of the target with the index finger of either hand. The trial was repeated 20 times. The patients were permitted to move their head and eyes during the pointing task while keeping the distance between the head and the screen at 40 cm. They were also permitted to touch the frame of the screen before pointing to the target. The point where the subjects touched was automatically recorded, and the average distance from the center of a target to the touched point was calculated by the computer. Paired t-tests were used to determine the significance of the differences in
the values of deviation. A $P$ value $\leq 0.05$ was considered significant. SigmaPlot 12.2 (Systat Software, Inc., San Jose, CA, USA) was used for the analyses.

**Mobility Test.** Blind patients tend to shift their trajectory while walking along a straight line, which is called a veering tendency. Using this phenomenon, we developed a new mobility test to evaluate the mobility of patients implanted with a retinal prosthesis. The mobility course was an indoor straight hallway that was 5 m long and 1.8 m wide. The side walls were covered with a black fabric, and the floor was covered with either a black or a gray carpet. A straight white line, 5 m long and 5 or 10 cm wide depending on testing conditions, was drawn down the center of the carpet. The width of the white line and the grayness of a carpet were determined by the residual natural vision of each patient. In Pt 1, a line width of 10 cm and black carpet were selected; in Pt 2, a line width of 5 cm and black carpet were selected, and in Pt 3, a line width of 10 cm and gray carpet were selected. To detect the position of the foot automatically, target markers were attached to the backside of the patients’ shoes. The target markers were circular with a diameter of 10 cm, with a black and white checkerboard pattern with a check size of 5 cm. A video camera (HX-A500, resolution 1280 $\times$ 720 pixels; Panasonic, Kadoma-shi, Japan) was mounted on the ceiling above the starting point, and it recorded the images continuously at 15 frames/second.

The patients wore an eye mask over the left eye, and they were instructed to examine the white line at the starting point and were instructed to walk along the line. The foot positions of the patients were calculated by analyzing the images using custom-made image processing software, which was developed by HALCON 11 (MVTec, Munich, Germany). In this image processing, the projection transformation was applied to the original images to correct the distortion and to obtain a virtual overhead view. The coordinates of the midpoint of the right and left markers that were attached to the patients’ shoes were determined by the residual natural vision of each patient. The walking trajectory was approximated by a second-order polynomial regression equation:

$$y = a_0 + a_1x + a_2x^2$$  

(1)

where $a_0$, $a_1$, and $a_2$ are coefficients and $x$ and $y$ are $x$- and $y$-coordinates of the patient’s position. The $x$-axis was parallel to the white line, and the $y$-axis was perpendicular to the white line. Regression analysis was performed and the coefficients were calculated by Excel 2013 (Microsoft, Redmond, WA, USA). The trial was repeated 10 times with the system turned on or off. When the participants deviated from the white line and touched the side wall before reaching the end point, they were instructed to stop walking. Trials were excluded from the analysis if the stop position was $\leq 5$ m from the starting point.

To compare the accuracy of the mobility in patients between the system ON and OFF conditions, the arrival point at 5 m from the starting point was estimated by extrapolating the regression curve using the regression equations shown in Figure 4. The $y$-coordinates of the estimated arrival points were compared between system ON and OFF conditions. Statistical significance of differences between the two conditions were
assessed by Welch’s t-tests of the JMP Pro version 11 (SAS Institute, Inc., Cary, NC, USA).

Table Test. A rice bowl, 10 cm in diameter and 5 cm in height, and chopsticks, 22 cm in length, were placed on a table covered with either a black or a gray sheet. The luminance of background was 3 cd/m² on the black sheet and 25 cd/m² on the gray sheet. The objects were set randomly either 10 cm to the left or 10 cm to the right of the center of the table. The subjects wore an eye mask over the left eye and viewed the table at a distance of 40 cm. Patients were asked the location of chopsticks (right or left) with the right hand. This trial was repeated 10 times with the system on or off. The percentage of correct answers on each task was analyzed statistically by a binominal test, and the criterion for statistical significance was 0.05. We tested whether each patient’s performance was better than the chance level (50%) on each task. These analyses were performed with JMP 8.0 program (SAS Institute, Inc.).

RESULTS

Position of Implanted Electrodes

We examined the position of electrode array after the implantation using OCT images in Pt 1 and Pt 3. In Pt 2, an OCT examination was not possible because of the development of cataract. The edge of the electrode array was assessed by the inflected position of the OCT image (Fig. 5). Using

FIGURE 5. OCT images (A, C) and corresponding fundus photographs (B, D) after surgery in Patient 1 (A, B) and Patient 3 (C, D). Red arrows in (A, C) and red points in (B, D) represent the estimated border of the electrode array in each patient. Green lines (B, D) represent the scanned position for the OCT images.

FIGURE 6. The estimated position of electrode array in fundus photograph using OCT images in Patients 1 (A) and 3 (B). The red dots represent the estimated border of electrode array reconstructed from the OCT image as shown in Figure 5. White squares represent the estimated area of electrode array in each patient.
multiple line scans, the two-dimensional image of the posterior edge of the implanted electrode array was assessed (Fig. 6).

Test of Functioning of Electrodes

Two weeks after the surgery, the number of electrodes that elicited a phosphene with currents $\leq 1\ mA$ and without eliciting a tingling sensation was 28 in Pt 1, 24 in Pt 2, and 25 in Pt 3. The threshold current to elicit a phosphene in these electrodes ranged from 0.7 to 1.0 mA ($0.84 \pm 0.15\ mA$; mean $\pm$ standard deviation) in Pt 1, 0.2 to 0.6 mA ($0.31 \pm 0.12\ mA$) in Pt 2, and 0.5 to 0.7 mA ($0.62 \pm 0.08\ mA$) in Pt 3. The threshold current to elicit a phosphene 1 year after the implantation decreased approximately 10% in Pt 1, increased by approximately 15% in Pt 2, and increased by approximately 20% in Pt 3.

Functioning of Implanted Device

In Pt 1, a connection error was detected in one of the lead wires of the power supply from the main device to the multiplexer at 6 months after the implantation surgery. It was caused by damage to the welded part at the connector. However, this connection error did not affect the functions of the multiplexer and the stimulating electrode because the device has a spare lead wire and automatically switched the damaged wire to the spare wire for power. In Pt 2 and Pt 3, this error did not occur during the follow-up period.

Other errors such as high electrode impedance, failure of multiplexer, or disconnection of lead wire to the electrode were not observed in any of the patients during the follow-up period.

Safety

Regarding safety during surgery, no complications were found intraoperatively. After the surgery, it was confirmed by skull X-rays that the device, cables, and electrodes were implanted and connected as planned (Fig. 2C). The fundus photographs and OCT images taken 1 week after surgery showed that the retina was attached and no retinal hemorrhage was observed in all patients. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed on Pt 1 and 3 but not in Pt 2 because of an allergy to fluorescein. In Pt 1 and 3, no changes were observed in the FA and ICGA images after the surgery.

Adverse Events During 1-Year Experimental Period

No serious adverse events that required surgery or hospitalization occurred in any of the three patients during the entire experimental period. In Pt 2, iridocyclitis developed in the right eye at 2 and 4 months after the surgery, which was successfully treated by topical medications. A posterior synechia and cataract developed later, which prevented OCT examinations. Ten months after the surgery, iridocyclitis recurred in the right eye and the intraocular pressure increased because of iris bombe. This was successfully treated by laser iridectomy and subconjunctival injection of corticosteroids. At the explantation surgery of devices performed 12 months after the initial surgery, cataract surgery was simultaneously performed. The ocular fundus and OCT examinations showed no changes in this eye after the explantation surgery.

In Pt 3, iridocyclitis developed in the right eye 6 months after the surgery, which was successfully treated by topical medications. Seven months after the surgery, a sudden hearing
loss occurred in the left ear, which was successfully treated by intravenous administration of corticosteroid by an otolaryngologist.

Results of Function Tests

**Square Localization Test.** In Pt 1, the square localization scores with the prosthesis turned on did not differ significantly from the score with the prosthesis turned off. In Pt 2, the pointed position was significantly closer to the center of the target with the system turned on than with system turned off at 1 month after the implantation, but the difference was not observed thereafter. In Pt 3, the pointed position was significantly closer to the center with system turned on than with the system turned off during the entire follow-up period (Fig. 7).

**Line Test.** The line deviation tests showed that the deviations from the straight line were not different when the device was turned on and turned off in Pt 1. In Pt 2, the deviation was significantly smaller with system on than with system off at 9 and 11 months after the surgery. In Pt 3, the deviation was significantly smaller with the system turned on than when the system was turned off at 2, 5, and 8 months after the surgery (Fig. 8).

**Table Test.** In Pt 1, the success rate for the table test was not significantly different between the device turned on and turned-off conditions. In Pt 2, the success rate was significantly better with the system on than turned off at 6 months after the surgery, but the success rate was not different at the other time points. In Pt 3, the success rate was significantly better with system turned on than with the system turned off during the entire follow-up period except at 12 months after the surgery, when the success rate in the turned-off condition was better (Fig. 9).

**DISCUSSION**

We implanted a 49-channel STS retinal prosthesis in three patients with clinically diagnosed advanced RP (Fig. 1); however, Pt 3 was later diagnosed with advanced Stargardt disease by gene analysis. The surgical procedures were similar to those for the nine-channel STS prosthesis12 except for the addition of a multiplexer IC that was connected to the electrode array. The multiplexer IC was approximately 6.0 mm wide and 5.5 mm long and was placed on the equatorial area of the sclera (Fig. 3). Neither a retinal detachment nor conjunctival dehiscence was observed in all patients after the surgical procedures, confirming the safety of our surgical methods.

The exposed height of the bullet-type platinum electrode was reduced from 0.5 mm in the 9-channel electrode array to 0.3 mm (49-channel STS) but the surface area was expanded by a femtosecond laser, which allowed us to increase the charge injection capacity (Fig. 2B). The threshold current to elicit phosphenes varied for each patient, but the average threshold current of the active electrode was similar between the 9-channel system12 (0.75 mA) and 49-channel (0.59 mA) channel
system. This suggests that the new system is functional as to its current injection ability. The connection between the internal device and the electrodes remained functioning during the 12-month testing period, indicating that the new system can withstand the surgical manipulations and the continuous eye movements.

Iridocyclitis developed in the implanted eye in two of three patients at 2 and 6 months after the surgery. Iridocyclitis was not observed in the two patients implanted with the nine-channel STS system during the 4-week follow-up period.12 This suggests that longstanding electrical stimulation of the pars plana area where the return electrode was implanted can cause inflammation. Because the functional results using the localization test were not different when we changed the return electrode from a vitreous electrode to the subdermal decoder package (data not shown), we are planning to change the position of the return electrode to the subdermal decoder package in the next clinical trial.

The position of the electrode array of the STS system could not be identified by fundus examinations because the electrodes were inserted in the scleral pocket. To determine a suitable position at which to insert the electrode array, we used transscleral monopolar stimuli to search the scleral area that consistently evoked low-threshold phosphenes intraoperatively. All three patients perceived phosphenes intraoperatively; however, OCT examinations after surgery showed that better functional results were obtained when the array was placed closer to the fovea (Figs. 6–9).

The number of electrodes that evoked phosphenes with currents ≤ 1 mA and without eliciting tingling sensation was 24 to 28 out of the 49 electrodes. This number limits the resolution and the extent of visual field. The tingling sensation is a somatosensory sensation that might originate from the stimulation of the trigeminal nerve, which passes through the choroid. Because the threshold currents to elicit somatosensory sensation and phosphenes by electrical stimulation to the anterior visual pathways depend on the duration of stimulation pulses,23 the optimal parameters should be determined to increase the number of electrodes that can elicit phosphenes without eliciting somatosensory sensations.

Functional testing using a spectacle-mounted video camera revealed that Pt 3 did significantly better in the square localization test with the system turned on than with the system off at all postoperative times (Fig. 7). The success rate of light localization test by Argus II24 or by Alpha IMS25 was higher compared with that of other functional tests in patients implanted with the retinal prosthesis, which is consistent with our results.

Patients 1 and 2 did not show a difference in the success rate in the square localization test with the system turned on and with the system off. Because the implanted electrode array was probably closest to the fovea centralis in Pt 3, the evoked phosphenes might be easier to identify as a small bright object in the central visual field. Similar results were reported for the subretinal prosthesis in which the functional results were better with the electrode array implanted closer to the fovea centralis.25

In the line test, significantly better results were obtained at 9 and 11 months after the implantation in Pt 2 and at 2, 5, and 8 months after the surgery in Pt 3 (Fig. 8). The better tracking
means that artificial vision with the STS retinal prosthesis is useful to track and follow a line by head scanning.

In the table test, the residual vision in the right eye in Pt 3, that is, with the device turned off, was able to discriminate objects when the background was black, so we decreased the contrast of the objects using a gray background in this patient. Under these conditions, the success rate was significantly better with the system turned on than with the system off during almost all of the follow-up period (Fig. 9). These results suggest that artificial vision with the STS retinal prosthesis is useful in discriminating low-contrast objects even when residual vision can be used to discriminate high-contrast objects.

In the three functional tests, Pt 1 did not show any significant difference between the system turned-on or turned-off conditions, probably because the electrode array was implanted slightly farther from the fovea and the elicited phosphens and the spontaneous phosphens were indistinguishable. In Pt 2, iridocyclitis occurred three times during follow-up period, which might influence the residual retinal function and account for the variations in the functional results (Figs. 7–9).

The limitation of this study is that just three patients were examined. In the next project, we are planning to increase the number of patients with a multicenter study and plan to investigate the factors affecting the functional results including age, threshold current to evoke a phosphene by TES before the surgery, and other tests.

In summary, the 49-channel STS retinal prosthesis was able to elicit phosphens in all three patients with advanced RP without major complications, and the device was functional for at least 1 year. Greater improvements in performing the visual tasks were observed in patients in whom the electrode array was implanted closer to the fovea centralis.

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