

A visual prosthesis for long term epiretinal stimulation in blind patients with retinitis pigmentosa

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Abstract

Purpose: To evaluate the performance of the first wireless Retinal Implant System in blind patients with retinitis pigmentosa. Objective of the study is to evaluate safety and efficacy as well as stability and optimal stimulus parameters for single electrode as well as simple pattern stimulation. Further objective is to control the wireless signal transmission for both data and energy and to test the feasibility of the surgical implantation method and the toleration of the implant by the eye over time. **Methods:** In a prospective study, 3 subjects with a visual acuity of hand movement or less received an epiretinal implant with 49 stimulation electrodes (IMI Intelligent Medical Implants GmbH). On predefined postoperative dates, stimulation sessions of 3-4 hours were performed, including threshold measurements, amplitude modulations, motion and pattern perception tests. All results were verified by repeating testing. ICG, fluorescein angiograms (HRA, Heidelberg Engineering) and OCT investigations (Stratus OCT and Cirrus OCT, Carl Zeiss Meditec) were also achieved. **Results:** A stable implant positioning of the electrode array over the whole followup period was identified. Fluorescein angiograms showed no signs of vascular leakage or tissue proliferation. OCT data proved a close proximity between the retina and the electrode film. No retinal tissue damage was observed. The provoked visual perceptions were pleasant. Reported perceptions were predominantly circles, yellow or white in colour. Threshold measurements showed safe and stable current levels. Point-to-point-discrimination was successful in all subjects. Motion as well as pattern perceptions showed success rates up to 100%. The patients were able to describe structures similar to letters. Data and energy transmission worked well. **Conclusions:** The implant allows safe and stable stimulation parameters in combination with good clinical results. This seems promising for upcoming implantations. The completely wireless data and energy transmission into the implant allows totally unrestricted eye movement and is therefore suitable as a long-term solution.

Keywords: epiretinal implant, retinitis pigmentosa, retinal prosthesis, retinal stimulation

1. Introduction

Retinitis pigmentosa (RP) and macular degeneration especially age related macular degeneration are the most common diseases, caused by a continuous loss of photoreceptor cells. With an incidence of 1 in 3500 live births and approximately 1.5 million people affected worldwide, RP is the leading cause of inherited blindness. RP is evoked by a genetic disorder and is characterized by a progressive visual field loss and decline of visual acuity leading to complete blindness in most patients. However the inner part of the retina, the bipolar and ganglion cells, remains intact in RP, so that the higher order neurons are still capable to process information to the brain and visual cortex. Thus the replacement of the degenerated photoreceptors by an electric stimulator might be a therapeutic option in RP and other degenerative retinal diseases. This idea is not new. The first reports on eliciting phosphenes by electric stimulation of the visual system date back to the 18th century [1]. Since then many different working groups have tried to elicit visual perceptions by electrical stimulation. This development was especially driven by the success of cochlear implants. Two main approaches emerged and proved successful in retinal stimulation systems; the epiretinal and the subretinal approach [2]. From a surgical point of view, the epiretinal approach is easier to perform and is therefore associated with a lower incidence of peri- and postoperative complications. We have been developing an epiretinal stimulator, that can be surgically implanted using standard vitrectomy techniques and is wirelessly receiving stimulation data and energy [3,4]. This paper reports on the clinical and stimulation results of a chronic epiretinal implantation of this wireless epiretinal prosthesis in blind patients with RP.

2. Materials and Methods

The Epiretinal implant

The device used in the study is developed and manufactured by IMI Intelligent Medical Implants GmbH, Bonn, Germany. It consists of an implanted component, the retinal stimulator, and several external components. The implantable retinal stimulator

(Figure 1) consists of a carrier onto which various micro-electronic components are mounted. The electronic components are used to receive data and energy as well as to stimulate the retina via micro-electrodes. The carrier is a flexible circuit film with built-in conducting paths. The embedded high frequency receiver coil of this carrier provides the required energy for the stimulation electronics. The coil is embedded in a supporting structure and positioned in the temporal area outside the eyeball in close proximity to an external sending coil which transmits the necessary energy. The infrared-receiver receives data containing visual information from an external transmitter via an infrared optical link. The infrared-receiver encodes the optical signals into electric stimulation currents and sends them to the retinal stimulator-chip. This chip processes the data and generates stimulation patterns for the electrode array placed on the retina. The array is composed of 49 platinum stimulation electrodes and is positioned on the epiretinal side of the retina in the area of the macula. The electrodes are in direct contact with the retina and activate the retinal nerve cells via electrical stimulation currents. The Retina stimulator is coated with Parylene C. The material was deposited on the device by plasma activation with following vapour deposition. The material is resistant against acids, blood, moisture and hydrocarbons. A LED indicator located near the array serves to control the proper functioning of the device by visual inspection within the eye. The encapsulated outer part of the retinal stimulator is sutured onto the sclera. The intraocular part with the electrode array is inserted into the eye via a scleral tunnel and fastened on the retina using a surgical retina tack (titanium tack, GEUDER®, Germany) and corresponding surgical tools. A ring made of medical graded silicone is placed on top of the tack as a retainer. The scleral tunnel is sutured watertight around the implant foil after correct positioning of both implant parts. The conjunctiva is closed over the external part.



Figure 1: The retinal stimulator with its epiretinal electrode array on the left side and the encapsulated chip and energy receiving coil on the right.

Subjects & Methods

Three patients suffering from RP were enrolled in a prospective study. All patients had a visual acuity of hand-movement or less. Patient's age ranged from 45 to 65. All patients signed informed consent.

The surgical procedure was performed in two steps. First a preparing surgery including pars plana vitrectomy, cryo- or endolaser retinopexy and, if needed a cataract extraction. The implantation procedure itself followed about 4 weeks after the initial preparing surgery. All surgeries were performed under general anaesthesia. On predefined postoperative dates, stimulation sessions of 3-4 hours were performed using a special stimulation software connected wirelessly to the implanted retinal stimulator. These stimulating sessions included threshold measurements, amplitude modulations as

well as motion and pattern perception tests. All results were verified by repeating testing. For threshold testing, the amplitude was increased in predefined steps until the subject reported a phosphene. Point-to-point-discrimination was tested by activation of two consecutive electrodes and the subject was asked, if the phosphene moved from right to left or from top to bottom in a forced-choice interview.

Motion discrimination was tested by consecutive activation of 4 electrodes in a linear horizontal or vertical direction. The subject was then asked, if the perceived motion was horizontal or vertical in a two-alternative forced-choice interview. Pattern recognition was tested by simultaneous activation of multiple electrodes in a linear horizontal or vertical bar orientation or a cross orientation. The patient was then asked, what kind of pattern he or she perceived in a three-alternative forced-choice interview. Even more complex patterns were tested in a free interview.

Furthermore indocyanine-green-angiographies (ICG, HRA2, Heidelberg Engineering), fluorescein angiographies (Visupac, Carl Zeiss Meditec) and optical coherence tomography (OCT) investigations (Stratus and Cirrus OCT, Carl Zeiss Meditec) were performed on predefined follow-up investigations. The postoperative follow-up was up to 36 months.

The study protocol complied with the principles of Good Clinical Practice and participants were treated in accordance with the tenets of the Declaration of Helsinki. The local ethics committee approved the study.

3. Results

Implantation Procedure

The preparing surgery was conducted without any notable events in all patients. The preparing retinopexy proved stable and safe retinal conditions for the later implantation. Thus no retinal detachment occurred. All implantations were performed without intraoperative complications and all implants were successfully placed epiretinally. The placement of the retinal tack and the fixation of the electrode array on the tack showed no difficulties. In one patient a progressing corneal opacity during surgery made a corneal abrasion necessary to keep the insight sufficient, but the postoperative corneal erosion reepithelialized quickly. Special attention was paid on the suture of the scleral tunnel to avoid postoperative leakage of intraocular fluid and testing for leakage directly after closure showed no percolating fluid in all subjects. Overall the implantation procedure proved feasibility and an easy learning curve for experienced retinal surgeons by using standard vitrectomy tools in combination with only few special and new implantation instruments.

Stimulating Sessions

Reported perceptions were predominantly circles, yellow or white in colour. The mean minimum stimulation threshold was 17 nC. The single threshold values showed a high variation according to the subject, the location of the electrode and the date of the stimulation session. An interindividual comparison of threshold values of the same electrode in different subjects showed differences in perception threshold, that was most likely caused by differences of electrode position and distance to the retina [5]. An intraindividual comparison of one electrode in the same patient on different session dates showed a slight change of threshold values even over time, which sometimes showed a „learning curve“-like lowering of threshold over time, but sometimes also showed higher threshold values on later session

dates. Point-to-point discrimination was successful in 85% to 89% (right/left, top/bottom). Motion perception was correct in up to 100% in both horizontal and vertical directions. The pattern recognition tests showed correct answers in 98,5% when stimulating a vertical bar, in 89,5% when stimulating a horizontal bar and in 55% when stimulating a cross bar. The lower success rate in correct recognition of the more complex cross pattern goes concordant with the results of the free interview tests of more complex patterns like a triangle or a square (Figure 2). These free answers often showed slight changes from the definite presented pattern, which is most likely caused by the stimulation of multiple not straight retinotopically organised ganglion cells and bipolar cells.

Pos.	Shape	Description	Response
1		Triangle	1. a 45 degrees slants, legs of a triangle 2. sloped rectangle 3. kind of triangle, 45 degree leg with additional a small additional object 4. horizontal line with slanted lines 5. side view of a roof from a house
2		Cross	1. 2 angled lines " / " 2. Angle 3. 2 angled lines " / " 4. 2 angled lines " / " 5. 2 angled lines " / " 6. 2 angled lines " / "
3		2 vertical, parallel lines	1. Rectangle, upside 2. vertical line with a view slanted lines at one side 3. like a vertical oriented comb (horizontal line with some vertical lines) 4. like a vertical oriented comb (horizontal line with some vertical lines)
4		Square	1. a triangle 2. a slanted line 3. a slanted rectangle 4. a cube 5. part of a circle, a cone
5		2 horizontal, parallel lines	1. a slanted rectangle, 45 degrees lines 2. slanted lines with slanted thin lines 3. 2 slanted, angled lines (like a roof top) 4. a screened square

Figure 2: Examples of free interview answers on complex pattern stimulations

Clinical Follow-Up

The ophthalmoscopic examinations as well as the fundus photographs showed a stable and well positioned electrode array over the whole followup period (Figure 3). Only a slight change of retinal vessel configuration near the implant was observed in one subject. There were no signs of tissue proliferation or cell migration onto the implant and electrode array as well as no signs of proliferative vitreoretinopathy. The fluorescein- and ICG-angiographies showed an unchanged and intact blood-retina-barrier in all subjects over the whole followup period. No signs of leakage were detected, especially no signs of choroidal neovascularisation. OCT investigations show the electrode array as a high reflective thin membrane over the retina. Typical optical shadows can be seen behind the conductant pathways (Figure 4). OCT data proved a close proximity between the retina and the electrode film, while differences in the distance between the electrode array and the retinal surface were not unusual and dependent on the exact location of the OCT scan. Even a slight compression of the retina at the edge of the implant foil could be seen on some OCT scans. In one case OCT scans showed a transient retinal edema. Overall no severe retinal tissue damage was observed.

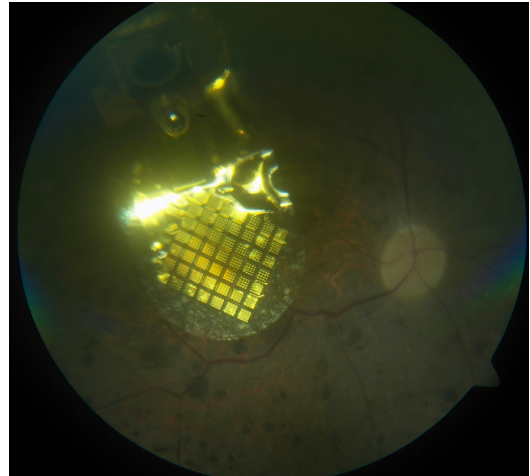


Figure 3: Fundus photography 2 years after implantation shows a stable and well positioned implant and electrode array in the macular area.

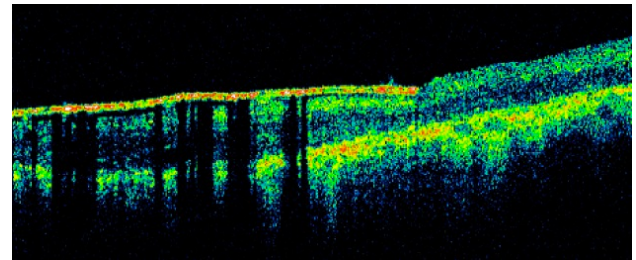


Figure 4: OCT of the implant foil. Notice the typical optical shadows of the conductant pathways and the slight compression of the retina on the edge of the implant

4. Conclusion

The implantation procedure itself proved feasibility and is easy to learn for the hands of an experienced vitreoretinal surgeon. This was achieved by the use of standard vitrectomy techniques only extended by a few special instruments as the tack positioner or implant guidance forceps. In comparison to subretinal implantation procedures, in which a retinal detachment needs to be performed and a postoperative silicone oil endotamponade is essential after implantation [6], the techniques for epiretinal implantation are easier and faster [7]. Furthermore the wireless data and energy transmission allows a complete wound closure without any cables or connectors penetrating through the wound and increasing the risk of postoperative infections. Nevertheless it is presumed that subretinal implantation can lead to postoperative choroidal neovascularisation (CNV) [8]. We can report no case of CNV in any of our subjects over the whole followup period. These facts point out the safety of the presented epiretinal implant device even during long term implantation and for the intended everyday use. Even more the completely wireless signal and energy transmission to the implant allows unrestricted eye movement and is therefore suitable as a long-term solution. The activation of the implant and the stimulation sessions are also very encouraging for further implant generations. The threshold values needed to elicit phosphenes are on a safe level and surprisingly much lower than in earlier studies [9]. This might result from an even closer electrode-retina contact by tack fixation in this chronic study compared to a handheld electrode

device in the acute study [4]. We found high success rates in point-to-point and motion recognition as well as in simple patterns similar to letters. This is a crucial point in improving patients' independence by restoring their ability to read [10,11]. The slightly incorrect answers in the free interview tests with complex patterns were most likely caused by the stimulation of multiple not straight retinotopically organised ganglion cells and bipolar cells, as already mentioned above. This phenomenon indicates the necessity of a learning image processor in the pathway between the camera and the electrode array for a visual prosthesis [12]. The captioned image cannot be stimulated directly onto the retina without considering the individual retinotopic conditions of each patient. Otherwise these slight changes in the perceived patterns will result in distortion and complete inability of recognition. Therefore a computed and learning image processor will be implemented in future generations of our implant.

In conclusion the presented results show a safe to implant and effective working wireless epiretinal implant device. The clinical and stimulation data are encouraging for upcoming long-term implantations and the intended every day use via a connected camera. Further improvement is expected with a higher number and efficacy of electrodes and a reduction of the implant's and especially the electronics' size [13]. Furthermore a learning image processor in the signal pathway will improve the resolution and recognition rate of more complex images.

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