Transchoroidal subretinal chip implantation in blind retinal pigmentosa patients. The choroidal challenge

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Purpose. *Active subretinal visual prostheses require a transchoroidal implantation due to their necessary connection to extraocular parts of the device for energy supply. When starting the program surgically the choroidal access was assumed to be one of the major problems.* ***Material and Methods.*** *26 legally blind retinal pigmentosa (RP) patients were included in the multicenter study and implanted with a chronic active prosthetic device via a transchoroidal access. 12 out of these 26 patients were operated by one surgeon who developed the transchoroidal procedure and had experience with it. Only this subgroup was analyzed to eliminate the learning curve effects of multiple surgeons.* ***Results.*** *All implantations were carried out successfully as far as the intended position of the implant and the stability of the retina were concerned. Feared major bleedings were not observed even when accidental perforation of the choroid occurred (1) in the area of the posterior pole. Minor problems concerning surgery were observed when advancing the guide foil or the implant subretinally. The causes were adhesions between retinal pigment epithelium (RPE) and the retina. These adhesions seem common in the area of dense pigmentation or scarring in RP patients. Other technical problems during the complex surgical procedure were obvious sub RPE-implantations most likely beneath the choroid. This occurred twice but both cases could be corrected during the implantation. This pitfall never led to bleedings or other unexpected effects that could be harmful for the patient.* ***Conclusion.*** *Problems resulting from the choroid are manageable and don't seem to be a limiting factor for this complex surgical procedure. Unintended perforations that occurred did not have any substantial threatening or harmful side effect. One of the causes may be the rather atrophic choroidal situation in RP. Proper design and geometry of the guide foil and the implant are relevant and are under improvement to minimize incidents resulting from this challenge. Thus, even difficult retinal situations are no contraindication for chip implantation.*

Keywords: retina implant, subretinal implant, visual prostheses, transchoroidal surgery.

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Various groups worldwide are developing visual prosthetic devices to restore vision for blind or visually handicapped patients who are blind due to photo receptor degeneration [1, 2]. All the retinal based implants currently in use try to activate remaining retinal neuronal cells by electric stimulation [3]. One main concern is the resulting visual field which is determined by the size of the implant. This fact has considerable impact on complexity of the surgery. Another decisive factor is the energy supply for the stimulation process. Technical problems involving biocompatibility and biostability or the implantation procedure itself have to be solved. According to the various approaches, different surgical techniques have been developed to guarantee a safe implantation of the device. Subretinal implantation was first carried out in humans with micro photo diode arrays (MPDA´s) by A. Chow 1997 [4], which were completely placed in an ab interno procedure into the subretinal space. The energy supply for the MPDA´s which were supposed to stimulate the degenerated retina was the available light falling into the eye.

Animal experiments of our group made clear that the stimulation process requires an additional energy supply to stimulate the retina under ambient light levels. Accordingly, our group chose not to implant the device evaluated in animal experiments [5]. Instead, the concept of an active subretinal implant was developed which transmits the necessary energy for the stimulation process from external electronic parts into the subretinal space. In this concept, a permanent (cable) connection into the subretinal space is mandatory. A suitable surgical procedure had to be

developed. In this concept a transchoroidal placement of the implant (combined ab externo and ab interno procedure) seems to be the method of choice [6]. In this way, the retina is taken care of and not affected or damaged during surgery. This provides optimal conditions for the stimulation process. Since this was a new and complex surgical maneuver, attention had to be focused on the crucial sequences. They have been studied in detail in animal experiments using different species for the same problem. Especially the bloodless penetration of the choroid had to be guaranteed to reach an optimal surgical result. The extraocular and extraorbital surgical procedure which describes the path of the subdermal cable is described in detail by F. Gekeler et al. [7].

MATERIAL AND METHODS

26 legally blind RP patients were recruited for the study. 12 of them were operated by one surgeon who had developed the transchoroidal access. The residual vision of the RP patients was determined to be of no use in daily life to meet the demands of the local ethic committee. The patient with the best residual vision had light perception without any light localization. All these patients with end stage RP had extensive diagnostic work up including family history for pattern inheritance, electric retinography, FA, OCT, SL examination and funduscopy. To ease the complex implantation process, cataract surgery with the implantation of a posterior chamber IOL was carried out several weeks prior to subretinal implantation surgery. This eases working in the very periphery of the retina when creating the site for the transchoroidal implantation. A written consent of each subject respecting the Code of Ethics of the World Medical Association (Declaration of Helsinki) was available.

The Implant. The complete implant is composed of different elements which fulfill the needs of the respective anatomical structure. The requirements of the subretinal space, the extraocular path and the subdermal path had to be fulfilled. In principle, the implant consists of a polyimide foil strip with direct stimulating electrodes on the tip of the foil strip followed by the chip for subretinal stimulation. Both these elements cover the implanted tip of the foil. The tail of the foil contains the conductive wiring which is connected to a subdermal silicone cable containing gold wiring. The distal cable ends in a micro plug which can be connected to the stimulation unit during the trials. The silicone cable leaves the skin in the retroauricular region. The micro plug was extra corporal. This plug was used in the first patients and replaced by a transdermal energy supply that has its receiver coil under the skin in the same region.

The ocular and subretinal part. The shape of the implant was designed and empirically tested in animal models [8]. The size of the chip determined the maximum width of the implant. A successful penetration of the choroid is eased by the design and shape of a guiding instrument that protects the retina during implantation. This instrument is called the guide foil. The design, especially the form of the tip of the implant, is helpful for the subretinal advancement. The available space on the tip of the implant left room for additional direct stimulating (DS) electrodes. These electrodes were important for parameter determination and basic electrophysiological experiments. The 16 DS electrodes are situated on the tip of the foil. In the later phase of the project these electrodes were removed. The DS electrodes are followed by the stimulation chip with 1550 photodiodes. The chip is square-shaped and has the photodiodes with the equal number of TiN electrodes arranged rectangularly. The chip is powered by external energy which is delivered via the supply lines on the polyimide foil. Light falling onto the chip (MPDA) drives the device. So the single photodiode worked like a switch pulling energy from outside if activated in the stimulation process. The 16 DS electrodes could be directly connected to an external stimulator and were used for light independent stimulation trials.

The width of the foil tail is determined by the wiring and the need for stability during the process of subretinal foil advancement and proper placement. The foil leaves the eye in the (pre-) equatorial region through the choroid and is covered for the following ca. 5 mm by a scleral flap. The extraocular foil has small polytetrafluorethylene patches glued onto it to ease episcleral fixation. This fixation is intended to neutralize the tensile stress. The foil reaches the fornix where it is rather loose to guarantee the mobility of the eye. The path of the subdermal cable starts at the scleral patch and ends at the retro auricular region. The cable has to be fixed to the bone with the help of screws to avoid tensile stress which could affect the more vulnerable PI-foil. In the orbit the cable forms a loop to guarantee eye movement.

The transition from MPDA to active subretinal implants. Surgery was developed using different animal models. Pigs were mainly used to develop or improve the critical surgical steps. For the required electrophysiological experiments, cats were of great value [2]. The experience of this model gave rise to the decision to develop an active implant. Information on retinal stimulation gathered from cat brains revealed that the MPDA concept without additional energy supply was not successful [4]. The decision to build a cable bound implant was the result of acute (intraoperative) stimulation film experiments in cats and pigs which were transformed step by step to a chronic experiment.

The surgical knowledge which was necessary to plan a transchoroidal procedure in humans was achieved by a series of implantations of cable bound stimulation film devices in domestic pigs. By engaging this animal model, the parameters for a bloodless penetration of the choroid were determined.

The transchoroidal subretinal implantation in humans in detail. One surgical team usually supported by an ENT surgeon is responsible for extraocular surgery (the path of the cable from the region of the ear to the orbit). This team starts the surgery and hands over to a second team for the intraocular surgery after finishing their part and opening

the conjunctiva. This process is described in detail in [8]. The stimulation foil and the following silicone cable enter the orbit beneath the upper temporal quadrant of the eye lid. The chip is covered by a protective sleeve which is removed immediately before the subretinal implantation. A standard 3-port vitrectomy is carried out and the vitreous is removed as far as possible. The position of the temporal lower sclerostomy is modified to guarantee the possibility of rotation downward of the globe during surgery. A critical step is the search for suitable (choroidal) penetration site which should allow the creation of a visible subretinal fluid bleb in the equatorial region. This bleb, which is created by injection of BSS through a 41G Teflon cannula (DORC, Netherlands, Dual bore BSS injection needle, 41G tip) is stabilized with viscoelastic solution (Healon, 10 mg/ml AMO, Uppsala, Sweden) injected with a subretinal injection needle (Subretinal injector, curved, Glaser, 32G tip). The size of the bleb is kept small, just big enough to meet the demands of retinal protection in the corresponding area which was determined in advance on the sclera as the suitable implantation site. Big blebs create additional problems during implant advancement. A trapezoid scleral flap with its basis corresponding to the subretinal bleb is created. The width at the basis is 4 mm (the implant size is 3.5 mm) and the length of the flap is 5 mm. The flap is prepared over the full thickness in the equatorial region to expose the choroid in a rectangular 1×4 mm window at its basis. Suprachoroidal tissue is removed completely in the region of the window. This maneuver is carried out in hypotony of the eye (the intermediate used scleral plugs are removed) to prevent the choroid from prolapsing. Care is taken to avoid any choroidal bleeding. The choroid is completely exposed in an area of 1×4 mm and radiodiathermy is applied in this region. The best and most constant results have been achieved with an Ellman Surgitron Radiofrequency device in the Fulguration mode 4m Hz (Ellman, NY, USA). In this mode with a spark gap waveform, maximum penetration and hemostasis is achieved. A ball electrode (2 mm) is used and discrete whitening of the choroid in the treated area is achieved. Thus the choroid can be punctured with a surgical knife without any bleeding. The subretinal space is entered by gaining access into the viscoelastic bleb from outside of the globe. This tiny choroidal opening is widened by a specially designed lancet-shaped guiding foil. Its rigidity and shape allows a safe subretinal advancement of this device into the desired subretinal posterior target area. So a smooth mechanical separation of the retina is achieved and the vulnerable electronic device can be advanced behind this shield into the desired macular region. After placement of the stimulation chip the shield can be withdrawn easily. The scleral flap is immediately closed by one situation suture (Vicryl 7.0) at the moment the guide film is removed. Gentle pressure onto the sclera next to the cut edge can remove the viscoelastic from the subretinal space if necessary. Most of the viscoelastic solution vanishes during the course of the surgery out of the choroidal opening. The infusion is turned on and inspection of the intraocular situation can be carried out. If the desired position is not yet reached, a repositioning by gently pulling back the implant and again advancing it is possible, best carried out with the guide foil in place. With the implant in its destination, the scleral flap is sutured several times with Vicryl 7.0 after removing the guide foil. The implant leaving the scleral flap is turned over in the direction of the fornix and fixed with patches onto the sclera. The extraocular region of the flap and the visible foil is covered by a donor scleral patch which was cut to the desired size. Other artificial material (e.g. Gore Tex) has been used successfully as well. This patch is also fixed to the sclera. Its purpose is to minimize scarring and protecting the overlying conjunctiva which is not sufficient alone to cover the implant structures permanently. In the region of the scleral fixation patch the foil part is followed by a silicon cable with spiral gold wires. 5 cm of the cable is buried in the fornix region without suturing creating a cable loop. This is it to guarantee eye movement. Silicone oil is used as a tamponade medium at the end of intraocular surgery to protect the retinal situation.

RESULTS

The feasibility of a transchoroidal implantation of retina implants was proven. All 26 transchoroidal subretinal implantations of which 12 performed by one surgeon were carried out successfully. All surgical maneuvers were in accordance with the originally planned procedure. The transfer of the critical sequences of the surgical steps from the situation in laboratory animals to humans turned out well and did not lead to unexpected situations. The parameters determined in animal models were extremely helpful in the human surgical situation. No unforeseen problems that endangered the health of the patients occurred. The vulnerable electronic components were left undamaged during the surgery. This was repeatedly monitored in post explantation function tests. A stepwise approach of the transchoroidal procedure is given in Figure 1, 2.

There are remarkable differences of the tissue of the RP patient which influence the surgery. It is merely possible to punch the retina with a 41G Teflon cannula due to an increased rubber like resistance of the tissue. When injecting the subretinal fluid through this cannula, the bleb appears in a different, flatter, way than in a normal retina which is known from retinal translocation surgery. The mechanical separation of the RP retina from the underlying pigment epithelium seems to be harder to achieve. A slightly increased resistance exists when advancing the guide foil. Incomplete penetration of the choroid with the implant results in a ping pong effect when advancing the foil. To avoid it, a clear sign of complete penetration is mandatory. A clear sign to penetrate into the subretinal space is when viscoelastic solution is emerging after the puncture of the choroid. Due to the fact that visual control of the foil advancement in the penetration site is not possible, these indirect signs seem to be important. Retracting the scleral flap and carrying out the maneuver under visual control leads to unintended loss of viscoelastic

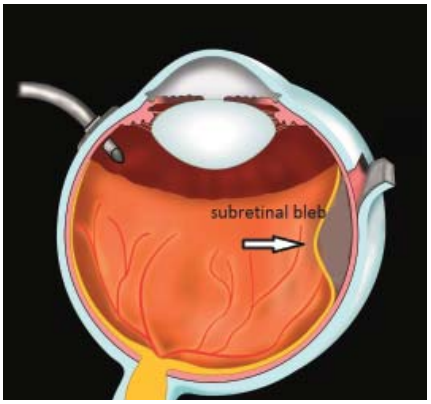


Fig. 1. Subretinal bleb containing viscoelastic solution and scleral flap before choroidal penetration.

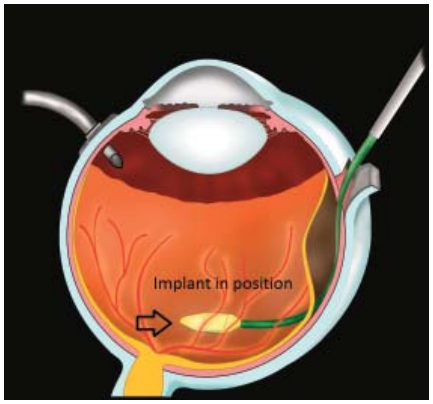
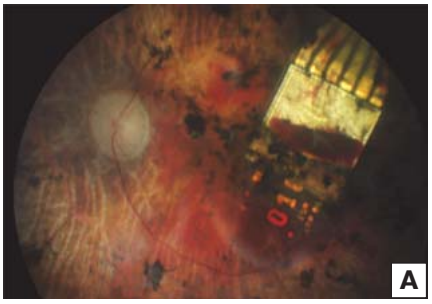
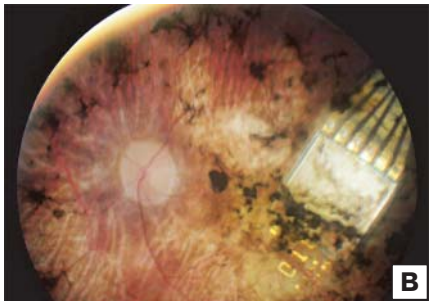


Fig. 2. Position off the implant after choroidal penetration and subretinal advancement (guide foil removed).





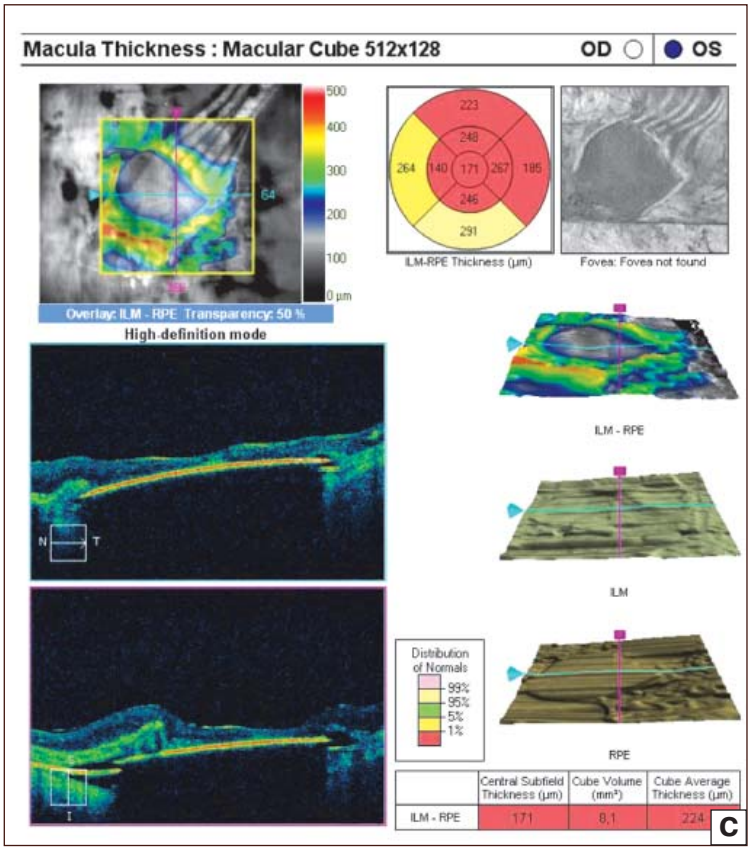


Fig. 3. Choroidal perforation with limited bleeding which resolved completely (A); choroidal bleeding resolved (B); OCT of choroidal perforation. Chip (high reflective red line). On the chip (bottom) exact boarder of penetration visible showing choroid and retina on the left side and retina only on the right side overlying the chip (C).

solution and hinders to pressurize the eye again. The implantation process is rather dynamic and best carried out beginning in hypotony (infusion closed, scleral plugs removed) for the choroidal puncture and after slightly injecting the guide foil turning over the scleral flap temporally suturing it so that the advancing forces are tangential. After temporally suturing the flap the eye can gently be repressurized. Done at the right time it seems to prevent the guide foil and the implant from running via falsa and rolling up in the originally created subretinal viscoelastic bleb. The advancement of the guide and the implant develops easier when having the eye repressurized after implantation of the guide further than the region of the subretinal viscoelastic bleb into the attached retina.

Choroidal problems in the 12-patient subgroup were one perforation in the area of the posterior pole (Fig. 3, A–C) and one intraoperative misplacement of the implant beneath the choroid (Fig. 4, A) and the RPE which was corrected within the same surgery (Fig. 4, B). The perforation did not lead to a major bleeding (Fig. 3, A, B). Additional problems were not monitored in the follow up phase for two years. Specifically, no additional bleedings followed. There was no neovarscular growth in the follow up. The initial bleeding resolved completely showing a stable situation (Fig. 3, B).

DISCUSSION

The transchoroidal access into the subretinal space in combination with a pars plana vitrectomy is a new developed surgical procedure to implant visual prosthetic devices to restore vision in patients blind from degenerative retinal disease. Severe theoretically possible complications lead to a lot of criticism in the period of the development of the surgical procedure especially in the preclinical phase of the animal experiments. The danger of a choroidal bleeding was discussed extensively. In this period the complex implantation procedure was divided into single steps which have been optimized in

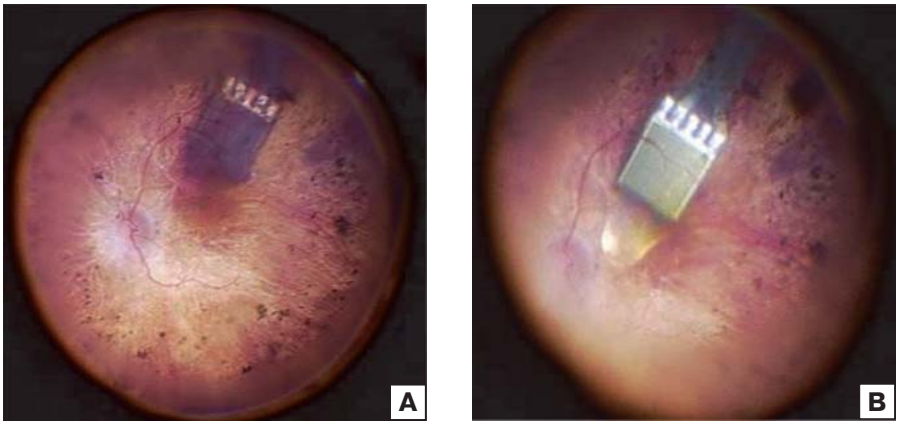


Fig. 4. Implant intraoperative beneath RPE and retina (A); Implant intraoperative beneath retina on RPE after repositioning (B).

the minipig model which was appropriate to evaluate the surgical steps. The development of the bloodless choroidal puncture was one of the key points and searching for the optimal strategy radiodiathermy was established to archive optimal surgical results. The optimized steps were combined again and adapted to each other. Thus a procedure resulted which could be transferred from the animal models to the human situation without adverse events. The feared disastrous choroidal bleeding and other major serious adverse events did not appear in any of the 26 cases that received the implant. In the subgroup of the 12 patients operated by one surgeon the perforation of the choroid in one patient appeared in an area with high pigmentation. Pigmented areas indicate adhesion between RPE and retina. This aspect was unknown before and was never seen in the animal model due to the missing RP phenomena. To avoid unintentional penetration of the retina during the implantation process a guiding tool was developed and continuously improved. This tiny instrument protects the retina during the implantation of the chip and is of outstanding importance for a successful implantation. An electronic implant like the one which was used for implantation has different rigid zones and is unimplantable without the help of the new developed tool. To achieve the ideal performance of the material, the rigidity and the flexibility were determined empirically. However not every retinal situation e.g. scarring or dense pigmented areas in RP is ideal for implantation. This became apparent during the course of the project. The number and severity of the observed adverse events do support the thesis that transchoroidal surgery has an acceptable safety profile. The choice of adequate animal models to acquire this information was decisive to reach this goal. Minipigs turned out to be the proper model to develop this surgical procedure. Primates that might be even nearer to the human situation were inappropriate due to known reasons of animal welfare. Cats, rabbits and other models which were used in the projects to answer special functional questions differ a lot from the human eye in respect of the surgical situation. To eliminate learning curve effects as far as possible only the surgeries of the most experienced surgeon who did most of the animal surgeries as well were taken into account.

With 26 surgically successful implantations out of 26 human implantations of the complete group a manageable procedure for experienced retinal surgeons is now available to implant electronic components of relevant size into the subretinal space. The persistent connection of the subretinal space to the extraocular environment has been shown to be manageable via this foil implantation procedure. The stability and safety of this situation in the postoperative period has been proven. This important step for a long lasting and stable implantation was reached by developing this new surgical access to the eye. Other modified applications for this procedure like instillation of drugs appeared later but have not been examined in this project.

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Трансхориоидальная субретинальная имплантация чипа слепым пациентам с пигментным ретинитом. Хориоидальный выбор

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Активный субретинальный зрительный протез требует трансхориоидальной трансплантации, поскольку его экстраокулярная часть обязательно должна быть соединена с источником питания. В ходе разработки стратегии хирургии автор предполагал, что хориоидальный доступ может оказаться одной из самых трудных проблем. Было прооперировано 26 пациентов с пигментным ретинитом (ПР), официально признанных слепыми. В ходе операции с помощью хориоидального доступа пациентам были имплантированы долговременные активные зрительные протезы. Все пациенты были обследованы в нескольких центрах. 12 из 26 пациентов были прооперированы одним и тем же хирургом, который сам разработал трансхориоидальную операцию и приобрел соответствующий опыт. Автор анализирует именно эту подгруппу пациентов, чтобы не принимать во внимание побочные эффекты, связанные с процессом обучения других хирургов. Все имплантации прошли успешно как с точки зрения оптимального расположения имплантата, так и с точки зрения стабильности сетчатки. Опасения серьезных кровотечений не оправдались даже в тех случаях, когда происходили перфорации хориоидеи в области заднего полюса. Небольшие хирургические осложнения наблюдались при проведении направляющей фольги или самого имплантата в субретинальное пространство. Они были вызваны адгезией ретинального пигментного эпителия (РПЭ) с сетчаткой. Такие адгезии нередко наблюдаются у пациентов с ПР в областях плотной пигментации или рубцевания. Другие технические трудности в ходе хирургического вмешательства были связаны с попаданием имплантата под РПЭ. Такие неудачные ситуации отмечались дважды, но они были скорректированы в ходе операции и не вызвали кровотечения или других нежелательных последствий для пациентов. В целом хориоидальной доступ не создает неразрешимых проблем и, как можно заключить, не является фактором, ограничивающим проведение этой комплексной процедуры. Наблюдавшиеся перфорации не вызвали реальных или потенциальных критических побочных эффектов; одной из причин этого может являться наличие у пациентов с ПР довольно атрофичной хориоидеи. Дизайн и геометрия направляющей фольги и самого имплантата имеют важное значение, поэтому они постоянно улучшаются с целью минимизации нежелательных эффектов. Таким образом, даже сложные ретинальные ситуации не являются противопоказанием к имплантации чипа.

Ключевые слова: ретинальный имплантат, субретинальный имплантат, зрительный протез, трансхориоидальная хирургия.

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