

Long-term follow-up after implantation of a telemetric intraocular pressure sensor in patients with glaucoma: a safety report

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ABSTRACT

Importance: To investigate the long-term safety of a novel intraocular telemetric pressure sensor.

Background: Acquisition of accurate intraocular pressure (IOP) data is vital for sufficient medical care of glaucoma patients. Non-invasive self-tonometry with a telemetric IOP sensor can provide important information regarding the individual IOP profile.

Design: Retrospective analysis of long-term follow-up data assessed during outpatient visits in a university hospital.

Participants: 6 patients with open-angle glaucoma were included. Unfortunately, 1 patient passed away shortly after completion of the original 1-year study.

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Methods: Within the scope of a prospective 1-year pilot clinical trial, a telemetric IOP sensor was inserted into the ciliary sulcus after intracapsular lens implantation during planned cataract surgery.

Patients were regularly examined as outpatients even beyond the duration of the 1-year study. Data concerning sensor functionality, safety parameters, and home self-tonometry were assessed.

Main Outcome Measures: Long-term sensor functionality and safety.

Results: Sensor measurements were always successful in every patient.

Additionally, home self-tonometry was conducted without any problems by every patient. The average follow-up period was 37.5 months (21–50 months). During this period, the average number of IOP measurements performed per patient was 1273 (223–2884 measurements). No severe adverse events were reported. A varying degree of pupillary distortion was observed after 6–12 months in every patient; this remained unchanged thereafter with only one exception.

Conclusions and Relevance: Telemetric IOP sensors showed good functionality and tolerability during long-term follow-up. Non-invasive self-tonometry with a telemetric IOP sensor can provide useful additional data for future monitoring of patients with glaucoma.

Keywords: glaucoma, intraocular pressure, self-tonometry, telemetry

INTRODUCTION

An estimated 60 million adults over 40 years of age worldwide suffer from glaucoma, with up to 8.4 million being bilaterally or legally blind.¹

Glaucoma is a chronic disease that requires life-long observation and treatment. Successful management requires a high degree of self-discipline and motivation on the patient's part, as well as intensive, individualized monitoring and patient care provided by the treating ophthalmologist. Antiglaucomatous therapy adherence suffers due to several factors.^{2,3} Patients have no symptoms, at least not until the development of severe visual field loss and visual impairment in the progressed disease stage. Even in developed countries, half of glaucoma cases remain undiagnosed.¹ Unfortunately, a definite cure is not currently possible; the main goal

of treatment (either conservative or surgical) is to prevent further deterioration. This can dampen patients' expectations and motivation, making their long-term medical care challenging for the treating physicians.

Glaucoma is a complex disease with several pathophysiological factors. Increased intraocular pressure (IOP) is considered the greatest risk factor for glaucomatous optic neuropathy.⁴ The exact role of IOP in the disease course is not completely understood. Clinical studies point out that short- and long-term IOP fluctuations may be an independent risk factor for the progression of glaucoma;^{5,6} however, there is some controversy about this assumption.⁷

Single IOP measurements used in clinical day-to-day routine only provide limited information and surely do not capture IOP fluctuations that may occur during the day or at night. Additional data are especially important for patients with unclear progressive glaucoma under seemingly good IOP values. A method combining non-contact tonometry with self-tonometry assessment that could provide reliable and repeatable IOP measurements may help us better understand the role of IOP fluctuation in the progression of glaucoma. In addition, self-tonometry may have a positive effect on a patient's compliance and motivation in dealing with this condition.

An intraocular telemetric pressure sensor could fulfill these above-mentioned requirements. However, as it will be only a diagnostic tool and not a therapeutic instrument, it must meet high safety standards. It is necessary to ensure a safe implantation procedure as well as a good short and long term safety profile. Long term evaluation is in the eyes of the authors particularly important. Are there late cases of inflammation or prolonged IOP decompensation? Is the telemetric sensor still working after being several years in the eye of the patients?

Regarding short time safety sensor properties, recently published 1-year follow-up results showed good safety and tolerability after the implantation of a telemetric IOP sensor in patients with glaucoma.⁸ Here, we describe and discuss the long-term follow-up data concerning safety, functionality, and home self-tonometry assessment.

METHODS

Study design

Within the scope of a prospective, single-center pilot clinical trial [ARGOS generation 1 study; Deutsches Register Klinischer Studien (German Clinical Trials Register) DRKS00003335; www.germanctr.de], a ring-shaped telemetric IOP sensor (ARGOS generation 1) was inserted into the ciliary sulcus after implantation of the intracapsular lens during planned cataract surgery in 6 patients with open-angle glaucoma.

After the completion of a 1-year clinical trial, the patients were regularly examined on an outpatient basis every 3–6 months (unfortunately, 1 patient passed away after completion of the 1-year study).

Data obtained over this long-term observation period were then retrospectively analyzed with regards to sensor functionality, safety parameters, and the results of home self-tonometry assessment (using a non-contact inductive reading unit).

Specifications of the telemetric IOP sensor

The properties and specifications of the intraocular telemetric sensor have previously been described.^{8,9} Briefly, the ring-shaped telemetric IOP sensor (ARGOS, 1st generation, Implants Ophthalmic Products GmbH, Hannover, Germany) is a miniature device with 8 pressure-sensitive capacitors included in a single application-specific integrated circuit (ASIC) combined with a circular micro-coil antenna. The device is powered by a high-frequency field emitted from the same reader unit that transmits the sensor data. This reader unit is held at a short distance in front of the eye during IOP measurements (measurement duration < 2s, Figure 1).

Figure 1: Reading unit, Implants Ophthalmic Products GmbH, Hannover Germany.



Safety assessment

The assessment of safety endpoints was performed at all outpatient control visits carried out during the follow-up period. These included medical history, BCVA (Snellen charts), visual field (static perimetry; protocol 24-2 SITA), IOP measurement [Goldmann applanation tonometry (GAT)], slit-lamp examination, ophthalmoscopy (retina, macula, and optic nerve with cup-to-disc ratio), optical coherence tomography, and the assessment of adverse events.

Sensor functionality and home self-tonometry

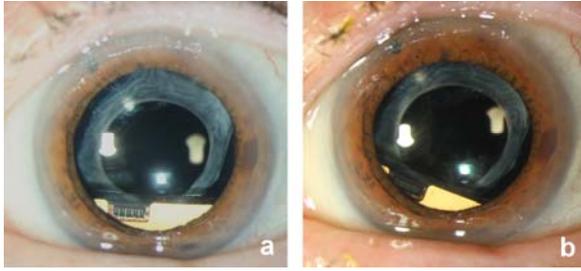
IOP measurements with the telemetric intraocular sensor were performed with the reading unit at every outpatient control visit. All patients received the reading unit for long-term self-tonometry and were encouraged to measure IOP at home on a regular basis and at different times of the day if possible. They were also instructed to perform a circadian IOP profile during daytime from time to time.

RESULTS

Safety and tolerability

In the long term, there were no incidents of late-onset endophthalmitis, chronic inflammation, corneal edema, pupillary block, angle closure, retinal detachment, bleeding, or macular edema. Dislocation of the intraocular lens or the telemetric pressure sensor was not observed in any case. However, a mild rotation of the sensor was observed in 2 patients (Figure 2).

Figure 2: Intraocular pressure sensor (generation 1) and intraocular lens (IOL) position in mydriasis of the same patient (pat. 2) at year 1 (a) and year 3 (b) postoperatively. During implantation, the single application-specific integrated circuit (ASIC) was rotated at the 6 o'clock position as seen in (a). Notice the mild rotation of the sensor in the year 3 image (b).



A mild to moderate pupillary distortion was observed in all patients after surgery. Furthermore, patients 1 and 4 showed transillumination of the peripheral iris owing to intraoperative pigment dispersion (Figure 3).

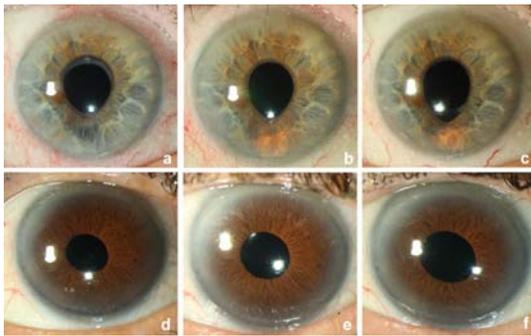
Figure 3: Transillumination of the peripheral iris (the sensor coil is visible) in patient 1 due to intraoperative pigment dispersion during sensor implantation.



In gonioscopy there were no further changes in the long-term follow-up compared to the findings at 1 year (gonioscopic findings at baseline and at 1 year have been described in details previously⁸).

Pupillary distortion remained stable over time (except in patient 4), with no further deterioration during long-term follow-up (Figure 4d–f). However, patient 4 showed progressive pupillary distortion and iris atrophy over time (Figure 4a–c).

Figure 4a-f: Pupillary distortion of patient 4 and patient 5 at three time points respectively (1 year, 2 years and 4 years after implantation of the intraocular pressure sensor ARGOS generation 1 in the ciliary sulcus during cataract surgery).



Glaucoma progression with varying degrees of bilateral deterioration of visual fields occurred in almost all patients, assumingly due to the underlying disease. The clinical data for all patients are summarized in Table 1. There was no evidence of a causal relationship with the sensor or the implantation procedure.

Patient 6 developed repeated uncontrolled intraocular pressure during follow-up.

Therefore, a canaloplasty in the study eye became necessary, along with a trabeculectomy with 5-fluorouracil in both eyes in the later course of the disease.

Both procedures were performed without complications. Sensor functionality was not affected by the canaloplasty or trabeculectomy.

Table 1: Patient data at baseline visit and at last visit

Patient No./ Sex/Age at baseline [y]	Study eye	Diagnosis	postoperative follow-up (baseline to last visit) [months]	IOP GAT [mmHg] baseline	IOP GAT [mmHg] Last visit	Visual field MD [dB] baseline	Visual field MD [dB] Last visit	Clinical course	Visual acuity baseline* (ETDRS)	Visual acuity last visit* (Snellen charts)
1/ f/ 75	OD	POAG	21	13	18	-3.34	-4.98	stable pressure values (GAT) under topical treatment (1 IOP lowering substance). No late complications	20/63	20/25 (ETDRS)
2/ f/ 76	OS	POAG	50	13	13	-4.94	-8.29	mild bilateral VF progression despite good IOP values (1 substance). No IOP decompensation, no late onset endophthalmitis	20/25	20/25
3/ f/ 71	OD	NTG	44	9	9	-28.08	-31.60	bilateral progression. GAT values always under 14mmHg (3 substances)	20/63	20/50
4/ m/ 72	OD	NTG	43	13	13	-22.59	-31.02	bilateral progression. Loss of central visual field in study eye. GAT values always under 15 mmHg (3 substances).	20/25	Count fingers
5/ m/ 70	OS	NTG	42	15	11	-2.17	-4.97	Mild vf progression, no late complications, adequate IOP lowering (2 substances)	20/20	20/20
6/ f/ 73	OS	POAG	25	19	20	-25.05	-30.41	bilateral progression, multiple eye-drop intolerances. Uncomplicated canaloplasty and trabeculectomy in study eye, trabeculectomy in the fellow eye	20/32	20/80

POAG: primary open-angle glaucoma, NTG: normal tension glaucoma, MD: mean deviation, VF: visual field, GAT: Goldmann applanation tonometry, IOP: intraocular pressure

*Note that some patients showed advanced glaucomatous visual field defects that at least partially affected center visual acuity.

Sensor functionality and home self-tonometry

Sensor measurements were successfully performed at all times and in every patient during long-term follow-up. The average follow-up period was 37.5 months, with a range of 21–50 months. Unfortunately, patient 1 passed away about 1 year after the completion of the 1-year observational study; therefore, no further long-term telemetric data or self-tonometry assessments were available for this patient.

All other patients successfully performed self-tonometry at home using the reader unit. They reported no discomfort or pain during the measurements.

During the follow-up period, an average of 1273 IOP readings were obtained with the telemetric sensor per patient (n_x = number of measurements performed, with x being the patient's identifying numeral: $n_1 = 223$, $n_2 = 1095$, $n_3 = 1884$, $n_4 = 1053$, $n_5 = 2884$, $n_6 = 548$). These total data represent the sum of the measurements performed during the repeated outpatient visits and the self-tonometry assessment values.

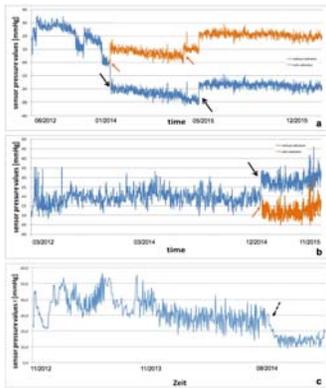
Figure 5 illustrates the telemetrically measured IOP values over time. The graphs resemble a series of seismographic curves. Due to the inhomogeneous measurement intensity across patients and over time, the time scale is not linear, but rather fitted to the data to allow better visualization of measurement fluctuations.

During long-term follow-up, there were shift phenomena in telemetric sensor values observed at 4 patients (figure 5, black solid arrows). In some cases, telemetric measurements displayed on the reading unit had negative values or values near zero. This was irritating for the patients. A calibration to current GAT values was performed in such cases (figure 5, orange color) and was needed only in three patients (pat. 3: 1 adjustment, Pat.4: 3 adjustments, pat. 5: 2 adjustments).

However, there was no defined IOP limit for performing these adjustments, as an adjustment of the sensor values to GAT is only possible and reasonable if the gap between measurements is stable over a long period. Fluctuations make an adjustment problematic. The adaptation of the sensor values to current GAT can be performed anytime by connecting the reading unit to a pc unit and all changes can be traced back. No direct manipulation of the intraocular sensor was performed. The values that the intraocular sensor measures remain unchanged. Only the IOP values

that the reading unit displays are adjusted. When the reading unit is connected to a pc unit all data can be controlled without lack of transparency.

Figure 5a-c: Representative graphic illustration of intraocular sensor pressure-values over time and their fluctuation [patient 5 (a), patient 3 (b) and patient 6 (c)]. Notice the shift phenomena that could be observed in 4 patients (black solid arrows). The orange arrows mark the time points of IOP calibration. At patient 6 the time point of the canaloplasty procedure is marked with a dashed arrow



As previously reported in the 1-year study results, there was a poor correlation of the IOP pressure sensor data when compared to GAT with strong fluctuations.⁸ This poor correlation persisted during long-term follow-up. Based on this finding, and on the small patient sample, the authors decided not to perform a detailed analysis of GAT data and sensor to GAT comparisons after the controlled 1-year study.

DISCUSSION

The lack of long-term clinical experience is a common characteristic of all innovative new methods, surgical techniques, and medical devices.

Although large amounts of data are available through preclinical research and animal testing, the reaction of a human organ over time is not always easy to foresee and predict based on the results of non-clinical studies.

Therefore, the focus and special interest of the authors was to describe long-term effects after the implantation of the above-mentioned telemetric IOP Sensor in patients with glaucoma. The authors were especially interested in reporting safety

and tolerability along with functionality of the medical device over a long-term follow up period.

There were incidents of inflammation in the early phase after implantation, as described before⁸. However, this inflammation was time-limited and resolved completely in all affected patients. Fortunately, long term follow-up did not reveal any late onset inflammation, chronic inflammation, or endophthalmitis.

The reported pupillary distortion must be interpreted as a sign of mechanical stress due to the pressure sensor. Nevertheless, the iris distortion did not lead to pupillary block or angle closure. At this point it is important to note that an ocular axial length less than 22 mm was an exclusion criterion in the original study.

Long-term tolerability was good with no patient complains about pain or discomfort during repeated follow-up visits.

In our opinion, there is no causal relationship between the observed deterioration of underlying glaucoma disease and the IOP sensor. The authors' main concern and fear regarding the sensor implantation was the possibility of a short-term or long-term IOP decompensation. Fortunately, these fears have not been confirmed. The patients that were included in the original study were patients with rather advanced glaucoma. Furthermore, the worse eye was chosen for the implantation. This decision was deliberate. The authors wanted to minimize the risk due to the lack of experience with the sensor and the implantation procedure. However, the low number of enclosed patients and the large heterogeneity of visual field defects at baseline prevent us from drawing definitive conclusions on how this procedure affects the progression of glaucoma in the long term.

A matched group of glaucoma patients could be useful to better differentiate the effect of the implanted sensor and should be considered in future studies. However, in this study patient selection for a control group would be difficult to implement due to the high inhomogeneous character of the study patient sample.

Nevertheless, the fellow eye of each patient served as an intraindividual comparison. At all patients, we observed similar progression of both eyes. This speaks against a direct effect of the implanted sensor.

During the follow-up, IOP measurements were successfully obtained in all patients and at all visits using the reader unit. Self-tonometry measurements were also

successful. After initial instructions for proper measurement, there were no reports of handling issues or discomfort by patients during the IOP assessment.

As described in the 1-year study results⁸, patient 4 showed a significant IOP shift immediately after the implantation; this was not observed in any other patient. We assumed that there was a malfunction in one of the eight capacitors of the ASIC, which was probably caused by the forceps during the sensor implantation procedure. Furthermore, throughout the long-term follow-up period, more similar IOP shifts of the sensor measurements were observed in 4 patients.

These IOP shifts, the early postoperative inflammation reaction, and the observed pupillary distortion can all be interpreted as signs of mechanical stress due to the size of the IOP sensor.

We do not wish to suggest that the prototype generation 1 sensor reliably measures the real IOP. Earlier manometric experiments in rabbits had revealed good IOP correlation between sensor and manometry, although a pressure drift over time had also been reported by the authors.⁹ We believe, that the clinical study was an important step. New techniques must evolve and prove themselves before reaching series production stage.

All these factors motivated a remodeling of the sensor's size and shape. Following the ARGOS generation 1 study data, a second-generation pressure sensor has been developed with a new design. Being both smaller in diameter and thinner with a new haptic design, the 2nd generation IOP sensor is currently being tested in a multicenter clinical trial.

The number of assessed values during home self-tonometry showed large fluctuations between patients. We assume that not all patients were equally motivated. To what extent the assessment intensity can reflect the patients' disease acceptance and the adherence to their treatment would only be speculative.

The key future question, provided that the sensor is safe and reliable, is whether there is a way to predict which patients with glaucoma can profit the most from a telemetric IOP sensor or whether this procedure is suitable for everyone. The given sample size of 6 patients was too small for a conclusive evaluation. One should remember that the implantation of the sensor remains an invasive procedure, even though it is combined with an indicated cataract operation to prevent a second

surgery. However, if the long-term data of the new designed sensor ensure a favorable safety profile, then the indication for implantation can also be expanded to pseudophakic patients. The limitation of the required cataract surgery excludes young patients and children, target groups that would benefit from long-term IOP data assessment and are usually open to new technology. In the author's eyes, especially patients with unclear deterioration of visual fields under seemingly well controlled IOP or persons with difficulty getting to the regular doctor appointments could benefit from this method.

Other methods and devices for self-tonometry also have limitations,¹⁰ especially regarding the need for corneal contact, and also the possible dependence on individual corneal properties (severe dry eye, scars, very thin or thick corneas, or laser-treated patients). In two recent studies with the non-invasive rebound tonometry (iCare HOME) several patients did not qualify for performing self-tonometry (20 of 76 patients in the publication by Dabasia et al¹¹ and almost 1 out of 6 patients in the study by Mudie et al¹²), either due to device handling difficulties or because the patients did not meet the advised IOP validation criteria.

The greatest advantages of the intraocular sensor are the ability of a non-contact IOP measurement, the independency from corneal properties, ease of use, and the large amount of measurements that can be performed.

The described follow-up study shows overall good safety and functionality of the telemetric IOP sensor (ARGOS generation 1) when used in long-term observations. The clinical trial results of the revised sensor (ARGOS generation 2) must demonstrate whether the above-mentioned issues concerning the mechanical stress have been resolved by adjusting the design of the intraocular sensor device, and furthermore, if a better correlation of the measured sensor IOP value to GAT can be achieved. In future, larger patient numbers and real-life data are needed for evaluating the long-term benefits of this novel method.

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