The CyPass-Stent

PROTOCOL
Version II
(08/07/2018)

Retrospective and prospective, monocentric study to evaluate the 5-year results of safety and efficacy following CyPass-stent implantation

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Retrospective and prospective, monocentric study to evaluate the 5-year results of safety and efficacy following CyPass-stent implantation

Subject	The Safety and efficacy of the supraciliary CyPass microstent five years postoperatively.
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1. BACKGROUND

In industrial countries worldwide and in Germany, glaucoma is the second most common cause of blindness. Glaucoma therapy with eye drops is the first line therapy. To achieve the target IOP (intraocular pressure) nearly half of the glaucoma patients require topical antiglaucomatous therapy with multiple drugs and different dosages. Therefore a consequent patient adherence is needed. With an adherence of only about 50% after one year of treatment, this is not sufficiently guaranteed. The resulting undertherapy may contribute to the progression of glaucoma damage. Therefore, surgical reduction of the intraocular pressure (IOP) is increasingly becoming an option for reducing topical therapy. The CyPass stent was developed as a less complicated surgical alternative to trabeculectomy.

We have been implanting the CyPass microstent at the Department of Ophthalmology in Neubrandenburg as a surgical glaucoma treatment procedure since 2009.

Since there is a negative pressure difference between the suprachoroidal space and the anterior chamber, the supraciliary CyPass microstent improves aqueous humor drainage into the suprachoroidal space.

In literature, we can only find follow-up data up to 2 years postoperatively for 'single' CyPass surgery [1, 2, and 3]. Long-term data are not yet available.

2. SYNOPSIS

2.1 Study objective

We designed this study to assess the long-term outcome after implantation of the supraciliary CyPass microstent beyond two years. The long-term results are of considerable importance for the evaluation and positioning of the CyPass stent procedure in the surgical glaucoma treatment armamentarium. We will collect data of a follow-up period of an average of 5 years.

The main research outcome is the determination of the efficacy of CyPass microstent implantation in reducing the intraocular pressure, the number of necessary antiglaucomatous medications and the progression of glaucoma in terms of visual field worsening and progression of glaucomatous optic disc changes.

Another main outcome is the safety of the procedure based on the intraoperative and postoperative complications.

Secondary outcomes include the development of the stent-associated blebs, the long-term success rate of the CyPass stent, and the clinical identification of stent failures.

2.2 Study population

- We plan to examine at least 84 eyes. Therefore, we invite patients with at least 130 study eyes (see sample size calculation 2.7).
- All patients after implantation of a CyPass microstent on at least one eye. Excluded are patients which had combined operation (phacoemulsification with intraocular lens implantation and CyPass stent implantation)
- We will not invite the patients of whom we already have the long-term data available because they had been examined in the past at the department of Ophthalmology. We will take the available data from the medical records.
- Patients with secondary surgery due to CyPass failure will not be invited for the examination. We will collect the available data up to the date of the new operation from the patient's records and classify these cases as failure.

- The following inclusion and exclusion criteria are considered for the prospective part of the study:

2.1.1 Inclusion criteria

- Patients 3 to 8 years following implantation of a CyPass-Stent between 2009 and 2014
- Willingness of patients to participate in the study and signing the written informed consent

2.1.2 Exclusion criteria

- Patients who live far away or with limited health conditions, to whom the trip to Neubrandenburg cannot reasonably be expected.
- Patients who moved to an unknown address.
- Deceased patients (with evaluation of the existing data).
- Patients who are not interested in participating in the study.

2.3 Study design

Monocentric study with two parts:

- Retrospective part: Collection of preoperative, intraoperative and postoperative data from the medical records
- Prospective part: Inviting patients according to inclusion and exclusion criteria for a single examination and collection of postoperative data after an average of five years

2.4 Study investigation plan

The pre- and intraoperative data, the data of the routine follow-up after 3 and 6 months postoperatively, as well as data of unscheduled examinations are taken retrospectively from the patient files.

- Collection of preoperative findings from the medical record:

  i. Patient name, date of birth, gender, operated eye and surgery date
  ii. General diseases and medications
  iii. Eye diseases and already performed eye operations, if any
  iv. Best corrected visual acuity
  v. Topical and systemic glaucoma therapy and duration of glaucoma therapy
  vi. Time of diagnosis of glaucoma, if available
  vii. Intraocular pressure using Goldmann tonometer and time of measurement
  viii. Central corneal thickness and pachymetric correction factor measured with the ultrasonic pachymeter or with Visante-OCT.
  ix. Classification of the chamber angle width according to Shaffer classification
  x. The lens condition or existing opacities of the natural lens or presence of an implanted intraocular lens at the time of surgery
  xi. Visual field using Humphrey perimeter or TAP (Tuebinger automatic perimeter)
  xii. Optic nerve configuration measured with the HRT-II (Heidelberg Retina Tomograph II)
  xiii. Retinal nerve fiber layer thickness measured with Stratus OCT

- Collection of intraoperative characteristics or complications from the surgical report

- Collection of available postoperative findings and complications
- A written or telephone invitation of the patients to a postoperative examination in the Department of Ophthalmology Neubrandenburg to collect the current, long-term postoperative findings
- The following examinations are performed during the study visit 5 years postoperatively:

  i. Ophthalmic history
  ii. Best corrected visual acuity
  iii. Topical and possibly systemic glaucoma therapy
  iv. Intraocular pressure using Goldmann tonometer
  v. Central corneal thickness and the pachymetric correction factor measured with the ultrasonic pachymeter or with the Visante-OCT
  vi. Visual field using Humphrey perimeter
  vii. Gonioscopic findings
  viii. The lens condition or opacities of the natural lens or of the implanted intraocular lens
  ix. Optic nerve configuration measured with the HRT-II (Heidelberg Retina Tomograph II)
  x. Nerve fiber thickness measured with Stratus OCT
  xi. Imaging and evaluation of the CyPass stent and associated bleb with the help of Visante-OCT/UBM (Ultrasound Biomicroskopy)

2.5 Safety relevant results

- Occurrence of accidents on the way from home to Neubrandenburg or the other way back and adverse events during the examination at the Clinic for Ophthalmology Neubrandenburg

2.6 Success of the treatment

We use two classifications to define treatment success:

- The first classification: dividing patients into 2 groups according to the need for postoperative glaucomatous medication: with and without medication. Then we divide each group into 4 subgroups according to the postoperative intraocular pressure achieved: patients with IOP >21mmHg, patients with IOP ≤21mmHg and >18mmHg, patients with IOP ≤18mmHg and >15mmHg, and patients with IOP ≤15mmHg.
- The second classification: definition of the treatment success according to the criteria of WGA (World Glaucoma Association) [4]. Complete success is achieved if the target IOP is reached without additional medication. Achieving the target pressure with additional local therapy is rated as qualified success. The loss of visual acuity to 'nulla lux' because of glaucoma progression, the need for systemic therapy with CAI (carbonic anhydrase inhibitor) to reduce pressure or the need for second glaucoma surgery are classified as complete failures.

2.7 Sample size calculation

We calculate the sample size by using the following formula [5]:

$$n = 21 \cdot \frac{\sigma^2}{d^2} = 21 \cdot \frac{8^2}{4^2} \approx 84\ patients$$

[$\boldsymbol{n}$= number of subjects $\boldsymbol{\sigma}$ = standard deviation $\boldsymbol{d}$ = relevant difference α= 0,05 $\boldsymbol{\beta}$=0,10] [6]

With a follow-up period of 5 years on average, we expect a response rate of 65%. Therefore the sample size will be 130 (n = 84 / 0.65 ≈ 130 patients)

3. OBSERVATION PERIOD

All patients potentially taking part in the study were treated with a CyPass micro-stent at the Department of Ophthalmology in Neubrandenburg between 2009 and 2014. Thus, we know the exact date of operation.

The duration of the observation period for each patient depends on the duration of the postoperative period up to the last follow-up visit in the Department of Ophthalmology Neubrandenburg in the context of the study. With follow-up visits, scheduled for the second half of 2016, we expect an average follow-up of more than five years.

4. Procedure

4.1 Screening

All patients who underwent CyPass microstent implantation without combination with cataract surgery, in the period between 2009 and the end of 2014 are potential candidates for the study. The selection of patients takes place according to the inclusion and exclusion criteria. Once a patient has met the criteria described above, we inform him in written form or by telephone about the study and ask him to participate.

4.2 Patient recruitment

The patient participates in the study when he fulfils the inclusion and exclusion criteria based on the findings and when he has signed the inform consent. We take out a proband insurance and travel insurance before the start of the study.

4.3 Patient pseudonymisation

After completion of the data collection, every patient record is provided with a unique patient identification code (pseudonymisation). This code is for study purposes only. After data collection, only the study physician and the study assistant can identify the patient.

4.4 Documentation

The data will be collected first via a data collection form (Appendix 1) and then via the Excel program. We collect the intraoperative information from the surgical documentation books, the surgical reports and the patient medical records.

- Surgery-Date
- Patient Name, date of birth, gender and address of the patient
- Operated eye (OD/OS)
- Anesthesia
- Intraoperative course, peculiarities or complications
- Preoperative findings
- Postoperative findings

4.5 Postoperative data collection

We collect the following data prospectively (at the five-year follow-up visit):

i. *Intermediate history:* First, asking the patients about the postoperative course and the regular check-ups at the registered ophthalmologist. If available, taking the intermediate eye pressure values and the course of the topical therapy, which may have been documented by the Glaucoma pass. Documentation of events such as bleeding or acute IOP-increase. Also documentation of intermediate treatments with date, if any, such as laser treatments.

ii. *Intraocular pressure:* Measuring the intraocular pressure twice in a row using a properly calibrated Goldmann tonometer (Carl Zeiss Meditec, Jena, Germany). The measurements should take place at the same time (± 1 hour) as preoperatively. Documentation of the average value of both measurements is required. If there is a difference of more than three mmHg between these two measurements, a third measurement is taken and the average of all three measurements is documented. The physican doctor measure the intraocular pressure and the assistant reads it.
The target pressure is determined according to the criteria of WGA (World Glaucoma Association) [7]. We initially classify the patients into three groups according to visual field damage (mean deviation):
   - mild damage (> -5 dB to -10 dB): target IOP ≤ 21mmHg and IOP reduction ≥ 20%
   - moderate damage (> -10 dB to -15 dB): target IOP ≤ 18mmHg and IOP reduction ≥ 30%
   - severe damage (>-15 dB): target IOP ≤ 15mmHg and IOP reduction ≥ 40%

iii. *Central corneal thickness:* A corneal topography is performed using Visante OCT (Model: 1000, Carl Zeiss Meditec, Jena, Germany). We define the thinnest part of the cornea as central corneal thickness. Alternatively, if the Visante OCT topography is not available (e.g., blepharospasm), three measurements are taken by means of an ultrasonic pachymeter (OcuScan, Alcon, Fort Worth, Texas, USA) to determine the central corneal thickness. The average of these three measurements is considered central corneal thickness.

iv. *Visual field:* The visual field examination is performed by using the Humphrey Perimeter (Humphrey Field Analyzer, Model 720i, Carl Zeiss Meditec, Jena, Germany) with threshold test centrally 24-2. The visual field is evaluated with the help of the MD value and the PSD value. The rate of progression is expressed in the form of dB / year [8]. As a significant clinical change (improvement or worsening), MD values of ≥ 3 decibels are assessed [9]. In addition, the visual field defects in the central 5-degree visual field are counted in all four quadrants (4 visual field points in total) and evaluated as follows: points with sensitivity level > 10 dB are classified with 0 point, while the points with ≤ 10 dB are evaluated with 1 point. The points are added and then divided by 4. Thus, in the evaluation, the normal regular central visual field will be rated with 0 and the advanced central scotoma in all four quadrants is rated as 1.0.

v. *Glaucoma therapy:* Number and name of the active ingredients of the prescribed topical and systemic antiglaucomatous medications preoperatively and at follow-up visits are assessed. The duration of the postoperative drug-free phase is documented. The systemic intake of acetazolamide (carbonic anhydrase inhibitor) is documented separately and evaluated as absolute failure.

vi. *Visual acuity:* First, the refraction is measured with an auto refractometer (KR-800S, Topcon, Tokyo, Japan). The best-corrected visual acuity is checked and adjusted with the best possible correction using Snellen chart. For the statistical evaluation, a visual acuity of hand motion is documented as 1/800, light perception as 1/1600, and Nulla-lux as 1/3200 [10].

vii. *The optic disc change*: Pre- and postoperative optic disc measurement is performed using the HRT II (Heidelberg Retina Tomograph II, Heidelberg Engineering GmbH, Heidelberg, Germany). The area of the optic disc and

the course of the rim area changes are documented and evaluated. Furthermore, the disc change is assessed and evaluated with the help of MRA (Moorfields Regression Analysis). The entire disc area is divided into 6 segments. First, the green segments lying within the standard range are rated with 0 points. The borderline yellow segments are scored 1 point and the pathologic red segments are scored with 2 points. The total number of points is added and then divided by 12. That means the normal non-glaucomatous papilla is rated with 0, the optic disc with terminal damage by glaucoma in all segments rated with 1.0.

viii. *The nerve fiber layer*: A measurement of the thickness of the peripapillary nerve fiber layer is carried out by the Stratus OCT (Model 3000, Carl Zeiss Meditec, Jena, Germany). The evaluation of nerve fibers is performed according to the number of damaged segments and the extent of damage of each segment. Each measurement results in 12 segments. The healthy segments (shown in green) are classified with 0 points, the moderately damaged segments (shown in yellow) are classified with 1 point and the markedly damaged segments in red are classified with 2 points. The total number of points is added and divided by 12, resulting in an average number of evaluable segments. The numbers of non-evaluable segments (shown in white), if any, are subtracted from the 12 segments and the total score is then divided by the number of segments that can be evaluated.

ix. *Description of the CyPass stent and the bleb*: By using the Visante OCT (Model: 1000, Carl Zeiss Meditec, Jena, Germany) the stent and the stent-associated bleb are morphologically visualized. It is assessed if the stent lumen is clear or if there is a CyPass occlusion. The size of the bleb is assessed and classified morphologically into 4 groups. While the largest bleb is assessed with 3 points, the absence of the bleb is rated with 0 points.

x. *Position of the stent:* The stent position is assessed by a gonioscopic examination of the angle of the anterior chamber with the Goldmann goniolens. Possible iris tissue growing and anomalies of the neighboring tissue (goniosynechiae) are documented as follows:
   - If there are no synechiae, it is classified with 0 points.
   - Goniosynechiae around the stent but without collar or lumen involvement are classified with 1 point.
   - Collar and / or lumen involvement of goniosynechiae is classified as 2 points.
   - Completely overgrowed and closed CyPass stent is classified with 3 points.

The depth of CyPass implantation is also assessed and documented using the number of visible rings. If the stent is not visible, it is rated with 0 points, if only the collar is visible, it is rated with 0.5 points. Depending on the number of rings visible, 1 to 3 points (one point per ring) are given.

New findings will be added to the data collection table in the Excel program.

5. STATISTICAL EVALUATION

For data protection reasons, all data of a patient are immediately pseudonymised after completing the data collection. The study assistant ensures that it is no longer possible to draw any conclusions about the respective patient from the data collected.

The data is statistically evaluated with the computer program STATISTICA (Version 10, StatSoft GmbH, Hamburg, Germany) using adequate statistical procedures.

Classification of the Follow-up-Visits according to the examination timeframe recommended by the WGA (World Glaucoma Association) [11]:

	D1	***W1***	***M1***	***M3***	***M6***	***M12***	***M18***	***M24***	***M36***
Ideal	1 day	7 days	28-31 days	90-92 days	181-183 days	yearly Date	547-548 days	yearly Date	yearly Date
Preferred	1-2 days	4-11 days	21-42 days	77-106 days	161-204 days	334-387 days	486-609 days	669-822 days	±91 days
Acceptable	1-3 days	4-14 days	15-60 days	61-122 days	123-272 days	273-456 days	457-639 days	640-913 days	± 181 days

6. ETHICAL ASPECTS

Prior to the start of the study, a vote will be obtained from the Greifswald Ethics Committee and the responsible supervisory authority according to the local law, regulations and authorities.

7. SAFETY

Since this is a retrospective and prospective data collection, rather than a clinical interventional trail, possible adverse events are limited to possible travel accidents and possible complications of the final follow-up visit, such as a conjunctival irritation, subjective impairment because of the pupil dilation or in very rare cases and corneal erosion after the measurement of the IOP or after gonioscopy. For the patients travelling to the examination, travel insurance and a proband insurance is taken out for the possible complications caused by the investigations. In case of conjunctival irritation, tear substitutes will be provided free of charge. In the very rare event of a corneal injury, tear substitutes and antibiotic-containing eye drops will be provided free of charge.

8. SIGNATURE OF THE PRINCIPAL INVESTIGATOR

I have read the study procedures described in this protocol and I agree to comply with them.

Prof. Dr. med. Helmut Höh

Principal Investigator Date,
Signature

Ahmed Medra

Sub-Iinvestigator Date, Signature

Ulrike Holland

Head of the research center Date, Signature

9. LITERATURE

[1] H. Höh, S. Grisanti, M. Rau und S. Ianchulev, „Zwei Jahre klinische Erfahrungen mit dem CyPass-Mikrostent: Sicherheit und operative Erebnisse eines neuen suprachorioidalen Mikrostents," *Klinische Monatsblätter für Augenheilkunde 2014; 231(4): S. 377-381.*

[2] H. Höh, S. Grisanti, S. D. Vold, A. Anton, M. Rau, K. Singh, D. F .Chang, B. J. Shingleton, S. Grisanti und T. Ianchulev, „Initial clinical experience with the CyPass Micro-Stent: safety and surgical outcomes of a novel supraciliary microstent," *Journal of glaucoma, 2016, 25. Jg., Nr. 1, S. 106-112.*

[3] J. García-Feijoo, M. Rau, S. Grisanti, H. Höh, C. Erb, P. Guguchkova, I. Ahmed, G. Grabner, H. Reitsamer, T. Shaarawy und T. Lanchulev, „Supraciliary Micro-stent Implantation for Open-Angle Glaucoma Failing Topical Therapy: 1-Year Results of a Multicenter Study," *American Journal of Ophthlamology 2015; 159 (6): S. 1075 - 1081.*

[4] T. Shaarawy, F. Grehn und M. Sherwood, Guidelines on Design and Reporting of Glaucoma Surgical Trials, Amsterdam: Kugler Publications, 2009, S. 17.

[5] M. Kutschmann, R. Bender, U. Grouven und G. Berg, „Aspekte der Fallzahlkalkulation und Powerberechnung anhand von Beispielen aus der rehabilitationswissenschaftlichen Forschung Rehabilitation," *Rehabilitation,* Bd. 45, pp. 377-384, 2006.

[6] P. M. David C Musch, M. Paul R Lichter, M. Kenneth E Guire, C. Carol L Standardi (RN und T. C. S. Group, „The collaborative initial glaucoma treatment study," *Ophthalmology,* Bd. 106, Nr. 4, pp. 653-662, 1999.

[7] T. Shaarawy, F. Grehn und M. Sherwood, Guidelines on Design and Reporting of Glaucoma Surgical Trials, Amsterdam: Kugler Publications, 2009, S. 17, 18.

[8] European Glaucoma Society, Terminologie und Leitlinien für das Glaukom, IV Hrsg., PubliComm, 2015, S. 64.

[9] European Glaucoma Society, Terminologie und Leitlinien für das Glaukom, IV Hrsg., PubliComm, 2015, S. 18.

[10] T. Shaarawy, F. Grehn und M. Sherwood, Guidelines on Design and Reporting of Glaucoma Surgical Trials, Amsterdam: Kugler Publications, 2009, S. 22.

[11] T. Shaarawy, F. Grehn und M. Sherwood, Guidelines on Design and Reporting of Glaucoma Surgical Trials, Amsterdam: Kugler Publications, 2009, S. 23, 79, 80.