Outcome and safety of the Baerveldt glaucoma implant

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Fabian - Januari 2023

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ISBN: 978-94-6458-917-7

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Printing: Ridderprint

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PROEFSCHRIFT

ter verkrijging van graad van doctor aan de Universiteit Maastricht
op gezag van de Rector Magnificus Prof. dr. Pamela Habibović,
volgens het besluit van het College van Decanen
in het openbaar te verdedigen
op vrijdag 10 maart 2023 om 13:00 uur

door

Annelie Nathanaele Tan
Geboren 9 oktober 1984 te Bilzen

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CHAPTER 1

Introduction

INTRODUCTION

Glaucoma is an optic neuropathy leading to irreversible blindness, due to progressive visual field loss, when untreated. The World Health Association statistics published in their recent report on global causes of blindness that glaucoma is the world leading cause of irreversible blindness. In 2015, 2.9 million people were blind due to glaucoma worldwide. [1] It is estimated that by 2040 the number of glaucoma patients will increase to 111.8 million people. [2]

History

The known history of glaucoma dates back to the early period from 400 BC to approximately 1600 AD. Originally, glaucoma could not be differentiated from cataract. Both diseases were assumed to be located in the lens which was believed to be the essential organ of vision (Figure 1). In that period, the term glaucoma was applied to afflictions that could be recognised by abnormalities in the papillary area and was used to refer to a general group of blinding ocular diseases. [3] The surgical treatment of cataract was first described in 800 BC. Couching (Figure 2) was performed; the surgeon would use a blunt needle and push the white lens backwards and downwards. [4] However, the failure of cataract operations to restore vision and the elevation of intraocular pressure as a distinct sign of ocular disease became gradually clear in the period from 1600 to 1854.

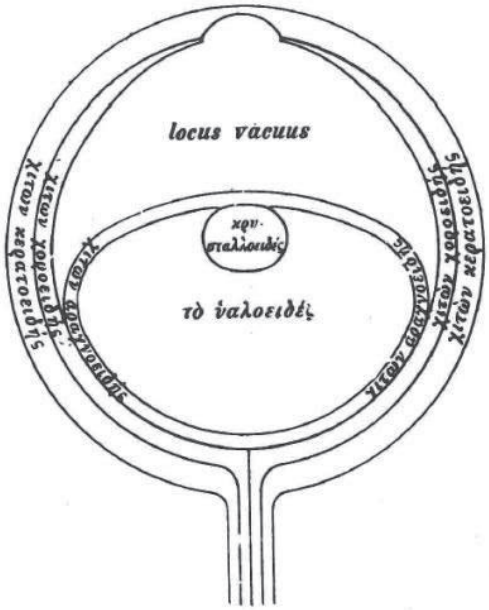

Figure 1

The anatomy of the eye after Celsus (2nd-century Greek philosopher), showing the lens in the centre of the eye [5]

Figure 2

Couching [3]

In 1826-1830, the German ophthalmologist Weller and the British ophthalmologist Guthrie recognised hardness of the eye to belong to glaucoma, and the British ophthalmologist Lawrence for the first time introduced the term acute glaucoma ("an acute inflammatory syndrome affecting the vitreous and choroid") and described a chronic form of the same condition [3]. Albrecht Von Graefe (1828-1870) was a pioneer of German ophthalmology. He observed a prominence of the papilla in glaucoma and described the glaucomatous disc in detail, including the pulsation of the retinal arteries in glaucomatous eyes. This phenomenon became a reliable clinically useful indicator of elevated intraocular pressure (IOP). With the aid of the then recently introduced ophthalmoscope, von Graefe divided glaucoma into three categories in 1857: acute, chronic and secondary glaucoma.

The Dutch ophthalmologist Donders (1818-1889) finally recognised that the chronic type of the disease (with increased ocular pressure) could occur without any inflammatory symptoms, and he suggested the name "Glaucoma simplex". He attributed the common cause of all glaucomas, i.e. elevated ocular pressure, to hypersecretion of intraocular fluid due to irritation of secretory nerves. [6]. In the 1890s, the Austrian ophthalmologist Schnabel was the first to describe in detail the nerve fibre breakdown with the formation of cavities as a characteristic of the glaucomatous process in the optic nerve.

Current classification

Nowadays, the classification of glaucoma is defined as primary (not associated with known ocular or systemic disease) or secondary glaucoma, associated with ocular or systemic diseases. Classification of glaucoma into subtypes is mainly based on differences in anatomy. Open angle glaucoma and angle closure glaucoma are the most common forms of glaucoma subtypes. [7, 8]

Currently, there is still no known causative treatment to cure glaucoma and restore lost vision. The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life. [9] Raised IOP is an important risk factor. Lowering IOP is the only known treatment to stop progression of the disease.

Medical treatment

Initially, most forms of open angle glaucoma are treated with topical agents. The European glaucoma society recommends to start with medical treatment or laser trabeculoplasty. [9]

History

Medical treatment first came available in the second half of the 19th century with the introduction of pilocarpine and physostigmine [3]. Pilocarpine first came on the market in 1870. Additionally, sympathetic agonists (e.g. epinephrine and later dipivefrine) could be used from 1903. Carbonic anhydrase inhibitors (CAIs, initially oral acetazolamide) became available in 1954. Acetazolamide is a potent IOP lowering drug but is also known for its systemic side effects. A combination of guanethidine/adrenaline (Suprexon®) became available from 1981 on, but this drug often caused severe redness of the conjunctiva and allergic reactions, making it less popular. After the development of new drugs in the nineties of the past century, it was withdrawn from the market in the Netherlands.

Current medical treatment

The introduction of β-blockers in 1976 revolutionised the treatment of glaucoma. [10] Topical CAIs and prostaglandins followed in the nineties. Together with new α-adrenergic agonists, these medications now are the main groups of anti-glaucoma drugs for current treatment. Pilocarpine is still in use for treatment of angle closure glaucoma. Currently used drugs act either through reduction of aqueous humour production (β-blockers, CAIs) or by enhancement of aqueous outflow (α-adrenergic agonists, miotics, prostaglandins) or both. [11] The highest topical reduction in IOP is obtained with prostaglandins, followed by non-selective β-blockers, α-adrenergic agonists, selective β-blockers and lastly carbonic anhydrase inhibitors. [12] Combination of two agents in one bottle, most often a β-blocker with another drug, are more and more available to further improve medical treatment. The use of oral Acetazolamide (a CAI) results in even more IOP reduction.

Laser treatment

Laser treatment is a suitable option in patients with intolerance or allergy to topical agents or poor compliance. It can also be used as a first line option or to additionally lower IOP when treatment with topical medication is insufficient. Several lasers are currently in use to treat glaucoma. Laser treatment of the trabecular meshwork (trabeculoplasty, LTP) is indicated for open angle glaucoma. When successful, it can induce a significant reduction in IOP. [13] LTP can be applied using the argon laser (ALT), which was introduced by Wise and Witter in 1979, or the newer selective laser (SLT), introduced by Latina and Park, in 1995. [14] In terms of the IOP lowering effect, SLT may be similar to ALT. [15]

Laser peripheral iridotomy (LPI) is mainly used for patients with angle closure glaucoma and is performed to treat or prevent an acute angle closure attack. [16]

The decision to opt for incisional glaucoma surgery depends on multiple factors, nevertheless glaucoma surgery should be considered whenever medical or laser treatment alone would appear unlikely to preserve sight in the glaucomatous eye. [9]

Incisional glaucoma surgery

History

The surgical treatment of glaucoma dates back to 1830 when William Mackenzie recommended a sclerotomy to release vitreous and relieve the pressure on the retina. [6] George Critchett first introduced the idea of drainage by an "iris inclusion", by drawing a blunt hook into a wound made at the limbus for a paracentesis [3]. In 1857, von Graefe introduced the iridectomy which remained the surgical treatment for (mainly acute) glaucoma until the further development of filtering operations in 1906. The principle of obtaining drainage through a fistulous scar with iris-inclusion to maintain flow of aqueous humour out of the eye was for the first time successfully applied by Félix Lagrange. He was the first to perform an iridosclerectomy in which uveal tissue remained incarcerated in the lips of the scleral wound (iridencleisis procedure, Figure 3).

Later a similar type of drainage scar by cauterizing the sclera was developed by Luigi Preziosi in 1924 and Harold Scheie in 1958. Another procedure was the technique of cyclodialysis, first attempted by Leopold Heine in 1905.

In 1909, Freeland and Elliot independently introduced the trephining surgery for Lagrange's scissors (Figure 4) [16]. In this operation, a large flap of conjunctiva and episcleral tissues was made, down to the limbus with dissecting the superficial layers of the cornea, after which a trephine hole was cut at the cornea-scleral margin, followed by a peripheral iridectomy.

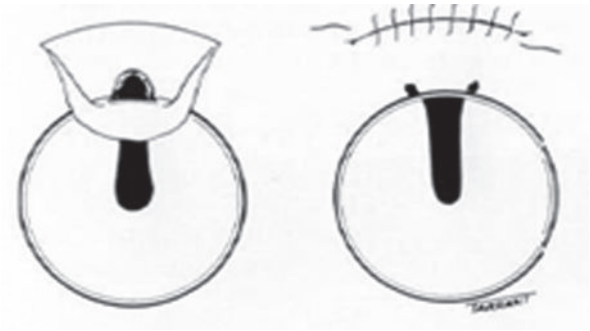

Figure 3

Iridencleisis [3]

An Italian surgeon, de Vincentiis, first conceived the technique of opening Schlemm's canal by the technique of trabeculotomy, in 1893. This method was further perfected by the American ophthalmologist Otto Barkan in 1936, who also introduced the technique of goniotomy, a technique by which the canal can be cut open from within [3]. This method is still in use today for the treatment of congenital glaucoma.

Current glaucoma filtration surgery

It wasn't until 1968 that Cairns introduced the trabeculectomy, the first glaucoma operation which proved to stop glaucoma progression and lower the IOP for a longer period of time with fewer post-operative complications. [17, 18] Trabeculectomy became (and still is) the gold standard procedure worldwide.

In this procedure, a block of tissue anterior to or including a part of the trabecular meshwork is removed, after which an iridectomy if performed, under a scleral flap, thereby facilitating outflow of aqueous humour from the anterior chamber into the subconjunctival space, creating a filtering bleb. However, initially success was often limited due to a high risk of bleb fibrosis and scarring. After the procedure, almost 60% of filtering blebs failed within 15 years. [19]

In 1987, Kitazawa reported that subconjunctival injection of 5-Fluorouracil (5-FU) appeared to improve the outcome on IOP following trabeculectomy in patients which had poor surgical prognosis due to increased risk of bleb fibrosis and scarring. [20] Chen et al. reported in 1990 that the use of mitomycin C (MMC) especially enhanced bleb survival. [21] In early studies, the outcome on IOP and complication rate were similar for MMC and 5-FU, with MMC showing less corneal complications compared to 5-FU. [22] However, in the following years MMC showed to be superior in obtaining complete and qualified surgical success and to have less postoperative complications compared to 5-FU. [23, 24]

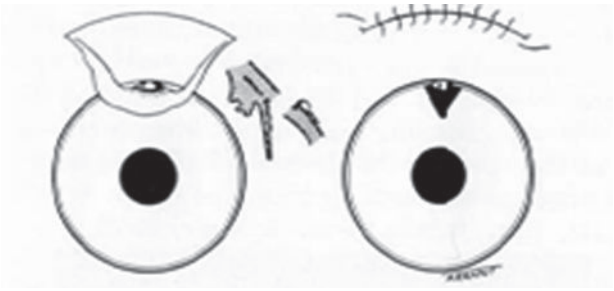

Figure 4a

Trephining surgery

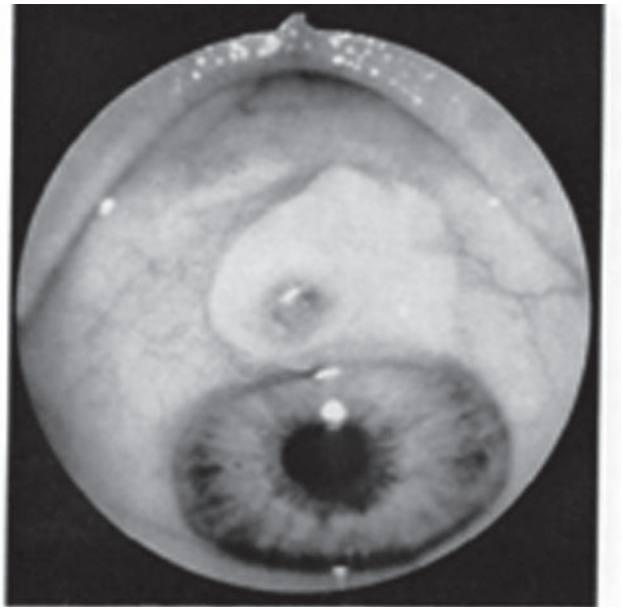

Figure 4b

Filtering bleb [3]

Glaucoma tube implants

A glaucoma tube implant is required when maximum medical or laser therapy is unable to reduce IOP and a trabeculectomy procedure is unlikely to succeed, such as in the presence of significant conjunctival scarring and/or inflammation. [25] Nowadays, it is more and more used as a primary procedure. Formerly, glaucoma tube surgery was mainly used in end stage glaucomatous eyes or in eyes with poor prognosis. [26, 27]

The pioneer of modern tube implants was Anthony Molteno who introduced the Molteno tube implant in the anterior chamber in 1969. The implant consisted of a translimbal tube which was attached to a thin circular acrylate plate of 8mm in diameter. The plate was sutured to the sclera and covered by Tenon's and conjunctiva. [28] A lot of variations and modifications followed in the following years. Aqueous shunts share a common design consisting of a silicone tube that is inserted into the anterior or posterior chamber through a scleral fistula, shunting aqueous humour to an episcleral plate that is located in the equatorial region of the globe, typically centered between (or under) two adjacent rectus muscles. Fibrous encapsulation of the equatorial plate produces a reservoir into which aqueous humor pools. The major resistance to aqueous outflow through these devices occurs across the fibrous capsule around the equatorial plate. [29-31]

Currently, glaucoma drainage devices are available in different sizes, materials and design, and with or without an IOP regulating valve. The nonvalved devices include the Molteno, Baerveldt, Shocket, and Eagle Vision implants. Unlike the nonvalved devices, the valved or flow-restrictive devices allow only unidirectional flow from the anterior chamber to the subconjunctival space with a minimum opening pressure. The most commonly used valved device is the Ahmed glaucoma implant, the most commonly used nonvalved device is the Baerveldt glaucoma implant (figure 5).

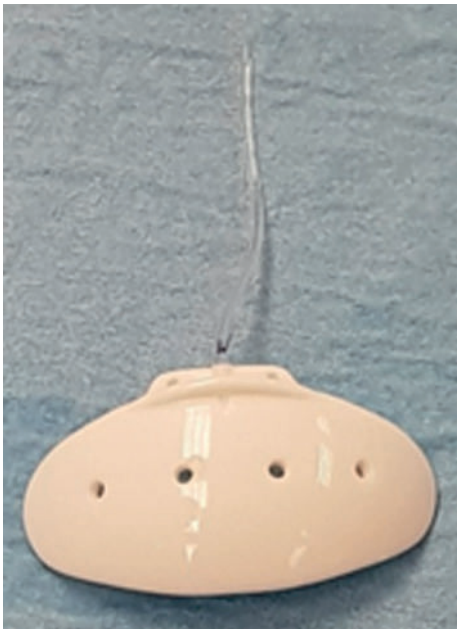

Figure 5

Baerveldt glaucoma implant

The Ahmed glaucoma valve allows an immediate IOP reduction. Due to the valved tube, there is a minimal risk on hypotony. These valved tubes are designed to open with an IOP of 10-12 mmHg and to close with an IOP of 8-9 mmHg, with an average flow of 2.75µL/minute, thus preventing post-operative hypotony. [25]

The non-valved tubes rely primarily on fibrous capsule formation around the plate to regulate IOP. Until the capsule forms during the first postoperative month there is a substantial risk for early hypotony. Therefore, a temporary ligature or stent is utilized to obstruct outflow until this capsule can form. The delay in initial IOP reduction is a disadvantage of the non-valved tube shunts like the Baerveldt, but long-term IOP control has been shown to be superior to valved devices. [25]

Multiple Baerveldt glaucoma implant types are available in different barium-impregnated silicone plate diameters and silicone tube diameters. The paediatric implant has a surface area of 250 mm^2 and a plate length of 22mm. The adult implant has a wider filtering surface of 350 mm^2 and a plate length of 32mm.

A BGI with a surface area of 500 mm^2 was also introduced, however due to a higher failure rate and a lower ability to maintain lower IOP for a longer period of time without the assistance of medication the 500 mm^2 is no longer in use. The theory was that the larger plates may increase higher fibrosis rate compared to the lower surface area Baerveldt implants. [32]

Adverse events

Although glaucoma tube surgery is currently gaining popularity as a primary procedure worldwide, it may still have serious and feared post-operative surgical complications, especially corneal complications. Severe corneal endothelial cell loss may lead to corneal oedema or decompensation. Persistent diplopia or tube exposure may also occur. Other complications (suprachoroidal haemorrhage, retinal detachment, cataract, hypotony and endophthalmitis) are probably similar to trabeculectomy. In a recent study, primary trabeculectomy + MMC surgery was compared to the Baerveldt glaucoma implant. In the first year of follow-up, the IOP was lower with the use of fewer glaucoma medications in the trabeculectomy group compared to the Baerveldt implant group; however the rate of serious complications was higher in the trabeculectomy group. [33]

In the Netherlands, the Baerveldt glaucoma implant has become the most popular tube implant. In several clinics, it also has become the most popular glaucoma filtering surgery, at the cost of trabeculectomy. However the Dutch study of Islamaj et al. shows us that the IOP and the failure rate were similar after Baerveldt glaucoma implants compared to trabeculectomy. [34]Further study is warranted to support this treatment paradigm shift.

Future perspectives

Currently new long tube implant designs are on the way. For instance the PAUL implant with a thinner silicone tube. However Minimally invasive glaucoma surgery (MIGS) is much more popular in the last decade. These devices are associated with a relatively high safety profile, shorter surgery time and a faster postoperative recovery. [35, 36] MIGS are designed to treat less severe glaucoma by enhancing physiological aqueous outflow with an approach that causes minimal tissue disruption. Three main approaches are performed. The first method is bypassing the trabecular meshwork (e.g. iStent, Hydrus microstent), the second is by increasing the uveoscleral outflow via suprachoroidal pathways, these approaches are not very successful. The last approach is by creating a subconjunctival drainage pathway (eg XEN gel stent, InnFocus). [37] These latest devices seem to have an IOP reduction which comes closest to the IOP reduction after conventional trabeculectomy surgery. There is still limited available evidence on the clinical and cost effectiveness of MIGS. [37]

The aim of the research in this present thesis was to further investigate efficacy and safety of the Baerveldt glaucoma implant, especially on the long term. Firstly, we evaluated reproducibility of methods to visualize the Baerveldt glaucoma implant in the anterior chamber to study its position with regard to long term success and possible corneal complications (Chapter 2). We then evaluated the movement of the BGI tube in the anterior chamber (Chapter 3) and the relation of the tube-corneal distance on the progression of endothelial cell loss (Chapter 4). The success in terms of IOP and preventing blindness of the Baerveldt glaucoma implant in secondary glaucoma (uveitic glaucoma and due to iris melanoma) is described in respectively Chapter 7 and Chapter 6. Finally, the long-term results of the Baerveldt glaucoma implant in general are presented in Chapter 5.

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CHAPTER 2

Reproducibility of anterior chamber angle measurements with anterior segment optical coherence tomography

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Investigative Ophthalmology & Visual Science, April 2011, Vol. 52, No. 5

ABSTRACT

Purpose

To study the reproducibility and variability of iridocorneal angle (ICA) measurements by using anterior segment optical coherence tomography (AS-OCT) by expert and nonexpert observers.

Methods

Twenty-three healthy volunteers (nonexperts with a basic knowledge of ophthalmology) acquired five consecutive AS-OCT images in the enhanced anterior segment single mode in the 180° to 0° meridian of the right eyes of their peers. Two experts and the 23 nonexperts analyzed the images. The ICA software tool was used to determine the angle opening distance (AOD) and the trabecular iris surface area (TISA) at 500 and 750 µm. A random intercept model was fitted to evaluate the variability of acquiring an image. For both the experts and the nonexperts, inter- and intraobserver variability of analyzing an AS-OCT image was determined with the coefficient of variation (CV). Reproducibility was qualified by using the intraclass correlation coefficient (ICC).

Results

There was no statistically significant difference in the variability of acquiring an image. The range of intraobserver variability in image analysis was from 9.4% to 12.5% in the experts and from 4.2% to 17.4% in the nonexperts. Interobserver variability was 10.7% in the experts and 10.2% in the nonexperts. The reproducibility was high, 0.875 and 0.942 in the experts and 0.906 in the nonexperts.

Conclusions

The overall reproducibility of the ICA measurements with the AS-OCT is good in open angles. Inter- and intraobserver variability showed similar mean values of reproducibility between the experts and nonexperts. The wide range of intraobserver variation in the nonexperts suggests that this group should undergo extensive instruction before routinely analyzing AS-OCT images.

INTRODUCTION

Although the current gold standard to assess the iridocorneal angle (ICA) is gonioscopy, this procedure is relatively invasive for the patient and the result relies on the physician's subjective assessment and experience. [1]

Recently, anterior segment optical coherence tomography (AS-OCT) has come into use for the assessment of the ICA in a more objective way.

AS-OCT enables in vivo measurement and objective assessment of the anterior eye segment through a noncontact technique. [2-5] The AS-OCT is becoming a promising technology for assessing the ICA and has the advantage of enabling scanning through an opaque cornea or examining painful eyes. [1,6,7] The built-in software of the AS-OCT system (Visante; Carl Zeiss Meditec, Inc. Dublin, CA) offers measurable parameters but also requires time-consuming and subjective user input, which may compromise measurement reproducibility. [9] A reliable measurement of the ICA and its subsequent clinical evaluation may eventually facilitate the choice of an appropriate treatment. ICA parameters, such as the angle-opening distance (AOD) and the trabecular iris surface area (TISA), are used to quantify the ICA and are measured with reference to the location of the scleral spur (figure 1). Since the scleral spur is used as the reference point for the relative position of the trabecular meshwork and is therefore vital for the diagnosis of angle closure, it represents an important anatomic landmark. However, the location of the scleral spur has to be determined by hand, and this necessity introduces an important human factor in the analysis of an AS-OCT image, possibly generating nonnegligible intra- and interobserver variance. Studies investigating the visibility of the scleral spur with AS-OCT showed a visualization between 70% and 78.9%. [6,9] Other studies have evaluated the reproducibility of the AOD and TISA with self-designed software and report reliable measurements with increasing variability when more than one observer identifies the scleral spur. [5,8,10,11] The purpose of the present study was to investigate the variability due to repeated AS-OCT image acquisitions from a single subject by a single operator, together with studying inter- and intraobserver reproducibility of generating ICA data with the standard software offered by Carl Zeiss Meditec, Inc. to determine the feasibility of using ICA assessment in daily practice.

METHODS

The study was conducted in accordance with the World Medical Association Declaration of Helsinki. Twenty-three healthy volunteers were recruited from the University Eye Clinic Maastricht and gave their informed consent. The volunteers, indicated as nonexperts, were medical students with only basic knowledge of ophthalmology. These nonexperts were given detailed instructions (including an instruction manual as well as an oral instruction) by an expert on how to acquire and analyze an AS-OCT image using a protocol that was especially designed for this study (citation protocol in Supplementary Materials, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5872/-/ DCSupplemental).

Since the location of the scleral spur was of crucial importance for this study, it was highlighted in our protocol by using clarifying illustrations (figure 1A, 1B). The protocol was designed to limit human influence on the image analysis to the choice of the positioning of the green dot on the scleral spur. Although small manual adjustments after placing the ICA tool are possible, such adjustments were not allowed in our protocol. If the observer was not satisfied with the placement of the marks of the ICA tool, the ICA tool was deleted, and the software was restarted until the observer was satisfied with the result. All subjects underwent five consecutive AS-OCT images of the right eye taken by one of their fellow nonexpert observers.

The five images were all acquired in the enhanced anterior segment single (EASS) mode, in the 180° to 0° meridian (from temporal to nasal), and under the same light conditions (>200 lux). The EASS automatically averages four frames per image, to minimize the noise– contrast ratio. All subjects had an undilated pupil and were asked to look at the internal fixation light. The images were analyzed with the AS-OCT software (ver. 2.0.1.88; Visante, Carl Zeiss Meditec, Inc.). The software included an ICA module. Once an image was acquired, the ICA tool had to be manually placed on the scleral spur, after which the software automatically generated the AOD and the TISA at 500 µm and 750 µm (figure 1C). All data were analyzed using a statistical software package (SPSS ver. 16.0; SPSS Inc., Chicago, IL).

Variability Due to Repeated AS-OCT Image Acquisitions by a Single Operator

For the assessment of variability due to repeated AS-OCT image acquisitions, the 23 nonexperts each acquired five images of the right eye of one of their fellow nonexpert peers. The two experts analyzed all 115 (23 x 5) acquired images in random order. A random intercept model was fitted to account for possible correlation introduced in the data due to repeated image acquisitions within one subject. The subjects (23 in total) were considered a random effect, whereas the expert observers (n = 2) and the repeated image acquisitions (n = 5) were taken as fixed-effect factors.

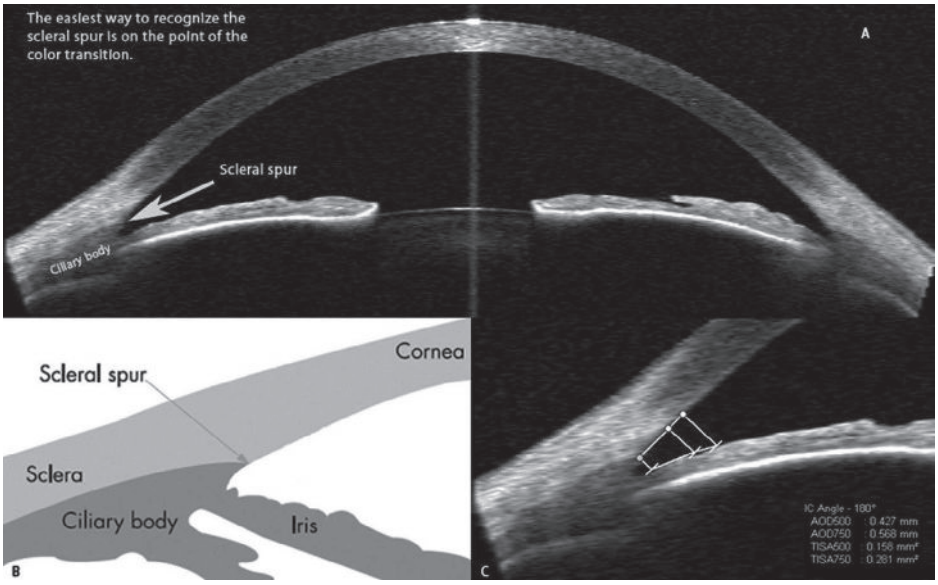

Figure 1

(A) Location of the scleral spur in an AS-OCT image. (B) Crosssection through angle structures illustrating the scleral spur position. Reproduced from Su DH, Friedman DS, See JL, et al. Degree of angle closure and extent of peripheral anterior synechiae: an anterior segment OCT study. Br J Ophthalmol. 2008;92:103–107, with permission from BMJ Publishing Group Ltd. (C) The ICA tool is shown with the green dot which had to be placed manually on the scleral spur by the operator. After this, the software generated the AOD500, AOD750, TISA500, and TISA750.

Variability and Reproducibility of Analyzing an AS-OCT Image

The images were randomly analyzed, with a time interval of 2 minutes between each image. To reduce the influence of observer memory with regard to the assignment of the scleral spur position, the program was shut down during the interval, after which the adjustments were newly set up and the images were randomly offered again. All (expert as well as nonexpert) observers assessed the nasal and temporal angles according to the protocol. Statistical analyses of the ICA data were subsequently performed for the separate groups of experts and nonexperts, to check for differences in reliability.

Expert Analysis

A random intercept model was also used to determine whether the observers were significant sources of variation in the ICA analysis. The subjects (n = 23) were a random effect, whereas the expert observers (n = 2) and the repeated image acquisitions (n = 5) were fixed-effect factors. In addition, the ICA data of the five repeated image acquisitions per subject (23 in total) were averaged for each expert. The standard deviation (SD) per subject was calculated and also averaged for the 23 subjects in total. The coefficient of variation (CV) was obtained by dividing

the SD by the mean. The mean CV was calculated afterward for both the experts, apart and together. These calculations were made for all parameters. Intraclass correlation coefficients (ICCs) were used as measures of intra- and interobserver reliability. ICCs, based on the available data of the repeated image acquisitions, were computed for each single observer as a measure of intraobserver reproducibility. For the computation of interobserver ICC, the ICA data was averaged over the five repeated image acquisitions. Finally, a Bland-Altman plot was used to facilitate visual interpretation of the interobserver agreement between the two experts.

Nonexpert versus Expert Analysis

From the five images that were acquired from each of the 23 subjects, one image was randomly chosen per subject. This procedure was repeated four times, to provide a reasonably random sample. Thereafter, all 23 nonexpert observers analyzed the five images in a random order. These images were used to study the inter- and intraobserver reproducibility of the ICA analysis performed by the nonexpert observers. The CV was calculated for each observer (n = 23) separately and for the whole group of nonexperts together. The ICCs of the image measurement replications were computed for each of the 23 nonexpert observers. For the comparison between experts and nonexperts, the experts analyzed the same images.

RESULTS

The sample consisted of 23 nonexpert subjects, of whom 9 were men and 14 were women with a mean age of 22.96 ± 1.89 years. None of them was known to have ocular disease. All images ± were assessed by the same 23 nonexperts and by 2 experts (1 man, 1 woman). In all AS-OCT images the scleral spur was identifiable, so that there was no need to exclude images due to nonvisibility of the scleral spur.

Variability Due to Repeated AS-OCT Image Acquisitions by a Single Operator

In the random intercept model that was used to assess the variability due to repeated AS-OCT image acquisitions, the images (n 5 for each of the 23 subjects) did not significantly (P > 0.8) differ from each other for all outcome parameters. This result shows that repeated acquisitions of the AS-OCT images were not a significant source of variability in the outcome parameters.

Variability and Reproducibility of Analyzing an AS-OCT Image Expert Analysis

In analyzing the ICA assessments made by the experts, the same random intercept model was used. The mean values of each of the four outcome parameters, as estimated by the random intercept model are shown in table 1. For parsimonious reasons, only the P-values for estimated differences in the means are displayed. A statistically significant difference between the observers was detected in two of the outcome parameters (TISA 500, TISA 750), with a third one on the verge of significance (AOD 500).

Table 1. Outcome Parameters as Estimated by the Random Intercept Model

	Expert 1	Expert 2	P value for the difference in means
AOD 500, mm	0.472 ± 0.036	0.486 ± 0.036	0.055
AOD 750, mm	0.680 ± 0.046	0.689 ± 0.046	0.362
TISA 500, mm^2	0.163 ± 0.014	0.173 ± 0.014	0.0005
TISA 750, mm^2	0.309 ± 0.024	0.321 ± 0.024	0.0095

Data are the mean ± SE for each expert.

Figure 2 shows the Bland-Altman plots for the four outcome parameters AOD 500, AOD 750, TISA 500, and TISA 750. There was a slightly significant difference in the AOD 500 (0.017 mm; P=0.01) which represents the difference between the two experts. The differences for the other outcome parameters were significant: 0.013 mm (P=0.01), 0.011 mm2 (P <0.01), and 0.014 mm2 (P <0.01) for AOD 750, TISA 500, and TISA 750, respectively. Since there were no significant differences between the nasal and temporal CVs, the CVs were averaged for both sides. The mean CV for the two experts was 10.4% ± 5.7% for the AOD 500, 9.4% ± 4.5% for the AOD 750, 12.5% ± 7.0% for the TISA 500, and 10.5% ± 5.3% for the TISA 750. There were no statistically significant differences between the two experts.

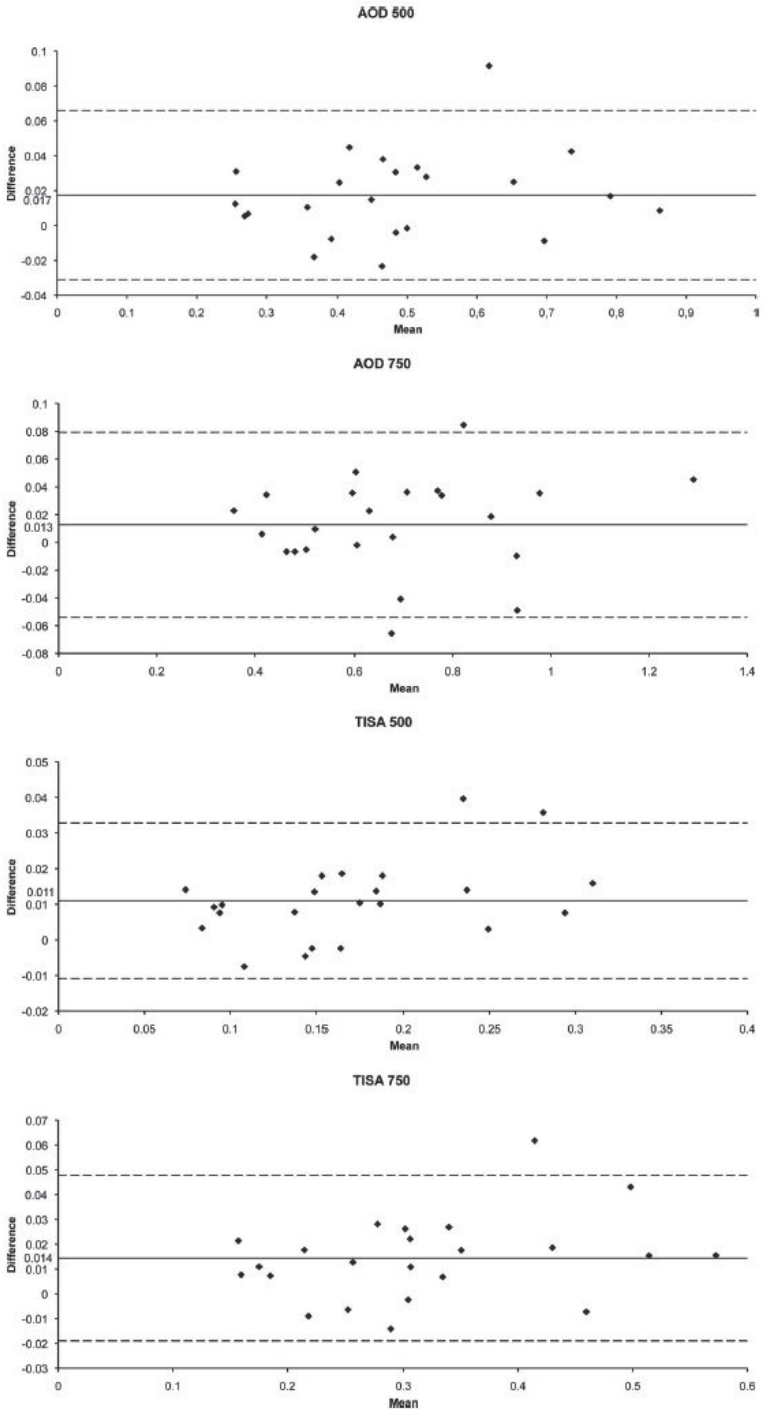

Figure 2. Bland-Altman plot of the four parameters, showing a high agreement between the two experts.

Intraobserver ICCs for expert 1 were 0.881, 0.844, 0.889, and 0.887 for AOD 500, AOD 750, TISA 500, and TISA 750, respectively. For expert 2, the intraobserver ICCs were 0.935, 0.909, 0.987, and 0.936 for these parameters. Given their high values (mean ICC 0.875 ± 0.021 in expert 1 and 0.942 ± 0.033 in expert 2), as well as the fact that the replications did not differ significantly in the modeling approach, one ICA reading per each subject was obtained after averaging over the five repeated measurements. Thereafter, the interobserver ICC was computed: 0.988 for AOD 500 and AOD 750, 0.978 for TISA 500, and 0.987 for TISA 750.

Nonexpert versus expert analysis

There were no statistically significant differences between the nasal and the temporal CVs; therefore, the CVs were averaged. The mean CV for the nonexperts was 9.8% ± 5.6% for AOD 500, 9.6% ± 4.8% for AOD 750, 11.5% ± 5.9% for TISA 500, and 9.9% ± 4.9% for TISA 750. Intraobserver ICCs ranged from 0.549 to 0.965, with a mean of 0.902 ± 0.09 for AOD 500, and from 0.572 to 0.972, with a mean of 0.897 ± 0.08 for AOD 750. The TISA 500 ICC ranged from 0.670 to 0.963, with a mean of 0.909 ± 0.08, and the TISA 750 from 0.635 to 0.973, with a mean of 0.913 ± 0.07. The box plot, shown in Figure 3 illustrates the intraobserver ICC of the 23 nonexperts for analysis of the four parameters. There were no statistically significant differences between the experts and nonexperts in intraobserver or interobserver CV (P = 0.09 to P = 0.3). Table 2 shows the absolute means of all nasal and temporal parameters for the experts and nonexperts. There were no statistically significant differences between the absolute means of the nasal and temporal parameters for the experts (P = 0.5 to P = 0.8) or the nonexperts (P = 0.4 to P = 0.8).

Table 2. Absolute Means of All Parameters

	AOD 500 (mm)	AOD 750 (mm)	TISA 500 (mm^2)	TISA 750 (mm^2)
Experts				
Nasal (n=40)	0.479	0.684	0.168	0.315
Temporal (n=40)	0.497	0.682	0.174	0.320
Nonexperts				
Nasal (n=460)	0.465	0.635	0.166	0.306
Temporal (n=460)	0.422	0.583	0.143	0.270

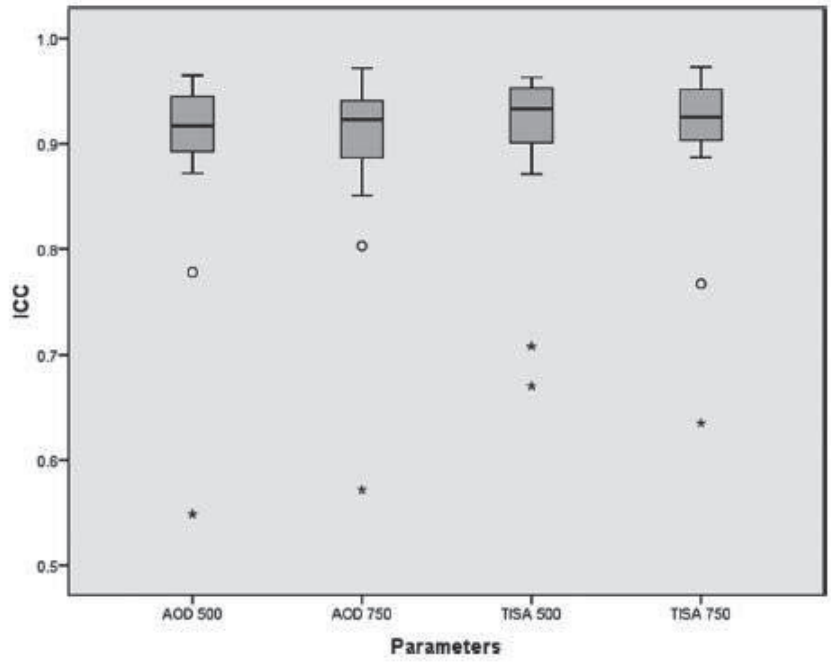

Figure 3. Box plot showing the intraobserver ICCs based on five image measurement replications of the nonexpert analysis.

DISCUSSION

Apart from a slight statistically significant intraobserver reproducibility difference for TISA 500 and the TISA 750, no significant difference in the variability of acquiring AS-OCT images made by the experts was found in our study. In a previous study, it was stated that when AS-OCT image acquisitions are performed by less-experienced operators, the percentage of nongradable images could be higher. The varying levels of observer experience would thus affect the performance of AS-OCT as a screening tool. [12]

Another study stated that the Visante OCT (Carl Zeiss Meditec, Inc.) can be operated by a technician with minimal expertise. [2] The latter findings correspond to our study. However, the fact that the nonexperts (medical students) received a solid instruction on how to analyze the image may have influenced our results.

The analyses of the ICA assessments showed a mean CV of 10.2% among the nonexperts in our reproducibility study. These results were similar to those of the expert analysis, which showed a mean CV of 10.7%. However, the range was larger in the nonexpert group. Radhakrishnan et al. [13] indicated an AOD 500 cutoff of 190 µm for detecting occludable angles. The 10% variation that we found in the analysis of our reproducibility study of the ICA will probably be acceptable in most cases in daily practice.

Previous studies have reported low intra- and interobserver variability in ICA measurements acquired by using AS-OCT, lending supporting evidence to their reliability. [2,3,5,8,10,14] However, in two of these studies the anterior chamber angle and the opening width were used, but both these parameters are unsuitable for irregular iris profiles. [2,3,5] Other studies have evaluated the reproducibility of the ICA with self-designed software. [5,10,11,15,16]

In previous studies, the anterior chamber was imaged with the anterior segment single protocol, whereas the enhanced mode (EASS) was used in the present study. [5-7,11,15,17] The EASS mode combines four anterior segment single scans and produces a better visualization of the scleral spur, making a more precise localization of the scleral spur by the observer possible. In our study, the scleral spur was visible in all images, in both the nasal and temporal angles. The use of the EASS mode probably contributed to the good results of the nonexperts.

We are also aware of limitations in the present reproducibility study. The images were taken in only one meridian (temporal to nasal), other meridians (i.e., inferior/superior were not investigated). Recent literature states that the temporal angle is the largest and the inferior

angle the smallest. [14] Our data suggest that there is no difference in the absolute values of the nasal and the temporal angles. However, the purpose of our study was not to compare different angles but to investigate the reproducibility of ICA parameters within one angle.

Another limitation of our study is that we included only young, healthy volunteers without ocular disease (i.e., narrow angle glaucoma). The analysis of ICA parameters of narrow-angle glaucoma patients may be less reliable due to a poorer visibility of the scleral spur.

Overall, the present results have shown that ICA measurements with the built-in Visante OCT software are useful for clinical practice. A standardized protocol for the analysis of AS-OCT images including a solid instruction for nonexperts should be helpful to further safeguard high reproducibility.

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CHAPTER 3

Baerveldt drainage tube motility in the anterior chamber

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European Journal of Ophthalmology, May-Jun 2014;24(3):364-70.

ABSTRACT

Purpose

To investigate the stability in position of the Baerveldt glaucoma drainage tube over time and to study movement of the drainage tube in the anterior chamber (AC) under varying light conditions.

Methods

This prospective study included 70 eyes with implantation of a Baerveldt glaucoma drainage tube in the anterior chamber. Anterior segment optical coherence tomography (AS-OCT) images were made preoperatively to quantify AC depth. AS-OCT images were made twice under photopic and twice under scotopic conditions, in the angle parallel to the Baerveldt tube to quantify drainage tube position, at 3, 6, 12, and 24 months postoperatively. Tube-corneal (T-C) and tube-iris (T-I) distances were measured. Additionally, the central AC depth and the peripheral angle opening (AOD 500) were determined. Two subgroups were distinguished according to tube position: free in the AC (group 1, n = 48) and transiridal (group 2, n = 22).

Results

After 24 months of follow-up, the drainage tube was found to move statistically significantly closer (0.12 mm) to the corneal endothelium in group 1 ($p<0.01$). There was no statistically significant difference in T-C distance over time in group 2. The T-C distance did not differ under photopic versus scotopic circumstances ($p = 0.32$). In both groups, the T-I distance was larger under scotopic conditions, a result of pupil dilation.

Conclusions

The Baerveldt glaucoma drainage tube remained in a stable position when a transiridal implantation was performed, whereas the tube moved closer to the endothelium when placed free into the AC. Transiridal implantation of the Baerveldt tube seems a safe alternative for tube implantation with respect to tube motility.

INTRODUCTION

Glaucoma drainage device (GDD) surgery is becoming an increasingly popular surgical procedure for the treatment of glaucoma. Initially, GDD surgery was preferably performed in eyes after failed trabeculectomy or in cases with uveitic, neovascular, or other forms of refractory glaucoma. In recent years, drainage tube implant surgery has gained popularity as a primary surgical procedure for glaucoma. Several implantation techniques can be chosen. The tube can be directly placed into the anterior chamber (AC) or fixed through the iris (transiridal approach), into the posterior chamber, or into the vitreous cavity in vitrectomized eyes. For this last purpose, a specially designed device may be used (Baerveldt pars plana implant with Hofmann elbow). The safety of tube surgery when compared to trabeculectomy or other glaucoma surgeries, however, is subject to debate. [1,2]

Additionally, it is unclear which implantation technique may be the safest. Corneal decompensation is a well-known complication after GDD surgery. Recent studies assumed the corneal endothelial cell loss after GDD surgery to be the result of the presence of a drainage tube in the AC, accelerating endothelial cell loss. [3,4,5,6] It is currently unknown to what extent tube mobility will contribute to endothelial cell loss. Additionally, drainage tubes implanted close to the corneal endothelium may cause tube-corneal touch. Sarkisian stated in a recent review on drainage tube complications that careful placement of a short drainage tube away from the cornea would at least prevent problems associated with tube-corneal touch. [7] Mendrinos et al reported that the tube-corneal distance remained stable during 6 months of follow-up after placing an Ahmed drainage implant. [8]

To our knowledge, no study has prospectively investigated the motility of the Baerveldt glaucoma drainage tube in the AC. We assumed that tube movement may be induced with constriction and dilation of the pupil, which could be simulated by observation under photopic and scotopic conditions. Therefore, the purpose of our study was to investigate the change in position of the Baerveldt drainage tube under varying light conditions (photopic and scotopic) of 2 different implantation techniques: directly into the AC or fixed through the iris (transiridial). Additionally, we studied the change in tube position between the 2 different implantation techniques over time.

METHODS

This prospective observational study was conducted in accordance with the World Medical Association Declaration of Helsinki. Glaucoma patients were eligible for inclusion if they were scheduled for Baerveldt GDD implantation with placement of the drainage tube into the AC. All surgery was conducted by a single surgeon (H.J.M.B.) at the University Eye Clinic Maastricht, the Netherlands. When patients required additional intraocular surgery (e.g., cataract surgery or keratoplasty), further measurements were discarded.

Surgical Technique

A fornix-based conjunctival flap was made in the superotemporal quadrant. A 101-350 mm^2 Baerveldt GDD was placed underneath the lateral rectus and superior rectus muscles and the Baerveldt GDD was sutured to the underlying sclera with a nylon 8-0 suture (Ethicon, Johnson & Johnson, Somerville, New Jersey, USA). The Baerveldt tube was tied off using a Vicryl 7-0 suture (Ethicon) and fixated to the sclera with one nylon 8-0 suture. The AC was entered using a 23-G needle and the Baerveldt tube, with an intraocular tube length of 3 mm (measured with a pair of compasses), was inserted into the AC, bevel up. To protect erosion of the tube, the extraocular part of the tube was protected with a patch of donor sclera before closing the conjunctival wound.

A tube position parallel to the iris plane, with the tube lying flat on the iris, was aimed for. However, in a number of cases this placement was difficult to obtain, with the tube ultimately being positioned free in the AC. Therefore, transiridal placement of the tube, using a preexisting peripheral iridectomy or creating a new one intraoperatively, was often preferred by the surgeon, especially for eyes with a shallow AC or a convex peripheral iris configuration. As the drainage tube was inserted transiridal or straight into the AC, we distinguished 2 groups according to the placement technique. In the first group (group 1), the tube was placed free into the AC; in the second group (group 2), the drainage tube was placed transiridal into the AC (figure 1).

Anterior segment optical coherence tomography scans

All patients underwent anterior segment imaging using VisanteTM optical coherence tomography (OCT) (Carl Zeiss Meditec Inc., Dublin, California, USA). During these examinations, the patients were asked to look at the internal fixation light (through an undilated pupil). Indentation of the eyeball during the examination was prevented.

Preoperatively, enhanced anterior segment single (EASS) scans were acquired in the 180°-0° meridian to measure the central AC depth and the peripheral angle. Anterior segment single scans were acquired in the angle parallel to the Baerveldt drainage tube in the AC

(figure 2) 3 months, 6 months, 12 months, and 2 years postoperatively to measure the tube-corneal endothelium (T-C), and tube-iris (T-I) distance. The EASS scan automatically averages 4 anterior segment single scans per image to minimize the noise-contrast ratio.

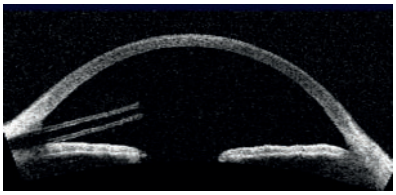
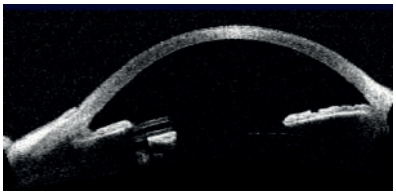
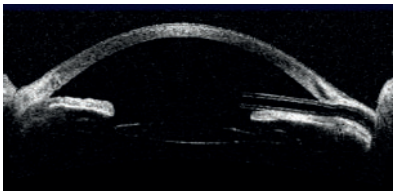
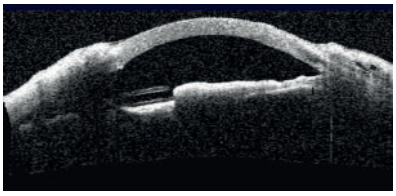
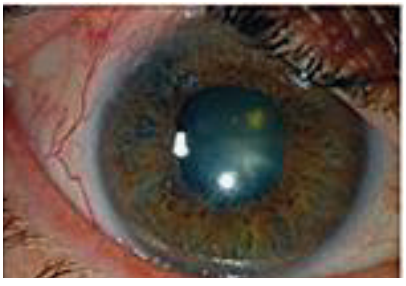
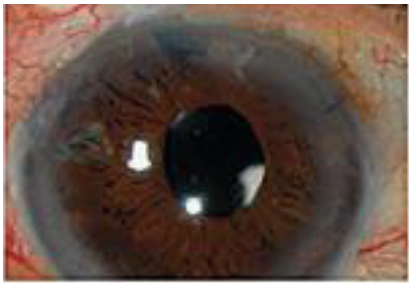
Drainage tube in the anterior chamber	Drainage tube transiridial
	
Drainage tube 'free' in the anterior chamber	Drainage tube transiridial, through new PI
	
Drainage tube parallel to the iris	Drainage tube transiridial, using pre-existent PI
	

Figure 1. Baerveldt tube position

At each visit, 4 anterior segment single scans were made, twice under scotopic conditions (<0.1 lux) and twice under photopic conditions (>200 lux), to search for possible tube movements under the same light circumstances as well as under varying light circumstances. The first scan was acquired under photopic conditions, the second scan under scotopic conditions, the third

scan again under photopic conditions, and, finally, the last scan under scotopic conditions. The time interval between each scan was 1 minute. The 1-minute time interval was required to reboot the VisanteTM OCT and was found to be sufficient to obtain an adequate dilation or constriction of the pupil.

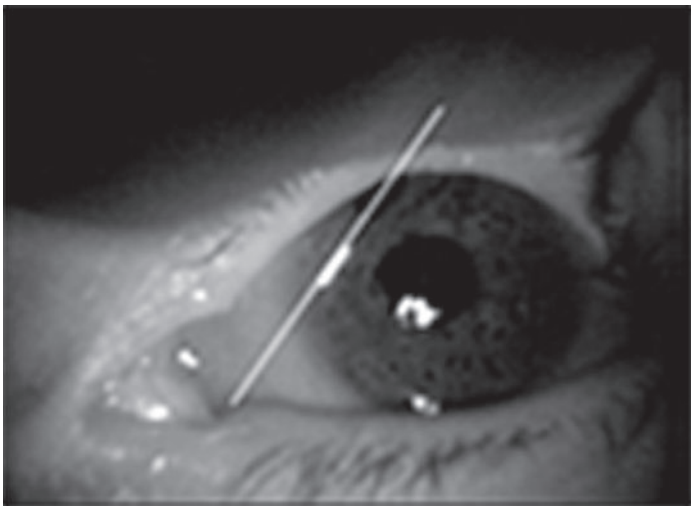


Figure 2. Visante ASS made in the angle parallel to the Baerveldt tube.

Scan analysis

All scans were analyzed using Zeiss software (version 2.0.1.88) as available on the VisanteTM OCT. This software has a claimed accuracy of 0.01 mm. For analysis of the EASS scans, the central AC depth was calculated using the chamber tool. The peripheral angle opening was measured using the iridocorneal angle tool (ICA). The ICA tool was placed on the scleral spur, after which the software automatically generated the angle opening distance at 500 µm (AOD 500).

In the anterior segment single scans, the distance between the superior tip of the Baerveldt drainage tube and the corneal endothelium (T-C distance) was determined using the safety center tool. The upper end of this tool automatically adheres perpendicular to the corneal endothelium after which the other end was dragged to the superior tip of the Baerveldt drainage tube (figure 3). Furthermore, the distance between the inferior tip of the Baerveldt drainage tube and the iris (T-I distance) was defined using the caliper tool (figure 3).

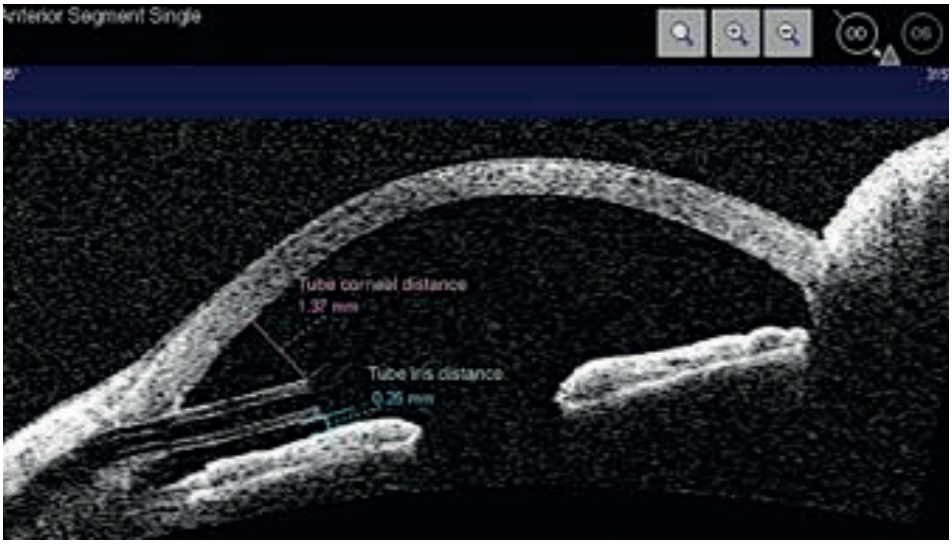


Figure 3. Tube corneal and Tube iris distance

Statistical analysis

The T-C distances for 2 photopic scans and 2 scotopic scans were analyzed using paired-sample t test. Differences in mean T-C distances under photopic versus scotopic circumstances were analyzed using paired-sample t test. The same statistical analyses were used for the T-I distance. For the analyses of the peripheral angle opening (AOD 500), paired-sample t test analyses were performed.

To determine changes in T-C distance and T-I distance over time, a linear mixed models (LMM) analyses was performed with subject ID as grouping factor and group and followup time as covariates, as well as their interaction term. All follow-up moments were included in the analyses. We also applied LMM analyses, stratified for the different groups, having only time as covariate. The resulting β-coefficients were used for visualization. All data were analyzed using the statistical software package SPSS® version 18.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Seventy consecutive eyes of 65 patients with a mean age of 58 years (range 26-80) were included, time range from January 2008 to January 2010. Fifty-eight percent of the patients were male. All included patients gave informed consent. The follow-up time was 24 months.

Baseline characteristics at the date of surgery are presented in table 1. In the first group (free into the AC), there were 2 phakic eyes, and in group 2 (transiridal), 1 eye was phakic. All other eyes were pseudophakic. We found no statistically significant differences between the 2 groups at baseline.

Table 1. Baseline characteristics

	Group 1: free into the AC	Group 2: transiridial
N	48	22
Mean age, y	56 ± 15	55 ± 18
% men	67	52
Mean AC depth, mm	3.60 ± 0.77	3.38 ± 0.65
Phakic eyes, n	2	1

AC = anterior chamber

T-C distance

The outcome of the LMM analyses is presented in Figure 4, where the trend lines shown are based on the β-coefficient of the model. After stratification, group 1 (free in the AC) showed a statistically significant decrease in T-C distance of 0.12 mm between 3 months and 24 months postoperatively ($p<0.01$). In group 2 (transiridal), the decrease was 0.045 mm ($p = 0.92$). Over time, the T-C distance decreased significantly more in group 1 when compared to group 2 ($p = 0.016$).

Comparison of the T-C distances revealed no statistically significant differences between both measurements under photopic conditions: 1.58 ± 0.58 mm (mean of measurement 1) versus 1.62 ± 0.58 mm (mean of measurement 2), $p = 0.50$, and under scotopic conditions 1.53 ± 0.61 mm (mean of measurement 1) versus 1.56 ± 0.60 mm (mean of measurement 2), $p = 0.54$.

At all follow-up times, the T-C distance did not significantly differ between photopic (1.59 ± 0.57 mm, mean of all measurements) and scotopic (1.54 ± 0.59 mm, mean of all measurements) conditions ($p = 0.41$). The T-C analyses under photopic and scotopic circumstances did not differ and therefore the presented results are limited to analyses of the values under photopic circumstances.

At all follow-up times, the T-C distance in group 1 (free in the AC) was larger than in group 2 (transiridal); however, these differences were not statistically significant (table 2). Table 2 shows the results of the absolute T-C distance in the 2 groups over time.

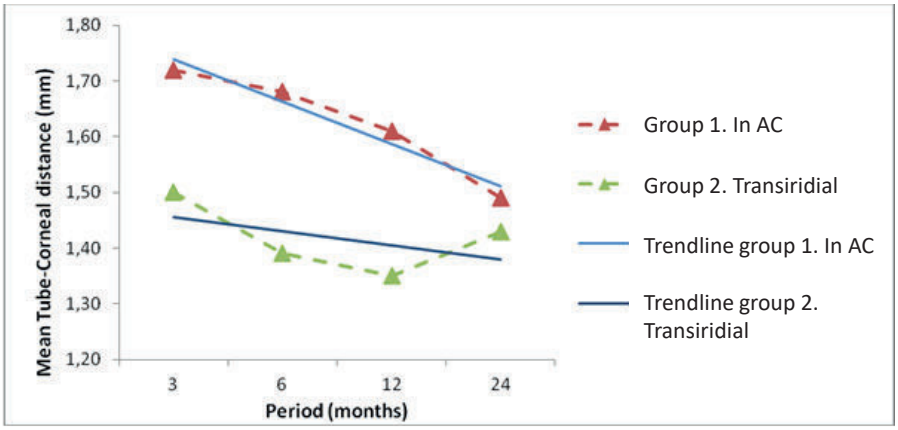


Figure 4. Mean Tube -corneal distance (mm) of the two groups

Table 2. Mean tube – corneal distances (mm), paired-sample T Test

	Group 1: Baerveldt tube in AC	Group 2: transiridial Baerveldt tube	p Value
3 months postoperatively	1.72 ± 0.62 (n= 48)	1.50 ± 0.56 (n= 22)	0.061
6 months postoperatively	1.68 ± 0.63 (n= 47)	1.39 ± 0.60 (n= 22)	0.065
12 months postoperatively	1.61 ± 0.59 (n= 47)	1.35 ± 0.66 (n= 21)	0.055
24 months postoperatively	1.49 ± 0.49 (n= 45)	1.43 ± 0.60 (n= 20)	0.54

AC= anterior chamber

T-I distance

Unlike the T-C distance, the T-I distance was significantly larger under scotopic (0.25 ± 0.35 mm) when compared to photopic (0.22 ± 0.36 mm) conditions ($p<0.001$). Between 3 months and 24 months postoperatively and after stratification, based on the LMM analyses, we found a statistically significant increase in T-I distance in both groups (0.076 mm [$p = 0.007$] in group 1 and 0.11 mm [$p = 0.01$] in group 2). There were no statistically significant differences over time between the 2 groups.

AOD 500

In group 2 (transiridal), the AOD 500 was smaller than in group 1 at all time points. These differences were not statistically significant (table 3).

Table 3. Peripheral iridocorneal angle measurements AOD 500 (mm), paired-sample T test

	Group 1: Baerveldt tube in AC	Group 2: transiridial Baerveldt tube	p Value
3 months postoperatively	0.72 ± 0.38 (n= 48)	0.61 ± 0.19 (n= 22)	0.11
6 months postoperatively	0.71 ± 0.30 (n= 47)	0.59 ± 0.23 (n= 21)	0.10
12 months postoperatively	0.66 ± 0.23 (n= 47)	0.61 ± 0.15 (n=21)	0.31
24 months postoperatively	0.67 ± 0.23 (n=45)	0.62 ± 0.25 (n=20)	0.41

AOD 500 = angle opening distance at 500µm

DISCUSSION

The present study shows that there is a shift of the Baerveldt drainage tube towards the cornea endothelium over time, which is dependent on the intraoperative tube placement. We evaluated the position of the Baerveldt drainage tube when placed free into the AC or transiridal. The inability of the anterior segment OCT to penetrate the iris stroma pigment makes it impossible to study the tube position in the posterior chamber or pars plana. [9] In cases where the Baerveldt tube was positioned free into the AC, the tube slowly migrated in the direction of the cornea endothelium, whereas when the tube was placed transiridal, no significant change in T-C distance over time was found.

We noticed a slight increase in T-C distance in the transiridal group from 12 to 24 months (figure 4), which we cannot explain from the present data. Further follow-up could possibly further elucidate this movement in the long term.

However, after 12 months of follow-up, the T-C distance already decreased significantly more in group 1 (free) when compared to group 2 (transiridal). We found no difference in T-C distance between photopic and scotopic conditions, indicating that light changes do not influence tube position with regard to the corneal endothelium. The significant increase in T-I distance under scotopic circumstances is the result of dilation of the pupil, causing the iris to move further away from the tip of the Baerveldt tube.

A larger T-C distance was found when the Baerveldt drainage tube was placed free into the AC. This might be explained by the preference of the surgeon to choose a transiridal approach in cases with a shallow AC. Although the AC was slightly shallower in the transiridal group (second group), there was no statistically significant difference in peripheral angle width between the 2 main groups. In contrast with the results of Mendrinos et al [8], who studied the position of the Ahmed drainage tube in the AC, we did not find a stable T-C distance for the Baerveldt GDD tube in the free AC group. A recently published article by Lopilly Park et al [10] described the position of the Ahmed glaucoma valve tube using the T-C angle. They found a smaller T-C angle (6.7°) over 12 months of follow-up, especially in uveitic eyes or eyes with previous penetrating keratoplasty. It is difficult to compare the decrease in T-C angle with the decrease in T-C distance observed in our study. However, we can assume that a decrease in T-C angle would also result in a decrease in T-C distance. In our study, we consciously choose the T-C distance over the T-C angle because previous published data revealed a low reproducibility in iridocorneal angle measurement using the angle software tool available on the anterior segment OCT. [11]

A possible drawback of our study was that it was carried out under ideal, almost laboratory circumstances. In real life, however, tube motion cannot be ruled out when patients rub their eyes or when there is contact between the patient's finger and the Baerveldt drainage plate.

Law et al [12] described 3 cases of drainage tube motion due to dissociation of the fibrovascular capsule and the plate in the fornix. They reported that the movement of the tubes was not associated with any intraocular tissue damage.

In our study, we did not observe any plate movement, although we did not investigate this in detail. Plate movement seems unlikely because the plate was positioned underneath the ocular rectus muscles and tightly fixated to the sclera with 2 nylon 8-0 sutures in all cases. Furthermore, the extraocular part of the tube was fixated to the sclera using a nonresolvable suture, preventing movement.

The movement of the tube towards the corneal endothelium therefore seems caused by forward bending of the tube instead of plate movement. Studies on the movement of phakic intraocular lenses (pIOL) in the AC have shown an increase of the distance between the pIOL edge and the corneal endothelium under dark circumstances or during accommodation. We could not extrapolate this observation to tube movement in our study. [13]

Another important observation from a recent study regarding pIOL implants into the AC is that a safe distance from implant to cornea should be respected to prevent excessive corneal endothelial cell loss. In this study, a mean distance of 1.43 mm led to a yearly endothelial cell density (ECD) loss of 1.0%, whereas a distance of 1.66 mm led to a yearly ECD loss of 0.2%. [14,15] Several studies reported an 8.3%-9% loss in ECD 5 years after the implantation of a phakic IOL.

It remains to be investigated if a similar safe distance should be respected with regard to the position of the tube of glaucoma implants. [13] Endothelial cell loss was reported after Molteno GDD insertion. [3] Recently, a decrease in central ECD of 7.5%-8.6% was found after 6 months and 12.6% after 12 months of Ahmed GDD implantation. [16,17] A substantial loss of endothelial cells is worrisome, since the treatment of corneal decompensation after GDD implantation remains difficult. Descemet stripping automated endothelial keratoplasty is the preferred technique; however, this technique requires an air bubble to press the donor tissue up against the patient's cornea. In eyes implanted with a GDD, the air bubble escapes through the tube to the subconjunctival space. A high rate of dislocation is reported, requiring a rebubbling. [16,18,19]

It might be expected that keeping a safe cornea–drainage tube distance will probably be the most important factor to prevent corneal decompensation in the long term. The present results suggest that transiridal placement of the drainage would seem a safe alternative to reach this goal. Alternatively, placement into the posterior chamber or pars plana insertion should be considered if possible.

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CHAPTER 4

Corneal endothelial cell loss after Baerveldt glaucoma drainage device implantation in the anterior chamber

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Acta Ophthalmologica, 2017 Feb; 95(1): 91–96.

ABSTRACT

Purpose

To investigate central and peripheral corneal endothelial cell density (ECD) in relation to Baerveldt (BV) glaucoma drainage device (GDD) tube corneal (TC) distance.

Methods

Prospective study of all patients scheduled for glaucoma tube surgery with 36 months follow-up. A BV GDD was inserted into the anterior chamber (AC). Anterior segment optical coherence tomography (AS-OCT) scans were made to determine the TC distance. Central and peripheral ECD was measured, preoperatively and at 3, 6, 12, 24 and 36 months postoperatively.

Results

Fifty-three eyes were included [primary open-angle glaucoma, (n = 13); secondary glaucoma, (n = 30); and primary angle-closure glaucoma, (n = 10)]. Central ECD significantly decreased during follow-up, with a mean decrease of 4.54% per year ($p < 0.001$), and 6.57% in the peripheral quadrant closest to the BV GDD tube (PQC, $p < 0.001$). In the PQC, a yearly decrease of 1.57% was shown after transiridial tube placement versus 7.43% after placement 'free' into the AC ($p = 0.006$). Endothelial cell (EC) loss was related to TC distance (mean 1.69 mm), with a central loss of 6.20% and 7.25% in the PQC per year with shorter TC distances, versus a central loss of 4.11% and 5.77% in the PQC per year with longer TC distances (outside mean _ 2SD, $p < 0.001$). A difference in EC loss by glaucoma subtype was not identified.

Conclusion

The TC distance is of significant influence on corneal ECD, a shorter TC distance causing more severe EC loss, especially in the PQC. Transiridial placement of the BV GDD tube seems safer than placement 'free' into the AC.

INTRODUCTION

Aqueous shunts are becoming increasingly popular in the surgical treatment of glaucoma. Although mainly used in cases of previously failed trabeculectomy or in cases with uveitic, neovascular or other forms of refractory glaucoma, they are increasingly used as a primary surgical procedure. Recent studies have demonstrated good shortterm results with early postoperative complication rates even lower than after trabeculectomy [1, 2].

One of the most worrisome long-term complications after aqueous shunt implantation is the development of corneal decompensation. A few studies have reported on corneal endothelial cell (EC) loss after aqueous shunt implantation [3-8]. The presence of the tube in the anterior chamber (AC) is thought to accelerate the loss of endothelial cells [3, 6, 9, 10]. Endothelial cell loss was reported after Molteno glaucoma drainage device (GDD) insertion [3]. Recently, an 8% decrease in central endothelial cell density (ECD) was found after 6 months and 12.6% after 12 months of Ahmed GDD implantation. In that study, the superotemporal area, which was closest to the tube, showed the largest ECD decrease [6, 9, 11].

In cases of corneal decompensation, the central corneal thickness (CCT) was increased. As far as we are aware of, no study prospectively investigated the corneal ECD after the implantation of the Baerveldt (BV) GDD in the long term. Therefore, the aim of the present study was to investigate the central and peripheral ECD and the CCT up to and including three years postoperatively after the implantation of the BV GDD. In addition, we studied the relation between the BV tube corneal (TC) distance and EC loss as well as the relation between tube position in the AC and EC loss.

PATIENTS AND METHODS

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Glaucoma patients were eligible for inclusion if they were scheduled for Baerveldt BG 101-350 (Abbott Medical Optics, Chicago, Illinois, USA) glaucoma implantation with placement of the drainage tube into the AC during the period 2009–2011. All surgeries were conducted by a single surgeon (HB) at the University Eye Clinic, Maastricht, The Netherlands. The central and peripheral ECD, the CCT and the TC distance were measured preoperatively and at 3, 6, 12, 24 and 36 months postoperatively. Patients requiring additional intra-ocular surgery during follow-up were included until the moment of the additional surgery and thereafter excluded from further analysis.

Surgical technique

A fornix-based conjunctival flap was made in the superotemporal quadrant. A 101–350 mm2 BV GDD was placed underneath the lateral and superior rectus muscles, and the plate was sutured to the globe with two nylon 8-0 sutures (Ethicon–Johnson & Johnson, Somerville, New Jersey, USA). The BV GDDtube was tied off using a Vicryl 7-0 suture (Ethicon–Johnson & Johnson, Somerville, New Jersey, USA) and fixated to the sclera with one nylon 8-0 suture. The AC was entered using a 23-G needle after which the BV GDD tube (with an intra-ocular tube length of 3 mm) was inserted bevel up into the AC.

To prevent conjunctival erosion, the extra ocular part of the tube was patched with donor sclera before closing the conjunctival wound. A tube positioned parallel to the iris plane, with the tube lying flat on the iris, was preferred. In pseudophakic eyes, especially with a more shallow AC, an additional technique was adopted to keep the tube away from the cornea by placing the tube transiridial through a peripheral iridectomy (PI). In eyes with a previously performed trabeculectomy, the previously created iridectomy was used, and in the other eyes, a new iridectomy was created using the 23-G needle that was used to enter the AC. There were no differences in AC maintainer between the two subgroups (BV GDD tube 'free' in the AC and transiridial placement of the tube). Subanalyses were performed for these two subgroups.

Corneal endothelium

The corneal endothelium and the CCT were analysed by specular microscopy (Konan Noncon ROBO Pachy SP-9000). A 'center-dot' method was used to measure the ECD. The ECD and CCT measurements were performed preoperatively and at 3, 6, 12, 24 and 36 months postoperatively. The central ECD was measured in all eyes and in four peripheral locations (at 2, 6, 10 and 12 o' clock) at 3 mm from the centre of the cornea (Fig. 1). Patients were asked to look at the internal fixation light. When they were unable to see the fixation light peripherally due to visual field loss, a peripheral measurement could not be obtained. Because of the known

variability in ECD data, three consecutive endothelial images of the central and each peripheral corneal quadrant were obtained and analysed using the dot method, after which the centres of 50 or more contiguous cells were marked. The mean values of these three measurements were used for further statistical analyses.

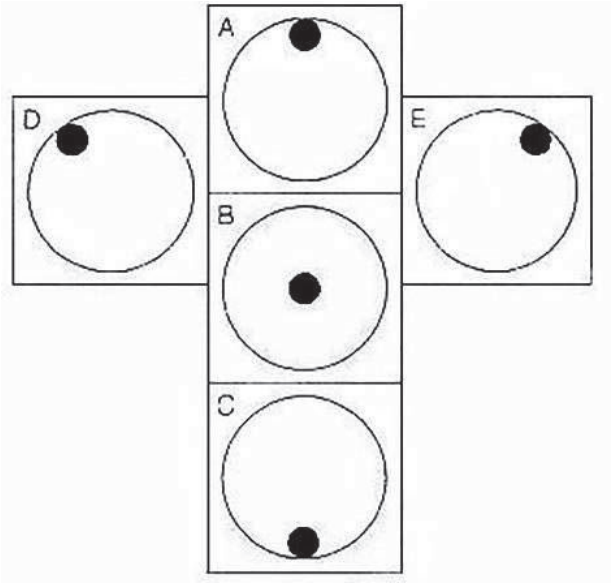

Figure 1

Endothelial cell density (ECD) measurement, (A) Superior corneal ECD, (B) Central corneal ECD, (C) Inferior corneal ECD, (D) Left superior corneal ECD, (E) Right superior corneal ECD.

Tube to cornea distance

All patients underwent anterior segment imaging using VisanteTM optical coherence tomography (OCT) (Carl Zeiss Meditec Inc, Dublin, California, USA). At all follow-up visits, the patients were asked to look at the internal fixation light (through an undilated pupil). The research assistants were instructed not to indent the eyeball during the examination. Two anterior segment single (ASS) scans were acquired in the angle parallel to the BV GDD tube in the AC, at 3, 6, 12, 24 and 36 months postoperatively, to measure the TC distance. The mean of these two TC distances was used for further statistical analyses.

Scan analysis

All scans were analysed using Zeiss software (version 2.0.1.88) as available on the VisanteTM OCT. This software has a claimed accuracy of 0.01 mm in measurements. The distance between the superior tip of the BV GDD tube and the corneal endothelium was determined using the

'Safety Centre tool'. The upper end of this tool automatically adheres perpendicular to the corneal endothelium after which the other end can be dragged to the superior tip of the BV GDD tube (figure 2). Extreme (short and long) TC distances were defined as outside mean ± 2SD.

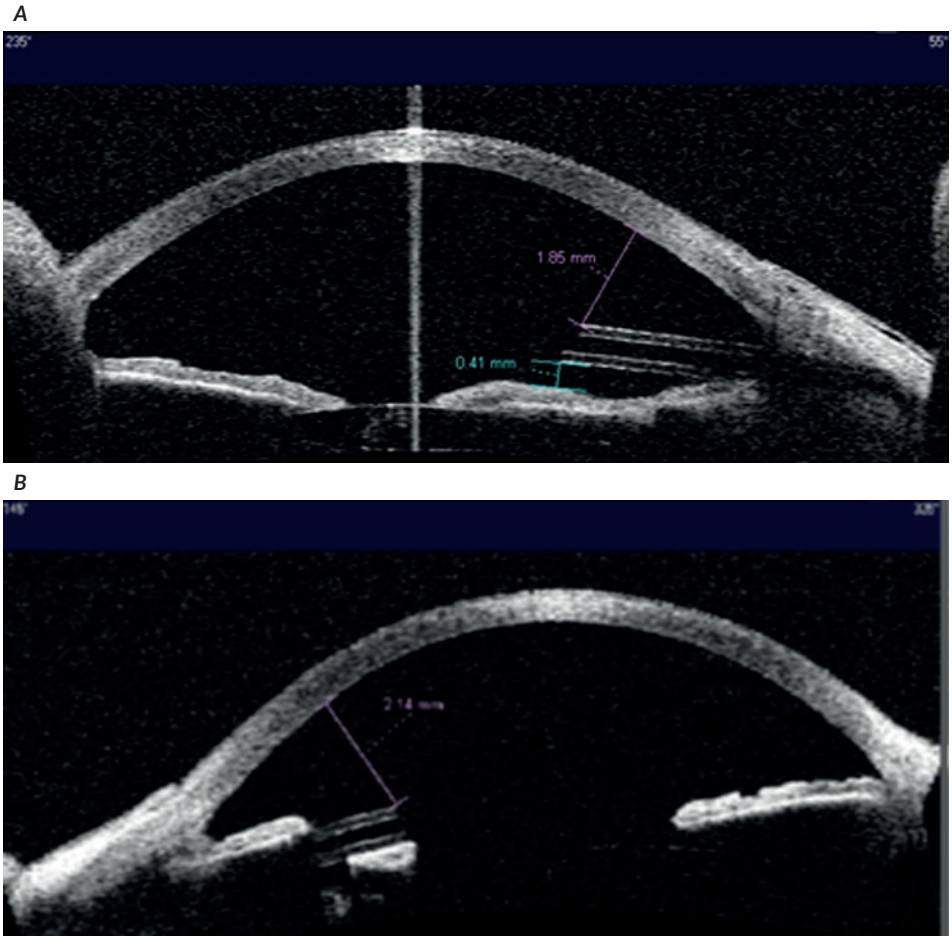

Figure 2

Anterior segment optical coherence tomography (AS-OCT) showing the Baerveldt tube and the tube corneal distance in pink. (A) Tube 'free' in the AC, (B) Transiridial placement of the tube.

Statistical analysis

To analyse the corneal ECD during the follow-up period, linear mixed model (LMM) analyses were performed. This model was chosen because it uses all available ECD data of each eye to fit the best linear model. The LMM was fitted with ECD as a dependent variable with time as covariate and assuming a random intercept per eye. To test for possible differences in EC loss, the TC distance was also included in the model as well as an interaction term "time" x "TC distance".

Our approach was to fit a linear mixed model using the following equation: $yi(t,d) = \alpha + \alpha i + \beta 1^*t + \beta 2^*d + \beta 3^*t^*d + \varepsilon i$, where yi(t,d) is the ECD count of an eye i after a follow-up of t months with TC distance d; α represents the intercept; αi represents the random intercept per eye; β1 is the effect of time after a follow-up of t months; β2 is the effect distance; β3 is the interaction effect of time and TC distance with a follow-up of t months and TC distance d; εi is the residual error.

All data were analysed using the statistical software package SPSS - version 18.0 (SPSS Inc., Chicago, IL, USA). Firstly, the central EC loss was determined for the total study group, after which the peripheral EC loss, for the quadrant closest to the BV tube (PQC) and the other quadrants, was assessed. Secondly, central and peripheral EC losses were compared between glaucoma subtypes [primary open-angle glaucoma (POAG), secondary glaucoma and primary angle closure glaucoma (PACG)]. The TC distance was included in the model to analyse the influence of TC distance on central and peripheral EC loss. Finally, central and peripheral EC losses were compared between patients with the tube positioned 'free' in the AC or with transiridial fixation. The central corneal thickness (CCT) was evaluated preoperatively and at all time-points during follow-up.

RESULTS

Baseline data

Fifty-three eyes of 35 patients (mean age 61±14 years, 54% female) were included. Fifty-one percent were right eyes. A total of 45 eyes were pseudophakic at the time of surgery, there were no aphakic eyes. Fifty-six percent of subjects had secondary glaucoma, 24.5% POAG and 18% PACG. Sixty-seven percent of eyes underwent trabeculectomy in the past. Baseline characteristics are listed in Table 1. All included patients gave their informed consent. Preoperatively, the mean central ECD was 2052±572 cells/mm^2, with no statistically significant difference between the peripheral quadrants and the central ECD. There were no statistically significant differences in baseline ECD in phakic versus pseudophakic eyes. The mean central ECD was 2176±105 in phakic eyes and 1887±181 in pseudophakic eyes (p=0.12). Preoperatively, the mean ECD was 2091±344 in the group where the BV GDD was placed "free" into the AC and the mean ECD was 2017±547 preoperatively in the transiridial group. A statistically significant difference in EC loss by glaucoma subtype could not be identified in baseline ECD.

The BV GDD tube was placed "free" into the AC in 31 eyes; in 22 eyes the BV GDD tube was placed transiridial (11 through pre-existent PI; 11 through a newly created PI). Preoperatively the AC depth was 3.6±0.6mm in eyes where the BV GDD was placed "free" into the AC, and 3.3±0.7mm in eyes with transiridial placement.

In the total study population, 2 eyes underwent a re-operation with repositioning of the BV tube because of a very short tube corneal distance (one eye had a tube corneal touch). One eye developed cornea decompensation after prolonged hypotony, which persisted after tying off the BV drainage tube. These eyes were excluded from further analyses.

Central and peripheral ECD

Table 2 shows the absolute central ECD during follow-up. The central ECD significantly decreased during follow-up, with a mean decrease of 4.54% per year (p<0.001). In the PQC a yearly decrease of 6.57% was found (p<0.001), versus 4.53% in the other peripheral quadrants. The decrease in the PQC was significantly larger compared to the central (p=0.005) and the other peripheral quadrants (p=0.003). The β coefficients of the LMM analysis and their 95% confidence interval (CI) are shown in table 3.

Table 1. Baseline characteristics

No of eyes (n)	53
Mean age in years (mean±SD)	61±14
Gender (% men)	46
Eye (% right eye)	51
Lens status (% pseudophakic)	84.9
Glaucoma type	
Primary open angle glaucoma (%)	24.5 (n=13)
Secondary glaucoma (%)	56.6 (n=30)
Primary angle closure glaucoma (%)	18.9 (n=10)
Previous trabeculectomy (%)	67.8
Endothelial cell density preoperatively (cells/mm^2)	
Tube "free" in the anterior chamber (mean±SD)	2091 ± 344
Transiridial placement of the tube (mean±SD)	2017 ± 547

Table 2. Central endothelial cell density (ECD) at different time points

Period	Mean ECD (cells/mm^2)±SD
Preoperatively	2052±572
3 months post-op	2016±592
6 months post-op	2012±607
12 months post-op	1911±640
24 months post-op	1898±657
36 months post-op	1771±662

Table 3. β coefficients and their 95% confidence intervals showing difference in ECD loss between the quadrant closest to the BV and the other quadrants

Parameter	Estimate	Sig.	95% Confidence Interval	
			Lower Bound	Upper Bound
Intercept	1939	<.001	1776	2101
$\beta_{1.}$ the effect of time after a follow-up of *t* months	-10.6	<.001	-12.6	-8.7
β_2, other quadrants	14.3	.408	-19.6	48.2
β_2, PQC	0			
β_3, the interaction effect time - other quadrants	3.23	.003	1.10	5.36
β_3,the interaction effect time - PQC	0			

PQC: peripheral quadrant closest to the BV GDD tube

Tube position and ECD

The central ECD showed a yearly decrease of 3.54% after transiridial placement and of 5.55% when the BV GDD tube was placed "free" into the AC. However, this difference was not statistically significant (p=0.37)

In the PQC we found a yearly decrease of 1.57% after transiridial placement and of 7.43% when the BV GDD tube was placed "free" into the AC. This was statistically different (p=0.006).

TC distance and ECD

The mean TC distance was 1.7 ± 0.6 mm for the whole study group at all follow-up time points. The mean TC distance at all follow-up moments was 1.7 ± 0.5 mm when the tube was placed "free" into the AC, and 1.6 ± 0.7 mm after transiridial placement. LMM analysis revealed that central and peripheral EC loss was significantly influenced by the TC distance (table 4): the shorter the distance, the higher the loss. A central loss of 6.20% and a loss of 7.25% in the PQC per year was found for a TC distance of 1.1mm, versus a central loss of 4.11% and a loss of 5.77% in the PQC of per year for a TC distance of 2.0mm (outside mean±2SD, p<0.001).

Table 4. β coefficients and their 95% confidence intervals showing the difference in ECD loss for different TC distances

Parameter	Estimate	Sig.	95% Confidence Interval	
			Lower Bound	Upper Bound
Intercept	2229	<.001	1988	2470
β_1 the effect of time after a follow-up of *t* months	-15.7	<.001	-20.8	-10.5
β_2 the effect of TC distance	-142.5	.008	-246.8	-38.2
β_3 the interaction effect	4.51	.004	1.46	7.55

Central corneal thickness

The CCT didn't statistically change over time. The mean pre-op CCT was 562.7 µm [549-576], 563.9 µm [547.7-580.1] after 1 year, 565.2 µm [546.2-584.1] after 2 years and 566.4 µm [544.7-588.1] after 3 years of follow-up; p=0.38.

DISCUSSION

This three-year follow-up study shows a significant decrease in corneal ECD in eyes with a BV GDD tube placed into the AC. Endothelial cell (EC) loss occurred most extensively in the PQC. Additionally, a tube position closer to the endothelium was found to accelerate EC loss; the shorter the distance, the higher the loss. The CCT did not statistically change over time; however, it may be that with further follow-up, several eyes may eventually develop corneal decompensation.

In normal adult corneas, the central human corneal ECD gradually declines at an average of approximately 0.6% per year [12]. Previous studies report a lower ECD in glaucoma patients compared to healthy subjects [13, 14]. The secondary glaucoma group of our study consists mainly of uveitic eyes, traumatic eyes and eyes after previous vitrectomy for retinal detachment. Our statistical analyses did not find a statistically significant difference in baseline ECD between secondary glaucoma, POAG or PACG.

Less EC loss was found after transiridial placement of the BV GDD when compared with placement of the BV tube 'free' into the AC. In a previous study by the same authors, it was demonstrated that the BV GDD tube remains in a stable position after transiridial placement, whereas the tube moves closer to the endothelium after placement 'free' into the AC [15]. The more stable position of the tube after transiridial placement may explain the lower EC loss in this subgroup. No excessive EC loss seems to occur in the early postoperative stage, implying that there is no additional EC loss according to the surgically induced trauma. An explanation for this might be the recovery capability of the corneal endothelium after intra-ocular surgery, when lost endothelium might be renewed by stem cells from a niche at the posterior limbus [16]. This phenomenon is also observed in a study of Storr-Paulsen et al., who studied the central ECD loss after mitomycin C-augmented trabeculectomy. An ECD loss of 9.5% was found 3 months after mitomycin C-augmented trabeculectomy, and 10% after 12 months [17].

To determine the course of postoperative EC loss, a linear mixed model analysis was chosen, as this provides the possibility to use all available data to fit a best linear model. A transiridial placement of the BV tube was only chosen for pseudophakic eyes, to prevent cataract formation in phakic eyes. The present results show a lower ECD decrease in comparison with a previous published paper by Lee et at [11], in which EC loss in eyes with an Ahmed glaucoma tube in the anterior chamber was studied. In their paper, a mean central EC loss of 15.4% was found 24 months after the implantation of an Ahmed glaucoma valve S2. In our study, the mean central EC loss after 24 months was 9.08% (4.54% per year).

Lee et al. found an ECD decrease of 22.6% in the superotemporal quadrant (closest to the Ahmed tube) at 24 months. The peripheral EC loss after 24 months was 13.14% in our study. However, we found the TC distance to be of crucial importance in the decline of the number of endothelial cells. A short TC distance of 1.1 mm led to a central EC loss of 6.20% per year and a peripheral EC loss of 7.25% per year. There are several reasons why our results differ from those of Lee et al. (2009) Their mean follow-up time was 19 months, whereas our subjects were followed for 36 months. Furthermore, the TC distance was not taken into account in their study. The different designs of the implants could also play a role.

The Ahmed tube is valved and might induce more fibrosis compared to the non-valved BV glaucoma implant [18]. Another possible explanation for the difference in EC loss might be the different material of the glaucoma drainage devices. Both the BV GDD and the Ahmed valve have a silicone drainage tube. The Ahmed-valved plate body and casing are made of polypropylene whereas the BV GDD plate is made of silicone. Despite the plate not being in contact with the corneal endothelium and being situated outside the anterior chamber, it is possible that due to backflow of aqueous humour through the drainage tube immunological inflammation occurs, which might contribute to the difference in EC loss as reported in our study as compared to the study of Lee [19].

Another important observation of our study is the influence of the TC distance on corneal EC loss. This finding underlines the results published by Doors et al. [20] demonstrating increased EC loss in the event of a shorter distance between a phakic intra-ocular lens and the corneal endothelium. A recent retrospective study published by Koo et al. [21] showed that tubes situated close to the cornea seem to lead to an increased EC loss. In our study, a shorter TC distance led to more EC loss, most severe in the PQC. After transiridial placement of the BV GDD tube, outcomes were better, which may be explained by the observation that the distance of the tube to the peripheral corneal endothelium from the entry site in the AC is in general larger than after direct insertion of the tube into the AC through the iridocorneal angle. A difference in EC loss by glaucoma subtype was not identified in our study. Even in uveitic eyes, where transiridial placement of the tube might probably elicit an inflammatory response, the ECD did not show a significant faster decrease as compared to POAG or PACG. But, as we have relatively small numbers, some caution must be taken into account by interpreting these results.

However, our findings support that tube placement far away from the corneal endothelium should be preferred to limit EC loss. To reach this goal, a transiridial approach (as an addition to sulcus placement or a pars plana approach) seems a valuable and safe option.

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CHAPTER 5

Long-term outcomes of Baerveldt glaucoma drainage implants: 10 years real-world results

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ABSTRACT

Purpose

To study the long-term results and complications after placement of a Baerveldt glaucoma implant (BGI).

Methods

Case series study, in which all patients who underwent BGI surgery before 2013 at the University Eye Clinic of the Maastricht University Medical Center in Maastricht, the Netherlands, were included. Patients were organized into two groups, a 10-year cohort and an additional 5-year cohort, to contradict a possible time-related bias in the 10-year cohort. Outcome measures included the evolution of IOP over the course of 5 years respectively 10 years, the cumulative rate of success, the number of IOP-lowering medications, and postoperative visual acuity (VA). Safety outcome measures included long-term occurrence and incidence of adverse events and complications.

Results

One hundred sixty-seven eyes from 167 patients (all Caucasians) were included, 80 eyes in the 10-year cohort and 87 eyes in the additional 5-year cohort. The most common diagnoses were open-angle glaucoma and uveitic glaucoma. IOP decreased from 30.0 ± 9.5 mmHg at baseline to 11.7 ± 4.2 mmHg at 5 years and 12.6 ± 4.5 mmHg at 10 years: in the 5-year cohort from 26.5 ± 10.3 mmHg to 10.3 ± 4.0 mmHg. The number of IOP-lowering medications dropped from 2.5 ± 0.8 at baseline to 0.7 ± 0.9 after five years and 0.9 ± 1.1 after 10 years; in the 5-year cohort from 2.7 ± 1.0 to 0.9±1.0 at 5 years. Mean corrected distance visual acuity (CDVA) slightly changed from logMAR 1.20 ± 1.04 at baseline to logMAR 1.00 ± 1.08 postoperatively at 5 years and decreased to 1.53 ± 1.14 after 10 years. In the 5-year cohort, the CDVA changed from logMAR 0.74 ± 0.82 to logMAR 0.90 ± 0.97. There were no statistical differences between the two cohorts. Corneal decompensation was the most frequently observed complication in every cohort. Other long-term complications were relatively few and mostly occurred within the first 5 years of follow-up. Phtisis bulbi was observed in 4 cases.

Conclusion

Sustained and stable control of IOP can be obtained with the BGI for up to 10 years after implantation, with IOP values between 12 and 13 mmHg. Corneal decompensation is the most important complication.

INTRODUCTION

For many decades now, the gold standard for the surgical treatment of glaucoma is trabeculectomy [1]. Ample experience with this procedure, including guarded antimetabolite use (often mitomycin C) and refinements over the years, has led to satisfactory long-term results with intraocular pressure (IOP) levels in the low teens in many cases, especially surgically naïve patients with open-angle glaucoma [2]. However, the introduction of long-tube glaucoma drainage devices (GDD), first by Molteno in 1969 [3], offered an important alternative to trabeculectomy. Several GDD designs have since become available. Nowadays, especially the Ahmed and Baerveldt GDD are commonly used. At first, GDDs were mainly used for patients with refractory glaucoma and after failed trabeculectomy. Over the years, it has been shown in a number of studies that GDD implantation may lead to similar successful IOP-lowering results when compared to trabeculectomy, and acceptable short- and long-term complications [4] [5, 6]. GGDs are also gaining popularity as a primary procedure [7].

However, although the amount of early and late complications may be comparable to trabeculectomy [4, 5], several, especially late complications are still feared (e.g. severe endothelial cell loss and subsequent corneal decompensation [8], tube or plate exposure, hypotony). Late endophthalmitis, probably related to tube exposure, contributes in most cases to failure [9].

Studies comparing the long-term results of the Ahmed versus the Baerveldt Glaucoma Implant (BGI) reported lower IOP outcomes with the BGI, but also more failures due to safety issues (hypotony, implant explantation, and loss of light perception) than with the Ahmed Implant [10, 11].

Although GDDs have proven their worth in current glaucoma practice, GDD implantations are placed at the end of the surgical treatment spectrum, due to the substantial amount of dissection, work and risks associated with the procedure [12]. Costs, availability, and surgeon's preference also play a role in the selection process [1]. After failure of a GDD, further treatment options are usually limited. Placement of a second (or even third) GDD may be considered, but often the only remaining alternative is a cyclodestructive procedure [1]. For this reason, it is interesting to study the outcome of GDD implantation on the very long term, as evidence after many years is still scarce, in a pragmatic trial.

Pragmatic trials offer the opportunity to study the effect of a treatment in a real-life situation, including influencing extraneous factors. The real-world insights are specifically relevant for treatments that have already acquired a place in the treatment armamentarium, in this case the GDDs [13].

The aim of this study was to evaluate the long-term results and long-term complications of the BGI, in a 10-year cohort and an additional 5-year cohort. These two cohorts were chosen to rule out a possible time-related bias, as indications and procedures may have changed slightly over the years. The 5-year cohort results were compared with the results of the first 5 years of the 10-year cohort to contradict a time-related bias in the 10-year cohort.

METHODS

To study the long-term effects of the BGI intervention, a pragmatic study approach was chosen with key components that include nonrestrictive eligibility criteria, implementation of the intervention under "real-world" conditions, monitoring in usual care, and outcomes that are usually ascertained using data collected during routine clinical care.

Therefore, all patients who underwent BGI surgery before 2013 at the University Eye Clinic of the Maastricht University Medical Center in Maastricht, the Netherlands, were included in this case series study. All patients gave their consent to use their medical data for scientific research. The study was conducted according to the principles of the Declaration of Helsinki (WMA, Brazil, October 2013). Data (IOP, topical and systemic IOP-lowering medications, visual acuity (VA), visual fields (VF) when available, complications, and subsequent ocular surgery) were recorded in electronic health records (EHR).

For the analysis, a data cut-off date was chosen to organize the patients into 2 groups, a 10-year cohort and a 5-year cohort, in which the implant surgery date was at least 10 years resp. 5 years before the data cut-off date (01/01/2018), regardless of the length of follow-up. No other inclusion criteria were applied, to avoid selection bias.

For the long-term results, only complications after year one were analyzed. Therefore, complications in the first postoperative year (early after the procedure as well as later that year) were not part of the analysis.

Surgical technique

A limbal or fornix based conjunctival flap was made in the superotemporal quadrant. A 250 mm2 or 350 mm2 plate BGI was placed 10 mm from the limbus, the 350 mm2 with its wings underneath the lateral and superior rectus muscles. In 10 (13%) cases a pars plana approach was chosen. The surgical technique has been described in detail elsewhere [8, 14]. All patients were operated by a single surgeon (HB).

Outcome measures

The primary outcome measure was the evolution of IOP over the course of 5 years resp. 10 years of follow-up. Secondary outcome measures include the cumulative rate of success, the number of applied topical IOP-lowering medications, and postoperative Snellen visual acuity (VA) at 5 years resp. 10 years after the surgery date.

Snellen VA was converted to logarithm of the minimum angle of resolution equivalents (logMAR) for calculating the mean and variances. Preoperative VA and occurrences of postoperative vision at 5 years resp. 10 years were determined. Secondary safety outcome measures included long-term occurrence and incidence of adverse events, (i.e., from the second year and further) that needed a glaucoma reoperation (such as device exposure).

Statistical analysis

Mean IOP was estimated by applying a linear mixed-effects model of time series where the linear time variable is representing the postoperative time elapsed from implant surgical date.

The subject-specific random deviation from the mean condition effect was modeled by the random effects in the model. It is common to have repeated measures on subjects in observational studies, where we would expect that the observation on an individual at time t would be quite strongly correlated with the observation on the same individual at time t□1. However, because of the observed significant serial correlation of the IOP in this longitudinal study, time series analysis is more appropriate.

The safety outcomes measures were presented by frequency and percentages. All analyses were conducted in R (R Core Team, 2017) with lme4 package [15] to perform linear mixed model (LME) analysis and figures were produced using the package ggplot2 [16].

RESULTS

Baseline parameters

A total of 184 eyes underwent glaucoma surgery with a BGI implant before 2013. For patients who underwent a BGI procedure in 2 eyes, only the first operated eye was included to avoid correlation. After removing the second eye with GDI from the analysis, 167 eyes from 167 patients were included in our study.

Setting data cut-off date (01/01/2018) resulted in a 10-year cohort with data from 80 eyes/patients (with at least 10 years of follow-up), and a 5-year cohort with 87 eyes (at least 5 years of follow-up).

Baseline demographics and patient characteristics were summarized in table 1. The most common diagnosis was open angle glaucoma. Of these, 14.1% were primary open angle glaucoma (POAG) cases in the 10-year cohort and 20.8% in the 5-year cohort, and 26.9% respectively 39.6% inflammatory secondary glaucoma cases. The mean age for this 10-year and 5-year cohort was 51.9 ± 19.9 years and 59.2 ± 14.5 years (median age: 55.5 and 61 years) respectively with a slight female predominance, and all patients were Caucasians.

A majority of patients had one or more IOP-lowering surgeries prior to BGI implantation. Previous surgeries included trabeculectomy (51% of eyes in the 10-year cohort and 45% of eyes in the 5-year cohort), and phacoemulsification with intraocular lens implantation (78% and 70% in the 10-year and 5-year cohort respectively.)

Withdrawal/failures

Table 2 summarizes the reasons for withdrawn from the study. Lost to follow-up as the reason for withdrawal is summarized by "death", "patient decision" and "move site" totals to 17.1% in the 10-year cohort and 10.6% in the 5-year cohort. Of the major failures of the BGI, evisceration is the most frequently mentioned, 9.2% in eyes of the 10-year cohort.

IOP evaluation

Table 3 summarizes the mean IOP and number of IOP-lowering medications at every yearly visit. Baseline preoperative IOP was 30.0 ± 9.5 mmHg [IQR 24–35] and the number of IOP-lowering medication classes was 2.5 ± 0.8. IOP dropped to 11.7 ± 4.2 mmHg at 5 years and 12.6 ± 4.5 mmHg at 10 years. The number of IOP-lowering medications decreased to 0.7 ± 0.9 after five years and 0.9 ± 1.1 after 10 years. In the 5-year cohort, IOP decreased from 26.5 ± 10.3 mmHg [IQR 20–32] and 2.7 ± 1.0 of IOP-lowering-medications to 10.3 ± 4.0 mmHg and 0.9±1.0 topical medication at 5 years.

Table 1: Baseline Demographics and Patient Characteristics

	Cohort		
Characteristics	**10-year**	**5-year**	**p-value**
number of patients/eyes	80	87	
Age, *years*, median [IQR]	55.5 [39.75, 66.5]	61 [51, 70]	0.021
age group, *years*, % (n)			0.068
-45	31.2% (25)	14.9% (13)	
46-65	41.2% (33)	44.8% (39)	
65-75	17.5% (14)	27.6% (24)	
76-	10.0% (8)	12.6% (11)	
eye % (n)			0.563
OD	56.2% (45)	50.6% (44)	
OS	43.8% (35)	49.4% (43)	
gender % (n)			0.403
female	52.5% (42)	44.8% (39)	
Male	47.5% (38)	55.2% (48)	
Glaucoma Type % (n)			0.221
Primary open angle	14.1% (11)	20.8% (10)	
Neovascular	7.7% (6)	0.0% (0)	
Uveitic	26.9% (21)	39.6% (19)	
Pigmentary	3.8% (3)	0.0% (0)	
Pseudoexfoliative	1.3% (1)	0.0% (0)	
Juvenile-onset open angle	12.8% (10)	10.4% (5)	
Primary angle closure	7.7% (6)	10.4% (5)	
Other	25.6% (20)	18.8% (9)	
Glaucoma Surgical History			
Trabeculectomy	51.3%	44.7%	0.593
Pars plana vitrectomy	28.9%	17.2%	0.2004
Corneal transplant	7.9%	6.4%	1
Phaco-emulsification	77.6%	70.2%	0.4795

IQR: interquartile range

Using the linear mixed model corrected for subjects as random effects, the number of medications as fixed effects, and tuned for the correlation of the postoperative years. The best fit was achieved with autocorrelation with 2 levels of moving average of postoperative years, resulting in an IOP (intercept) of 11.8 mmHg ($p<0.001$) and a IOP slope of 0.068 mmHg per follow-up year ($p=0.3699$). Five and 10 years IOP estimates were 12.1 ± 3.7 mmHg and 12.3 ± 3.9 mmHg in the 10-year cohort. In the 5-year cohort, the IOP estimates were 10.5±4.1 mmHg after 5 years (p-=0.1043 with Welch two-sample t-test).

Table 2: Failures

			Cohort
Discontinuation	**5-year**		**10-year**
Period	**(0-5y)**	**(0-5y)**	**(5-10y)**
	N=47	N=76	N=56
continuation % (n)	87.2% (41)	73.7% (56)	67.8% (38)
withdrawn % (n)	12.8% (6)	26.3% (20)	32.1% (18)
Reasons for withdrawal % (n)			
Failures	2.1% (1)	9.2% (7)	7.1% (4)
Evisceration	0.0% (0)	5.3% (4)	5.4% (3)
Explantation	0.0% (0)	1.3% (1)	0.0% (0)
Pthisis bulbi	2.1% (1)	2.6% (2)	0.0% (0)
second implant	0.0% (0)	0.0% (0)	1.8% (1)
Death	2.1% (1)	2.6% (2)	5.4% (3)
move site	6.4% (3)	13.2% (10)	10.7% (6)
patient decision	2.1% (1)	1.3% (1)	8.9% (5)
		p-value = 0.3638	
			p-value = 0.2653

Although mean IOP at baseline and at 5 years were lower in the 5-year cohort than the mean IOP in the first 5 years of the 10-year cohort, these differences were not statistically significant (figure 1).

Visual Acuity

Mean corrected distance visual acuity (CDVA) in the 10-year cohort slightly changed from logMAR 1.20 ± 1.04 at baseline to logMAR 1.00 ± 1.08 postoperatively at 5 years and decreased to 1.53 ± 1.14 after 10 years ($p < 0.001$).

Ten percent (8 eyes) had at baseline a Snellen VA of 0.5 decimal (20/40) or better and 9% and 4% at 5 years and 10 years, respectively. None of these results at any of the time points were statistically significant.

In the 5-year cohort, the CDVA changed from logMAR 0.74 ± 0.82 at baseline to logMAR 0.90 ± 0.97 after 5 years. Thirty-six percent (17 eyes) and 21.3% (10 eyes) had a Snellen VA of 0.5 or better at baseline and after 5 years respectively (table 4).

Table 3: Mean IOP and medication use

10-year cohort		IOP (mmHg)			medications
Visit	**n**	**mean** ± SD	**marginal mean**	**confidence interval**	**mean** ± SD
Baseline	76	30.0 ± 9.5			2.5 ± 0.9
Year 1	70	12.6 ± 5.2	11.92	(10.7, 13.2)	0.7 ± 0.9
Year 2	67	12.2 ± 4.7	11.95	(10.8, 13.1)	0.7 ± 0.9
Year 3	54	12.6 ± 4.2	11.99	(10.9, 13.1)	0.6 ± 0.8
Year 4	58	11.8 ± 3.6	12.03	(11.0, 13.1)	0.7 ± 0.9
Year 5	48	11.7 ± 4.2	12.07	(11.0, 13.1)	0.7 ± 0.9
Year 6	45	12.3 ± 5.3	12.11	(11.1, 13.1)	0.7 ± 0.9
Year 7	46	12.5 ± 5.6	12.15	(11.1, 13.2)	0.7 ± 0.9
Year 8	42	12.7 ± 4.5	12.19	(11.1, 13.3)	0.8 ± 1.0
Year 9	39	12.9 ± 6.0	12.23	(11.1, 13.4)	0.9 ± 1.0
Year 10	41	12.6 ± 4.5	12.27	(11.1, 13.5)	0.9 ± 1.1
5-year cohort					
Baseline	47	26.5 ± 10.3			2.7 ± 1.1
Year 1	47	10.4 ± 4.1	10.17	(8.9, 11.4)	0.9 ± 0.9
Year 2	45	10.8 ± 4.8	10.25	(9.1, 11.4)	0.9 ± 0.9
Year 3	46	11.2 ± 4.4	10.33	(9.2, 11.5)	0.9 ± 0.9
Year 4	41	10.8 ± 4.4	10.41	(9.2, 11.6)	0.9 ± 1.0
Year 5	40	10.3 ± 4.0	10.48	(9.2, 11.8)	0.9 ± 1.0

Mean IOP during follow-up, estimate and 95% confidence interval of IOP from Linear Mixed Model analysis and mean number of IOP-lowering medications

Table 4: Visual Acuity

	10-year cohort		5-year cohort	
	logMAR	**Snellen>0.5 (20/40)**	**logMAR**	**Snellen>0.5 (20/40)**
Visit	**mean ± SD**	**% (n)**	**mean ± SD**	**% (n)**
Baseline	1.20 ± 1.04	10.5% (8)	0.74 ± 0.82	36.2% (17)
Year 1	1.12 ± 1.09		0.92 ± 0.94	
Year 5	1.00 ± 1.08	14.5% (11)	0.90 ± 0.97	21.3% (10)
Year 10	1.53 ± 1.14	12.5% (7)		

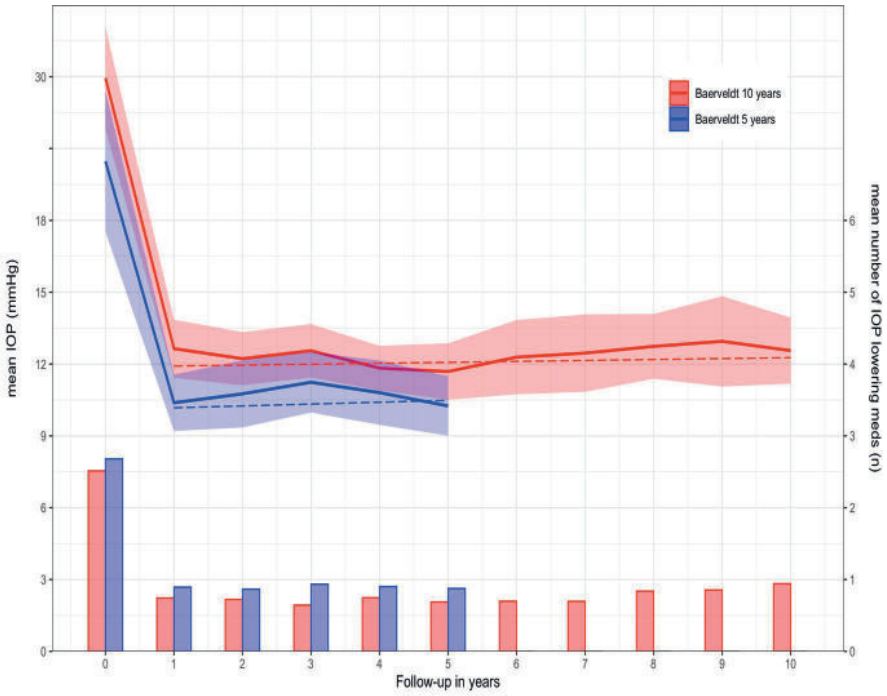

Figure 1. Mean IOP during follow-up and mean number of IOP-lowering medications. Shaded area corresponds to the 95% confidence intervals. Model best fit results are presented by the dotted lines.

Complications and additional surgical procedures

In our long-term analysis, (severe) clinical complications that occurred after the first year of follow-up were summarized in table 5. Furthermore, the additional surgical procedures that were undertaken after occurrence of complications were listed in the second half of table 5. Corneal decompensation occurred in 8% of the eyes, in both the first and the second 5 years of follow-up. Revisions of the BGI were done in 10% of the eyes in the first 5 years; none were performed in the second five years. The most frequently performed surgical revisions were tube shortening, tube replacement or re-patching of the tube (after erosion of overlying conjunctiva and Tenon's capsule). Hypotony was observed in nearly 3% in the first 5-year cohorts, however, more tube revisions and ligations were performed in the 5-year cohort. Enucleation or evisceration, for painful blind eyes, was performed in 5% of cases in the 10-year cohort, in both the first and second 5 years of follow-up.

Table 5: Complications and additional procedures

	Cohort		
	5-year	10-year	
Period	**(0-5y)**	**(0-5y)**	**(5-10y)**
Complications			
Corneal decompensation	8.5% (4)	7.9% (6)	5.4% (3)
Retinal detachment	0.0% (0)	0.0% (0)	0.0% (0)
Tube erosion	0.0% (0)	1.3% (1)	0.0% (0)
Conjunctiva defects	0.0% (0)	1.3% (1)	0.0% (0)
Hypotony	0.0% (0)	2.6% (2)	0.0% (0)
Choroidal detachment	2.1% (1)	0.0% (0)	0.0% (0)
Suprachoroidal haemorrhage	0.0% (0)	0.0% (0)	0.0% (0)
Cystoid macular edema	0.0% (0)	1.3% (1)	1.8% (1)
Pthisis bulbi	2.1% (1)	3.9% (3)	0.0% (0)
Diplopia	2.1% (1)	0.0% (0)	0.0% (0)
Endophthalmitis	0.0% (0)	0.0% (0)	0.0% (0)
Additional surgical procedures			
Tube revision	4.3% (2)	10.5% (8)	0.0% (0)
Tube ligation	0.0% (0)	2.6% (2)	1.8% (1)
Tube patch graft	0.0% (0)	1.3% (1)	0.0% (0)
Explantation	0.0% (0)	1.3% (1)	0.0% (0)
Corneal transplant	0.0% (0)	3.9% (3)	1.8% (1)
Enucleation/Evisceration	0.0% (0)	5.3% (4)	5.4% (3)

DISCUSSION

The aim of this study was to evaluate the long-term effects of the BGI. An advantage was that we were able to retrieve the data of most of the patients. The reason for this is that most patients were followed at the university hospital, relatively few were referred back to their initial hospital. To show that the population included in this study was not different from any other and that possible bias was reduced to a minimum, the first five years of the 10-year cohort were compared to the 5-year cohort. Our study demonstrated sustained and stable long-term IOP results after BGI implantation. Mean IOP dropped substantially, from values around 30 mmHg to the low teens (12.6 ± 4.5 mmHg), with significantly less IOP-lowering medications (0.9 ± 1.1) after 10 years of follow-up.

After 10 years, the IOP remained almost at the same level as after the first year. The best fit modeling resulted in an IOP increase in of 0.07 mmHg per year, not statistically significant (p=0.5970). That equals an increase of 0.7 mmHg of IOP in 10 years.

In this study, all consecutive patients undergoing BGI implantation were included, without a specific patient selection. This created a unique opportunity to provide and summarize real-world long-term data from patients with a BGI, in a common ophthalmic practice environment. However, the majority of patients included in this study had refractory glaucoma. Alternative treatment options for these patients were very limited. This may have negatively influenced the outcome of the study. With the gaining popularity of the BGI for less advanced cases, general long-term results may be further improved. Although the differences between our two study cohorts were not statistically different after 5 years, there were small differences that may reflect this slowly changing indication for earlier tube surgery.

Another limitation of this study is its retrospective nature. Although we were able to retrieve most results, we may have missed data and further in-depth interpretation of data is not possible. As we assume that patients who were followed elsewhere had satisfactory results, this may also have negatively influenced our study results.

As the focus of this study was on long-term effects and complications (the long-term survival of the BGI), the comparison between preoperative and postoperative IOP was therefore not appropriate. The same reason applies to the early complications (onset < 1 month, e.g., hypotony due to insufficient tube ligation) and the complications up to one year (e.g., encapsulated bleb, retinal detachment). Other frequent complications however, such as corneal decompensation, seldomly occur within the first year of follow-up. Additionally, the effectiveness and safety of the BGI in the first postoperative year has been analyzed and published in a number of studies by now [17].

Several glaucoma drainage device studies with long-term results usually report 5 years follow-up and compared the Ahmed device with the BGI. The study by Purtskhvanidze [18] had a follow-up of 10 years and longer and a similar inclusion period (2001-2014) as our study. In their study, success for glaucoma control was defined as a postoperative IOP ≥ 5 mmHg and ≤ 21 mmHg with or without application of IOP-lowering medications. They reported glaucoma to be controlled in 86, 79, and 73% of eyes at 1, 5 and 10 years, respectively. The mean preoperative IOP was 30.8 ± 6.9 mmHg and decreased to 14.3 ± 5.4 mmHg at last postoperative follow-up. Although the preoperative IOP levels are comparable with ours, the 10 years IOP follow-up values are higher.

Christakis [11] reported a mean IOP reduction after 5 years from 31.8 ± 11.8 mmHg at baseline to 13.2 ± 4.7 mmHg, with a mean number of IOP-lowering medications of 1.5 ± 1.4 in a pooled data analysis of a BGI comparison study. These 5 years postoperative values correspond with ours.

In the Tube versus Trabeculectomy study [5], IOP decreased after 5 years from 25.1 ± 5.3 mmHg preoperatively to 14.4 ± 6.9 mmHg postoperatively, with 1.4 ± 1.3 medications. These IOP values are slightly higher than our 5-year results, with a lower baseline value.

A recent study of Islamaj [19] comparing primary BGI versus primary trabeculectomy showed in the BGI eyes a mean IOP rate of 12.9 ± 3.9 mmHg after 5 years of follow-up, and similar results in the trabeculectomy patients. These IOP values match to the findings of our study. In the Primary Tube Versus Trabeculectomy Study [2] the mean IOP after 3 years was 14.0 ± 4.2 mmHg, with 2.1 ± 1.4 glaucoma medications. This IOP level is higher than in our study, with a much lower baseline IOP (23.3 ± 4.9 mmHg with 3.1 ± 1.1 medications).

The mean baseline VA of 1.20 logMAR implies that our patients already had a low VA, a loss of more than 2 lines Snellen was therefore less relevant for this category of patients. In TVT study the mean VA at baseline was 0.20 ± 0.42, which is much better than in our study at enrollment. Additionally, because of the low vison of most of our patients, visual field testing was not often performed (anymore). Analysis of visual field progression was therefore not relevant in this study.

In the Tube versus Trabeculectomy study [5], a total of 22 (16%) late postoperative complications, occurring after more than 1 month, were seen in the tube group. The most commonly observed late complications in that study were corneal decompensation, diplopia, tube erosion and cystoid macular edema. In our study, corneal decompensation was the most frequent complication. Additionally, we observed a few cases with hypotony, choroidal detachment, and diplopia. Hypotony after BGI implantation is a feared complication that has also been demonstrated in

other studies [10, 11, 20]. Phthisis bulbi occurred in 3 eyes of the 10-year cohort and in one eye of the 5-year cohort. These eyes already had poor vision and progressed to blindness during follow-up. As mentioned before, at the time they had surgery, no other treatment options were feasible for these patients to rescue their vision.

In conclusion, the BGI demonstrates sustained control of IOP for up to 10 years after implantation. The IOP at 5-year follow-up as demonstrated in our study can be predicted to be between 12 and 13 mmHg, with on average less than one topical IOP-lowering medication. These findings are confirmed by former studies. The 10-year follow-up data showed that IOP values will remain stable in the second half of the follow-up, at the same level as after the first five years. Corneal decompensation is the most common complication after placement of a BGI.

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CHAPTER 6

Baerveldt implant for secondary glaucoma due to iris melanoma

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Clinical Ophthalmology. 2010;4:407-409

ABSTRACT

Background

Proton beam therapy (PBT) is effective in the treatment of iris melanoma. Reported complications after PBT are radiation-induced cataract and raised intraocular pressure (IOP). Filtering glaucoma surgery has generally been avoided because of fears of seeding.

Case report

A 37-year-old man presented with a self-discovered, pigmented lesion on his right iris. Four years later, the pigmented lesion was diagnosed as an iris melanoma, because of documented growth. The patient was treated with PBT but developed secondary glaucoma one month later. The IOP could not be controlled despite maximal medical therapy and selective laser trabeculoplasty (SLT). Finally, Baerveldt implant surgery was performed, resulting in an IOP lowering to 10 mmHg and stabilization of the glaucomatous visual field loss.

Conclusion

Our case demonstrates that Baerveldt implant surgery is a reasonable therapy for glaucoma following successful radiotherapy of iris melanoma.

INTRODUCTION

Iris melanoma comprises 3% to 10% of all uveal melanomas and is the most common primary malignancy of the iris. [1,2] It tends to have a ten-year metastasis rate of 3% to 6%. [1-3] Possible therapies for iris melanoma include iridectomy, iridocyclectomy, plaque brachytherapy, proton beam therapy (PBT), and enucleation. PBT is generally selected if the tumor is too extensive for surgical excision or if such surgery is rejected because the surgical iris coloboma is expected to cause unacceptable photophobia or cosmetic deficit.

The main complications after PBT are radiation-induced cataract and raised IOP. Trabecular scarring may play a role in the latter. [4] Secondary glaucoma occurs in 7% of eyes with untreated iris melanoma and in 30% of patients with microscopically confirmed iris melanoma, occurring mostly because of tumor infiltration of the trabecular meshwork with outflow obstruction. [5,6] Traditionally, filtering glaucoma surgery has been avoided in patients with iris melanoma because of fears that such aqueous drainage might encourage subconjunctival or intraorbital tumor seeding. [2,3] Nevertheless, insights into the biology of uveal melanomas and outcome studies after PBT encouraged us to treat a patient with a Baerveldt tube implantation because of rapidly deteriorating vision and uncontrollable glaucoma.

Case report

A 37-year-old man discovered a pigmented iris lesion in his right eye. The best corrected visual acuity (BCVA) was 6/6. Ophthalmologic examination showed a pigmented iris lesion between the 5.30 and 6.30 o'clock meridians with a basal diameter of 3.5 mm and a thickness of 1.4 mm. Gonioscopy showed pigment deposition in the inferior and nasal parts of the iridocorneal angle. The IOP was 25 mmHg. Ultrasonography showed no involvement of the ciliary body. The left eye was normal. Initially, the tumor showed no growth; however, four years after presentation, the iris lesion had changed to a diffuse tumor, extending from the 4.30 to 6.30 o'clock meridians with seeding onto the iris surface from the 3.30 to 7.00 o'clock meridians. The pupil also became oval (figure 1a). Gonioscopy showed pigment deposition in the iridocorneal angle between the 1.00 and 10.00 o'clock meridians. The BCVA decreased to 6/7.5. The patient refused a biopsy for histological examination.

Because of documented growth, the tumor was diagnosed as an iris melanoma. The entire anterior segment was treated with PBT (53.1 Gy, administered in four fractions over four days). One month later (figures 1b and 1c) the patient developed secondary glaucoma with IOP levels fluctuating between 20 and 43 mmHg, despite maximal medical therapy. The optic disc showed normal cupping. SLT was performed, placing 25 shots with a total energy of 15 mJ in the nasal quadrant. The IOP decreased slightly but only transiently.

Further treatment of the temporal quadrant did not lead to a reduction of IOP. Meanwhile, the optic disc cupping had become pathological and glaucomatous visual field loss had progressed from mild loss to very extensive loss within two months. Since the patient was keen to preserve the remaining vision in this eye, despite advice about a possible risk of extraocular spread, we finally placed a Baerveldt tube in the anterior chamber (figures 1d and 2). The IOP decreased to 13 mmHg. After one year of follow-up, the IOP was stable at 10 mmHg with the additional use of dorzolamide and timolol. The visual field showed no further deterioration. The BCVA was 6/15. The patient declined systemic screening for metastasis; however, he remains under intensive ophthalmic surveillance.

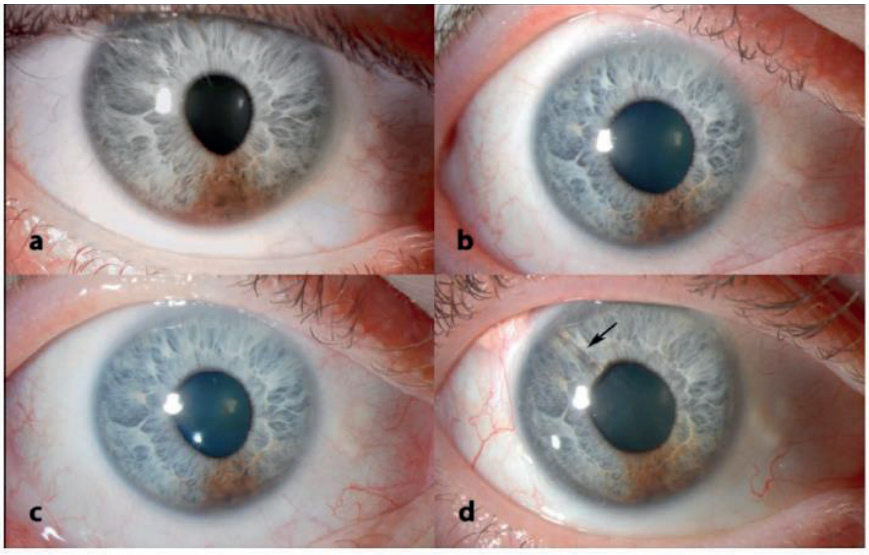

Figure 1. Slit lamp figures. Figure 1a shows the iris lesion when diagnosed as iris melanoma. Figure 1b shows the lesion after PBT. Figure 1c shows the lesion after PBT. Figure 1d shows the Baerveldt tube in the temporal/superior quadrant

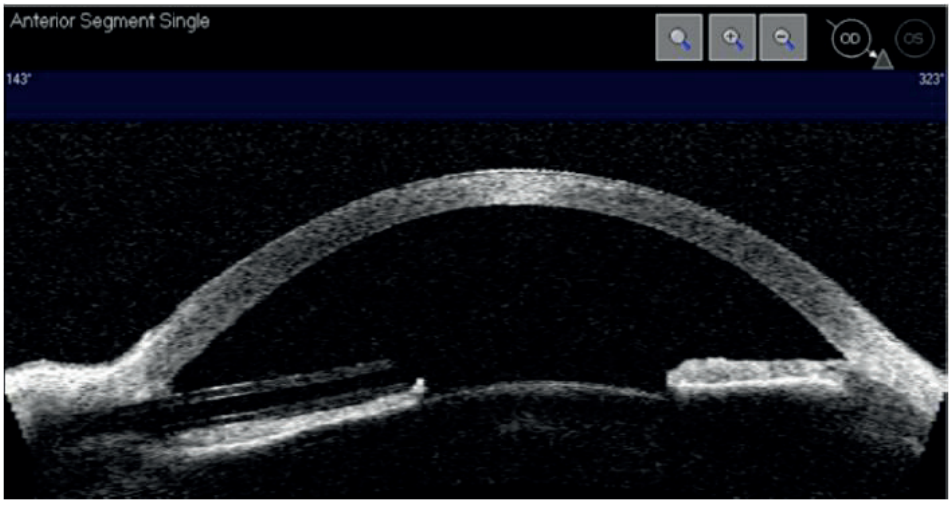

Figure 2. A Visante OCT scan showing the Baerveldt tube in the anterior chamber on the left.

DISCUSSION

Secondary glaucoma after PBT for iris melanoma can be difficult to control with medical therapy. [7] We report successful lowering of the IOP in such a case by using a Baerveldt glaucoma implant. To our knowledge this approach has not been reported previously. As a rule, drainage surgery is avoided after treatment of iris melanoma, probably because of concerns that tumor cells might seed through the drainage fistula and metastasize to other parts of the body.

Therefore, we initially attempted to lower the IOP by SLT. Insights from genetic studies on uveal melanomas suggest, however, that these tumors metastasize almost exclusively if they show loss of chromosome 38 or class II gene expression profile. [9] There is growing evidence that metastasis starts at a very early stage, before the patient even presents to the ophthalmologist. [10] For these reasons, there are now considerable doubts that glaucoma drainage surgery would enhance risks of metastasis spread to the rest of the body by providing an exit route from the eye.

Another concern is that the iris melanoma can recur and seed through the tube into the subconjunctival and orbital tissues. We consider these risks to be small, firstly, because local tumor recurrence is rare after PBT and, secondly, because the tumor was located far from the internal opening of the tube (figure 1d). In any case, the patient is being monitored closely so that appropriate treatment can be administered without delay in case of re-growth of the tumor. Further studies with more patients and long-term follow-up are indicated to evaluate the safety and efficacy of the Baerveldt glaucoma implant for the treatment of secondary glaucoma after PBT for iris melanoma.

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CHAPTER 7

Outcomes of severe uveitic glaucoma treated with Baerveldt implant: can blindness be prevented?

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Acta Ophthalmologica. 2018 Feb;96(1):24-30.

ABSTRACT

Purpose

To evaluate long-term outcomes on efficacy and safety of severe uveitic glaucoma treated with a Baerveldt glaucoma implant (BGI).

Methods

A retrospective study of 47 eyes of 47 patients with uveitic glaucoma treated by a BGI between September 2002 and September 2015. Main outcome measures were intraocular pressure (IOP), number of glaucoma medications, course of the uveitis, visual acuity (VA) and complications.

Results

Mean IOP dropped from 30.6 ± 8.1 mmHg with 3.6 ± 1.1 glaucoma medications at baseline to 10.6 ± 4.3 mmHg with 1.0 ± 1.3 glaucoma medications after a mean follow-up of 63.6 _ 43.1 months. In the majority of cases, IOP remained stable during follow-up. However, especially in several patients with viral uveitis, episodes with IOP peaks were observed during a flare-up despite a functioning implant. These peaks remained below preoperative levels. During follow-up, 16 patients (34%) experienced a clinically significant VA loss, mainly because of late-stage glaucoma or hypotony maculopathy. Early postoperative complications were transient choroidal effusion (n = 5), shallow/flat anterior chamber (n = 4), hyphaema (n = 2) and suprachoroidal haemorrhage (n = 1). The most important late postoperative complication was hypotony maculopathy (n = 5), three of these in juvenile idiopathic arthritis (JIA) patients.

Conclusion

The BGI is an effective and safe treatment for patients with refractive secondary glaucoma due to uveitis. In a majority of patients, VA remains stable and a low and stable IOP is maintained over time with an acceptable number of complications. In particular, patients with viral uveitis and glaucoma should be closely monitored for IOP peaks that may occur during episodes of a flare-up of uveitis, whereas at the other end of the spectrum, patients with JIA seem much more prone to hypotony maculopathy.

INTRODUCTION

Despite its relative rareness, uveitis can lead to sight-threatening complications. Approximately 10% of uveitis patients will ultimately become blind. The most serious sight-threatening complication is glaucoma: 10–30% will develop secondary glaucoma, and eventually, one-third of patients with uveitic secondary glaucoma will become (severely) visually impaired or (in the worst scenario) blind. Juvenile idiopathic arthritis (JIA), Fuchs heterochromic cyclitis and herpetic uveitis have even higher reported rates of secondary glaucoma development [1-5]. Longterm corticosteroid treatment may be needed to control the uveitis but can also lead to uncontrollable high IOP.

The balance between uveitis activity and IOP rise is often difficult to manage with medications. Medical treatment fails in approximately 25% of patients with uveitic glaucoma. These patients need surgical treatment to control IOP [4, 6]. Trabeculectomy without antifibrosis medication such as mitomycin C or 5-fluorouracil has a poor outcome [7, 8].

However, even with antifibrosis medication, reported qualified success rates vary greatly, ranging from 38% to 79% at 5 years [9-13]. Postoperative inflammation influences surgical success greatly as fibrosis develops more rapidly in inflamed eyes [14]. Therefore, maximum control of uveitis before surgery is warranted, and after surgery, careful suppression of the postoperative inflammation is extremely important for successful surgery. Glaucoma drainage implants have become an important surgical alternative to treat secondary glaucoma.

Although these implants have initially only been used after failed trabeculectomy, in case of uveitic glaucoma they are increasingly used as a primary surgical procedure [15]. The three most frequently used glaucoma drainage implants are the Ahmed valve glaucoma implant (New World Medical, Rancho Cucamonga, CA, USA), the Molteno glaucoma implant (Molteno Ophthalmic Ltd., Dunedin, New Zealand) and the BGI (Abbott Medical Optics Inc., Santa Ana, California, USA). Studies reporting on the outcome of the BGI for uveitic glaucoma are scarce. Because of its larger plate surface area, this implant may be more successful for IOP control on the long term compared to the smaller implants that may fail earlier due to subconjunctival fibrosis and scarring.

The aim of this study was to evaluate long-term efficacy and safety of the BGI for patients with uveitic glaucoma, in relation to the course of their uveitis.

PATIENTS AND METHODS

A retrospective study for which we reviewed the medical charts of all patients diagnosed with (chronic) uveitis and treated with a BGI in the period between September 2002 and September 2015 at the University Eye Clinic Maastricht, the Netherlands. In case of bilateral uveitic glaucoma, the first operated eye was included in the analysis. Patients with a follow-up of at least 6 months were included. All patients gave their consent to use their medical data for scientific research. The study was conducted according to the principles of the Declaration of Helsinki (WMA, Brazil, October 2013).

The following data were collected: IOP, topical and systemic medications (prior to and after surgery), VA, visual fields (VF) when available, complications and subsequent ocular surgery. These data were collected at baseline (with baseline IOP as the mean IOP of two visits prior to surgery), 1, 3 and 6 months postoperatively and every year thereafter. Data on demographics, cause of uveitis, history of ocular surgeries, size of BGI and placement of the tube were collected as well. If patients were no longer followed in our clinic, the referring ophthalmologist was contacted to obtain data, after having received the patients' permission.

Surgical technique

A limbal- or fornix-based conjunctival flap was made in the superotemporal quadrant. A 250-mm2 or 350-mm2 plate BGI was placed 10 mm from the limbus, the 350 mm2 with its wings underneath the lateral and superior rectus muscles. The plate was secured to the sclera with two nylon 8 x 0 sutures (Ethicon – Johnson & Johnson, Somerville, NJ, USA). The tube was sutured to the sclera with one nylon 8 x 0 suture and tied off with a Vicryl 7 x 0 suture (Ethicon – Johnson & Johnson). In case IOP lowering was immediately needed, one or two venting slits were made, or an orphan trabeculectomy was created. The anterior chamber was entered with a 23-G needle after which the Baerveldt tube was inserted close and parallel to the iris, with a preferred intraocular tube length of 3 mm. Several tubes (especially in more narrow anterior chambers) were placed transiridially through a peripheral iridectomy to secure a stable position and to prevent corneal endothelial cell loss [16, 17].

In three cases, a pars plana approach was chosen. Before closing the conjunctiva watertight with a running Vicryl 7 x 0 suture, the extraocular part of the tube was patched with donor sclera and sutured to the underlying sclera with four interrupted Vicryl 7 x 0 sutures. Postoperative topical antibiotics were given for 10 days, and topical steroids (dexamethasone or prednisolone acetate) were started 4–6 times daily and slowly tapered over a period of 8–12 weeks.

However, in most cases steroids were permanently continued bid or qd to control the underlying uveitis. If deemed necessary because of severe inflammation, oral prednisolone was added in the postoperative hypertensive phase. If patients were on oral immunosuppressive drugs preoperatively (e.g. methotrexate, prednisolone, adalimumab or infliximab), these were continued postoperatively at the discretion of the prescribing physician. If necessary, postoperative glaucoma medication was added to reach target IOP.

Outcome measures

Main outcome measures were IOP, number of postoperative glaucoma medications, VA loss, progression of VF loss, complications and uveitis activity. Three different definitions of success were used: postoperative IOP of ≥5 mmHg and ≤21 mmHg, or ≤18 mmHg, or ≤15 mmHg and a minimal IOP reduction of 30% from baseline.

Failure was defined as two consecutive study visits without meeting the success criteria, with or without glaucoma medication (qualified success), starting after 3 months, with the first visit considered as the moment of failure. Total loss of vision, additional glaucoma surgery and removal of the BGI were also considered failures.

Statistical analysis

A linear mixed-model analysis (LMM) was used to analyse IOP, glaucoma medication, VA, VF progression and topical steroids. They were each fitted as a dependent variable with time as a factor and assuming a random intercept per eye. Success rates were determined by the Kaplan–Meier survival method. A p-value of 0.05 or less was considered statistically significant. Baseline VA was also compared to VA at the last recorded visit to determine whether patients had a clinically significant loss of VA. Clinically significant loss was defined as a decrease of >0.20 LogMAR from baseline [18]. The medical charts of these patients were analysed in more detail to provide an explanation.

RESULTS

Forty-seven eyes of 47 patients, mean age 51.8 ± 16.6 years, 57% male, and 49% right eyes, with a mean follow-up of 63.6 ±43.1 months (range 6–144 months) were included. From these, twelve patients had bilateral uveitis. In two patients, a BGI was implanted in both eyes: the first operated eye was included in the study. Demographic data are shown in table 1.

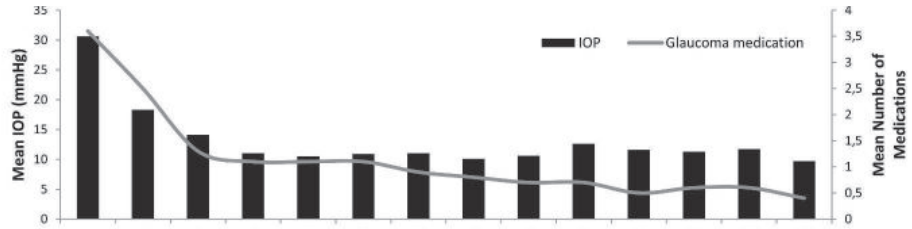
A majority (72%) of patients had a history of one or more ocular surgeries: 70% cataract surgery, 28% one or more trabeculectomies (range 1–3), 21% pars plana vitrectomy, 9% encircling band and scleral buckle and one (2%) penetrating keratoplasty (PKP). The most important causes of uveitis were idiopathic (28%), Fuchs heterochromic iridocyclitis (17%), sarcoidosis (15%) and JIA (7%).

The tube was placed in the anterior chamber in 43 cases, of which 10 tubes were placed transiridial. In three eyes, a pars plana approach was chosen: in one case, the tube was placed in the ciliary sulcus. In two cases, an orphan trabeculectomy was performed. Three patients received a 250-mm2 Baerveldt plate, once because of inadequate conjunctiva quality, twice because of the diagnosis JIA. All surgeries were performed by a single surgeon (HB).

IOP and glaucoma medication

Mean IOP dropped from 30.6 ± 8.1 mmHg at baseline to 10.6 ± 4.3 mmHg (65% reduction) at the last follow-up visit ($p < 0.001$, paired t-test) (figure 1). Patients with hypotony maculopathy were excluded from this analysis. Seventy-nine per cent of patients reached an IOP of ≤15 mmHg and ≥5 mmHg. IOP kept decreasing significantly until the sixth month (all $p < 0.011$, LMM). Thereafter, no further significant reduction was recorded and IOP remained stable. The number of glaucomamedications decreased from 3.6 ±1.1 at baseline to 1.0 ±1.3 at the last follow-up visit ($p < 0.001$, paired t-test), with 53% of patients totally off medications. Medication use decreased sharply until the third postoperative month (all $p < 0.011$, LMM). Thereafter, a statistically nonsignificant tendency for a further reduction was noticed. No patient used more glaucoma medications postoperatively compared to preoperatively, 40% used fewer topical medications, and the remaining 7% used the same number of topical medications but were off oral acetazolamide.

Until the third postoperative month, there was a high need for topical steroids. In three patients with significant ocular inflammation, oral prednisolone was also added for several months until the inflammation subsided. In seven eyes, despite the BGI, IOP fluctuations (peaks >5 mm than mean IOP over the years) kept occurring during bouts of uveitis: four (57%) with viral uveitis (HSV, CMV and rubella), one with Bartonella and two with idiopathic uveitis. In the other eyes, IOP remained low and stable, with little fluctuation over the years.



	Baseline	1 month	3 months	6 months	12 months	24 months	36 months	48 months	60 months	72 months	84 months	96 months	108 months	120 months
Number of patients	47	47	47	47	41	39	34	29	23	19	17	13	8	7
IOP (mmHg) mean ± SD [a]	30.6 ± 8.1	18.3 ± 9.5	14.1 ± 7.6	11.0 ± 4.3	10.5 ± 4.8	10.9 ± 4.9	11.0 ± 4.3	10.1 ± 4.2	10.6 ± 2.9	12.6 ± 5.0	11.6 ± 5.0	11.3 ± 3.7	11.7 ± 5.2	9.7 ± 5 .8
Medications mean ± SD [b]	3.6 ± 1.1	2.5 ± 1.8	1.3 ± 1.4	1.1 ± 1.2	1.1 ± 1.3	1.1 ± 1.3	0.9 ± 1.0	0.7 ± 1.1	0.7 ± 1.1	0.7 ± 1.1	0.5 ± 0.8	0.6 ± 1.0	0.6 ± 0.9	0.4 ± 0.8
Pt. with 0 med. (%)	2	23	45	49	44	49	47	62	65	63	71	69	63	71

Figure 1

Mean IOP and mean number of glaucoma medications over a period of 10 years.

[a] Patients with hypotony maculopathy were excluded.

[b] Oral glaucoma medication was counted as one extra medication.

7

Success rate

With an upper limit of 21 mmHg, qualified success for 1 and 5 years was 89% (95% CI: 0.80–0.98) and 75% (95% CI: 0.60–0.90), respectively (figure 2). The reasons for failure after 5 years of follow-up in this group were hypotony maculopathy (n = 5), loss of light perception (n = 4) and removal of the implant (n = 3). With an upper limit of 18 mmHg, the qualified success was 87% (95% CI: 0.77–0.97) and 74% (95% CI: 0.59–0.89), respectively. With an upper limit of 15 mmHg, the qualified success rate dropped to 67% (95% CI: 0.53–0.81) and 51% (95% CI: 0.35–0.67).

Uveitis disease activity and systemic medication

Seventeen patients (36%) used systemic immunosuppressive agents preoperatively to control their uveitis and/or underlying disease. Six used oral steroids, five adalimumab, three methotrexate, one infliximab and two acyclovir (table 2). In the period after BGI implantation, five other patients were treated with oral steroids to suppress excess ocular inflammation and prevent a flare-up.

One patient started with adalimumab postoperatively and once valacyclovir was given. Thus, a total of 24 patients (51%) used systemic immunosuppressive or antiviral agents postoperatively: 11 (46%) used corticosteroids, 10 (42%) used biologicals, and three (13%) used antiviral medication. Additionally, in most cases topical steroids were used as a maintenance therapy (87% at 1 year); however, 8.5% experienced a flare-up within the first year and had to use topical steroids 4–6 times a day (none of them had viral uveitis).

Over the next years, the yearly flare-up rate fluctuated from 2.9% to 17.1%. IOP remained stable in these eyes despite the high topical steroid use, with the exception of patients with viral uveitis who still had IOP fluctuations with peaks. Of the 24 patients with systemic immunosuppressive agents, only two with viral uveitis and one with Bartonella experienced large IOP fluctuations. Thus, the other five patients with IOP peaks did not use any type of systemic medication.

Table 1

Demographic characteristics

	n (%)
Patients	47
Male	27 (57)
Female	20 (43)
Eyes	47
Right	23 (49)
Left	24 (51)
Age	
Mean ± SD, yrs	51.8 ± 16.6
Range, yrs	15 – 83
Follow-up	
Mean ± SD, months	63.6 ± 43.1
Range, months	6 – 144
Cause of uveitis	
Unknown	14 (30)
Fuchs uveitis syndrome	8 (17)
Sarcoidosis	6 (13)
JIA	4 (9)
Bechterew's disease	3 (6)
HSV	4 (9)
Syphilis	1 (2)
Polyarthritis	1 (2)
Rheumatic disorder	1 (2)
UGH syndrome	1 (2)
Bartonella	1 (2)
Cytomegalovirus	1 (2)
Sarcoidosis + Bechterew	1 (2)
Rubella	1 (2)

Table 1

Continued

	n (%)
Lens status	
Phakic	14 (30)
Aphakic	3 (6)
Pseudophakic	30 (64)
Previous glaucoma surgery	
No. of patients with a TE	13 (28)
1 x TE	11 (23)
2 x TE	1 (2)
3 x TE	1 (2)
Previous other surgery	
Pars plana vitrectomy	10 (21)
Encircling band	4 (9)
Cataract surgery	33 (70)
Penetrating keratoplasty	1 (2)
Type of BGI	
350 mm^2	41 (87)
250 mm^2	3 (6)
Pars Plana 350 mm^2	3 (6)

SD-standard deviation; JIA juvenile idiopathic arthritis; HSV herpes simplex virus; TE trabeculectomy; BGI Baerveldt glaucoma implant.

Visual acuity (VA) and visual field progression

Using mixed-model analysis, a statistically significant loss of VA was recorded only after 9 years (p = 0.022). Mean VA loss after 9 years was 0.86 LogMAR (95% CI: 0.12–1.60). At the last follow-up visit, VA had remained stable in 23 patients and was improved in eight patients after cataract surgery, as compared to baseline. Sixteen patients (34%) experienced a clinically significant VA loss at the last follow-up visit (table 3), starting after a mean follow-up of 41 ±32 months. From these, four ultimately went blind. Three patients were preoperatively already severely visually impaired (ranging from hand motion to light perception in late-stage glaucoma). The fourth eye went blind from a postoperative suprachoroidal haemorrhage. The main reasons for VA deterioration for the other patients were hypotony maculopathy (n = 5), progression of VF loss despite a stable control of IOP in late-stage glaucoma (n = 4), and exacerbations of uveitis with uncontrolled IOP (n = 3; twice HSV uveitis, once Bartonella). One eye had a postoperative exacerbation of idiopathic uveitis for which oral steroids were started, and this is probably the reason of VA loss; however, no IOP fluctuations were recorded in this case. For one eye, no reason could be found. All 16 patients were pseudophakic (n = 13) or aphakic (n = 3).

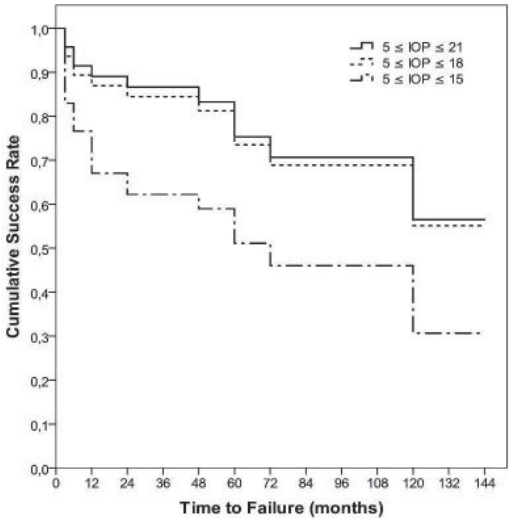


Figure 2

Cumulative qualified success rates.

Qualified success was defined as an IOP ^{3}5 mmHg and £ 21, 18 or 15 mmHg, a reduction of more than 30% from baseline, with or without glaucoma medications and without subsequent glaucoma surgery, loss of light perception or removal of the implant.

Table 2

Systemic medication at baseline

	n (%)
Oral prednisolone	6 (13)
Infliximab	1 (2)
Adalimumab	5 (11)
Methotrexaat	3 (6)
Acyclovir	2 (4)
Total number of patients	17 (36)

Twenty-two patients had at least one preoperative maximum 12 months before surgery) and two postoperative VF tests with the 30-2 protocol of the Humphrey VF analyser (HFA; Carl Zeiss Meditec, Jena, Germany). Due to the differences in postoperative time of the VF testing for these patients, the postoperative period was divided into periods of 2 years. Mean preoperative mean deviation (MD) for these patients was -13.25 (95%CI: -16.73 to -9.76). The MD dropped to -15.76 (95% CI: -20.75 to -10.78) during the first two postoperative years. During the two consecutive postoperative years thereafter, the MD

remained relatively stable with a mean of -15.98 (95%CI: -20.90 to -11.05). After 4 years of follow-up, only nine patients had at least one VF test. However, the difference between preoperative and postoperative VF tests was never significant (LMM, p > 0.275).

Table 3

Visual acuity at baseline and at last visit

	Baseline (n = 47)	Last visit (n = 47)
Mean VA (LogMAR)	0.60 ± 0,66	0.90 ± 1.20
VA range (LogMAR)	0.00 – 3.20	-0.08 – 3.51
		n (%)
Better VA[a]		8 (17%)
Same VA		23 (49%)
Worse VA		16 (34%)
	n (%)	n (%)
≤ 0,18 LogMar (20/30)	14 (30%)	14 (30%)
>0,18 <1,30 LogMar	26 (55%)	22 (47%)
≥1,30 LogMar (20/400)	7 (15%)	11 (23%) [b]

Last visit is defined as the mean of all last recorded visual acuity of each patient with a mean follow-up of 63.6 months.
a Difference of more than 0.2 LogMAR with baseline VA.
b Four blind eyes.
VA visual acuity; SD standard deviation.

Complications

Table 4 lists early (within 3 months) and late (after 3 months) postoperative complications. A total of 11 patients (23%) had a serious complication (defined as a complication for which a reoperation was needed or with a clinically significant VA loss [19, 20]). Thirteen patients (28%) had one or more early complications, the most serious being a suprachoroidal haemorrhage that needed to be drained. Five eyes developed mild choroidal effusion, which spontaneously resolved in all cases. A shallow or flat anterior chamber, for which reformation with viscoelastics was needed, was seen in six eyes. Because of partial conjunctival dehiscence, one eye needed extra conjunctival suturing. In three eyes, a spontaneously resolving hyphaema occurred.

Fourteen patients (30%) experienced one or more late complications. To repair persistent hypotony, the tube was tied off in three eyes, which was successful only once. The most severe late complication was hypotony maculopathy (n = 5), in three of these cases occurring in patients with JIA. One painful blind eye with preexistent corneal decompensation was eviscerated. Because of tube erosion, a new scleral patch graft revision was needed in two cases. In one of

them, the BGI plate eroded again and was finally removed. An encapsulated bleb developed in one eye with an encircling band and scleral buckle. This was resolved by removing all scleral material and placing a new BGI via the pars plana.

In one case, cornea decompensation occurred after BGI implantation. Two cases with previous corneal decompensation underwent PKP, once a PKP was performed after a patient developed a herpetic corneal ulcer.

Table 4

Complications divided into early (<3 months) and late (>3 months) onset

	< 3 months n (%)	> 3 months n (%)
Persistent mild diplopia [a]	7 (15)	
Choroidal effusion	5 (11)	0 (0)
Shallow/flat anterior chamber	4 (9)	2 (4)
Hypotony maculopathy	0 (0)	5 (11)
Corneal decompensation [b]	0 (0)	4 (9)
Tube endothelial touch	0 (0)	2 (4)
Conjunctiva/wound dehiscence	1 (2)	0 (0)
Tube erosion	0 (0)	2 (4)
Suprachoroidal hemorrhage	1 (2)	0 (0)
Cystoid macula edema	0 (0)	1 (2)
Encapsulated bleb	0 (0)	1 (2)
Cornea ulcer	0 (0)	1 (2)
Hyphema	2 (4)	1 (2)
Total number of patients [c]	13 (28)	14 (30)
Number of patients with serious complications [d]	11 (23)	

a Only one patient needed an intervention; strabismus surgery.
b Three with pre-existing corneal decompensation.
c Some patients had more than one complication.
d Serious complication was defined as a complication for which a reoperation was needed or with VA loss (> 0.20 LogMAR).

DISCUSSION

Our study shows that the treatment of uveitic glaucoma is challenging, but in most patients with uveitic glaucoma, the BGI maintains a low and stable IOP over many years, with a significant reduction in glaucoma medications. Only a few studies have reported on the long-term results of the BGI in uveitic glaucoma. Besides the long follow-up, the strengths of our study are the size of the study population and the extensive analysis of VA and complications.

To analyse the retrospective collected data as efficiently as possible, we used linear mixed-model analysis (LMM). The advantage of this model is that all available data are included in the analysis. Still, due to the nature of retrospective studies and the heterogeneity of the study population, the results have to be interpreted with caution.

An important finding in this study is that IOP was substantially reduced and remained stable with a reduction between 59% and 68% during a ten-year follow-up period. However, IOP fluctuations can still occur after BGI implantation in a number of patients with uveitic glaucoma, for which mainly patients with viral uveitis seem to be at risk. However, IOP peaks during bouts of uveitis did not reach preoperative levels. Lewkowicz et al. also reported higher IOP in patients with viral uveitis compared to nonviral uveitis [21]. A successful control of the uveitis and its underlying disease seems to be of crucial importance in the success of treatment of uveitic glaucoma. In recent years, systemic therapy has improved a lot after the introduction of biologicals as an addendum to the treatment armamentarium.

In our study, 46% of patients who used systemic medication preoperatively used corticosteroids and 42% used biologicals. These medications seem very beneficial to prevent vision loss from IOP peaks; however, in a few patients, the underlying uveitis seems to have been the reason for further visual deterioration despite stable IOP. Our results compare to the one-year results of other studies that reported an IOP reduction between 57% and 69% after 1 year [13, 22]. Iverson et al. reported a stable reduction over a period of 5 years as well [13]. The IOP reduction for the Molteno glaucoma implant in uveitis patients seems slightly lower than for the BGI. At 1 year, the reported IOP reduction ranges from 50% to 56% [23, 24]. Molteno et al. also reported an IOP reduction after 10 years of follow-up of 54% from baseline [23].

There are four studies with a follow-up of 2 years or more with the Ahmed valve implant, reporting an IOP reduction ranging from 46% to 67% [25-28]. Thus, the BGI probably results in a larger reduction in IOP than the other glaucoma drainage implants, possibly through its larger plate size. Recently, a large meta-analysis in a general glaucoma population compared the Ahmed valve with the BGI and reached the same conclusion [29]. However, this study reported more complications in the Baerveldt group. In most studies, success rate is defined as an IOP of 21

mmHg or lower. In our study, and in most other studies, the majority of patients have advanced glaucoma. Therefore, we believe that the aim of the BGI should be a low target pressure to prevent progression. Thus, a stricter upper limit of 18 mmHg or even 15 mmHg seems a more realistic definition of success. For the sake of comparison, we included a success rate with an upper limit of 21 mmHg.

Still, it is difficult to compare these data because of differences in baseline characteristics, in particular the number of previous surgeries and the cause of uveitis. Our qualified success rate at 1 year (89%) is similar to those of Ceballos et al. and Iverson et al.; 92% and 91% at 1 year, respectively. At 5 years, a success rate of 75% was recorded, which is similar to the one we found [13]. In the Iverson study, 26% of patients continued their systemic uveitis medication. Caballos et al. do not mention systemic medication in their study. The qualified success at 1 year for the Ahmed valve implant ranged from 50% to 100% [25-28, 30]. The success rate for the Molteno implant at 1 year ranged from 79% to 97% [7, 23, 24, 31, 32]. Molteno et al. reported a success rate of 87% and 77% at, respectively, 5 and 10 years [23].

The short-term success rates are quite similar for the three implant types. It seems that the Molteno implant has a better longterm success rate, but this is only based on a single study. Only a few articles report on VA loss, all with slightly different definitions. In the study of Ceballos et al., 21% of the patients had a profound loss of VA [22]. Fifteen to 40% of patients with a Molteno glaucoma implant experienced VA loss [7, 31]. Five studies report the VA loss for the Ahmed valve implant. The percentage of patients with VA loss ranges from 0% to 26% [25-27, 30, 33].

In our study, 16 patients (34%) had a clinically significant VA loss at the last recorded visit. This number appears slightly higher than reported for the Ahmed valve implant. Most of this can be accounted for by the longer follow-up in our study, as mean VA loss only became significant after 9 years. Multiple earlier surgical procedures influenced this number as well, together with severe baseline pathology (other than uveitis), progression of VF loss in several patients and several cases with postoperative complications (hypotony maculopathy and suprachoroidal haemorrhage). A recent study of Pathanapitoon et al. showed that 41% of patients with uveitic glaucoma became blind at least in one eye, which was significantly higher compared to the uveitis eyes without secondary glaucoma (18%). A total of 69% of these eyes underwent glaucoma surgery [34]. With regard to VF progression, we have to be careful to draw conclusions due to the lack of sufficient data. The majority of patients performed at least one VF test at baseline, from only 22 patients at least two postoperative VF tests were available for analysis. The main reasons for this were end-stage glaucoma, further follow-up by the referring ophthalmologist, or a short follow-up period. However, we observed a tendency towards a drop in MD (-3.40 dB) in the first 2 years after implantation, with a stabilization thereafter. From existing literature, we could not corroborate this finding with earlier work. In a preliminary study by the group of

Jansonius (F.G. Junoy Montfolio, R.P.H.M. Müskens and N.M. Jansonius, abstract presented at 210th meeting of the Dutch Ophthalmological Society, Maastricht 2016), it was suggested that an increase in inflammation caused by the BGI may cause visual field progression in the early postoperative phase. If this is confirmed, this further underlines the need to sufficiently suppress inflammation, especially in uveitic eyes.

The complications recorded in this study are similar to those in two large prospective studies, the Tube Versus Trabeculectomy (TVT) study [35] and the Ahmed Baerveldt Comparison (ABC) study [20]. At 5 years, the serious complication rate for the BGI was 22% and 29% in the TVT and ABC study, respectively. In our study, 23% had a serious complication. An important difference in late postoperative complication is the number of patients with hypotony maculopathy. Both studies reported approximately 1% hypotony maculopathy in the Baerveldt group. We recorded 11% (n = 5) hypotony maculopathy patients, three of them with JIA. A 250 mm2 was tried for two patients with JIA, but one patient still developed a hypotony maculopathy with this smaller implant. Hypotony is a known complication, even without surgery: with 10% per year of patients with JIA, this patient category is especially at risk [36]. Because of its chronic symptomatic character, undertreatment is possible, and ciliary body atrophy can occur [37]. Our patients with JIA underwent BGI surgery late in the course of the disease. A more aggressive and earlier medical and surgical approach of these patients may possibly lead to a better outcome [38, 39].

In conclusion, the BGI has shown to be a long-term effective and safe treatment for refractive secondary glaucoma due to uveitis. Continued systemic immunosuppressive treatment seems beneficial to prevent a flare-up and uncontrolled IOP. The main reasons for postoperative vision loss in this population most probably are severe disease at baseline, uncontrolled uveitis/inflammation despite stable IOP, continued IOP fluctuations with IOP peaks (e.g. in viral uveitis), whereas at the other end of the spectrum, especially patients with JIA seem much more prone to hypotony maculopathy.

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CHAPTER 8

General discussion

GENERAL DISCUSSION

The treatment of open angle glaucoma has evolved over the years. During the last decades, the availability of new drugs and drug combinations, and the subsequent intensification of medical treatment has led to a decrease in the number of traditional glaucoma filtering surgeries, especially trabeculectomy. [1, 2] A 52% drop in trabeculectomy rates has been observed from 1994 until 2003, with a further decrease of 52% in 2021 (Medicare data). Simultaneously, a 231% increase in the number of tube surgeries was seen between 1994 and 2003, and a 54% further increase in 2012. But the most dramatic increase, from 2013 on, has occurred with new, minimally invasive surgery procedures. [3-5] We will elaborate upon this later in this paragraph.

The current European guidelines [6] advise to start glaucoma treatment with topical medication and/or laser treatment. Incisional glaucoma filtering surgery is usually reserved for patients with advanced and worsening disease, often after treatment with three or even four medications. This approach is questionable, as there is emerging evidence that this may cause a delay in the referral of patients for glaucoma surgery until a late stage of the disease. A recent European report showed that from all referrals, only 41.5% were considered on time .[7] The treatment period was significantly longer (median: 7 years) in the "old" European Union countries than in "new" European Union countries or non-European Union countries, and the glaucomatous damage was more advanced. These findings suggest that further efforts are necessary to improve glaucoma care in Europe.

Furthermore, long-term topical glaucoma medications and preservatives in eye drops may cause side effects, including burning, redness and blurred vision [8] and/or exacerbate pre-existing ocular surface disease (OSD); such as dry eye and chronic allergy [9]. The preservative benzalkonium chloride (BAC) is toxic and may lead to a reduction in the success rate of filtering surgery. An additional problem is nonadherence with glaucoma medication, which may also lead to progression of visual field loss. [10, 11]

It can be concluded that intensification of medical treatment has not resulted in better treatment outcomes so far. Too many patients still go blind from glaucoma, with up to 24% unilateral and 10% bilateral blindness at the end of their lives. [12] There is a large need for safe and effective surgery.

Glaucoma surgery

Traditional glaucoma surgery (especially trabeculectomy) is not very popular, as the worldwide numbers show. This might be explained by the high level of surgical skill and experience that is needed to successfully perform trabeculectomy. There is a learning curve and the use of antifibrotic drugs (which are commonly used now to improve the outcome), may cause additional

problems. Intensive postoperative monitoring is needed and possibly severe complications may arise (e.g. bleb related infection). The procedure may also have a negative impact on quality of life. However, especially as the technique has been refined over the years, good results can be obtained, with sustained IOP levels in the low teens. [13] Currently, trabeculectomy remains the gold standard procedure for the treatment of primary open angle glaucoma, and for cases where a very low IOP is needed. However, tube surgery may now be the first choice for all other open angle glaucomas. [14-16]

IOP reduction and serious complications may be similar in most cases, but after trabeculectomy more early complications have been observed and more bleb-related infections, whereas after tube surgery other problems may occur, e.g., erosion of the tube, tube obstruction, diplopia, and corneal decompensation.

Another concern causing ophthalmologists to refrain from glaucoma surgery, is visual loss that might occur directly afterwards, induced by the procedure. However, a recent study showed that glaucoma surgery indeed induced an immediate postoperative drop in mean deviation of visual field defects, but 1.5 year later the rate of progression of the visual field loss had slowed down whereas this was not the case in non-operated patients. [17] This implicates that early surgical intervention in glaucoma could prevent visual deterioration and blindness on the long term.

Nowadays, the Ahmed glaucoma valve (AGV) and the Baerveldt glaucoma implant (BGI) are the most frequently used GDDs worldwide. The main difference between these two devices is that the AGV has a built-in valve which immediately regulates the postoperative flow, whereas the BGI requires a temporary ligature around the tube to prevent hypotony during the first postoperative weeks. The Ahmed Baerveldt Comparison study and the Ahmed versus Baerveldt study both evaluated and compared the efficacy and safety of the AGV and the BGI. Overall, after 5 years of follow up, the AGV tended to fail because of inadequate IOP control whereas on the other hand the BGI had more serious complications which needed reoperation. [18, 19] From these studies can be concluded that the choice of the optimal GDD should be made on an individual basis, taken multiple cofactors into account such as glaucoma diagnosis, presence of conjunctival scarring, durability of the implant, preoperative IOP level, the necessity to immediately lower IOP, and ocular comorbidity.

This thesis focuses on the outcome and safety of the BGI. The BGI can be pictured well in the anterior chamber using anterior segment optical coherence tomography (AS-OCT). In our study, a spectral-domain OCT (SD-OCT) was used. The SD-OCT showed good reproducibility of anterior chamber angle measurements **(chapter 2)** and tube-corneal and tube-iris distances could be accurately assessed, with reproducible outcomes **(chapter 3**). Recently, new and more

sophisticated AS-OCT machines have been developed. The swept source-OCT (SS-OCT) is now often for images of e.g., anterior chamber structures, intraocular lenses, tubes, and tumors. SD-OCT devices use a broadband near-infrared super luminescent diode as the light source with a spectrometer as the detector. On the other hand, SS-OCT instruments apply a tunable swept laser as the light source with a single photodiode detector. [20]

An important aspect of our study was the finding that the BGI tube migrated towards the corneal endothelium over time when placed free in the anterior chamber. The tube-corneal distance decreased. A safer approach is to place the BGI transiridial. When the tube is fixed to the iris, it cannot migrate towards the endothelium, which should protect endothelial cells. However, this study was carried out under ideal circumstances, without indentation of the eye. We cannot rule out tube motion or tube-endothelial contact when patients rub their eye. [21] In daily practice, we should warn patients to refrain from rubbing their eyes. If they cannot comply with this, tube surgery is contraindicated.

Increased corneal endothelial cell (EC) loss is significantly correlated with shorter tube-corneal distance, as shown in **chapter 4**. The shorter the distance, the higher the loss. A central EC loss of 6.20% per year was found with a mean corneal distance of 1.69 mm, in contrast to a 4.11% loss with longer tube-corneal distances. The EC loss was found to be most profound in the superior corneal quadrant which was closest to the BGI. Transiridial placement of the tube showed lower EC loss compared to placement of the tube free in the anterior chamber. [22] These data indicate that the tube should be placed away from the corneal endothelium and can be safely fixed to the iris. A long tube- corneal distance may prevent severe corneal EC loss, and thus corneal decompensation.

Our findings are comparable to recently published studies. Iwasaki et al. reported a more profound EC loss in the quadrant closest to the Baerveldt tube compared to central ECD (13.1% vs 10.3% after one year). [23] This study also demonstrated that pars plana placement of the BGI is not significantly related with EC loss, indicating a relationship between tube-corneal distance and EC loss. Hau et al also found that anterior chamber BGI insertion was associated with EC loss greatest close to the tube. Tube insertion in the vicinity of, or anterior to Schwalbe's line, and short tube length were also associated with significant EC loss with time. [24]

These data clearly indicate that placement of the silicone BGI tube in the anterior chamber can lead to significant EC loss over time, especially if the tube is short and has been placed close to the endothelium. A stable position of the tube in the anterior chamber, close to the iris or transiridial, will prevent the tube from migrating towards the corneal endothelium (as shown in chapter 3). However, other mechanisms may also play a role in chronic EC loss. It has been hypothesized that placement of a phakic intraocular lens may lead to EC loss due to changes in

aqueous humor flow. [25] Additionally, pro-inflammatory cytokines in glaucomatous aqueous humor and the silicone material of the tube may lead to a chronic subclinical inflammatory response. Silicone has a high affinity for plasma proteins, promoting inflammation. [26, 27]

Similar to the advice given when implanting phakic IOLs in patients, we recommend to scheduling patients with a BGI for (bi)annual follow-up measurements of the corneal endothelium, especially if the tube has been inserted "free" into the anterior chamber. [28] By regular monitoring, severe EC loss can be detected timely, and a surgical revision can be planned during which the tube is relocated to the ciliary sulcus or to the vitreous cavity (if applicable). Anterior segment imaging can also be helpful as tube position and distance to intraocular structures (especially cornea and iris) can be assessed over time (chapter 2).

Recently, a new GDD, also made from silicone, but with a thinner tube, has been introduced into the clinic: the Paul glaucoma implant. [29, 30] It will be interesting to compare EC loss and tube positioning in the long term between this new device and older GDDs, like the BGI. In addition, new and less invasive subconjunctival implants, with a thinner tube and made from new materials (e.g. SIBS), may offer new alternatives. A first study indicated that EC loss after placement of a SIBS MicroShunt may be comparable to EC loss after trabeculectomy. [31]

As GDDs stay permanently in the body after implantation, it is of great interest to study if complications, due to the implant(design) and/or its material, may arise over time. The silicone material of the BGI may lead to prolonged subclinical inflammation, as already mentioned. However, in studies regarding complications after placement of silicone breast implants, it was also shown that silicones can migrate from the implant through the body, inducing a chronic inflammatory process, which may lead to rheumatic autoimmune diseases. [32]

In the 5-year studies comparing the AGV and BGI, more failures were reported in the BGI group due to safety issues (hypotony, implant explantation, and loss of light perception) (ref Budenz et al. 2015, Christakis et al. 2017). As both devices are made from silicone, these findings are most likely explained by the differences in implant design.

Due to the recent shift in guidelines, making tube surgery now the preferred choice of filtering surgery for most forms of open angle glaucoma, outcomes may have improved, especially during the last decade. To study possible differences (due to this treatment paradigm shift) in long-term results and complications of the BGI, we compared a 10-year cohort (all patients operated in the University Eye Clinic of Maastricht, and by a single surgeon), and an additional 5-year cohort, with more recently operated patients **(chapter 5)**. The 5-year cohort results were compared with the results of the first 5 years of the 10-year cohort to contradict a time-related bias in the 10-year cohort. Mean corrected distance visual acuity slightly decreased over the years in all

groups but was better in the 5-year cohort. There was a trend towards lower IOP levels in the 5-year cohort, however a sustained and stable IOP in the low teens was obtained in all groups. There were small differences between the 5-year and 10-year cohorts, with more primary open-angle cases and less neovascular glaucoma cases and vitrectomized eyes in the 5-year cohort. Although these differences may reflect the changing indications for preferred earlier treatment with tube surgery, they were not statistically different.

Corneal decompensation was the most common complication, occurring in 8% of eyes, in both the first and the second 5 years of follow-up, however, cornea transplant was only performed in the 10-year group. Revisions of the BGI (e.g., tube shortening, tube replacement or re-patching of the tube) were also more often performed in the 10 year-cohort, during the first 5 years. Enucleation or evisceration, for painful blind eyes, was performed in 5% of cases in the 10-year cohort, while none were performed in the 5-year cohort. Although these numbers are small, they may also indicate that less healthy eyes were included in the 10-year cohort.

Overall, the BGI performs well over many years, and optimal patient selection (earlier in the treatment algorithm) may further improve treatment outcomes. Although made of silicone, the impact of the material on the long term seems not very significant, but severe complications do occur, especially corneal decompensation. We will have to await if a new generation of tube implants, made of newer material, might further improve results.

We also studied the role of the BGI in special cases. In a case report we presented a patient with secondary glaucoma due to an iris melanoma, treated with proton beam therapy **(chapter 6).** After the implantation of a BGI, the IOP remained low and the already severe visual field loss stabilized. [33] Sharkawi et al. prospectively studied the outcome of BGI implantation in secondary glaucoma cases due to iris melanoma, treated with proton beam therapy. In this series of 31 eyes, 86% achieved surgical success, 1 year after BGI. [34] These findings indicate that the BGI may be a safe treatment option for this category of patients.

The incidence of secondary glaucoma due to uveitis is estimated to be 18.3%. [35] The balance between uveitic activity and subsequent IOP rise (with often high IOP peaks) can be difficult to manage with medication and remains a therapeutic challenge. Medical treatment fails in approximately 25% of patients with uveitic glaucoma and those patients eventually need surgical treatment. [36] Our study, presented in **chapter 7**, showed an IOP decrease from 30.6 mmHg preoperatively to 9.7 mmHg at 10 years of follow up. The number of glaucoma medications reduced from 3.6 preoperatively to 0.4 at 10 years. Visual acuity deteriorated in 34% of cases. One of the main reasons for visual acuity loss was hypotony maculopathy, which was more pronounced in juvenile idiopathic arthritis (JIA) patients. In such cases, the implantation of a BGI with a smaller endplate is advised. [37] A meta-analysis published by Ramdas et al. reported the

outcomes after placement of a GDD in uveitis patients. They found no statistically significant difference in efficacy of the GDD in patients with or without uveitis. A decrease of 42% in IOP was found in eyes with uveitic as well as in non-uveitic glaucoma. They suggested that macular edema may have been underreported. In another study, mean IOP was found to drop from 29.5 mmHg preoperatively to 14.4 mmHg after 5 years. Thirteen eyes suffered from early hypotony of which only one eye developed hypotony maculopathy. [38, 39]

These studies confirm that the BGI is also a safe treatment for uveitic glaucoma. Nevertheless, patients need to be followed up closely to prevent tiresome complications.

Future perspectives

The efficacy and safety of glaucoma filtration surgery has improved over the years. New glaucoma drainage devices and implantation methods have been developed, making tube surgery now the first choice for many glaucoma patients who need to undergo filtration surgery. Tube surgery is especially indicated for secondary glaucoma and more challenging cases. However, despite the current surgical techniques and choice of devices, serious complications may still occur after GDD surgery. Optimal patient selection and close postoperative monitoring is mandatory to obtain successful outcomes and detect possible complications in an early stage. Baseline endothelial cell density (ECD) and anterior chamber depth should be assessed, and placement of the tube away from the cornea, transiridial or into the ciliary sulcus should be opted for. If applicable, placement into the vitreous cavity in previously vitrectomized eyes can also be considered. We recommend that patients who will undergo GDD implantation should be informed preoperatively about the risk of EC loss and be advised to comply with a strict long-term follow-up regimen with ECD measurements on a regular (bi)annual basis. Thus, patients as well as surgeons need to be motivated for lifelong monitoring.

There has been a paucity in the development of new GDDs. Current innovations include the Paul implant, made from silicone but with a thinner tube, and the Rheon Medical eye Watch, which is the first GDD with the possibility to actively alter postoperative outflow. The eye Watch is currently being tested in Europe and its results may be promising. [40]

However, despite these improvements in traditional glaucoma filtration surgery, most attention has been focused on the development of new, minimally invasive glaucoma surgery (MIGS) procedures. [41] There are many new options. [42] Most MIGS are based on a Schlemm's canal/trabecular meshwork (TM) approach. These MIGS include miniature implants, as well as excising/cleaving or dilating procedures. Suprachoroidal implants have also been developed, but recently one implant has been taken off the market because of severe endothelial cell loss during follow-up. [43] The TM/canal-based procedures have fewer risks, shorter surgery time and a faster postoperative recovery. [44, 45] However, they are also less effective when compared

to traditional filtration surgery. [46] Less invasive, bleb forming procedures have also been introduced to the market. These include miniature tube shunts (without an endplate and made from new materials) for subconjunctival/sub-Tenon's placement. The XEN-gel stent is made from gelatin and the Preserflo MicroShunt from SIBS. [47] These subconjunctival procedures are more promising in efficacy; however, they need to be augmented by mitomycin c application to obtain successful results. There is emerging evidence that they may be a less invasive alternative to trabeculectomy or GDD, however more studies (including head-to-head comparisons) are needed to prove this. [31, 48, 49] Several randomized controlled studies are currently under. [50, 51]

The future of glaucoma surgery is promising. Next to traditional trabeculectomy, tube shunts like the BGI have proved their value. The BGI offers safe and sustained IOP lowering for many patients, provided that patients comply with strict postoperative monitoring, especially for EC loss. The new MIGS and less invasive procedures will find their place in the treatment paradigm, and we will be able to offer a broad variety of treatment opportunities to our patients. Hopefully this will eventually lead to a further reduction of severe visual impairment and blindness.

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CHAPTER 9

Summary & Samenvatting

SUMMARY

Glaucoma is a complex and possibly devastating eye disease, in which degeneration of the optic nerve leads to progressive and irreversible visual field loss. Currently, it is the leading cause of irreversible blindness worldwide. Raised intraocular pressure (IOP) is its most important risk factor and lowering IOP is the only proven treatment to stop progression of the disease. Medical and surgical treatment options have increased over time. Trabeculectomy has proven its worth over the past decades and still is the first choice for the surgical treatment of open angle glaucoma. However, long-tube glaucoma implants have become an interesting alternative, for primary glaucoma and especially for secondary and refractory glaucoma. This thesis focuses on the surgical treatment of glaucoma with the Baerveldt glaucoma implant.

Chapter 1 is a general introduction and gives an historical overview on glaucoma and its treatment options.

Chapter 2 shows the reproducibility of anterior chamber angle measurements with the Visante anterior segment OCT. The overall reproducibility in experts and non-experts was good in open angles.

The Baerveldt tube motility was investigated using the Visante anterior segment OCT under varying light conditions in **chapter 3**. The drainage tube remained stable when inserted transiridial, but moved closer to the endothelium when the tube was placed free in the anterior chamber.

Chapter 4 reports on corneal endothelial cell loss after placement of the Baerveldt tube in relation to tube-corneal distance and the quadrant of placement. A shorter tube-corneal distance causes more severe endothelial cell loss, especially in the peripheral quadrant closest to the tube. Transiridial placement of the tube seems safer than placement 'free' into the AC to avoid extensive endothelial cell loss.

The long-term outcomes of the Baerveldt glaucoma implant are presented in **chapter 5**. A sustained and stable control of intraocular pressure can be obtained for up to 10 years after implantation, with values between 12 and 13 mmHg. Corneal decompensation is the most important complication.

A case report in **chapter 6**, shows that placement of a Baerveldt glaucoma implant is a safe and effective method to treat glaucoma that may arise after proton beam therapy for iris melanoma.

Chapter 7 demonstrates that the Baerveldt glaucoma implant is an effective and safe treatment for patients with refractive secondary glaucoma due to uveitis. Patients with viral uveitis and glaucoma should be closely monitored for intraocular pressure peaks that may occur during episodes of a flare-up of uveitis. Patients with juvenile idiopathic arthritis seem much more prone to hypotony maculopathy.

Chapter 8 discusses the main findings of this thesis, and future perspectives. The Baerveldt glaucoma implant is a good choice for the surgical treatment of glaucoma, and is also suitable for special cases. However, correct tube-placement is essential to prevent severe endothelial cell loss, and lifelong monitoring is advocated. Refining tube designs and novel minimally invasive methods may prevent complications.

Finally, **the impact paragraph (addendum)** shows the impact on society of the results of this thesis. There is still a large and unmet need for a proper treatment of glaucoma. However, IOP lowering works and this thesis shows that the Baerveldt glaucoma implant performs well over many years, underlining that safe and effective glaucoma surgery helps to combat blindness. Future refinement of glaucoma surgery devices and methods may further improve outcomes.

SAMENVATTING

Glaucoom is een complexe en mogelijk verwoestende oogziekte waarbij degeneratie van de nervus opticus lijdt tot progressieve en irreversibel gezichtsveldverlies. Momenteel is glaucoom de meest voorkomende oorzaak van irreversibele blindheid wereldwijd. Verhoogde intraoculaire druk (IOP) is de meest belangrijke risico factor, en verlaging van de IOP is de enige bewezen therapie om progressie van de ziekte te stoppen. De medicamenteuze en chirurgische behandelopties zijn in de laatste decennia toegenomen. Trabeculectomie heeft in de afgelopen decennia zijn waarde bewezen en is nog steeds de eerste keuze voor de chirurgische behandeling van open kamerhoek glaucoom. Lange-tube implantaten zijn echter een interessant alternatief geworden voor primair glaucoom en voornamelijk voor secundair glaucoom en refractair glaucoom. Dit proefschrift richt zicht op de chirurgische behandelding van glaucoom met het Baerveldt glaucoom implant.

Hoofdstuk 1 is een algemene inleiding en geeft een historisch overzicht van glaucoom en de behandelmogelijkheden.

Hoofdstuk 2 toont de reproduceerbaarheid van de metingen van de voorste oogkamer hoek met de Visante anterieure segment OCT. De algehele reproduceerbaarheid bij experten en niet-experten was goed in open kamerhoeken.

De motiliteit van de Baerveldt tube werd onderzocht met behulp van de Visante anterieure segment OCT onder wisselende lichtomstandigheden in **hoofdstuk 3**. De drainage tube bleef stabiel wanneer deze transiridiaal werd ingebracht, maar kwam dichter bij het endotheel wanneer de tube vrij in de voorste oogkamer werd geplaatst.

Hoofdstuk 4 rapporteert over het verlies van corneale endotheelcellen na plaatsing van een Baerveldt glaucoom implant in relatie tot de afstand van de tube tot het hoornvlies en in relatie met het kwadrant van plaatsing. Een kortere afstand tussen tube en hoornvlies veroorzaakt ernstiger verlies van endotheelcellen, voornamelijk in het perifere kwadrant het dichtst bij de Baerveldt tube. Transiridiale plaatsing van de tube lijkt veiliger dan plaatsing “ vrij” in de voorste oogkamer om uitgebreid endotheelcelverllies te voorkomen.

De lange termijn resultaten van het Baerveldt glaucoom implantaat worden gepresenteerd in **hoofdstuk 5**. Een aanhoudende en stabiele controle van de intraoculaire druk kan worden verkregen tot 10 jaar na implantatie, met waarden tussen 12 en 13 mmHg. Hoornvlies decompensatie is de belangrijkste complicatie.

Een case report in **hoofdstuk 6** laat zien dat het plaatsen van een Baerveldt glaucoom implant een veilige en effectieve methode is om secundair glaucoom vanwege protonen bestraling voor een iris melanoom te behandelen.

Hoofdstuk 7 laat zien dat het Baerveldt glaucoom implant een effectieve en veilige behandeling is voor patiënten met secundair glaucoom vanwege uveitis. Patiënten met een virale uveitis en glaucoom dienen nauwlettend gecontroleerd te worden voor intraoculaire druk pieken die kunnen ontstaan tijdens uveitis opvlammingen. Patiënten met juveniele idiopathische uveitis lijken vatbaarder voor hypotone maculopathie.

Hoofdstuk 8 rapporteert de belangrijkste bevindingen van dit proefschrift en de toekomstperspectieven. Het Baerveldt glaucoom implant is een goede keuze voor de chirurgische behandeling van glaucoom en is tevens ook geschikt voor speciale casus. Correcte plaatsing van de tube is echter essentieel om ernstig verlies van endotheelcellen te voorkomen. Levenslange monitoring wordt aanbevolen. Het verfijnen van tube ontwerpen en nieuwe minimaal invasieve methoden kunnen complicaties voorkomen.

Tenslotte laat **het addendum (impact paragraaf)** zien wat de resultaten van dit proefschrift zijn qua impact op de samenleving. Er is nog steeds een grote onvervulde behoefte aan een goede behandeling van glaucoom. Echter, dit proefschrift toont aan dat het Baerveldt glaucoom implantaat een goede IOP-daling bewerkstelligd en dat het jarenlang goed werkt. Dit onderstreept dat veilige en effectieve glaucoomchirurgie werkt om blindheid te bestrijden. Toekomstige verfijning van implantaten en methoden voor glaucoomchirurgie kunnen de resultaten wellicht nog verder verbeteren.

ADDENDUM

Paragraph of impact

PARAGRAPH OF IMPACT

Glaucoma is a degenerative optic neuropathy that is characterized by progressive visual field loss. When inadequately treated, the disease will lead to visual impairment and eventually blindness. Currently, glaucoma is the leading cause of irreversible blindness worldwide. It is estimated that by 2040 the number of affected glaucoma patients will increase to 112 million people [1]. Even in the Netherlands, a country with highly developed health care facilities, approximately 25% of people eventually go blind in one eye, 10% even become bilaterally blind at the end of their life, despite treatment [2].

Thus, there remains a large and unmet need for a proper treatment of glaucoma. Currently, the only proven treatment is by lowering intraocular pressure (IOP) to a target level where further visual field progression is halted. Treatment is usually started with (topical) medication and/or laser, however incisional surgery should be considered when target IOP is not reached or the disease keeps progressing. Surgical treatment should also be considered as an early option for patients who do not visit their ophthalmologist until in a late stage of the disease. Unfortunately, this still happens often as there are usually no symptoms until severe visual impairment sets in. It is estimated that for each diagnosed patient there is another patient out of care who is not aware of having glaucoma. Awareness, and early diagnosis and treatment should therefore be further promoted.

However, the unacceptable high proportion of patients that still severely progress despite diagnosis and treatment brings to light another problem: patients and ophthalmologists often shy away from surgical treatment, because they fear complications, vision loss and loss of quality of life after the procedure. As a result, medical treatment (often with multiple drugs) is continued, even when facing progression. This reasoning is understandable, as glaucoma surgery did not have a good reputation in the past.

Several decades ago, trabeculectomy became the gold standard procedure for the surgical treatment of glaucoma (see the introduction of this thesis for an historic overview of surgical techniques). However, trabeculectomy often failed, due to fibrosis and scarring of the filtering bleb. Almost 60% of filtering blebs failed within 15 years [3], and further treatment options were usually limited to high-risk cyclodestructive procedures. [4]

Early pioneers like Molteno and Baerveldt dramatically changed the landscape of glaucoma surgery from the second half of the twentieth surgery. The revolutionary concept of draining aqueous humour via a flexible silicone tube out of the anterior chamber of the eye to a subconjunctivally located endplate proved a successful answer to the widespread problem of failing filtering blebs.

During the years, glaucoma drainage devices (GDD) have become increasingly popular. The Baerveldt glaucoma implant (BGI) has become one of the most commonly used devices worldwide. Also, it has been the subject of many studies that investigated efficacy and safety when compared to other devices and trabeculectomy [5-8]. These studies have clearly demonstrated the value of the BGI for the current treatment of glaucoma.

However, the route to success of GDDs (and the BGI in particular) cannot be seen separately from the developments in other fields of ophthalmology, especially cataract and vitreoretinal surgery. Results of GDDs were further improved after the shift of cataract surgery from extracapsular (large incision) surgery to small incision clear cornea phacoemulsification, no longer needing to open the conjunctiva and thereby reducing the risk of conjunctival scarring. The same applies to retinal surgery, which has largely moved away from buckling procedures to small-incision vitreoretinal procedures, also sparing the conjunctiva. GDD placement can successfully be opted for before, after or directly combined with cataract or retinal surgery.

The research in the present thesis has offered important new insights for surgical glaucoma treatment with the BGI. A stable position of the tube in the anterior chamber, close to the iris or transiridial, will prevent the tube migrating towards the corneal endothelium (**chapter 3**). New imaging devices, such as Swept Source OCT, can accurately monitor tube position and distance to intraocular structures (especially cornea and iris) over time (chapter 2). The current thesis also clearly demonstrated for the first time that endothelial cell loss is a very important cause of failure of the BGI, leading to corneal decompensation in about 8% of cases (**chapters 4 and 5**). We strongly recommend to incorporate regular measurements of endothelial cell count (yearly) into routine clinical practice after placement of a GDD (BGI), especially if the tube has been inserted "free" into the anterior chamber, somewhere between cornea and iris. Doing this, severe endothelial cell loss can be detected timely and a surgical revision can be planned during which the tube is relocated to the ciliary sulcus or to the vitreous cavity (if applicable).

This thesis also demonstrated that the BGI can be safely used for many cases of secondary glaucoma. Most patients with uveitic glaucoma are better off after placement of a BGI (**chapter 7**) and a BGI can even be safely and successfully applied after treatment of intraocular tumors (**chapter 6**).

Finally, this thesis clearly showed that IOP results after BGI placement are stable and sustained in the low teens for many years, saving many patients from blindness (**chapter 5**).

Currently, evidence is emerging that early surgical intervention is indeed superior to the continuation of medical treatment. A recent study from the Netherlands demonstrated that the surgical event (often a BGI) has a small impact on visual function, however after approximately 1.5 years of follow up the surgical group performed better than the medication group, with less progression of visual loss. [9]

At the beginning of the third decade of the 21st century, trabeculectomy is still considered the gold standard procedure worldwide. [10] Through the years, the surgical technique has been greatly improved and with the additional application of antimetabolites (mitomycin C or 5 FU), success rates have been improved as well and severe complications have become less common. [11] It is also a low-cost procedure, making it available for many glaucoma surgeons worldwide. However, to obtain optimal results, good surgical skills and experience with the procedure are required.

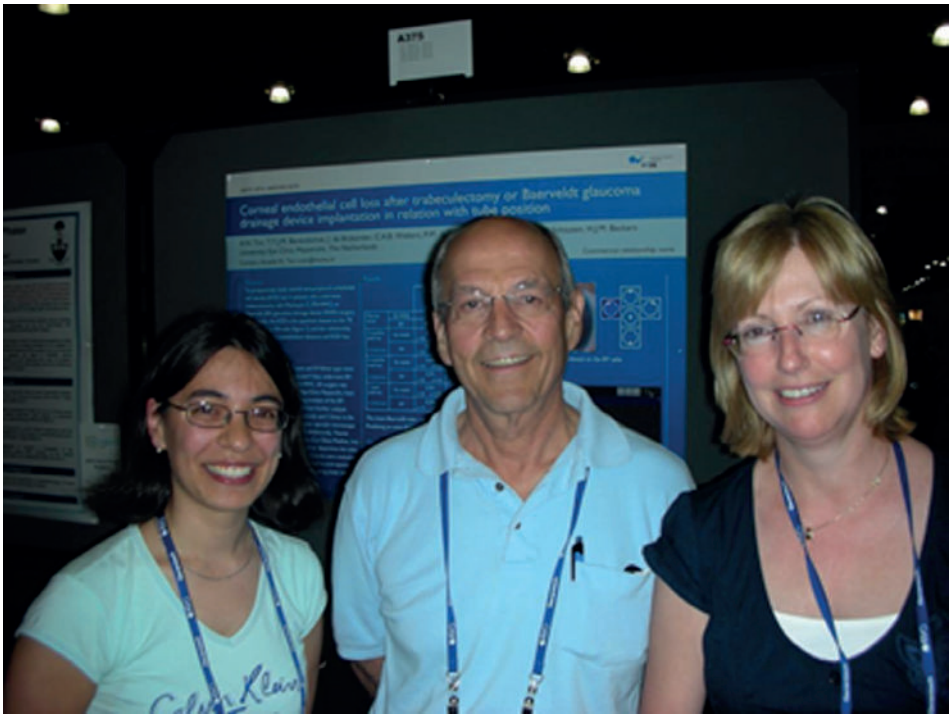
During the last three decades, trabeculectomy rates have been steadily declining while the number of GDD surgeries keeps growing, also for primary cases. In the Preferred Practice Pattern of the American Academy of Ophthalmology (2020) it is stated that currently there is insufficient information on superior results of GDDs versus trabeculectomy. [12] Selection of the desired procedure should be done in a process of "shared decision making" between the patient and the treating ophthalmologist. However, there is a growing consensus that trabeculectomy should probably be reserved for cases with primary open angle glaucoma, pseudophakic patients (after clear cornea incision phacoemulsification), cases in which very low IOP levels are needed, or cases in which there is objection to placement of a foreign body. [13] In all other cases, a GDD like the BGI may be considered, including primary surgeries.

However, factors like availability, experience with a surgical procedure and costs also play a role. Up till now, the higher costs of GDDs, including the BGI, has limited their usage in developing countries. New inventions like the Aurolab aqueous drainage implant, a cheap device that strongly resembles the BGI and was recently developed in India, may offer a reasonable alternative for these countries. [14]

In recent years, less invasive and minimally invasive, newer surgery procedures (MIGS) have come to the market. These new procedures claim to be safer than the traditional options, and are often used in combination with cataract surgery, earlier in the treatment algorithm. However, they are also very costly and mostly lead to IOP reductions in the mid/high teens. [15] Although strongly gaining popularity, the place of these newer devices and procedures within the treatment armamentarium of glaucoma has still to be established.

Although the BGI has amply proven its value, refinement of GDDs is also underway. Interpretation of results in literature, including the findings of this thesis, have paved the way for new designs, with smaller tube lumens and improved endplates. An example is the PAUL glaucoma implant, which has recently come to the market. [16] Also, new materials and combination with medications are being considered.

George Baerveldt must have been very satisfied with the impact his invention has had on the global community for the treatment of glaucoma and the prevention of blindness. He would also have been very interested in all new developments. However, unfortunately he is no longer among us and we cannot share the results of this thesis with him anymore.



ARVO 2010: Annelie Tan, George Baerveldt, Henny Beckers

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ADDENDUM

Dankwoord

DANKWOORD

De voltooiing van dit proefschrift zou niet tot stand gekomen zijn zonder de hulp van vele mensen. Een aantal mensen wil ik in het bijzonder bedanken.

Als eerste wil ik mijn promotor Prof. Dr. H.J.M. Beckers bedanken. Beste Henny, de basis van dit proefschrift werd tijdens mijn wetenschapsstage gelegd. Samen zaten we op een kamer in het Dr. Tansgebouw en met jou ben ik naar mijn eerste internationale congres gereisd waar er nog papieren posters gedragen moesten worden. Bij jou ligt de fundering van mijn glaucoom passie, zowel wetenschappelijk als klinisch. Dank dat je jarenlang achter mijn broek hebt gezeten en me bent blijven steunen. Het proefschrift was nooit zo mooi geworden zonder jouw begeleiding.

Mijn 2 andere promotoren: Prof. Dr. C.A.B. Webers en Prof. G.P.M. Luyten. Beste Carroll, dank voor het vertrouwen dat je in deze Belg had. Jouw systematische denkwijze en praktische aanpak hebben me veel bijgebracht. Beste Gré, ondanks dat je er bij mijn proefschrift langs de zijkant bij betrokken was, heb je me altijd gesteund om het af te krijgen. Je stortvloed aan (soms niet zo haalbare) ideeën waren altijd een inspiratiebron.

Dr. Tos Berendschot, mijn co-promotor. Al vroeg tijdens mijn geneeskunde studie ging mijn interesse uit naar de oogheelkunde. Samen met jou en John hebben we destijds een onderzoekje opgezet dat de retinale bloedvaten bij hypertensie patiënten onderzocht. Jouw eindeloze enthousiasme, je statistisch brein en nuchtere kijk hebben me altijd gefascineerd. Dankzij jou ben ook ik nu bedreven in de mixed model analyses.

De leden van de beoordelingscommissie: Prof. dr. W.H Backes, Prof. dr. A.E. Boonen, Dr. M.M. Dickman, Prof. dr. N.M. Jansonius en Prof. dr. N.E. Schalij-Delfos. Dank dat jullie bereid waren om mijn proefschrift kritisch te lezen en te beoordelen.

Prof. Dr. F. Hendrikse, het voormalige hoofd en de opleider van de Universiteitskliniek voor Oogheelkunde Maastricht. Dank dat u mij de kans gegeven hebt om dit promotietaject en de opleiding tot oogarts te starten.

Alle stafleden die bijgedragen hebben aan mijn opleiding tot oogarts: Carroll, Fleur, Henny, Igor, Isabelle, Jan, Martin, Noël, Peter, Roel Erckens, Roel Kloos, Rudy en Sascha in Maastricht en Eric, Eva, Paul, Rogier, Sander en Theresia in Eindhoven. Jullie hebben me opgeleid tot oogarts en ik dank jullie voor alle moeite die jullie daarvoor genomen hebben. Dank voor het vertrouwen dat jullie in mij hadden.

Mijn mede-onderzoekers Aukje, Elton, Hellen, Lukas, Margriet, Mari, Mor, Muriël, Nienke, Paul, Rob, Thijs, Frenne en Frank. Dank voor de gezellige lunch momenten op de Unie, de koffie pauzes, de zelfgemaakte tompoezen, de welkome afleiding na werktijd en de gezamenlijke congressen. Met velen van jullie heb ik ook mijn opleiding tot oogarts voltooid. We beleefden samen de nodige ups en downs. Het feit dat je er niet alleen voorstond, en er zielsverwanten waren schepte een band. Het is fijn dat we ondanks de afstanden ook nu nog goed contact hebben onderling!

Al mijn mede AIOS, met name mijn "lichting": Jelle, Agnes, Stefani, Vanessa, Koen en Diana, nu collega oogartsen. Met jullie heb ik lief en leed gedeeld, eerst nog op de oude poli en erna in de mooie oogtoren. Ochtendpoli's die tot ver in de middag doorliepen, memorabele AIOS vergaderingen en gezellige etentjes maken dat ik deze tijd als zeer intensief en prettig ervaren heb. Het feit dat er iemand tot feestsmurf benoemd werd, geeft aan dat het niet alleen maar *drama lama* was… Dank daarvoor!

Beste Yanny, wij kennen elkaar al sinds de periode in het Dr. Tansgebouw. Jij in Rudy zijn kamer, ik in die van Henny. Mijn 1ste phaco deed ik onder jouw supervisie. Wie had kunnen bedenken dat we in Leiden kamergenoten en de beste vriendinnen zouden worden. Jij altijd netjes, praktisch en voor alle problemen een oplossing. Ik met mijn rommelbureau waar jij probeerde orde in te scheppen… Jij zorgde ervoor dat er in onze kamer altijd een overlevingspakket was: chocolade, snoep, mango, macha, dadelcake, sesam tegen de grijze haren… We denken vaak hetzelfde en kunnen elkaars zinnen aanvullen. Het is superfijn dat jij naast mij wilt staan als paranimf.

Beste Mireille, je was bij dit onderzoek betrokken vanaf het allereerste begin. Wat hebben we veel cellen geteld en eindeloos achter de Visante gezeten om alle data te vergaren en te analyseren. Uren heb je in alle kwadranten het endotheel geteld en kreeg je patiënten verhalen tot in den treure mee. Ik ben je dankbaar voor al je hulp, je luisterend oor, de gezelligheid en je nuchterheid. Dank dat je vandaag, bij de verdediging van mijn promotie, mijn paranimf wilt zijn.

Mijn liefste Leidse collega's: Greetje, Gré, Irene, Jacco, Khanh, Leonoor, Marina, Nicoline, Stijn, Yanny, Yvonne, Elon, Jan-Willem, Camiel. Ik ben jullie enorm dankbaar dat ik in zo een warm bad terecht ben gekomen waar ik me op alle professionele gebieden kon ontplooien. Waar we ondanks alle drukke klinische en wetenschappelijke taken, elkaar ook persoonlijk zagen. We konden altijd bij elkaar terecht en hadden het gezellig. Jullie hebben me altijd met raad en daad bijgestaan en hebben de promotie struggles van dichtbij meegemaakt en hebben zelfs op het allerlaatst nog over de stellingen meegedacht. Daarnaast ook veel dank om altijd voor mij en de jongens klaar te staan! Jullie waren altijd bereid om samen te zoeken naar oppas mogelijkheden (bij jullie thuis, bij ons of in het LUMC). De stafgang was voor de jongens hun 2de thuis. Ook de vele ijsjes, stafdiners en borrels waren altijd gezellig. Ik mis jullie nu al! Aan mijn high tea vriendinnen, de volgende is in Houthalen!

Nicoline, een speciaal woordje van dank voor jou. Dank voor al je vertrouwen en je vriendschap. Jou op volgen als chef de poli leek een onmogelijke taak. Je hebt immers de bijzondere gave om overal een oplossing voor te verzinnen zonder een enkel detail over het hoofd te zien. Dank voor al je steun, de gevatte grapjes en constructieve discussies.

Aniki, als jonge klare kwam ik bij jou in het Erasmus voor een uveitis fellowship. Met alle vragen kan ik bij je terecht, waar ook ter wereld je bent. Meestal krijg ik dan een antwoord inclusief een foto van waar je op dat moment mee bezig bent. Ook jij bent me altijd blijven steunen in het promotietraject. Dank!

Juliette, Loes, Marlous, Michiel, Pauline en Valeria, medeauteurs van mijn artikelen. Rob Jongen, de eerste database was nog in Access, we eindigden met een mooi 10-jaars artikel. Dank voor al je hulp.

Ellen, Veronique, Annelies, Brigitta, Judith en Marlies. Dank voor jullie organisatorisch talent om elke afspraak gepland te krijgen in mijn volle agenda, jullie luisterend oor en jullie praktische en logische oplossingen voor mijn "complexe" problemen.

Alle medewerkers van de Oogheelkunde, het OK-complex, de interventie unit en de (kinder-) reumatologie in het LUMC, dank voor de prettige samenwerking! Het gevoel van samenhorigheid en jullie onuitputtelijke inzet is uniek.

Mijn toekomstige collega's in het Laurentius ziekenhuis: David, Diana, Hank, Marieke, Palwasha en Rutger. Ik kijk er naar uit om in jullie team te mogen werken!

Tanja en Nick, Desiree en Robin, Ghais en Ilona, onze vriendschap gaat terug tot ons eerste OWG. Dank voor jullie vriendschap, de jaarlijkse weekendjes weg zijn inmiddels legendarisch. We passen volgens mij inmiddels niet meer in 1 huisje met alle kinderen.

Con cảm ơn Bố mẹ, anh Yen và chị Luyen, anh Dung và chi Thrinh, và chú Lich và thím Van Anh đã luôn ủng hộ và luôn luôn sẵn sàng giúp đỡ. Con rất vui khi được nhìn thấy các cháu hoà đồng với nhau. Thời gian sắp tới các cháu sẽ chơi chung với nhau nhiều hơn và gia đình mình sẽ sum họp nhiều hơn ở nhà mới của vợ chồng con.

Yuhan en Lianne, het is niet met woorden te beschrijven hoe dankbaar en trots ik ben met jullie als broer en zus. Jullie sportieve inzet en volharding hebben me doen beseffen dat alles mogelijk is in het leven, als je je er maar goed genoeg voor inzet en je niet opgeeft. Het blijft vertrouwd en fijn om met jullie over badminton en andere dingen te praten die niets met oogheelkunde of dokter zijn te maken hebben. Want wat weet een simpele oogarts daar nu van… En ondanks jullie

drukke schema's, maken jullie altijd tijd voor mij! In de schaduw staan van een bekende broer en zus is overigens ook goed voor mijn nederigheid. Yuhan en Willemijn, ook voor jullie wordt dit een spannend jaar met veel veranderingen. Het is fijn om deze nu dichterbij (letterlijk) te mogen meemaken. Lianne en Indra, in Parijs zitten wij op de eerste rij!

Lieve mam en pap. Dank voor jullie onuitputtelijke liefde, vertrouwen en steun. Jullie hebben me laten zien dat je met hard werken veel kan bereiken. Er is voor jullie nooit iets teveel en ik kan altijd op jullie hulp, relativering en wijs advies rekenen. De afgelopen jaren zijn jullie vaker komen logeren in Voorschoten. Ik ben jullie enorm dankbaar dat ik in zo een liefdevol gezin heb mogen opgroeien en ben blij dat jullie dezelfde normen en waarden ook aan de jongens doorgeven.

Lieve Lai, al jaren ben je mijn zielsverwant. Wat hebben we al veel meegemaakt samen, van zuur-base evenwicht tot opvoedkwesties en feng shui. Wetenschap heeft ook jou altijd geboeid en samen konden we er goed over sparren! Je leerde me soms dat er ook puur zakelijke dingen zijn en maakt van elke aankoop een afding feestje. We hebben prachtige reizen gemaakt. Wat kijk ik er naar uit om meer tijd met elkaar door te kunnen brengen in ons nieuwe paleisje. Dank voor al je liefde!

Natan en Fabian, mijn ondeugende jongens. Mama haar boek is af, we kunnen nu gaan genieten in ons nieuwe huis. Lieve Natan, mijn grote, sportieve en wijze jongen. Je bouwt in no time de meest ingenieuze LEGO bouwwerken waar mama niet eens van weet hoe je het überhaupt kan verzinnen. Blijf zo vrolijk en nieuwsgierig als je bent. Lieve Fabian, wat ben jij een energieke en eigenwijze jongen. Dol op lezen, spelletjes spelen en knuffelen (en pasta). Met je eerlijkheid en enthousiasme pak je iedereen in. Jij geeft nooit op… nu nog leren eten! Mama is fier op jullie en kijkt er naar uit om nog meer avonturen te beleven.

Het oog, Natan 3 jaar

ADDENDUM

Curriculum vitae

CURRICULUM VITAE

Annelie Nathanaele Tan was born on October 9th 1984 in Bilzen, Belgium. After finishing high school at the Heilig Graf instituut (mathematics-science) in Bilzen, she started medical school in 2003 at Maastricht University, the Netherlands. During medical school she was offered a place in the honours program international track medicine with internships in the United Kingdom, Australia and Belgium. She received her medical degree in May 2009. She developed interest in the field of Opthalmology and she started a scientific research project under supervision of Dr. T.T.J.M. Berendschot and Dr. J. de Brabander in 2006. During medical school she completed senior clinical internships in ophthalmology at the University clinic in Ghent, Belgium and at the University Eye Clinic Maastricht. Her scientific internship started in 2008 under supervision of Prof. dr. H.J.M. Beckers and Prof. dr. C.A.B. Webers and was the beginning of this doctoral thesis which she started in June 2009. In December 2009 she started her residency in Ophthalmology at the University Eye Clinic Maastricht and Catharina hospital in Eindhoven. The author continued her PhD project during her residency and thereafter and presented her work at various meetings and conferences. In December 2014 she became an ophthalmologist and from January 2015 onwards she was appointed a staff position at Leiden University Medical Center, The Netherlands. Her subspecialties were glaucoma and uveitis. Meanwhile she completed a uveitis fellowship (2015) under supervision of Prof. dr. A. Rothova at Erasmus MC and worked at Bronovo hospital (October 2015-June 2016). In 2021 she became medical manager of the outpatient clinic at Leiden UMC. From March 2023 onwards, she will start working in Laurentius Hospital in Roermond, the Netherlands. Currently the author is living in Voorschoten with her husband Lai and her sons Natan and Fabian.

ADDENDUM

List of publications

LIST OF PUBLICATIONS

Tan AN, Hoevenaars JG, Webers CAB, Damato B, Beckers HJM.
Baerveldt implant for secondary glaucoma due to iris melanoma.
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Long-term outcomes of Baerveldt glaucoma drainage implants: 10 years real-world results
Submitted

Natan - Januari 2023