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Canaloplasty for Treatment of Open Angle Glaucoma

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Abbreviations

BCVA	Best Corrected Visual Acuity
ICG	Indocyanine green
IOP	Intraocular pressure
MIST	Micro-invasive suture trabeculotomy
Nd: YAG	Neodymium-doped yttrium aluminium garnet
NPGS	Non-penetrating glaucoma surgery
OAG	Open angle glaucoma
SC	Schlemm’s canal
TDM	Trabeculo-Descemet membrane
TM	Trabecular meshwork
TSCPC	Transscleral cyclophotocoagulation

1. Introduction and aim of work

1.1. Glaucoma

1.1.1. Definition

The term “glaucoma” refers to a large number of diseases. The common feature of all glaucomas is a distinctive progressive optic neuropathy, which derives from various risk factors. Glaucomatous optic neuropathy is associated with a gradual loss of the visual field, which can lead to total, irreversible blindness if the disorder is not diagnosed and treated properly (Azuara-Blanco et al., 2001). Glaucomatous optic neuropathy is not the disease; it is the end-result of several as yet unidentified cellular disease processes (Schacknow and Samples, 2010).

Historically, glaucomatous eyes were hardly to recognize till the invention of ophthalmoscopy by Helmholz in the nineteenth century, and its use by Albrecht von Graefes to describe the atrophy and cupping of the optic nerve head (Shaffer, 1996). As our understanding of the disease pathomechanisms increases and technology advances, treatment strategies become more sophisticated.

1.1.2. Epidemiology

Glaucoma is the second leading cause of blindness worldwide after cataract, with approximately 8.4 million people bilaterally blind from glaucoma (Quigley and Broman, 2006). Glaucoma is estimated to affect about 60.5 million people worldwide representing 2.65% of the adult population older than 40 years in 2010 (Quigley and Broman, 2006, Resnikoff et al., 2004). In Germany, glaucoma is estimated to be the third leading cause of blindness in 2000 with an incidence of 1.6/100,000 (Krumpaszky et al., 1999). Twenty percent of all cases of legal blindness in people aged 75 years and older were due to glaucoma (Krumpaszky et al., 1999).

1.1.3. Anatomy of the anterior chamber angle

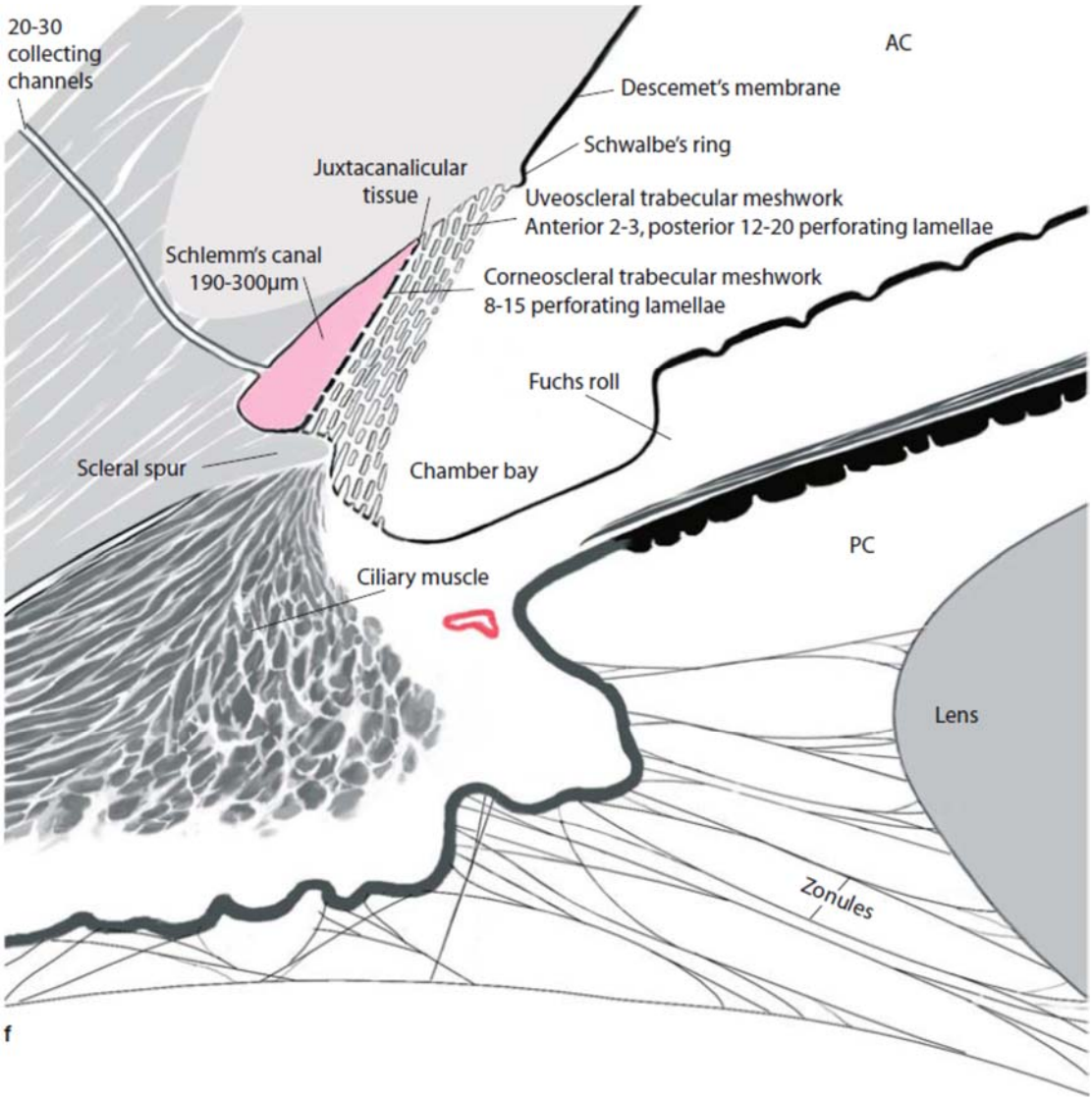

Figure (1) Microanatomy of iris root, trabecular meshwork: Fuchs' roll (*FR*), uveocorneal (*UC*) and scleral corneal portion (*SC*) of trabecular meshwork, collector channels (*CC*), scleral spur (*SS*), ciliary muscle (*CM*), Schwalb's line (*SL*), Schlemm's canal (*pink*); ciliary arterial circle of ciliary body (*red*) may be located in front of the ciliary muscle, but usually is embedded in the ciliary muscle. Note that the thinnest portion of the iris is located peripheral to Fuchs' roll.(Naumann et al., 2011)

The anterior chamber angle as viewed by gonioscopy (Alward and Allen, 1994, Kanski, 2007):

- Root of the iris

The iris generally inserts at a variable level into the face of the ciliary body.

-Anterior border of ciliary body

There are two major muscle groups in the ciliary body: the circular muscle fibers, which are responsible for accommodation, and the longitudinal muscle fibers, which control the outflow of aqueous by pulling open the trabecular meshwork and Schlemm's canal.

- Scleral spur

The longitudinal muscle of the ciliary body attaches to the scleral spur and opens the trabecular meshwork by pulling on the Trabecular Meshwork.

-Trabecular meshwork

It is a sieve-like structure at the angle of the anterior chamber extending between the scleral spur and Schwalbe's line and it is composed of the following three portions:

a *Uveal meshwork* is the innermost portion and consists of cord-like endothelial cell-covered strands arising from the iris and ciliary body stroma, and extending from the root of the iris to Schwalbe's line. The intertrabecular spaces are relatively large and offer little resistance to the passage of aqueous.

b *Corneoscleral meshwork* forms the larger middle portion which extends from the scleral spur to Schwalbe's line. The layers are sheet-like and composed of connective tissue strands also with overlying endothelial-type cells. The intertrabecular spaces are smaller than those of the uveal meshwork, conferring greater resistance to flow.

c *Juxtacanalicular (cribriform) meshwork* is the outer part of the trabeculum, and links the corneoscleral meshwork with the endothelium of the inner wall of the Schlemm's canal. This offers the major proportion of normal resistance to aqueous outflow, consisting of cells embedded in a dense extracellular matrix with narrow intercellular spaces.

-Schlemm's canal

A circumferential 190-350 μm diameter tube at the base of the scleral sulcus, Schlemm's canal collects aqueous and drains it into the venous system. Schlemm's canal is bridged by septa, which provide some support.

-Schwalbe's line

Schwalbe's line occurs in a 50-150 μm transition zone (zone S) between the trabecular meshwork and the corneal endothelium. It is the anterior border of the trabecular meshwork and the posterior border of Descemet's membrane.

1.1.4. Flow of aqueous humor

Aqueous humor is produced by the ciliary body and is secreted into the posterior chamber. Most of this fluid then flows into the anterior chamber and drains out of the chamber angle via one of two outflow pathways (Alward and Allen, 1994, Choplin and Lundy, 2007a, Kanski, 2007):

Trabecular (conventional) route:

Approximately 90% of aqueous outflow is through the trabecular meshwork. This flow is pressure-dependent, increasing as intraocular pressure increases. Aqueous humor flowing through the trabecular meshwork enters Schlemm's canal and from there flows into the scleral, episcleral, and conjunctival venous systems. For aqueous to exit the eye by this route, the intraocular pressure must be higher than the episcleral venous pressure. At pressures below episcleral venous pressure (8-15 mm Hg) all aqueous outflow must be via non-conventional routes.

Uveoscleral (unconventional) route:

Accounts for the remaining 10% in which aqueous passes across the face of the ciliary body into the suprachoroidal space and is drained by the venous circulation in the ciliary body, choroid and sclera.

1.1.5. Classification of glaucoma

Based on the newest guidelines of the European Glaucoma Society, glaucoma is classified as follows (Society, 2014):

1. Primary congenital forms

-Primary congenital glaucoma / childhood glaucoma

-Glaucoma associated with congenital anomalies

2. Primary open-angle glaucoma

-Primary juvenile glaucoma.

-Primary open angle glaucoma / high-pressure glaucoma

-Primary open angle glaucoma / normal-pressure glaucoma

-Primary open angle glaucoma – suspect

3. Secondary open angle glaucoma

-Secondary open angle glaucoma caused by ocular disease

-Exfoliative glaucoma

-Pigmentary glaucoma

-Lens induced secondary open angle glaucoma.

-Glaucoma associated with intraocular hemorrhage

-Uveitic glaucoma

-Glaucoma due to intraocular tumors

-Glaucoma associated with retinal detachment.

-Open angle glaucoma due to ocular trauma

-Iatrogenic secondary open angle glaucoma

-Glaucoma due to corticosteroid treatment

-Secondary open angle glaucoma due to ocular surgery and laser

-Glaucoma caused by increased episcleral venous pressure

4. Primary angle closure

-Acute angle closure

-Intermittent angle closure

-Chronic angle closure

-Status post acute angle closure attack

5. Secondary angle closure

-Secondary angle closure with papillary block

-Secondary angle closure with anterior “pulling” mechanism without papillary block:

e.g. neovascular glaucoma, peripheral anterior synechia, etc.

-Secondary angle-closure with posterior “pushing” mechanism without papillary block:

e.g. Aqueous misdirection glaucoma, iris and ciliary body cyst, silicon oil or gas tamponade implanted in the vitreous cavity, uveal effusion syndrome, retinopathy of prematurity (Stage V).

1.1.6. Spectrum of glaucoma

Glaucoma is a wide spectrum of clinical entities that include many ocular and systemic conditions. At one end of this spectrum is the quiet, painless eye of a patient with primary open-angle glaucoma who may be unaware of his disease. Because of its quite slow progression of optic nerve damage, glaucoma is

commonly called the “silent thief of vision” and patients may not present until late stage of disease. At the other extreme is the patient with acute angle closure glaucoma who presents with eye pain, decreased vision, and possibly even systemic symptoms such as nausea and vomiting (Choplin and Lundy, 2007b).

Being the commonest form of glaucoma in Europe and worldwide (Quigley and Broman, 2006) , primary open angle glaucoma was a main focus of research in the last decades.

1.1.7. Pathophysiology of aqueous outflow resistance in open angle glaucoma

The exact site of aqueous outflow resistance in glaucoma is still unclear and continues to be an area of intense study (Tombran-Tink et al., 2008). Histological, experimental, and theoretical studies of the aqueous outflow pathways point toward the juxtacanalicular region and inner wall of Schlemm’s canal as the likely site of highest aqueous outflow resistance. It forms at least 50% of the aqueous outflow resistance in normal eyes and the bulk of the pathologically increased resistance in glaucomatous ones (Johnson and Johnson, 2001, Grant, 1963). In the memorable experiment of Morton Grant, he tried to find out the point of greatest outflow resistance in the Schlemm’s canal. He dissected the trabecular meshwork in enucleated human eyes so that the depth of dissection was correlated with perfusion of the same eye to measure outflow facility. Grant used a perfusion pressure so that the IOP is kept between 15-25mmHg. There was no change in the outflow resistance until he penetrated the inner wall of Schlemm’s canal. He thus found that approximately 75% of the resistance to aqueous outflow was either at or just proximal to the inner wall of the canal in both healthy human eyes and those with open-angle glaucoma (Grant, 1963). He concluded that bypassing the proximal resistance of the anterior wall of Schlemm’s canal with a technique such as trabeculotomy could eliminate ¾ of the aqueous outflow resistance in eyes with glaucoma.

1.1.8. Current treatment concepts for glaucoma

Lowering intraocular pressure (IOP) is currently the only option proven to be effective to slow or halt the deterioration of visual function in glaucoma (Garway-Heath et al., 2015).

A long time ago, the debate arose on whether to consider a primary surgery for open angle glaucoma or to follow the conventional practice pattern of firstly offering the medical treatment, and in some cases the laser treatment for patients. Medical therapy is still the first line of treatment in the developed world, while in poor countries surgery may come as a first treatment option, where non compliance to therapy and costs of a long term medical treatment may be unaffordable. Lichter el al did not find a significant benefit from the aggressive primary trabeculectomy surgery for open angle glaucoma after 4 years, compared with the primary medical treatment (Lichter et al., 2001). In contrast, Jay et al (Jay and Murray, 1988) concluded that early operation provides a significantly better protection of the visual field. Moreover Hitchings (Hitchings, 1993) stated that a long period of local medical treatment for glaucoma could be a risk factor for failure of filtration glaucoma surgery because of chronic irritation to the conjunctiva and the episclera. In concordance, Sherwood et al (Sherwood et al., 1989) found a significant increase in the number of macrophages, lymphocytes, and fibroblasts in the conjunctiva and Tenon's capsule in patients who received long term glaucoma topical therapy. This may stimulate the unwanted excessive healing at the site of surgery. It is known that a healed trabeculectomy is a failed one.

The problem remains to weigh between the potency of different therapeutic modalities to halt the progression of glaucoma and the risk of potential complications. It can be argued, that the risk of complications is higher for surgical procedures than medications. However, the common use of the "maximum *tolerated* medical therapy" results in poor adherence, ocular irritation and greater financial burden for the health system.

Bylsma (Bylsma, 1999) suggested that if the safety margin of glaucoma surgery could be increased significantly without sacrificing efficacy, surgical intervention for glaucoma might be considered earlier.

1.2. Surgical treatment of glaucoma

Until recently, the surgical options were limited to filtration surgery including trabeculectomy or glaucoma drainage devices such as the Ahmed glaucoma valve, the Baerveldt implant, or the Molteno implant. Currently, trabeculectomy with or without antimetabolites such as 5-fluoruracil or mitomycin-C is still considered the gold standard for surgical lowering of intraocular pressure. Results of new glaucoma surgical techniques still have to be validated in reference to the IOP lowering efficacy and safety of trabeculectomy.

1.2.1. Trabeculectomy

Cairns first published a description of trabeculectomy technique 1968 (Cairns, 1968). Trabeculectomy is designed to divert aqueous from the anterior chamber to the subconjunctival space. The success of the procedure depends upon aqueous flowing to the subconjunctival space, distributing within the space, and being reabsorbed. The main disadvantage of the subconjunctival space as an aqueous outflow-rout is that, the resistance to aqueous outflow depends on the variations in the wound-healing response of Tenon's tissue. This makes the results highly unpredictable. Antifibrotic agents such as mitomycin-C (Reibaldi et al., 2008) and 5-fluoruracil (Koutsonas et al., 2013) have been introduced to modulate the wound healing response (Lama and Fechtner, 2003). However, the effect of anti-fibrotic therapy is nearly as unpredictable as the wound-healing response itself (Tombran-Tink et al., 2008).

Trabeculectomy technique has well known problems and complications as well. In about up to 30% of cases, trabeculectomy fails to achieve adequate intraocular pressure lowering (Jampel et al., 2012). Furthermore, Increased IOP is not an uncommon postoperative complication. This usually occurs as a result of occlusion of the fistula internally by hemorrhage, fibrin, vitreous incarceration,

a plug of iris or retained viscoelastic material. Rarely, increased IOP might be the result of a postoperative malignant glaucoma.
Hypotony due to excessive filtration is another typical complication after filtering surgery. Prolonged hypotony can cause visual impairment due to macular folds, macular edema or choroidal hemorrhage (Vijaya et al., 2011). Blebitis is a rare but potentially sight-threatening complication that can lead to endophthalmitis, if not treated appropriately. Also, cataract formation (Jampel et al., 2012) can be accelerated after trabeculectomy. Additionally, trabeculectomy necessitates longer inpatient period and frequent follow-up visits.(Drake, 1992, Kanski and Bowling, 2011)

1.2.2. Non-penetrating glaucoma surgery

Meanwhile, non-penetrating glaucoma surgery (NPGS; deep sclerectomy and viscocanalostomy) has been developed seeking for a better safety compared to trabeculectomy. However, the improved safety profile of these procedures comes at the expense of worse IOP lowering effect.

The efficacy of NPGS depends on filtration of aqueous through a trabeculo-descemet membrane (TDM) into a suprachoroidal scleral lake. Viscocanalostomy depends moreover on a local deroofing and viscodilation of Schlemm's canal through injection of viscoelastic substance into two surgically created ostia in the canal (Shaarawy et al., 2003). In the classic viscocanalostomy described by Stegmann, the superficial scleral flap has to be tightly sutured in order keep the viscoelastic substance in situ and to force aqueous percolation into the created sclera lake (Stegmann et al., 1999). Sharaawy described a loose suturing of the superficial sclera flap trying to use the subconjunctival space as an additional outflow route and thus theoretically increasing the chance of success (Shaarawy et al., 2003).

Nevertheless, insufficient filtration through the TDM is common, and so, Nd:YAG laser goniopuncture is often required to open the TDM window, thus

converting the procedure from NPGS into a fistulating one (Alp et al., 2010, Anand and Pilling, 2010).

1.3. Canaloplasty

Canaloplasty has been developed on the basis of viscocanalostomy. It aims to a more anatomical restoration of aqueous outflow pathway with a notably high safety profile. Recent advances in technology have enabled the development of a device that allows 360° cannulation of Schlemm's canal in order to expand the entire circumference with viscoelastic and also to allow a suture to be delivered within the canal. The function of the suture is to exert centripetal force maintaining expansion of the canal. This approach enhances physiologic aqueous outflow through the natural pathway in contrast to trabeculectomy which relies on an artificial fistula diverting aqueous outflow to the subconjunctival space.

1.3.1. Surgical technique

Lewis et al (Lewis et al., 2007) first described the technique for canaloplasty. Briefly, a one-half thickness scleral flap is dissected. A deep flap is then dissected down to a depth very close to the ciliary body/choroid and carefully carried forward anteriorly until Schlemm's canal is unroofed. The ostia of the canal are then carefully dissected and viscodilated to allow easy access of the microcatheter. The deep flap dissection is then further carried forward into clear cornea to expose a small segment of Descemet's membrane creating a trabeculeo-descemetic window. A specially designed microcatheter (iTrack, iScience Interventional, Menlo Park, California, USA) is then circumferentially introduced into Schlemm's canal. The beacon tip of the microcatheter is illuminated by a laser-diode based microillumination system (iLumin, iScience Interventional, Menlo Park, California, USA). A 10-0 polypropylene (Prolene) suture is tied to the catheter tip, after the entire canal has been catheterized.

The catheter is then retracted into the canal in a smooth continuous movement. As the tip and the suture are retracted, Healon GV (Advanced Medical Optics, Santa Ana, California, USA) is injected every 2 clock hours through an inbuilt viscoelastic injector. The polypropylene suture in the canal is tightened, causing distention of the trabecular meshwork inwards and further distention of the canal. This can be verified intraoperatively using the i-Ultrasound system enabling accurate suture tensioning. After satisfactory tightening of the suture has been achieved, the deep flap is excised creating a scleral lake. The superficial flap is then closed tightly with good tissue apposition to achieve a watertight closure.

Canaloplasty is often combined with cataract surgery, which might increase the efficacy of the procedure (Lewis et al., 2009, Lewis et al., 2011, Lewis et al., 2007, Shingleton et al., 2008).

1.3.2. IOP lowering mechanisms

Although the exact mechanism of IOP lowering effect of canaloplasty is not clearly understood, an improvement of the Schlemm's canal outflow facility seems to be the main mechanism of action. The 360 degree catheterization and the viscodilation dissect the septa within the canal and cause a permanent dilatation. Tensioning of the canal through the suture keeps it open, so that the flow of aqueous can travel into the canal circumferentially, then to the collector channels and aqueous veins. It is assumed that it also increases the permeability of the trabecular meshwork similarly to pilocarpine (Lewis et al., 2007). Lewis et al compared the results of canaloplasty with and without insertion of a tensioning suture into Schlemm's canal (Lewis et al., 2007). Cases without the suture achieved a mean IOP reduction of 24% after 12 months, compared to 40% in cases with canal distention.
The percolation of aqueous through the Descemet window into the scleral lake plays an important role for the IOP decrease. An enhanced aqueous humor

filtration through the sclera and conjunctive is assumed because of the increased conjunctival microcysts formation after canaloplasty (Brusini, 2014). A conjunctival bleb can be seen, if the sclera flap is not sutured water-tight. If this bleb does not disappear with time, one can assume that the IOP lowering effect of the procedure is mediated by the unintended filtration.

The difficulty to determine the exact mechanism of canaloplasty lies in our inability to monitor the exact aqueous outflow routes. It has been attempted to visualize the aqueous outflow routes through injecting fluorescein in the anterior chamber (Benedikt, 1976). Grieshaber et al. injected fluorescein sodium tracer directly into the Schlemm's canal through a microcatheter. The so called canalography permits video recording and evaluation of the aqueous outflow pathway (Grieshaber et al., 2009). However, since the dye is directly injected into the Schlemm's canal, the aqueous outflow properties of the inner wall of the canal cannot be assessed with this technique. The dye is also prone to leak into the anterior chamber and the suprachoroidal space rather to completely follow the natural outflow route. Recently, Zeppa et al. injected indocyanine green (ICG) coupled with a viscoelastic solution using a microcatheter into the Schlemm's canal in 10 patients undergoing canaloplasty. The distribution of the dye was monitored with near-infrared light (Zeppa et al., 2016). However, the speed and pressure of the injection, the effect of the cannulation and the intra operative pressure fluctuation were factors that affected the results. It is still not possible to assess the aqueous outflow in vivo.

1.3.3. Potential candidates

The most promising results with canaloplasty have been achieved in patients with primary open angle glaucoma, pseudoexfoliation glaucoma and pigmentary glaucoma (Brusini, 2014). Canaloplasty can also be successfully performed in patients with failed trabeculectomy in whom Schlemm's canal has been left undamaged from previous filtrating surgeries (Brusini and Tosoni, 2014).

1.3.4. Contraindications

Canaloplasty is contraindicated in patients with angle closure glaucoma (although it can be still considered in some patients after a laser or surgical iridectomy). Eyes with damaged Schlemm's canal during previous ocular surgery or extensive laser trabeculoplasty with peripheral anterior synechiae are not suitable candidates for canaloplasty. Also, ocular hypertension due to an increased episcleral venous pressure and other forms of secondary glaucomas are contraindications for canaloplasty (Brusini, 2014, Godfrey et al., 2009).

1.3.5. Current results

The first comprehensive evaluation of canaloplasty was presented by Lewis et al (Lewis et al., 2011). They have included 157 eyes with open angle glaucoma in their study. Patients with angle closure and uveitic glaucoma, as well as patients who had undergone more than two laser trabeculoplasties were excluded. The mean IOP decreased from 23.8 ± 5.0 mmHg on 1.8 ± 0.9 medications to 15.2 ± 3.5 mmHg on 0.8 ± 0.9 medications. This was a decrease of 36.1% of the mean IOP. In 30 eyes canaloplasty was combined with phacoemulsification. Phaco-canaloplasty achieved an IOP decrease from 23.5 ± 5.2 mmHg on 1.5 ± 1.0 medications to 13.6 ± 3.6 mmHg on 0.3 ± 0.5 medications at three years postoperatively representing a 42.1% reduction of the mean IOP. However, the IOP lowering effect of the combined procedure was not significantly superior to that of the stand alone operation.

In another study, Brusini reported 4 years results of 214 eyes who underwent canaloplasty (Brusini, 2014). The mean IOP decreased from a mean of 29.4 ± 7.9 mmHg under 3.3 ± 0.9 medications preoperatively to 17.0 ± 4.2 mmHg under 1.3 ± 1.5 medications postoperatively. However, 17 patients underwent

trabeculectomy after 3 to 58 months after canaloplasty because of poor IOP control.

Similar results were achieved by Bull et al. in a prospective study which included 109 patients with a 3-years follow-up (Bull et al., 2011). Mean IOP at baseline was 23.0 ± 4.3 mmHg under 1.9 ± 0.7 medications which decreased to 15.1 ± 3.1 mmHg on 0.9 ± 0.9 medications at 3 years postoperatively.

1.3.6. Safety

One of the major advantages of canaloplasty is the absence of the usual vision-threatening complications of filtrating glaucoma surgery, such as choroidal detachments, shallow or collapsed anterior chambers, and prolonged hypotensive periods (Koerber, 2012). Nevertheless, a series of operative difficulties and complications which are specific for canaloplasty have been described. Canaloplasty is a surgically challenging technique. It needs a relatively long learning curve and special surgical skills when compared to trabeculectomy. Unsuccessful circumferential Schlemm's canal catheterization is reported to range between 10% and 26% (Brusini, 2014, Bull et al., 2011, Grieshaber et al., 2010c, Lewis et al., 2009, Lewis et al., 2011, Lewis et al., 2007, Shingleton et al., 2008). This is attributed mostly to surgical inexperience or anatomical obstacles such as stenosis of Schlemm's canal or deviation of the microcatheter into the anterior chamber or into a collector channel. Other postoperative complications reported in the literature include suture 'cheese-wiring through the trabecular meshwork in up to 12%, Descemet's membrane detachment in up to 9.1%,(Brusini, 2014, Grieshaber et al., 2010c, Lewis et al., 2011, Lewis et al., 2007) and hyphema in up to 70% (Bull et al., 2011, Grieshaber et al., 2010c, Lewis et al., 2009, Lewis et al., 2011, Shingleton et al., 2008) Hyphema is generally transient and resolves within a week in the majority of cases.

1.4. Aim of work

Most published reports assessed the short- and (Brusini, 2014, Bull et al., 2011, Grieshaber et al., 2011a, Koerber, 2012, Lewis et al., 2011, Shingleton et al., 2008) midterm results of canaloplasty (Shingleton et al., 2008, Grieshaber et al., 2011a, Koerber, 2012). In the first study of this thesis, we discuss the long-term safety and efficacy of canaloplasty. This is the longest follow up for canaloplasty in the literature.

The main intraoperative complications of canaloplasty are the failure to perform a 360° catheterization of Schlemm's canal or the inability to introduce a tensioning suture within the canal. In the second study of this thesis, we studied the conversion of canaloplasty into trabeculotomy as a method to deal with these complications.

2. Results and Discussion

2.1. [Treatment efficacy and safety of canaloplasty for open-angle glaucoma after 5 years. (Voykov B., Blumenstock G, Leitritz MA, Dimopoulos S, Alnahrawy O., published in Clin Exp Ophthalmol)](Voykov et al., 2015a)

Introduction

Circumferential viscodilation and tensioning of Schlemm's canal with a flexible microcatheter (canaloplasty) is one of the recent advances in non-penetrating glaucoma surgery. It seeks to improve the outflow of aqueous humor through the trabecular meshwork and a Descemet window into and around Schlemm canal and out through the collector channel system. (Shingleton et al., 2008)

Thus, in theory, canaloplasty restores the trabeculocanalicular outflow pathway. However, suture tensioning of Schlemm canal may also alter the anatomy of the trabecular meshwork (Brusini, 2014, Grieshaber et al., 2010b). It has been proposed that this alteration might offer mild, late reduction of intraocular pressure (IOP) remotely after surgery (Grieshaber et al., 2010b). Another possible outflow mechanism in canaloplasty involves the intra-scleral space created after excision of the deep scleral flap. From here, an enhanced aqueous humor filtration across the sclera and conjunctiva has been observed (Mastropasqua et al., 2012). The exact contribution of each mechanism is not clear. Nevertheless, published data demonstrate good efficacy and safety of canaloplasty in the short and mid-term (Grieshaber et al., 2010b, Lewis et al., 2011, Bull et al., 2011, Brusini, 2014, Lewis et al., 2009, Lewis et al., 2007, Shingleton et al., 2008, Mastropasqua et al., 2012). However, anatomical changes in the trabecular meshwork and/or the intra-scleral space might be causes of failure in the long-term as seen in the course of non-penetrating deep sclerectomy for example (Roy and Mermoud, 2006). That has aroused our interest to investigate, if there is a decline of efficacy of canaloplasty in controlling open-angle glaucoma in the long-term. In the present study, the safety and efficacy of canaloplasty in the treatment of adult patients with open-angle glaucoma (OAG) were investigated.

Patients and Methods

In this study, all medical records of consecutive patients who underwent canaloplasty after January 2009 in the Centre for Ophthalmology at the University Hospital Tübingen were reviewed. Inclusion criteria included diagnosis of insufficiently controlled open-angle glaucoma (OAG) on maximal tolerated medical therapy and a minimum follow-up of five years. Exclusion criteria included all other forms of glaucoma and previous intraocular surgery except phacoemulsification. Previous cyclophotocoagulation was not an exclusion criterion. Patients that underwent filtration surgery were considered as

failure. Written informed consent was obtained after a comprehensive discussion of the experimental nature of the procedure from all patients before surgery. We documented age at surgery, gender, type of glaucoma, preoperative and postoperative best corrected visual acuity (BCVA), intraocular pressure, number of glaucoma medications, lens status, and intra- and postoperative complications for each patient. Combination glaucoma medications were enumerated as individual medications.

This work adhered to the tenets of the Declaration of Helsinki and the requirements of the local institutional review board.

Operative technique

The surgical procedure followed the technique described by Lewis et al (Lewis et al., 2007). Briefly, after conjunctival dissection at the 12 o'clock limbus, a non-penetrating two-flap dissection of the sclera was prepared to expose Schlemm's canal. The iTrack-microcatheter (Ellex iScience, Inc., Fremont, CA, USA) was used to dilate the full circumference of the canal. Dilation was facilitated by the injection of 1.4% sodium hyaluronate (Healon GV, Advanced Medical Optics, Inc., Santa Ana, CA). After circumferential catheterisation, a 10-0 Prolene suture (Ethicon, Inc., Somerville, NJ) was tied to the microcatheter tip and the device was withdrawn, pulling the suture into the canal. Then, the suture was cut from the microcatheter and the two ends were tightened to distend the trabecular meshwork inward. The deep flap was excised and the superficial flap and conjunctiva were sutured watertight.

Efficacy

The success of surgical outcome was defined as complete when no additional medication was required or qualified when additional medication was required to achieve the specific IOP definition. Success was also defined at two IOP cut-off points (IOP ≤ 21 mm Hg and IOP ≤ 18 mm Hg, and at least a 25% reduction

from baseline). These cut-off points were used in order to allow comparison with previous studies on canaloplasty. Three specific time points were used to define success outcomes: at one, three and five years after surgery.

Statistical analysis

Continuous data were compared by analysis of variance (Student's t-test). Contingency table analysis and logistic regression were used to evaluate factors potentially associated with success and failure. Values for *p* of less than 0.05 were considered to reflect significant differences. The statistical analysis was performed with the JMP 11.0 statistical package (SAS Institute Inc., Cary, NC, USA).

Results

Demographics

Canaloplasty was performed in 60 eyes in the observed period. Of those, 20 had a follow up of at least five years and fulfilled the inclusion criteria. Only these eyes were included for further analysis. Demographic characteristics of the patients included are summarised in table 1. None of the eyes underwent canaloplasty combined with cataract surgery. Two eyes had undergone a single transscleral cyclophotocoagulation three and five years before canaloplasty.

Demographic	Value
General	
Eyes, n (%)	20
Right	7 (35)
Left	13 (65)
Women, n (%)	11 (55)
Men, n (%)	9 (45)
Age (y)	
Mean ± SD	60 ± 11
Range	44-82
Diagnosis, n (%)	
POAG	15 (75)
Pigmentary glaucoma	2 (10)
Exfoliation glaucoma	2 (10)
Uveitic glaucoma	1 (5)
Baseline	
IOP, mm Hg	
Mean ± SD	25.7 ± 6.6
Mean medications ± SD	3.4 ± 0.5
Previous glaucoma surgery, n (%)	2 (10)
Transscleral cyclophotocoagulation	2 (10)
Phakic, n (%)	14 (70)
Pseudophakic, n (%)	6 (30)
BCVA (LogMAR) ± SD	0.27 ± 0.35

Table 1. Patients' demographics.

IOP and Antiglaucoma Medications

Figures 2 and 3 show the efficacy results.

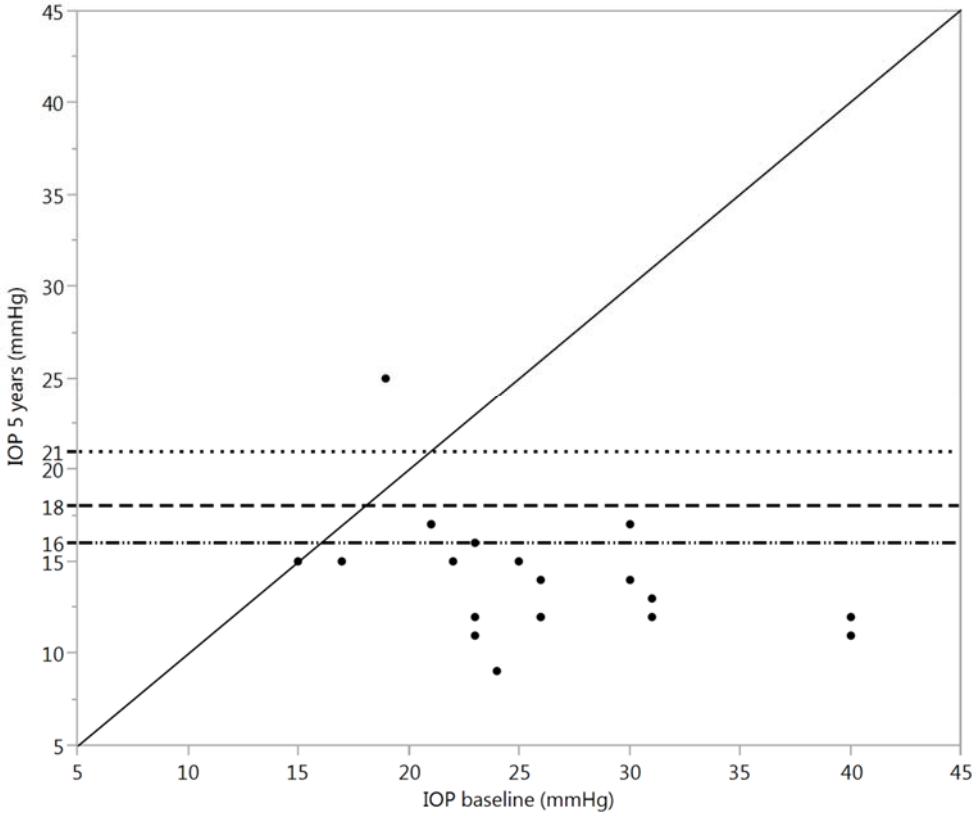

Figure (2) Scatter diagram of pre and postoperative IOP at 5 years with different cut off points (≤16, ≤18 and ≤21 mmHg).

The mean IOP decreased from 25.7 ± 6.6 mmHg (standard deviation [SD]) at baseline to 15.5 ± 3.8 mmHg (n=19) at one year (p<0.001), 15.1 ± 4.4 mmHg (n=18) at three years (p<0.001), and 14.2 ± 3.4 mmHg (n=18) at five years (p<0.001). The differences between one, three and five years were not significant. Mean number of medications decreased from 3.4 ± 0.5 at baseline to 1.5 ± 1.6 at one year (p<0.001), 1.6 ± 1.4 at three years (p<0.001), and 1.7 ± 1.3 at five years (p<0.001).

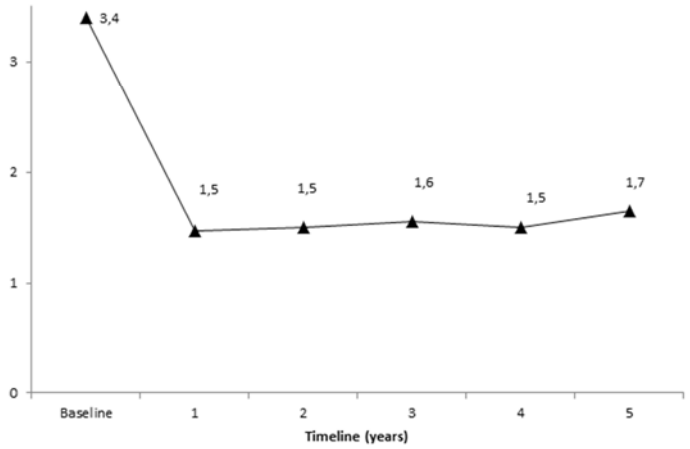

Figure (3) Mean number of medications at different time points.

Visual acuity

BCVA decreased from 0.27 logMAR at baseline to 0.28 logMAR at three years (p=0.58) and 0.47 logMAR at five years (p=0.06).

Success

Success results for the different time periods and definitions are presented in table 2.

Complete and qualified success rates were 10% and 95% for the softest criterion (IOP ≤ 21 mmHg), respectively. The rates were 5% and 75% for the strictest criterion (≤18 mm Hg and ≥25% IOP reduction).

	Success rate %		
	1 year n=19	3 years n=18	5 years n=18
Complete success			
≤21 mm Hg	37	28	10
≤21 mm Hg and ≥25% IOP reduction*	26	22	5
≤18 mm Hg	37	28	10
≤18 mm Hg and ≥25% IOP reduction*	26	22	5
Qualified success			
≤21 mm Hg	90	89	95
≤21 mm Hg and ≥25% IOP reduction*	73	66	75
≤18 mm Hg	79	82	95
≤18 mm Hg and ≥25% IOP reduction*	68	66	75

Table 2. Success results at 1, 3 and 5 years.

Complications

Complications are presented in table 3. The overall complication rate was low.

Complication	
Early postoperative, n (%)	
Transient hypotony	1 (5)
Microhyphema	5 (25)
Macrohyphema	2 (10)
Transient IOP elevation	0 (0)
Detachment Descemet membrane	0 (0)
Late postoperative, n (%)	
Endophthalmitis	0 (0)

POAG = primary open-angle glaucoma; IOP = intraocular pressure; Microhyphema = <1 mm layered blood in anterior chamber; Macrohyphema = ≥1 mm layered blood in anterior chamber

Table 3. Ocular-related surgical and postsurgical complications.

The most common early postoperative complication was hyphema, which was observed in 7 (35%) eyes. Transient hypotony was observed in one (5%) eye in the early postoperative phase, which resolved spontaneously within one week after surgery. We did not observe any case of endophthalmitis or other sight-threatening complications. We did not see any cases of dislocation of the Prolene suture after five years.

Further surgery

Thirteen (65%) eyes needed further surgery because of insufficient IOP control during the follow-up period of 5 years. Median time to further surgery was 24 months (95%-confidence interval 1-51 months). One eye was treated with a single transscleral cyclophotocoagulation. In 12 eyes micro-invasive suture trabeculotomy was performed first, followed by trabeculectomy with mitomycin C in two eyes and TSCPC in another four.

Discussion

Canaloplasty is one of the recent advances in non-penetrating glaucoma surgery. There is increasing evidence for the efficacy and safety of canaloplasty in the literature (Bruggemann et al., 2013, Bull et al., 2011, Grieshaber, 2012, Grieshaber et al., 2010a, Grieshaber et al., 2010b, Koerber, 2011, Lewis et al., 2011, Matlach et al., 2013, Tetz et al., 2013, Brusini, 2014). In the current study, we investigated the long-term safety and efficacy of canaloplasty in the treatment of OAG. Our results show that the efficacy of the procedure slowly decreases in time. We did not observe any case of endophthalmitis or other sight-threatening complications.

In the current study, a lowering of the mean IOP was achieved from 25.7 ± 6.6 mmHg on 3.4 ± 0.5 medications to 15.1 ± 4.4 mmHg on 1.6 ± 1.4 medications after three years. The complete and qualified success rates for IOP ≤ 21 mmHg were 28% and 89%, after three years, respectively. Our results compare well to previously reported studies. Lewis et al. demonstrated a significant reduction in the mean IOP from 23.5 ± 4.5 mmHg on 1.9 ± 0.8 medications at baseline to 15.5 ± 3.5 mmHg on 0.9 ± 0.9 medications after three years. The reported complete success rate in a group of patients with successful suture implantation without cataract surgery was 40.4% for IOP ≤ 21 mmHg, and 95.5% had qualified success at three years (Lewis et al., 2011). Bull et al. reported similar results in a group of 82 eyes with canaloplasty alone. They achieved a lowering

of mean IOP from 23.0 ± 4.3 mmHg on 1.9 ± 0.7 medications to 15.1 ± 3.1 mmHg on 0.9 ± 0.9 medications at three years.(Bull et al., 2011) Complete and qualified success for IOP ≤ 21 mmHg was achieved in 40.5% and 98.6% of the eyes at three years, respectively (Bull et al., 2011). Grieshaber et al. demonstrated similar efficacy rates for canaloplasty in black African patients after three years (Grieshaber et al., 2010b). Brusini reported a complete success of 44.8% and a qualified success of 86.2% for IOP ≤ 21 mmHg (Brusini, 2014). The complete success rates in our study were lower compared to the above studies. A possible explanation for this is a learning curve effect since we included some of our first canaloplasty patients in the study. Another possibility is that IOP in our patient population was generally more difficult to control compared to the studies of Lewis et al. and Bull et al. since the number of baseline medications in the current study was notably higher (3.4 vs 1.9 for the above mentioned studies). (Bull et al., 2011, Lewis et al., 2011). After five years, the majority of eyes required additional medication for IOP control. The complete and qualified success rates were 10% and 95%, respectively. The mean IOP was 14.2 ± 3.4 mmHg on 1.7 ± 1.3 medications. During the follow up, 13 (65%) eyes needed further surgery because of insufficient IOP control. In 12 of those eyes micro-invasive suture trabeculotomy (MIST) was performed as previously described (Voykov et al., 2014).

Although we did not compare canaloplasty and standard filtration surgery in the current study, based on our and literature results, canaloplasty has a lower efficacy of both (Ayyala et al., 2011, Matlach et al., 2015, Matlach et al., 2013, Rulli et al., 2013, Schoenberg et al., 2013, Thederan et al., 2014).

The complication rate after canaloplasty was very low in the current study and compared favourably to previous studies (Brusini, 2014, Bull et al., 2011, Lewis et al., 2011). Hyphema was the most common complication which occurred in one third of the eyes. In a study by Grieshaber et al., microhyphema on the first postoperative day was found to be predictive of success (IOP lower than 16 mmHg without medications) after a mean follow-up of 20.6 months (Grieshaber et al., 2011b). In our study, microhyphema was not a positive prognostic

indicator. However, comparison between both studies is difficult, because of the different definitions of success and microhyphema, which was defined as less than 1 mm layered blood in the present study and had no such strict definition in the study by Grieshaber et al "reported range 1-2.5 mm" (Grieshaber et al., 2011b). The frequency of microhyphema (85.1%) appears to be quite high in the latter study compared to the majority of published results, including ours (Bull et al., 2011, Lewis et al., 2011). We did not observe any sight threatening complications during the follow up of five years.

Of the studied factors, including age, gender, number of preoperative medications, baseline IOP, and hyphema, none were predictive for success in our study. Further studies, designed to evaluate the indicators for success and failure, are necessary for optimising preoperative patient selection.

Limitations of the study include the small sample size as well as a possible selection bias adherent to the retrospective design. Further prospective studies with a larger number of cases are warranted to evaluate the long term safety and efficacy of the procedure as well as specific risk factors for failure.

In conclusion, our results show that canaloplasty lowered IOP in this series of patients but many patients (65%) needed further surgery to control IOP. We did not observe any sight threatening complications of the procedure.

2.2. [Exit strategies in canaloplasty: intraoperative conversion into 180-degree trabeculotomy or 360-degree trabeculotomy in cases of unsuccessful catheterisation of Schlemm's canal: influence of degree of canal cleavage (Alnahrawy O, Blumenstock G, Ziemssen F, Szurman P, Leitritz MA, Dimopoulos S, Voykov B., published in Graefes Arch Clin Exp Ophthalmol)](Alnahrawy et al., 2015)

Introduction:

Canaloplasty is a novel surgical technique that aims to lower IOP using a non-penetrating approach through circumferential catheterisation of SC and placement of tension suture to restore natural aqueous outflow pathways. This obviates the need of external fistulisation which has more frequent early and late postoperative bleb related complications (Bettin and Di Matteo, 2013, Bruggemann et al., 2013, Lewis et al., 2011, Lewis et al., 2007, Shingleton et al., 2008). But what if catheterisation of SC fails or the placement of a tension suture is unsuccessful? Both scenarios are challenging surgical problems in the course of surgery, occurring in 10% to 26% of eyes undergoing canaloplasty surgery (Brusini, 2014, Bull et al., 2011, Grieshaber et al., 2010c, Lewis et al., 2009, Lewis et al., 2011, Lewis et al., 2007, Shingleton et al., 2008). Suture cheese wiring through the trabecular meshwork (TM) is another complication, which precludes suture placement (Brusini, 2014, Grieshaber et al., 2010c, Lewis et al., 2009, Lewis et al., 2011). Growing surgical experience helps to increase the technical success; however, anatomical obstacles such as SC stenosis remain difficult to overcome (Koerber, 2012, Lewis et al., 2009, Lewis et al., 2011, Lewis et al., 2007). Meanwhile different surgical “escape” strategies such as viscocanalostomy and deep sclerectomy have been described, but no gold standard has yet been established (Bull et al., 2011, Lewis et al., 2009, Lewis et al., 2011). Table 4 (Bruggemann et al., 2013, Brusini, 2014, Bull et al., 2011, Grieshaber et al., 2010c, Grieshaber et al., 2013, Lewis et al., 2009, Lewis et al., 2011, Lewis et al., 2007, Shingleton et al., 2008) shows the literature overview of the currently documented surgical and postsurgical difficulties/complications in canaloplasty.

In this study the safety and efficacy of intraoperative conversion of unsuccessful canaloplasty into 180 degree metal or 360 degree suture trabeculotomy were investigated.

Patients and methods:

A total of 183 eyes that underwent canaloplasty surgery in the Centre for Ophthalmology, University Hospital Tübingen from November 2008 to July 2013 were studied. 122 eyes were operated using the Glaucolight (DORC International, Zuidland, The Netherlands) microcatheter, and 61 eyes using the iTrack (iScience Interventional, Menlo Park, CA), microcatheter.

In this retrospective case series 35 patients with primary open angle glaucoma, pseudoexfoliative or pigmentary glaucoma, with uncontrolled IOP, who underwent intraoperative conversion of canaloplasty into 180 degree metal or 360 degree suture trabeculotomy were included.

Eyes were divided into two groups: Group A comprised 17 eyes, which had unsuccessful circumferential SC catheterisation because of intracanalicular stenosis or catheter deviation into a collector channel or into the anterior chamber. These eyes were converted into 180 degree metal trabeculotomy. Group B comprised 18 eyes, which had a cheese wiring or partial suture or microcatheter extrusion through the TM during withdrawal. In this case the procedure was converted into 360 degree trabeculotomy.

Patients with other forms of glaucoma or with previous glaucoma surgery were excluded. None of the patients had a simultaneous lens operation in both groups. Success was defined as the percentage of eyes that reached a target IOP ≤ 21mmHg or IOP ≤ 21 mm Hg and at least 25% reduction from baseline. Success was classified as complete when no glaucoma medications were needed postoperatively, and qualified when one or more glaucoma medications were still used.

This work adhered to the tenets of the Declaration of Helsinki. According to German legislation and the requirements of the local IRB, completely anonymised data was used for this study.

	Complication (%)						
	Unsuccessful catheterisation or tension-suture placement	Cheese wiring through TM	Hyphema	IOP increase	Hypotony	Choroidal effusion	Descemet detachment
Brüggemann et al. 2013(Bruggemann et al., 2013)	n.a.	n.a.	26.7	n.a.	6.7	n.a.	6.7
Brusini 2014(Brusini, 2014)	16.4	0.9	21.9	5.6	9.8	none	5.1
Bull et al. 2011(Bull et al., 2011)	11.1	n.a.	18.3	7.3	none	none	3.7
Grieshaber et al. 2010(Grieshaber et al., 2010c)	none	2.2	27.8	4.4	none	none	2.2
Grieshaber et al. 2013(Grieshaber et al., 2013)	n.a.	n.a.	85.1	n.a.	n.a.	n.a.	n.a.
Lewis et al. 2007(Lewis et al., 2007)	21.3	1.1	3.2	3.2	1.1	1.1	1.1
Lewis et al. 2009(Lewis et al., 2009)	15	1.6	15.8	10.3	0.8	n.a.	1.6
Lewis et al. 2011(Lewis et al., 2011)	15.3	1.9	22.3	12.8	0.6	n.a.	3.2
Shingelton et al. 2008(Shingleton et al., 2008)	26	none	33.6	n.a.	none	n.a.	1.9

Table 4. Literature overview of documented surgical and postsurgical complications in canaloplasty (n.a. = not available, TM = trabecular meshwork)

Surgical technique:

The canaloplasty surgical procedure followed the technique described by Lewis et al (Lewis et al., 2007). Briefly; a two-flap dissection was carried out until SC was deroofed. The two ostia of the canal were dilated with high molecular weight hyaluronic acid (Healon GV), followed by an attempt to circumferentially introduce a microcatheter into the SC. The iTrack (iScience Interventional, Menlo Park, CA), or the Glaucolight microcatheter (DORC International, Zuidland, The Netherlands) were used. If this attempt failed, a Neuhann U-shaped trabeculotome (Geuder, Heidelberg, Germany) was introduced into SC through about 90° circumference and its tip was swung gently into the anterior chamber cleaving the TM once superotemporally and again superonasally completing a trabeculotomy of maximum 180 degree (group A) following the original trabeculotomy technique described by Harms and Dannheim (Harms and Dannheim, 1970)

If successful 360 degree catheterisation was achieved, but tension suture could not be placed because of cheese wiring or partial suture extrusion through the TM (group B), then the suture was retrieved cleaving the entire circumference of SC and thus creating a 360 degree trabeculotomy. The operation was then completed identically for both groups with excision of the deep scleral flap and watertight suturing of the superficial flap. All patients received postoperative local treatment with antibiotic and steroid eye drops over two weeks. Pilocarpin 1% was instilled for 4-6 weeks to hinder synechia formation at the iris base.

Outcome and Statistical analysis:

Main outcome measures included IOP, number of glaucoma medications, visual acuity and success after 6- and 12-month follow-up. The data record for each eye included patient age at surgery, gender, glaucoma type, surgical procedure, IOP, glaucoma medication, visual acuity, possible complications and postoperative interventions. For combination glaucoma medications, the single active ingredients were enumerated.

For statistical analysis, chi-squared test, Fisher's exact test, and Wilcoxon rank-sum test were performed with the JMP 11.0 statistical package (SAS Institute Inc., Cary, NC, USA). Values for *p* of less than 0.05 were considered to reflect significant differences.

Results:

Demographic data for both groups are shown in table 5. There were no significant differences in patients' gender, mean age, lens status, aetiology of OAG or logMAR of best corrected visual acuity (BCVA) between both groups preoperatively.

Canaloplasty was attempted with the Glaucolight microcatheter in 15 eyes and with the iTrack microcatheter in 2 eyes in group A. In all eyes of group B, the Glaucolight microcatheter was used.

Mean BCVA changed from 0.09±0.15 and 0.31±0.52 at baseline to 0.17±0.35 and 0.29±0.3 at 12 months postoperatively for group A and group B, respectively. These changes were not statistically significant.

Demographic data

	180° Trabeculotomy	**360° Trabeculotomy**	**p-value**
General			
Eyes, n	17	18	
gender			*0.44*
Women, n (%)	14(82)	12(67)	-
Men, n (%)	3(18)	6(33)	-
Age (y)			
Mean ± SD	62±13	59 ± 16	*0.52*
Range	44-79	24-82	
Diagnosis, n			*0.57*
POAG	15	13	-
Pigmentary dispersion glaucoma	0	2	-
Exfoliation glaucoma	2	3	-
Phakic, n (%)	12(71)	16(94)	*0.23*
Pseudophakic, n (%)	5(29)	1(6)	*0.09*
Preoperative BCVA (log MAR, mean ± SD)	0.31±0.15	0.09±0.52	*0.14*

POAG = primary open-angle glaucoma; BCVA= Best Corrected Visual Acuity; log MAR= Mean logarithm of the minimal angle of resolution

Table 5. Patients' demographics.

Table 6 shows the median values of pre- and postoperative IOP and number of glaucoma medications in both groups at 1, 6 and 12 months.

	180° Trabeculotomy			360° Trabeculotomy		
	n	Median IOP (range)	Median number of medications (range)	n	Median IOP (range)	Median number of medications (range)
Baseline	17	22 (16-34)	4 (2-4)	18	22 (15-48)	3 (1-4)
Postoperative follow-up						
1 Month	17	12 (3-26)	0 (0-3)	18	14 (11-38)	0 (0-4)
6 Months	16	15 (4-23)	0 (0-3)	15	13 (10-22)	1 (0-4)
12 Months	15	14 (8-27)	2 (0-4)	10	14.5 (9-21)	1 (0-3)

Table 6. Outcome measures. IOP in mmHg; Number of glaucoma medications

A significant IOP reduction of 36% has been achieved in group A, from 22.0mmHg (ranging from 16 to 34 mmHg) at baseline to 15.0mmHg (ranging from 9 to 21mmHg) at 12 months. In group B, IOP reduced from 22.0mmHg (ranging from 15 to 48mmHg) at baseline to 14.5mmHg (ranging from 8 to 21mmHg) at 12 months representing 34% reduction.

The median number of glaucoma medications decreased significantly by half in group A and by two thirds in group B at 12 months.

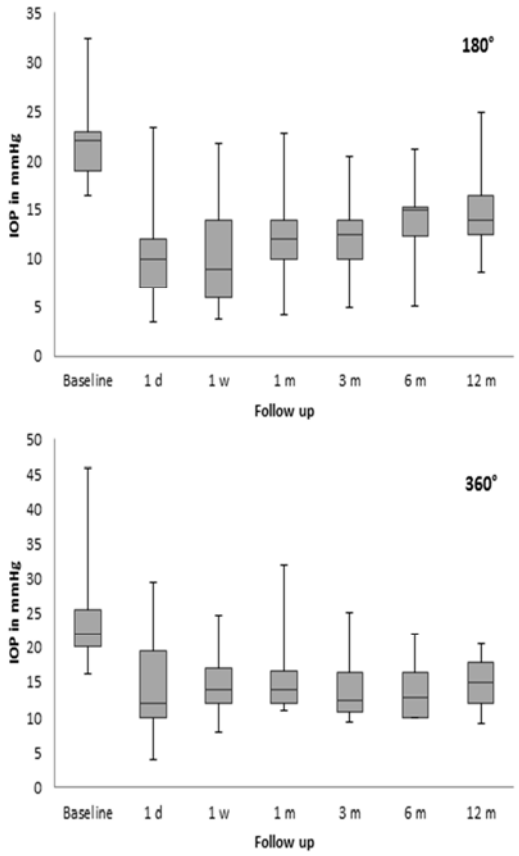

Figure. 4 Boxplot diagram showing IOP distribution at different time intervals. The whiskers indicate minimum and maximum values; the length of the boxes represents the interquartile range, i.e., the middle 50 % of the data. 180° indicates trabeculotomy degree in group A, and 360° the trabeculotomy degree in group B.

The overall success results at 6 and 12 months for both groups are shown in Table 7. There were no statistically significant differences between groups A and B regarding success results at all time points.

	Success Rate (%)			
	180° Trabeculotomy		**360° Trabeculotomy**	
	6 Months (n=16)	12 Months (n=15)	6 Months (n=15)	12 Months (n=10)
Complete success				
≤21 mm Hg	62.5	40	40	50
≤21 mm Hg and ≥25% IOP reduction*	56.3	33.3	40	40
Qualified success				
≤21 mm Hg	93.8	86.7	86.7	80
≤21 mm Hg and ≥25% IOP reduction*	75	60	66.7	60

*Reduction from maximum baseline IOP

Table 7. Success results at 6 and 12 months. All differences between both groups were not statistically significant.

Complications:

Operative and postoperative complications are summarized in Table 8. One eye in group A had a trabeculodescemet's membrane perforation, however it was small and the operation could be continued as previously described. The same eye had a presumed cyclodialysis with transient hypotony in the first postoperative week, but IOP increased above 6mmHg in all next follow-up visits.

	Complications n (%)	
	1180°Trabeculotomy	**360°Trabeculotomy**
TDM rupture	1 (6%)	0
Possible cyclo/iridodialysis	1 (6%)	0
Microhyphema	8 (47%)	8 (44%)
Macrohyphema	5 (29%)	6(33%)
Transient hypotony	2 (12%)	3(17%)
Transient IOP elevation	0	2(11%)

Table 8. Operative and postoperative complications. (TDM = trabeculodescemet membrane.) All differences between both groups were not statistically significant.

Two eyes in group A and three eyes in group B showed a transient postoperative hypotony (IOP ≤5mmHg) which normalised spontaneously within the first week. Transient IOP elevation occurred in two eyes in group B and could be rapidly controlled with medical treatment.

Persistent IOP elevation or frequent IOP spikes >21mmHg were recorded in one eye at 6 months and one eye at 12 months in group A, and in two eyes at 6 months in group B. Three eyes underwent transscleral cyclophotocoagulation and a total of four eyes were ultimately considered to have failure at mentioned time points. None of the postoperative complications was significantly associated with a specific risk of failure. No serious complications, such as endophthalmitis, aggressive iridocyclitis, malignant glaucoma or loss of vision were observed in both groups.

Discussion:

Canaloplasty is a novel procedure that aims to improve the physiological aqueous outflow, while avoiding the problem of conjunctival scarring related to bleb dependent operations. However, the advent of novel techniques usually invites new complications, which need to be dealt with. The current study investigates a new approach to deal with two challenging problems at different stages in the course of canaloplasty surgery. In our series, converting eyes with unsuccessful circumferential catheterisation of SC into 180 degree trabeculotomy, and eyes with suture cheese wiring through the trabecular meshwork into 360 degree trabeculotomy achieved a significant and sustained IOP control with a high safety profile over one year.

Brusini considered a conversion into deep sclerectomy or viscocanalostomy as his backup alternative for those eyes with unsuccessful SC catheterisation or impossible suture placement.
In addition, Lewis et al. and Bull et al. completed the surgery in such eyes performing viscocanalostomy. However, no results have yet been published for these eyes (Brusini, 2014). Of course, deep sclerectomy or viscocanalostomy can be alternative approaches if the anterior chamber has not been compromised. However, in the case of cheese wiring through the trabecular meshwork during the withdrawal of the microcatheter, a 360-degree trabeculotomy is automatically produced.

Deep sclerectomy with or without implant and viscocanalostomy have shown effective IOP control with fewer complications in naïve eyes compared to trabeculectomy; however Nd:YAG laser goniopuncture is often required after both procedures due to the frequent insufficient filtration through the trabeculodescemet's membrane (Alp et al., 2010, Anand and Pilling, 2010, David et al., 2008, Hamel et al., 2001, Lachkar et al., 2004, Mendrinos et al., 2008, Shaarawy et al., 2001, Shaarawy and Mermoud, 2005, Stegmann et al., 1999). Furthermore, a significantly superior efficacy of canaloplasty in

comparison to viscocanalostomy (fellow eye of the same patient) was demonstrated by Koerber (Koerber, 2012).

We tried a different treatment algorithm in eyes with difficult catheterisation and converted the procedure into trabeculotomy. *Ab-externo* trabeculotomy is a popular non-penetrating option in the treatment of adult OAG (Harms and Dannheim, 1970). Its effectiveness in controlling IOP by lowering the aqueous outflow resistance through cleaving the TM has been reported in the literature (Chihara et al., 1993, Chin et al., 2012, Iwaki et al., 1991, Schwenn and Grehn, 1995, Tanihara et al., 1993, Tanito et al., 2002a, Wada et al., 1994). Suture trabeculotomy was first described by Smith in 1960, refined by Beck and Lynch in 1995 and Chin et al. in 2012 to involve the entire circumference of SC (Beck and Lynch, 1995, Chin et al., 2012, Smith, 1960). Girkin et al. and Dao et al. used the iTrak microcatheter to achieve a 360 degree trabeculotomy with good results in congenital glaucoma (Dao et al., 2013, Girkin et al., 2012).

Theoretically, a procedure that opens the entire circumference of SC is expected to achieve a better IOP control than a 180 degree technique does (Chin et al., 2012). This, however, is not seen in our series. The differences between groups A and B regarding IOP reduction and number of postoperative glaucoma medications were not statistically significant. We cannot rule out that the anatomic differences hindering successful catheterisation in group A were associated with a different patient profile.

Although it is difficult to compare between different studies because of different techniques, populations and success criteria, our results compare well to viscocanalostomy, which is the most frequently described alternative to uncompleted canaloplasty (Bull et al., 2011, Lewis et al., 2009, Lewis et al., 2011). In our series, a complete success of 40% and 50%, and a qualified success of 86.7% and 80% at 12 months were achieved in group A and group B, respectively. Using the same definition of success, viscocanalostomy results showed a complete success rate ranging from 21.4% to 59% and a qualified success ranging from 71% to 88% (Luke et al., 2003, Moradian et al., 2013, O'Brart et al., 2002, Sunaric-Megevand and Leuenberger, 2001). Furthermore,

canaloplasty studies that included patients with IOP baseline similar to our case series, showed an IOP lowering effect and a medication reduction highly compatible with our result (Bull et al., 2011, Lewis et al., 2007, Shingleton et al., 2008).

Complications reported in the current study were infrequent and temporary. Hyphema was the most common postoperative complication , as it is related to surgery of SC (Dannheim and Harms, 1969). There was no association between the amount of blood and the extent of SC tearing.

IOP fluctuation is a reported complication after trabeculotomy; however, we observed a relatively stable IOP postoperatively, with an overall low rate of transient IOP elevation or hypotony (Tanihara et al., 1993, Tanito et al., 2002b). It should be noted that of all 35 eyes included in the current study, canaloplasty had been attempted with the Glaucolight device in 33 eyes and with iTrack in 2 eyes. In our opinion, this difference is due to the greater stiffness of the iTrack device, which allows an easier catheterisation of SC.

Limitations of this study include the short follow-up, small sample size as well as the possible selection bias adherent to the retrospective design. Further prospective studies with a larger number of cases and longer follow-up would be necessary to evaluate the long term safety and efficacy of the procedure as well as specific risk factors for failure.

In conclusion, the increasing popularity of canaloplasty necessitates new strategies to deal with its complications. The currently described approach showed a promising IOP control with a high safety profile after one year and could be considered in cases of unsuccessful canaloplasty surgery.

All authors have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

3. Summary

Canaloplasty has widened our treatment options for glaucoma. The bleb avoiding nature of the procedure results in a high safety profile. Canaloplasty allows also a rapid recovery after surgery. It can therefore, be offered for selected glaucoma patients even early in the course of the disease.

This work aimed to assess the long term safety and efficacy of canaloplasty in the treatment of open angle glaucoma. The procedure was moderately successful in lowering the IOP in the long-term. Additional topical anti-glaucoma medications were necessary to achieve satisfactory IOP control over time. Ultimately, more than half of operated eyes had to undergo a second surgery to keep the IOP within satisfactory levels after 5 years. However, it should be considered, that no procedure can guarantee permanent IOP control. Therefore, canaloplasty can be used to gain time before further surgery becomes necessary. We consider canaloplasty as a part of a so-called triple escalating glaucoma treatment: canaloplasty followed first by MIST and then by trabeculectomy (Voykov et al., 2015b).

Canaloplasty, however, is a surgically challenging procedure. Catheterisation of Schlemm's canal is not always possible. Surgical experience, individual anatomical variations and the catheter type/rigidity used are important variables that determine the success of the operative technique. In the second study, we analyzed two possible "escape" strategies in cases of catheterisation failure or cheese wiring of the prolene suture through the trabecular meshwork. Our results showed that converting the procedure into 180° or 360° trabeculotomy, achieved a good IOP lowering effect. The number of topical antiglaucoma medications was significantly reduced as well. The safety and efficacy of the procedure was as high as the originally intended canaloplasty.

4. Zusammenfassung

Die Kanaloplastik ist ein neues Verfahren in der Glaukomchirurgie mit einem hohen Sicherheitsprofil. Ein wesentlicher Vorteil dieses Verfahrens liegt in der

schnellen postoperativen Genesung, die eine verbesserte Lebensqualität für die Patienten bedeutet.

In dieser Dissertationsarbeit werden die Ergebnisse von zwei Studien zur langfristigen Wirksamkeit der Kanaloplastik sowie zum Umgang mit einer befürchteten intraoperativen Komplikation. In der ersten Studie konnte gezeigt werden, dass der drucksenkende Effekt der Kanaloplastik im Verlauf allmählich nachlässt, so dass nach 5 Jahren bei mehr als die Hälfte der Patienten eine zweite Operation erforderlich wurde. Die Kanaloplastik demonstrierte ein sehr hohes Sicherheitsprofil. Visusbedrohende Komplikationen, wie aus der fistulierenden Chirurgie bekannt, sind nicht zu erwarten. Da keine chirurgische Maßnahme eine permanente Druckregulation bisher gewährleisten kann, bietet die Kanaloplastik eine stufenweise Glaukomtherapie. Die erste Stufe bildet die erfolgreich durchgeführte Kanaloplastik. Sobald der Effekt der Kanaloplastik nachlässt, kann der Faden aus dem Schlemm'schen Kanal entfernt werden (mikroinvasive Faden-Trabekulotomie) gefolgt von einer klassischen Trabekulektomie falls zum späteren Zeitpunkt erforderlich.

Die Kanaloplastik ist jedoch chirurgisch anspruchsvoll. Chirurgische Erfahrung, individuelle anatomische Variationen und Steifheit der verwendete Katheter, sind wichtige Faktoren, die den Erfolg des Eingriffs bestimmen. In bis zu 15% der Augen kann der Schlemm'sche-Kanal nicht kathetarisiert werden, oder der Spannungsfaden kann nicht eingesetzt werden. In diesen Fällen kann der Eingriff in in eine 180- oder 360-Grad Trabekulotomie umgewandelt werden. Die Ergebnisse der zweiten Studie zeigen, dass diese Strategie eine signifikante Drucksenkung mit einer deutlichen Reduktion der Augentropfen erreichen kann.

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6. Erklärung zum Eigenanteil

Die Arbeit wurde in der Universitäts-Augenklinik Tübingen unter Betreuung von Prof. Dr. med. Faik Gelisken und Dr. med. Bogomil Voykov durchgeführt.

Die Konzeption der Studien erfolgte in Zusammenarbeit mit Dr. med. Bogomil Voykov.

Die Datensammlung und die Analyse der Ergebnisse wurden von mir durchgeführt. Das Manuskript der ersten Publikation wurde von Dr. Voykov und mir verfasst.

Das Konzept, die Datenerfassung und Analyse sowie die Verfassung des Manuskripts der zweiten Studie ‘‘Exit strategies in canaloplasty: intraoperative conversion into 180-degree trabeculotomy or 360-degree trabeculotomy in cases of unsuccessful catheterisation of Schlemm’s canal: influence of degree of canal cleavage’’ wurden von mir durchgeführt.

Die statistische Auswertung erfolgte in Kooperation mit dem Institut für Biometrie der Universitätsklinikum Tübingen.

Ich versichere, das Manuskript selbständig (nach Anleitung durch Prof. Gelisken und Dr. Voykov) verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Den 22.04.2017

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