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DEEP SCLERECTOMY

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CONTENT

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications. They will be referred to in the text by Roman numerals:

I. Suominen S, Harju M, Ihanamäki T, Vesti E. The effect of deep sclerectomy on intraocular pressure of normal-tension glaucoma patients: 1-year results. Acta Ophthalmol. 2010 Feb;88(1):27-32.

II. Suominen S, Harju M, Kurvinen L, Vesti E. Deep sclerectomy in normal-tension glaucoma with and without mitomycin-c. Acta Ophthalmol. 2014 Nov;92(7):701-6.

III. Harju M, Suominen S, Allinen P, Vesti E. Long-term results of deep sclerectomy in normal-tension glaucoma. Acta Ophthalmol. 2018 Mar;96(2):154-160.

IV. Suominen SM, Harju MP, Vesti ET. Deep sclerectomy in primary open-angle glaucoma and exfoliative glaucoma. Eur J Ophthalmol. 2016 Nov 4;26(6):568-574.

V. Suominen SMA, Harju MP, Hautamäki AME, Vesti ET. Changes in anterior ocular structures and macula following deep sclerectomy with collagen implant. Eur J Ophthalmol. 2018 Jan;28(1):47-51.

ABBREVIATIONS

5-FU	5-fluorouracil
AC	Anterior chamber
ACD	Anterior chamber depth
AL	Axial length
ALPI	Argon laser peripheral iridoplasty
BAC	Benzalkonium chloride
BCVA	Best corrected visual acuity
BP	Blood pressure
BSS	Balanced salt solution
DS	Deep sclerectomy
DSCI	Deep sclerectomy with collagen implant
EXG	Exfoliation glaucoma
EXS	Exfoliation syndrome
GP	Goniopuncture
HRT	Heidelberg Retina tomograph
IOP	Intraocular pressure
LOXL1	Lysyl oxidase-like
MIGS	Minimally invasive glaucoma surgery
MMC	Mitomycin-C
NTG	Normal tension glaucoma
OCT	Optical coherence tomography
ONH	Optic nerve head
POAG	Primary open-angle glaucoma
SD	Standard deviation
SLT	Selective lasertrabeculoplasty
TDM	Trabeculo-Descemet's membrane
UBM	Ultrasound biomicroscopy
YAG	neodymium-doped yttrium aluminum garnet

ABSTRACT

This study was undertaken to determine outcome of deep sclerectomy (DS) with and without mitomycin C (MMC), especially in patients with normal tension glaucoma (NTG). DS has been a method for treating eyes suffering from glaucoma for many years, but the intraocular pressure (IOP) lowering effect of DS to NTG eyes with low preoperative IOP has not been studied previously. MMC is widely used in glaucoma surgery. When aiming for low postoperative IOP, however, MMC may introduce postoperative adverse effects on operated eyes. Although the majority of glaucoma patients scheduled for surgery have primary open-angle glaucoma (POAG), exfoliation glaucoma (EXG) is common in Nordic countries. The number of DS studies on EXG eyes is limited, and the number of eyes in these studies has been low. IOP lowering with DS results in a decrease in best corrected visual acuity (BCVA) during the first postoperative weeks, the reasons for which are not thoroughly known.

The aims of this thesis were to investigate 1) the effect of DS in NTG eyes, 2) the possible additional IOP-lowering effect and adverse effects of MMC use, 3) the effect of DS in POAG and EXG eyes and 4) changes to BCVA, and anterior and posterior structures of the eye after DS.

DS reduced IOP efficiently in NTG eyes, an effect that could be noticed throughout our follow-up: postoperative IOP with and without MMC was 9 to 10 mmHg respectively, after 6 to 9 years of follow-up.

Hypotony was more common during the first postoperative months when MMC was used. In the MMC group, IOP was lower until 5 years postoperatively; after that, no difference was evident in IOP. Goniopuncture (GP) was common in both groups. In the MMC group 87%, and the non-MMC group 100% of eyes needed GP during follow-up. Needling was needed in 16 of 34 eyes and tended to be repeated more often in the non-MMC group. Four eyes lost two or more lines of best-corrected visual acuity (BCVA). The rate of serious postoperative complications was low.

DS also lowered IOP efficiently in POAG and EXG eyes. Mean postoperative IOP was 16.8 mmHg in POAG, and 16.5 mmHg in EXG after 3 years´ follow-up. That GP and re-operations were more common in EXG may indicate a stronger fibrotic response or altered function of the Descemet's membrane in these eyes. Studying possible variables to explain surgical success with the Cox regression model revealed that an IOP of 2 to 14 mmHg one week postoperatively indicated a lower rate of losing surgical success.

BCVA decreased when IOP was lowered with DS, but had returned to its preoperative level 4 weeks postoperatively. Axial length was shortened by 0.1 mm, and a steeper corneal meridian changed from 44.6 to 44.9 D. Thickness of the central cornea decreased 6 μm when measured with Scheimpflug. Changes in macular structures in optical coherence tomography (OCT) were small: four patients initially developed macular folds and two persisted until 4 weeks postoperatively, but visual acuities remained good.

Based on these studies, we demonstrated that DS is effective in lowering IOP in NTG, EXG, and POAG. Even very low IOP between 9 to 10 is achievable. Use of MMC results in lower IOP and fewer postoperative interventions, such as GP and needlings. MMC use was without significant risk of serious complications or adverse effects. Rate of GP is close to 100 % when follow-up is long. EXG eyes may have altered fibrotic response to DS, which may favor MMC use. DS is a safe procedure, with only relatively small changes in anterior and posterior structures and a low rate of irreversible decrease in BCVA.

INTRODUCTION

Glaucoma is one of the leading causes of irreversible blindness. Worldwide, 58 million people had POAG in 2015 but this number is estimated to rise to 75 million by 2025 (Kapetanakis et al. 2016). The majority of growth in patient number comes from the developing world. In Finland there were 84.000 glaucoma patients in 2013 with a higher prevalence among those over 70 years of age (Hirvelä et al. 1994). The number of glaucoma patients has been increasing by 2.5% annually, and their number in Finland is expected to rise to 100,000 in 2020. Glaucoma is mostly asymptomatic in the early phase of the disease, and half the patients are unaware of their glaucoma, even in developed countries (Mitchell et al. 1996).

The only evidence based method of treatment commonly used for glaucoma is IOP reduction. A 25% decrease in IOP from the pre-treatment level slows the progression rate of glaucomatous visual field damage (Heijl et al. 2002). A decrease in IOP can be achieved with topical glaucoma medication, laser treatments, or surgery to slow visual field damage progression.

The principle of glaucoma surgical procedures is to reduce IOP by raising aqueous outflow. This is achieved by reducing aqueous outflow resistance by partially or completely penetrating the eyewall.

Although effective in IOP reduction, several adverse effects are associated with glaucoma surgery: shallowing of the anterior chamber, intraocular bleeding, bacterial infections, hypotony, and hypotony-related complications. Deep sclerectomy (DS) evolved in order to avoid the postoperative hypotony which occurs with other forms of glaucoma surgery.

The aim of deep sclerectomy is an increase in the aqueous outflow caused by reducing outflow resistance. This is performed during surgery by peeling the posterior trabeculum and the roof of Schlemms canal after formation of a deep scleral pocket. Since the inner part of the trabecular meshwork is left intact, resistance to the aqueous outflow is partly maintained (Rossier et al. 2000) and IOP decreases slower than with trabeculectomy. DS is classified as a non-penetrating technique, since during uneventful DS, the eye wall is not completely penetrated.

This study was undertaken to find the effect of DS when aiming for low postoperative IOP. MMC is commonly used in glaucoma surgery, especially with this aim. A detailed study of the additional effect of MMC use with DS on lowering IOP, as well as its adverse effects, was needed. I aimed to study the IOP-lowering effect of DS in EXG, which is a common glaucoma subtype in Finland. Transient loss of BCVA is common after successful DS, and my aim was to learn the factors explaining it.

REVIEW OF THE LITERATURE

1 GLAUCOMA

Glaucoma is a chronic and progressive ophthalmic disease. It affects the eye by triggering apoptosis of ganglionic cells that travel from the retina to the optic nerve (Quigley et al. 1995). Clinically, it has a specific pattern of optic nerve head damage and subsequent deterioration in the visual field. Patients can be unaware of having glaucoma, since glaucoma can be asymptomatic for many years. The most common forms of glaucoma in Finland, primary open-angle glaucoma (POAG), exfoliation glaucoma (EXG), and normal-tension glaucoma (NTG), do not usually cause pain or other symptoms, and can therefore remain undetected until late in the disease, when subjective vision is affected.

High intraocular pressure (IOP) is a risk factor for glaucoma (Sommer 1989), but 30 to 50% of glaucoma patients, the ones suffering from NTG, have IOP in the normal range (Bonomi et al. 1998, Rotchford & Johnson 2002).

Other risk factors for glaucoma are age (Rudnicka et al. 2006), myopia (Mitchell et al. 1999), exfoliation (Ekstrom 2012), and family history (Tielsch et al. 1994).

Glaucoma is diagnosed in a clinical examination by an ophthalmologist assisted with visual field evaluation by automated perimetry and examinations of the optic nerve head and retinal nerve fiber layer with optical coherence tomography (OCT), Heidelberg retina tomography (HRT), and/or ocular fundus photography.

1.1 Maintenance of intraocular pressure

IOP is regulated by a balance between aqueous production and outflow. Aqueous is produced by non-pigmented epithelial cells of the ciliary body behind the iris. Aqueous production has been measured in healthy eyes as between 2.4 to 2.8 µl / min (Toris et al. 1999). The aqueous flows through the pupil to the anterior chamber and leaves the eye via two passive pathways: conventional and unconventional pathways.

The conventional (trabecular) pathway consists of aqueous flowing through the trabecular meshwork into the canal of Schlemms. From this canal, aqueous is removed to the episcleral veins and into the venous circulation (Bill & Hellsing 1965).

The unconventional (uveoscleral) pathway consists of direct aqueous outflow through the uveal meshwork and anterior part of the ciliary muscle, to the suprachoroidal space and then out of the eye through the sclera (Bill & Hellsing 1965). Functions of these pathways have been considered different, so that outflow through the unconventional pathway is independent of IOP, unlike with the conventional pathway (Brubaker 2001). However, in another study, aqueous outflows of both pathways were decreased among patients with ocular hypertension (Toris et al. 2002). The unconventional pathway contributed 42% of the total outflow in patients with ocular normotension and 25% of those with ocular hypertension.

The mean volume of the anterior chamber is 196 µl (Fontana & Brubaker 1980), but the anterior chamber in those 20 to 30 years of age is larger compared to those over 60 (247 µl ±39 vs. 160 µl ±39, $p<0.00001$) (Toris et al. 1999). Theoretically, the entire aqueous volume of the anterior chamber changes every 60 to 90 minutes.

1.2 Open-angle glaucoma subtypes

Glaucomas with normal anterior chamber angle structures and angle width are termed open-angle glaucomas. These can be further divided into primary and secondary open-angle glaucomas (Foster et al. 2002).

1.3 Primary open-angle glaucomas

These glaucomas are chronic, progressive optic neuropathies with common characteristic changes in the optic nerve head and retinal nerve fiber layer. No other ocular disease or congenital anomaly is present. Retinal ganglion cell death leads to visual field loss, and these glaucomas can be asymptomatic until visual field loss is severe.

High IOP is the most important risk factor (Sommer et al. 1991). Other risk factors are age (Rudnicka et al. 2006), race (African ancestry) (Rudnicka et al. 2006), myopia (Mitchell et al. 1999), positive family history (Tielsch et al. 1994), diabetes (Klein et al. 1994), optic disk hemorrhage (Hollands et al. 2013) and lower diastolic perfusion pressure (Tielsch et al. 1995).

The most common form of primary open-angle glaucomas is the high-pressure variant of the disease. IOP is measured in ophthalmic examinations above the statistically determined "normal" level of 21 mmHg. Characteristic glaucomatous changes are detectable by means of further ophthalmologic studies. This high-pressure variant is clinically referred to as primary open-angle glaucoma (POAG). In POAG, IOP is too high because aqueous outflow in trabecular meshwork is impaired.

The normal pressure variant of primary open-angle glaucoma is often clinically termed normal tension glaucoma (NTG). It can be debated whether NTG is one spectrum of POAG or is a different disease entity. IOP is measured in the normal range, (21 mmHg or below) in ophthalmologic examinations with NTG. Hemorrhages of the optic nerve head may be present.

Diastolic perfusion pressure plays a role in developing glaucomatic damage of the optic nerve head in both NTG and POAG. Perfusion pressure is blood pressure minus IOP, and low diastolic perfusion pressure is a risk factor for glaucoma (Tielsch et al. 1995). Blood flow to the optic nerve head (ONH) is autoregulated to remain stable despite changes in the IOP and blood pressure (BP). However, as the ONH blood flow autoregulation is defective in glaucoma (Hafez et al. 2003), an increase in IOP or decrease in BP will compromise ONH blood flow. Thus, problems in blood pressure autoregulation (nocturnal dippers) may explain some glaucoma damage occurring at lower IOP levels. IOP affecting the shape of the lamina cribrosa (Quigley & Addicks 1981) and development of retinal damage in the peripapillar area (Buus & Anderson 1989) have been under speculation as explanations for glaucomatous damage in optic nerve. The effect of translaminar pressure (difference of intraocular and intracranial pressures) in NTG has been speculated upon, but it seems controversial (Pircher et al. 2017).

If primary open-angle glaucoma is diagnosed between the ages of 10 and 35 it is considered primary juvenile glaucoma.

1.4 Secondary open-angle glaucomas

Secondary open-angle glaucomas are caused by ophthalmic or systemic diseases, drugs, or treatments. By definition, the anterior chamber angle is open, with no angle pathology present. ONH changes and visual field deterioration may resemble those found in primary open-angle glaucomas.

Open-angle glaucoma with the presence of exfoliation material is called exfoliation glaucoma (EXG). The pathogenesis of exfoliation syndrome (EXS) is by formation of dandruff-like exfoliation material in the ocular structures, first discovered by Finnish ophthalmologist Lindberg in his thesis of 1917 (Tarkkanen & Kivelä 2002).

When exfoliation material accumulates in the trabecular meshwork, ocular outflow can be reduced. This can lead to a slow but severe IOP rise. EXS is associated with weakening of lens zonules, which leads to an increase in risk of complications in cataract surgery, ultimately even luxation of the crystalline lens or IOL into the vitreous cavity. In slit-lamp examination, exfoliation material is detectable on the crystalline lens surface or pupillary border. The pupillary border can have a "moth-eaten" appearance in slit-lamp examination, and pupillary dilatation can be substantially weakened.

EXS prevalence is geographically restricted; it is common in Nordic countries (Hirvelä et al. 1995, Arnarsson et al. 2007) but also in Greece its prevalence is 11.9% among those over 60 (Topouzis et al. 2007). In Australia and Asia, however, EXS is uncommon (Mitchell et al. 1999, Miyazaki et al. 2005).

Mutation of the lysyl oxidase-like (LOXL1) gene, found in 2007 (Thorleifsson et al. 2007), explains most of the EXS in Nordic countries. The LOXL1 mutation is common in many other areas without a high prevalence of EXS, and recently environmental factors, epigenetics, and other genes are considered to explain EXS development in part (Anastasopoulos et al. 2015).

Exfoliation syndrome promotes IOP, and this leads to an increased risk of glaucoma (Ekstrom 2012). Exfoliation syndrome may also reduce stiffness of the lamina cribrosa (Braunsmann et al. 2012) and affect glaucoma development.

In EXG, visual field damage and damage progression can be more severe than in POAG (Olivius & Thorburn 1978).

Pigmentary glaucoma is another form of secondary open-angle glaucomas. Pigment granules are released from the posterior surface of the iris, possibly due to the iris rubbing against crystalline lens zonules (Campbell 1979). As pigment granules are released into the aqueous fluid, they accumulate in the trabecular meshwork, and aqueous outflow thus decreases. Pigment glaucoma may induce an acute periodical rise in IOP, with sensations of pain and haloes around lights. Iris retroillumination or accumulation of melanin pigment on the corneal endothelium may occur in slit-lamp examination. Accumulation of melanin is visible with gonioscopic examination of anterior chamber angle.

2 MEDICAL TREATMENT OF GLAUCOMA

2.1 Drugs affecting aqueous production

Decreasing aqueous production is a useful way to reduce IOP. Beta-blockers (timolol, timolol maleate, betaxolol), alpha-agonists (brimonidine, apraclonidine) and carbonic anhydrase inhibitors (dorzolamide, brinzolamide, acetazolamide) are common glaucoma medications. They reduce aqueous production of ciliary epithelium. Their IOP-lowering effect is between 22 and 25% (Lippa et al. 1992, Schuman 1996, Scoville et al. 1988).

Apraclonidine and brimonidine also have some effect in increasing aqueous outflow and lowering episcleral venous pressure (Toris et al. 1995).

2.2 Aqueous outflow increasing drugs

Another alternative to reduce IOP is to raise aqueous outflow in the anterior chamber angle.

Miotics (pilocarpine and derivatives) were the first topical glaucoma medications. They cause increased aqueous outflow by enhancing the outflow facility of the trabecular meshwork, doing so by affecting the longitudinal muscle of the ciliary body (Gaasterland et al. 1975). Miotics reduce IOP by 20 to 30%, but their clinical use has declined because of undesirable side-effects: miosis, burning sensations, brow ache, and headache.

Prostaglandin analogs (latanoprost, travoprost, tafloprost, unoprostone) form a group of drugs that reduce IOP by raising uveoscleral outflow (Toris et al. 1997). Bimatoprost is a prostamide and has a slightly different metabolism from prostaglandins (Brubaker et al. 2001). Its IOP-lowering mechanism is to raise uveoscleral outflow, and its IOP-lowering effect is equal; however, it is clinically included among the prostaglandins. The IOP-lowering effect of prostaglandins as monotherapy has been better than that of beta-blockers (Alm & Stjernschantz 1995, Boland et al. 2013).

2.3 Combination therapy

Glaucoma medications can be combined in order to achieve a greater IOP-lowering effect (Alm et al. 1995). Combination therapy can be instilled in individual components or fixed combinations. One common fixed combination product, latanoprost-timolol maleate (Xalcom), reduced IOP 1.9 mmHg more than did timolol maleate and 1.2 mmHg more than did latanoprost alone (Higginbotham et al. 2002). Latanoprost, travoprost and taflurost are available in fixed combinations with timolol (Brief et al. 2010, Pfeiffer et al. 2010, Pillunat et al. 2017). All prostaglandin fixed combination therapies show an additional IOP lowering effect compared to monotherapy alone, with good patient tolerability. Brinzolamide and dorzolamide are used with timolol in fixed combinations, and their IOP lowering effects have been similar (Manni et al. 2009). The only fixed combination without timolol combines brimonidine and dorzolamide.

2.4 Side-effects of topical glaucoma medication

Topical glaucoma medications can have many adverse effects, both local and systemic, and some of them are severe; contact allergy and eye redness are the most common. Miotics can produce accommodation spasm, visual disturbances, miosis, headache, and brow ache as local adverse effects (Zimmerman & Wheeler 1982). Gastrointestinal symptoms have been reported as systemic side-effects.

Beta-blockers may have severe systemic side effects: cardiovascular ones and worsening of asthma symptoms (Waldock et al. 2000). Carbonic anhydrase inhibitors´ systemic side-effects include electrolyte imbalance, blood glucose level variations, and neurologic symptoms (Epstein & Grant 1977).

Prostaglandins commonly produce local adverse effects: contact allergy, eyelash growth and bristle, changes in iris- and eyelid pigmentation and hyperemia (Alm & Stjernschantz 1995, Inoue et al. 2012).

Some of the adverse effects introduced by glaucoma medication are due to benzalkonium chloride (BAC), which is used as a preservative in glaucoma medication products. BAC may cause corneal irritation, conjunctival redness, and allergic reactions (Uusitalo et al. 2010).

Since adverse effects can be severe, some patients become intolerant to glaucoma medication and need laser or surgical treatment for glaucoma later.

3 LASER TREATMENT OF GLAUCOMA

3.1 Laser trabeculoplasty

Laser trabeculoplasty is glaucoma therapy aimed at the safe lowering of IOP. Argon laser trabeculoplasty was introduced in 1979 (Wise & Witter 1979). Argon laser applications are delivered to trabecular meshwork under topical anesthesia with help of a gonioscopic lens in order to increase aqueous outflow.

Later, selective laser trabeculoplasty (SLT) was developed (Latina & Park 1995). SLT is a laser procedure that aims to reduce IOP by causing an increasing aqueous outflow. This is achieved by applying Q-switched 532 nm energy pulses to the trabecular meshwork in the anterior chamber. After instillation of anesthetizing drops, gonioscopic lens is introduced into the eye. Then approximately 50 to 100 laser pulses are applied to 180 or 360 degrees of trabecular meshwork. SLT treatment does not create mechanical damage to the structures of the trabecular meshwork (Kramer & Noecker 2001), and the IOP-lowering effect is explained by biomechanical and cellular alterations (Wong et al. 2015).

The IOP-lowering effect of SLT is between 3.6 and 6.8 mmHg after 1 to 3 years of follow-up (Bovell et al. 2011, Katz et al. 2012, Koucheki & Hashemi 2012). The most common adverse effects of SLT are anterior chamber inflammation in 0 to 89%, transient IOP rise in 0 to 62%, and eye pain in 0 to 58% of patients (Bovell et al. 2011, Koucheki & Hashemi 2012, Wong et al. 2015). However, IOP reduction after SLT is transient, with a failure rate of 44 to 50% after 1 to 3 years of follow-up, when failure is determined as IOP reduction of less than 20% or continuation of glaucoma medication (Bovell et al. 2011, Koucheki & Hashemi 2012). Since SLT is well tolerated, it can be used as first-line treatment of open-angle glaucomas or in addition to topical glaucoma medication.

3.2 Laser cyclophotocoagulation

Cyclophotocoagulation can be performed by laser. Among different wavelengths in use, are 810 nm infrared, 647 nm krypton, and 670 nm diode laser. Lasers can function in a continuous mode (Mistlberger et al. 2001, Schlote et al. 2001) or in a recently developed micropulse mode (Tan et al. 2010). The IOP-lowering effect of laser cyclophocoagulation procedures is achieved by lessening aqueous production of ciliary body by damaging aqueous-producing epithelial cells.

Treatment is performed, after retrobulbar anesthesia, by holding laser probe against the conjunctiva a few millimeters posterior to the limbus. Then laser energy is provided through the sclera to affect the underlying ciliary body. Treatment is rather straightforward and can be repeated if necessary. Laser cyclophotocoagulation is usually reserved for late-stage glaucoma when other methods of treatment have failed or are considered inefficient. However, cyclophotocoagulation can be used as the primary treatment in neovascular glaucoma (Yildirim et al. 2009).

Success, an IOP of <21 or 22 mmHg, can be achieved in 68 to 80% of eyes after a one-year follow-up with medication allowed (Mistlberger et al. 2001, Schlote et al. 2001, Tan et al. 2010). After 2 years of follow-up, the success rate declines, however, to 50% (Mistlberger et al. 2001), with 25% of treated eyes in need of two or more cyclophotocoagulations during first 3 to 4 years (Raivio et al. 2008). Adverse effects are anterior chamber inflammation at 64-100%, loss of >2 lines of visual acuity at 13-19%, hyphema at 7-18% and phthisis bulbi in 0-8% (Mistlberger et al. 2001, Schlote et al. 2001, Delgado et al. 2003, Tan et al. 2010).

4 INDICATIONS OF GLAUCOMA SURGICAL TREATMENT

The most important indications for glaucoma surgery are as follows: overly high IOP despite maximal topical glaucoma medication, progression of visual field defect and intolerance to topical glaucoma medication. The IOP-lowering effect of glaucoma medication can weaken when used for many years, and although good IOP control has been achieved after initiation of topical medication, glaucoma surgery may be necessary after a few years (Brooks & Gillies 1988). If the visual-field defect progresses despite the maximum tolerated IOP medication, glaucoma surgery may be indicated (Jay & Murray 1988). In glaucoma patients, IOP may show diurnal variation, and the optic nerve may suffer damage when IOP is elevated even for a short time (IOP spike). For some patients, glaucoma surgery reduces these IOP spikes and the diurnal IOP fluctuation more than does topical glaucoma medication (Medeiros et al. 2002). Glaucoma medication may cause adverse effects on treated eyes such as redness, irritation, and inflammation. These effects can be induced by the glaucoma medication itself (Alm & Stjernschantz 1995) or by benzalkonium chloride used as a preservative (Uusitalo et al. 2010).

Some elderly people may have difficulties using topical medication on their eyes. Patients with diseases affecting their cognitive behavior (Alzheimers disease, alcohol abusers, mental illnesses) may be unable to comply with regular medication use.

5 PENETRATING FILTRATION SURGERY

5.1 Trabeculectomy

Trabeculectomy, introduced in 1968 (Cairns 1968), has become the gold standard among glaucoma surgical procedures. The conjunctiva is opened with a limbus- or fornix-based incision. As with DS, it is very important to achieve good hemostasis in order to avoid postoperative scarring. The scleral flap is performed with a surgical knife. The thickness of the flap is about half- to one-third of scleral thickness, and the flap can be rectangular or triangular. Paracentesis to the anterior chamber is performed so that the volume and shape of the anterior chamber can be maintained when needed. The flap is lifted and turned over the peripheral part of the cornea. After formation of the scleral flap, the antimetabolites MMC or 5-fluorouracil (5-FU) can be applied. Polyvinyl alcohol sponges soaked with MMC are then inserted under the scleral flap and conjunctiva for 1 to 3 minutes, then removed, and the antimetabolite is carefully washed away with a balanced salt solution (BSS). MMC concentration in use varies between 0.02 to 0.4 mg/ml (Kitazawa et al. 1993, Robin et al. 1997). The surgical opening is continued to the peripheral part of the cornea, and finally a perforation is performed to the anterior chamber. A full-thickness block is removed by a punch instrument from the peripheral part of the cornea and anterior part of the sclera. Perforation to the anterior chamber or corneoscleral block removal usually results in rapid flow of aqueous from the wound. Then surgical iridectomy is performed by forceps and scissors. Closure of the scleral flap is secured with two or more non-absorbable sutures. By adjusting the tightness of these sutures, the surgeon can affect the amount of aqueous filtration and IOP in the immediate postoperative time-period. The conjunctiva is closed with continuous or interrupted absorbable sutures. The use of subconjunctival devices with trabeculectomy is comparable to the application of MMC with regard to long-term success rate (Ji et al. 2015). The later-introduced safe-surgery trabeculectomy is another alternative. The anterior chamber maintainer and adjustable sutures, which can be loosened postoperatively, lead to fewer postoperative complications and allow adjustment of aqueous outflow (Stalmans et al. 2006).

The IOP-lowering effect of trabeculectomy is well documented (Bindlish et al. 2002, Stalmans et al. 2006, Gale & Wells 2008, Landers et al. 2012). In the longer term, mean IOP is between 10 and 12 mmHg after 3 to 5 years (Bindlish et al. 2002, Gale & Wells 2008). Complications of traditional trabeculectomy include hyphema in 25%, hypotony 24 to 43%, hypotony maculopathy 9%, and choroidal

detachment 14% (Bindlish et al. 2002, Edmunds et al. 2002, Landers et al. 2012). With the later-introduced safe surgery trabeculectomy, some complication rates are lower: hyphema 5% and choroidal detachment 3 to 9% (Stalmans et al. 2006, Gale & Wells 2008).

Cataract progression occurs postoperatively: in 5 years after trabeculectomy, 55% of eyes need cataract operation (Bindlish et al. 2002), and within 3 years after safe-surgery trabeculectomy (Gale & Wells 2008), only 18% need a cataract operation. With modern postoperative antibiotics, endophthalmitis is rare after trabeculectomy, with an incidence of 0.3 to 1.5% (Bindlish et al. 2002, Edmunds et al. 2002, Stalmans et al. 2006).

5.2 Glaucoma tube surgery

Glaucoma tube surgery is another alternative to filtration procedures. In tube surgery, aqueous fluid flows out of the anterior chamber through a tube connected to an outflow chamber; this facilitates outflow. When the tube is inserted, the conjunctiva is opened in similar fashion as with filtration surgery. The outflow chamber is sutured to the surface of the sclera with two knots. An opening to the anterior chamber is performed by needle. (A flap of sclera can be created to help protect the tube from penetration of the overlying conjunctiva during the postoperative period.) The tube is inserted under the scleral flap and through the opening to the anterior chamber. Care needs to be taken that the tube, when inserted, does not touch any intraocular structures: the corneal endothelium, the iris or the lens. Tube-length must be adjusted accordingly. The most common types of tube in use are the Molteno, Molteno3, Ahmed, and Baerveldt implants (Molteno 1969, Smith et al. 1993, Coleman et al. 1995, Välimäki 2012). The Molteno and Baerveldt allow direct outflow of aqueous via the tube to the outflow chamber. This may result in postoperative hypotony, so some modifications can avoid this complication with these implants. The outflow tube can be ligated with an absorbable suture, or the tube can be internally occluded with a removable suture (Hong et al. 2005).

The Ahmed is designed differently: to avoid postoperative hypotony, this outflow tube has a one-directional flow restrictor designed to open at a pressure of 8 mmHg (Coleman et al. 1995).

Other modifications to the original implants to achieve lower postoperative IOP include introduction of a larger outflow chamber with the Baerveldt, and a double outflow chamber with the Molteno (Heuer et al. 1992, Smith et al. 1993).

After insertion of tube implants, a hypertensive period may occur 1-13 weeks postoperatively and it is more common after Ahmed than Baerveldt implantation (Nouri-Mahdavi & Caprioli 2003). During this period, the IOP can rise to between 35-55 mmHg before falling to a lower level after the 12th – 16th postoperative weeks (Molteno et al. 1976).

Previously, tube surgery was reserved for more complex cases of glaucoma and for reoperation when filtration surgery had failed. Nowadays, a shift towards primary tube surgery has been validated by previous results (Molteno et al. 2011, Gedde et al. 2012b, Välimäki & Ylilehto 2014, Islamaj et al. 2018). Postoperative IOP after insertion of Baerveldt shunt was 14.4 mmHg ±6.9 after 5 years' follow-up in the multicenter Tube Versus Trabeculectomy study (Gedde et al. 2012b). The same study showed that the Baerveldt implant had a better success rate compared to trabeculectomy with MMC in patients with prior cataract surgery or trabeculectomy. The number of early postoperative complications and reoperation for glaucoma was higher following trabeculectomy with MMC than Baerveldt procedure (Gedde et al. 2012a, Gedde et al. 2012b). Insertion of a sequential glaucoma drainage implant in a piggyback manner is possible if extra drainage with lower IOP is needed during the follow-up (Välimäki 2015). The tube can also be introduced into the posterior chamber, and the IOP control appears comparable to conventional anterior chamber placement (Kolomeyer et al. 2015, Rososinski et al. 2015). In addition, postoperative 50% corneal graft failure rate has been reported after this pars plana approach (Sidoti et al. 2001).

6 DEEP SCLERECTOMY

6.1 Surgical technique

The conjunctiva is opened either from the limbus or from the conjunctival fornix. Care must be taken to avoid excessive bleeding, which could promote postoperative scar-formation.

The superficial scleral flap is first incised with a surgical knife. A superficial flap is usually rectangular and 5 x 5 mm (Kozobolis et al. 2002, Ollikainen et al. 2011), but even a 4 x 5 mm superficial flap has been used (Audren et al. 2006). A superficial flap, in thickness, is approximately one-third the scleral thickness.

The superficial flap is then opened and turned aside.

Mitomycin-C (MMC) can be used to lessen postoperative scarring. Polyvinyl alcohol sponges soaked with MMC (0.02 to 0.4 mg/ml) (Anand 2011, Mansouri et al. 2011) are placed under the conjunctiva and superficial scleral flap for one to three minutes. Then the sponges are removed, and the subconjunctival and intrascleral spaces are rinsed thoroughly with balanced salt solution (BSS).

Then the deeper flap is excised in similar fashion. The deeper flap can be smaller than the superficial flap (Anand et al. 2011, Ollikainen et al. 2011), and the shape of the deeper flap is rectangular (Shaarawy et al. 2001, Anand et al. 2011) or triangular (Kozobolis et al. 2002). The depth of the deeper flap is about 95% of scleral depth, so that the chorioidea can be faintly observed through the remaining sclera.

The deeper flap is excised anteriorly until the canal of Schlemm. Excision is continued further anteriorly to the peripheral cornea in order to perform a trabeculo-Descemet's window. Then the base of the deeper flap is cut in the clear cornea to achieve an intrascleral empty space where fluid from the anterior chamber can percolate after the operation.

Structures of Schlemm's canal are identified after excision of the deeper flap. Then the outer part of the trabecular meshwork is seized with fine forceps. The outer part of the trabecular meshwork is carefully peeled, but if too much tissue is peeled, this leads to a small or large tear of Descemet´s window. A smaller tear is easier to handle, since the anterior chamber is usually maintained. A large tear leads to shallowing of the anterior chamber, and the operation usually has to be converted to a trabeculectomy with widening of the scleral opening to the anterior chamber and subsequent surgical iridotomy. If excision of the outer part of the trabecular meshwork is too superficial, this may lead to inadequate outflow of anterior chamber fluid and a too-high postoperative IOP. When the trabecular

meshwork is peeled correctly, and no perforation to the anterior chamber occurs, fluid from the anterior chamber begins to slowly percolate through the inner part of the trabecular meshwork, which can be seen with a surgical microscope. The anterior chamber is maintained, and risk of bleeding into the anterior chamber is minimal, because fluid percolation is controlled by the remaining trabecular meshwork.

Space created inside the sclera can be postoperatively maintained by inserting an implant into the remaining scleral bed and securing it with a knot.

Then, whether or not an implant is inserted, the superficial flap is closed. It is sutured with non-absorbable material from the corner(s) and the knots are buried. The conjunctiva is finally closed with absorbable sutures. Suturing of the conjunctiva can be done with interrupted or continuous sutures. This final suturing must be careful in order to avoid tearing of the conjunctiva or a too loosely closed conjunctiva, both of which could lead to postoperative leakage of aqueous out of the eye.

Aqueous should not flow uninterrupted out of the eye, since this could lead to sight threatening complications, such as endophthalmitis (Soltau et al. 2000). If such postoperative leaking of aqueous is encountered, there are several options for treatment. It can be treated with follow-up only, with placement of a therapeutic contact lens, or by suturing the conjunctiva in the operating room with the aid of an operating microscope. A filtering bleb can be seen under the conjunctiva on the first postoperative day.

6.2 Implant types

In DS, part of the sclera and cornea is removed surgically under the superficial flap, and a sclerocorneal space, or pocket, is created. In order to maintain this sclerocorneal pocket open and to avoid postoperative scarring, implants have been developed: the principle of the implants is absorbable material partially filling the sclerocorneal pocket during the first postoperative months, after which the implant is absorbed. In studies concerning the IOP-lowering effect of implants, results are controversial. In two studies, use of collagen implants resulted in a better postoperative success rate and IOP control (Sanchez et al. 1996, Shaarawy et al. 2004). All studies, however, do not find the same result (Mesci et al. 2012).

Several implants are in use at present. The Aquaflow collagen implant (STAAR Surgical AG, Nidau, Switzerland) is a 1-mm wide and 4-mm long cylinder of collagen (Demailly et al. 1996, Karlen et al. 1999). It is placed radially on the exposed scleral bed of the deep sclerectomy dissection and secured with a 10/0 non-absorbable suture. Resorption of the implant takes 6 to 9 months, during which the intrascleral space is held open to enhance filtration (Chiou et al. 1998b).

Another material for implants is the hyaluronic acid used in the SK-GEL implant (Corneal Laboratories, Paris, France). The SK-GEL implant is positioned in the deep sclerectomy dissection but with no suture needed (Sourdille et al. 1999). It is biocompatible, begins to dissolve after 6 months postoperatively and is replaced by scar or resorbed in 2 of 30 patients during the first 12 months (Marchini et al. 2001).

The third option is the hydrophilic acrylic implant T-flux (IOLTech Laboratories, La Rochelle, France). It is a non-absorbable T-shaped implant 8 mm in width and 2.75 mm in height (Ravinet et al. 2004). The arms of the T-flux are inserted into the openings of the Schlemms canal, and it is secured with a non-absorbable suture to the scleral bed (Mendrinos et al. 2008).

6.3 Trabeculo-Descemet's membrane

When the outer layer of the trabecular meshwork is peeled during DS, a thin layer of tissue remains as a barrier between the anterior chamber and the deep sclerectomy pocket. This barrier is called the trabeculo-Descemet's membrane (TDM) or trabeculo-Descemet's window. It is a transparent layer of inner trabecular meshwork. An intact TDM is considered to be a major factor explaining the different complication profiles observed when comparing DS and trabeculectomy, especially concerning flat anterior chamber and postoperative choroidal detachment (Mermoud et al. 1999).

6.4 Aqueous resorption mechanisms

Several resorption routes exist after aqueous has flowed through the TDM. When aqueous flows through the TDM and under the scleral superficial flap, most of it flows beside the sutured superficial flap into the subconjunctival space, and a subconjunctival bleb is formed. After DS, a subconjunctival filtering bleb can already be found in most of the cases on the first postoperative day. These subconjunctival blebs vary in height and appearance; a clinically shallow and diffuse appearance is more desirable than a high profile with thick walls. For study purposes, subconjunctival blebs can be divided into four categories using ultrasound biomicroscopy: low reflective, high reflective, encapsulated, and flattened, described after trabeculectomy with MMC (Yamamoto et al. 1995). This filtering subconjunctival bleb can persist even years after successful DS (Chiou et al. 1998b, Marchini et al. 2001).

During deep sclerectomy, a deep scleral flap is removed surgically, and an intrascleral space, or intrascleral bleb, is formed. When aqueous percolates through the TDM, it flows through this intrascleral bleb. One suggestion is that

new intrascleral drainage vessels grow after DS, possibly affecting aqueous outflow (Delarive et al. 2003). Several types of implant can hold this intrascleral space open. One year postoperatively, an intrascleral bleb could be found with ultrasound biomicroscopy in 90% of the eyes treated with an intrascleral implant (Kazakova et al. 2002). Postoperative formation of an intrascleral bleb seems to be clinically important for DS success. The height of the intrascleral bleb as measured by OCT has been correlated with lower postoperative IOP (Mavrakanas et al. 2010).

During DS, 10% or less of scleral thickness is left intact in the area of the deeper scleral flap. Aqueous humor can flow into the suprachoroidal space postoperatively via an outflow route that can be examined by ultrasound biomicroscopy (UBM). A suprachoroidal bleb imaged as suprachoroidal hyporeflectivity in UBM examination is apparent in 50 to 80% of eyes after DS (Chiou et al. 1998b, Perez-Rico et al. 2014). The clinical role of suprachoroidal outflow, however, is still not clear.

The Schlemms canal is opened and part of its wall is removed with DS. This might allow aqueous to drain from intrascleral space into the Schlemms canal and further into the episcleral veins (Mendrinos et al. 2008). This route of aqueous outflow may be important after viscocanalostomy (Stegmann et al. 1999), but its relevance after DS is unknown.

6.5 Goniopuncture

During the postoperative period, filtration of anterior chamber fluid under the conjunctiva can decrease. Very commonly this occurs because outflow resistance in Descemet's window has increased. Treatment is perforation of Descemet's window with YAG-laser goniopuncture (GP).

GP is performed as follows: the eye is anesthesized with oxybuprocain eye drops (or similar). One or a few drops of pilocarpine are instilled into the eye to stabilize the iris. The gonioscopic lens is introduced into the eye, and the Descemet's window is visualized. Then one pulse or several pulses are fired at the Descemet's window with a neodymium-doped yttrium aluminum garnet (YAG) laser. When a hole is achieved in the Descemet's membrane, fluid outflow from the anterior chamber can be visualized with a gonioscopy lens; IOP decreases within minutes.

GP turns deep sclerectomy from a non-perforating technique to perforating, because a hole between the anterior chamber and subconjunctival bleb is opened. GP is normally performed in the postoperative period weeks or even years after the initial operation, when the conjunctiva has healed.

Mean time of GP after DS is 10 to 12 months, mean IOP before GP ranges from 20 to 23 mmHg and decreases about 10 mmHg in the immediate post-GP period (Anand & Pilling 2010, Di Matteo et al. 2016). In these studies, mean IOP was between 11 and 14 mmHg 2 years after GP. The rate of GP after DS has a

large variation from 24 to 87% with a tendency toward a higher percentage with longer follow-up (Rekonen et al. 2006, Bissig et al. 2008, Ollikainen et al. 2011, Bettin et al. 2016).

After GP, several possible complications can occur, of which iris incarceration into the hole of the Descemet's window (13%), hypotony (4%) and microscopic hyphema (4%) are the most common (Anand & Pilling 2010, Di Matteo et al. 2016). The rate of iris incarceration into the Descemet's window after GP can possibly be reduced with preoperative laser iridotomy and Argon laser iridoplasty (Di Matteo et al. 2016).

If parts of the iris are incarcerated into the hole of the Descemet's window, and IOP rise occurs, there are several treatment options. First, argon laser applications can be applied to the peripheral iris with a gonioscopy lens (Argon laser iridoplasty) (Anand & Pilling 2010). Second, the iris can be treated with YAG laser applications in a manner similar to this on the base of iris as well as by creating a new opening in the Descemet's window (Vasquez Perez et al. 2013). The third option is surgical removal of iris tissue from the Descemet's window in the operating room if IOP remains too high despite laser treatments.

6.6 Needle revision

Postoperative subconjunctival scarring can lead to formation of a cystic filtration bleb, which is usually balloon-like, with clearly distinguishable walls. Cystic bleb formation can be treated with needle revision.

The eye is anesthesized with drops similarly as with GP. The patient is seated with their head positioned on the biomicroscope, or alternatively in the operating room. The upper eyelid is lifted with a cotton swab. The subconjunctival space is then entered with a straight or bent needle, one 27 g in our hospital, usually from the temporal side. The cystic bleb is punctured with the needle, and its wall can be opened further by cutting it with the side of the needle. This leads to increasing fluid filtration under the conjunctiva, which can be observed with the biomicroscope. If sufficient fluid filtration or a subsequent IOP drop is not achieved, the needle can be inserted under the scleral flap.

After needling, antimetabolites, 5-fluorouracil (5-FU), or mitomycin-c (MMC) (Koukkoulli et al. 2015), can be injected under the conjunctiva. These antimetabolites are used to lessen scar formation of the conjunctiva. Postoperatively, patients receive antibiotic and cortisone drops for a few days to several weeks.

Only one study concerns long-term effects of needle revision after DS (Koukkoulli et al. 2015). In that study of needle revision with MMC adjunction, a complete success rate of IOP < 18 mmHg or 20% reduction without glaucoma medication allowed was achieved in 57% of cases after 3 years of follow-up. The mean number of needle revisions needed was 1.6, ranging from 1 to 4. Needle revision had significant complications: delayed hypotony in 7.6% and endophthalmitis in 1.5% (one eye). MMC concentration was 0.01 or 0.02 mg/ml in most cases.

6.7 Surgical revision

Sometimes postoperative scar formation is too thick to be treated with needling alone. If fluid filtration under the conjunctiva is dramatically decreased, and needle revision has been insufficient, the patient may need surgical revision of the filtration bleb. Surgical revision is carried out in the operating room. The eye is anesthesized with drops or with a parabulbar block. The conjunctiva is opened surgically, and the underlying scar tissue or thickened tenons capsule or both are excised. The superficial scleral flap can be opened. The conjunctiva is closed with sutures as in the initial DS. When surgical revision is performed, the antimetabolites MMC or 5-FU can be injected under the conjunctiva.

To the best of my knowledge, no published studies consisting only of DS patients seem to exist. One study of surgical revision does include DS patients, although the majority, 45 of 54 eyes, had initially been performed by trabeculectomy or trabeculectomy combined with cataract procedure (Anand & Arora 2007). A thickened tenons capsule was excised in 41% of those eyes, MMC was used in all eyes, the scleral flap was opened and iridectomy performed when necessary. In that study all DS surgeries were performed with trabeculectomy as a revision operation. After 4 years, 39% of eyes achieved complete success; 43% of eyes required glaucoma medication.

7 INDICATIONS FOR DEEP SCLERECTOMY

Traditionally, treatment of glaucoma begins with topical medication and laser treatments, such as SLT. Surgery may be necessary if IOP remains too high despite maximal tolerated glaucoma medication, if the visual-field defect progresses and medication cannot be added, if glaucoma medication cannot be tolerated because of adverse effects, or if compliance prevents its topical use (problems instilling eye-drops, Alzheimers, decrease in cognitive status).

7.1 Open-angle glaucoma (POAG)

In open-angle glaucoma resistance to aqueous outflow is considered too high, and the anterior chamber angle in POAG is considered anatomically normal, open and without angle anomalies affecting aqueous outflow.

DS has a good IOP-lowering effect in POAG patients (Kozobolis et al. 2002, Bissig et al. 2008, Anand et al. 2011, Ollikainen et al. 2011, Bettin et al. 2016). In studies with the majority of their patients diagnosed as POAG, postoperative IOP after one year ranges from 13 to 17.3 mmHg with or without glaucoma medication (Kozobolis et al. 2002, Bissig et al. 2008, Anand et al. 2011, Ollikainen et al. 2011, Bettin et al. 2016). In the longer term, after 3 years, postoperative IOP ranges from 11.1 to 18.7 mmHg with or without glaucoma medication. In one study, IOP 10 years postoperatively was 12.2 mmHg (±4.7) with or without glaucoma medication (Bissig et al. 2008).

7.2 Normal tension glaucoma (NTG)

Among NTG patients, visual-field damage progresses with lower IOP than in POAG, and the target IOP is lower, usually between 10 and 14 mmHg. Trabeculectomy has been the gold standard among glaucoma-filtering procedures for NTG patients (Shum & Leung 2013), because the IOP-lowering effect of trabeculectomy among these patients is well documented (Membrey et al. 2000, Shigeeda et al. 2002, Jongsareejit et al. 2005, Jayaram et al. 2016).

Some studies prior to 2010 included NTG patients (Bissig et al. 2008, Anand et al. 2011), but they were not analyzed as a subgroup. To the best of my knowledge there is no study of the IOP-lowering effect of deep sclerectomy in NTG patients alone.

The IOP-lowering effect of trabeculectomy has been reported in NTG patients (Membrey et al. 2000, Shigeeda et al. 2002, Jongsareejit et al. 2005, Jayaram et al. 2016) to be sufficient, with mean IOP of 10.6 -11.1 mmHg 3 years after the operation with success rates of 39 to 65 % with or without medication (Membrey et al. 2000, Jayaram et al. 2016).

7.3 Exfoliation glaucoma (EXG)

In EXG, accumulation of exfoliation material occurs in the juxtacanalicular tissue under the inner wall of Schlemm's canal (Schlotzer-Schrehardt & Naumann 1995). This is the site of greatest resistance to aqueous outflow, and also the anatomical location at which DS is targeted. In several studies of DS with EXG patients, similar success rates were achieved with DS in EXG and POAG patients (Drolsum 2006). A more recent prospective study found similar results (Ollikainen et al. 2011), although goniopuncture was more common in the EXG group. Although these were relatively small studies with only 37 EXG patients as a maximum, they indicate that DS has a good effect on EXG.

The number of studies on DS with EXG patients is limited. However, they show good IOP lowering effect (Drolsum 2006, Mendrinos et al. 2009, Ollikainen et al. 2011). One year postoperatively, IOP has been between 11 and 12 mmHg and in the longer term, after at least 3 years of follow-up, IOP has ranged from 11 to 15.5 mmHg (Drolsum 2006, Mendrinos et al. 2009, Ollikainen et al. 2011), with a pressure drop of 13-17 mmHg with or without medication. The number of eyes in these studies has been 22 to 37.

7.4 Deep sclerectomy in other forms of glaucoma

There are relatively few reports of DS in uveitic glaucoma patients, although it seems that good IOP control in the medium term can be achieved by DS with MMC. In a retrospective study of 43 eyes, preoperative IOP decreased from 33.6 mmHg to 16.4 after 5 years follow-up, with 51% of eyes achieving IOP <19 mmHg without medication (Mercieca et al. 2017). In another prospective study of 33 eyes, IOP decreased from 37.2 mmHg to 14.7 mmHg after mean follow-up of 33 months (Al Obeidan et al. 2015), and 72% of eyes had final IOP < 21 mmHg without medication.

There is a small number of published studies on pediatric glaucoma. One study of modified deep sclerectomy has been reported to show relatively good IOP control. With a preoperative IOP of 31.9 mmHg, 70% of eyes achieved an IOP between 6 and 19 mmHg after 3 years of follow-up (Feusier et al. 2009). However, their deep sclerectomy technique was modified so that perforation to the anterior chamber and a surgical iridotomy were performed at the time of surgery.

Deep sclerectomy has been used in glaucoma associated with Sturge-Weber syndrome, but the result was not favorable (Audren et al. 2006). Postoperatively, 6 out of 9 operated eyes (66%) required another glaucoma surgical procedure after 2 years follow-up, with Kaplan-Meier survival of 0%.

8 CONTRAINDICATIONS TO DEEP SCLERECTOMY

Neovascular glaucoma is associated with the growth of small blood vessels in the anterior parts of the eye; these can grow into the anterior chamber angle. Because IOP reduction with DS is related to a functional conjunctival bleb and window of the Descemet's membrane, neovascular glaucoma is a contraindication for DS.

Angle-closure glaucoma is associated with narrowing or total closure of the anterior chamber angle. To achieve good IOP control with DS, a proper window of the Descemet's membrane must be created. This can be impossible when the anterior chamber is narrow or closed, so angle-closure glaucoma and angle anomalies are contraindications for DS.

Contact lens wear is not a direct contraindication, but wearing contact lenses can be difficult postoperatively. Filtering bleb after trabeculectomy may introduce difficulties in contact lens fitting and wear (Pederson 2005). To my knowledge no studies of worsening dry eye symptoms after DS exist. However, dry eye symptoms in some patients may worsen after trabeculectomy in conjunction with MMC (Lam et al. 2015). Postoperative follow-up with performance of GP when necessary are mandatory after DS (Rekonen et al. 2006, Bissig et al. 2008, Ollikainen et al. 2011, Bettin et al. 2016). Patients' ability to control visits should be taken into account when DS is scheduled.

9 VISCOCANALOSTOMY

The first results of viscocanalostomy appeared in 1999 (Stegmann et al. 1999). The conjunctiva is opened in the usual manner and a superficial and deep scleral flap are made. Then the canal of Schlemm is unroofed. Viscoelastic material is injected into both of the opened lumens of the canal of Schlemm. Viscoelastic material is considered to open the canal of Schlemm and facilitate aqueous outflow from the anterior chamber. The superficial scleral flap is sutured tightly. Viscocanalostomy is based on the assumption that by increasing aqueous outflow with viscoelastic dilatation of Schlemm's canal, no filtering bleb is necessary. Postoperative injections of 5-FU can reduce bleb fibrosis (Shaarawy et al. 2003).

In studies of viscocanalostomy, postoperative IOP has been from 15.4 to 16.2 mmHg after 5 years of follow-up, and two-thirds achieved IOP <18 mmHg without medication (Wishart et al. 2008, Grieshaber et al. 2015). The main adverse effects were microhyphema, microperforation, and cataract formation. A shallow anterior chamber and hypotony are very rare (Wishart et al. 2008, Grieshaber et al. 2015).

10 CANALOPLASTY

Canaloplasty, a modification of viscocanalostomy, was introduced in 2007 (Lewis et al. 2007). The first phases of canaloplasty and viscocanalostomy are the same, up to the formation of the deeper scleral flap. Then, the opening of Schlemm's canal is entered by a flexible catheter with a small light source in its tip. This catheter is carefully introduced into Schlemm's canal until it travels the total 360 degrees; then it is retracted from the other opening of Schlemm's canal, and a suture is tied to the tip. The catheter is then withdrawn from the Schlemm's canal and the catheter pulls the suture into Schlemm's canal. Viscoelastic material can be injected into the canal while the catheter is withdrawn. The ends of the suture are tied to secure it in place and apply tension to the inner wall of Schlemm's and to open its lumen. Then the scleral flap and conjunctiva are closed in the same way as with viscocanalostomy.

In studies of POAG eyes, a mean postoperative IOP of 13.3 to 14.5 mmHg was reached after 18 to 36 months follow-up with or without glaucoma medication (Grieshaber et al. 2010, Koerber 2012). Postoperatively, transient microhyphema was reported in 70% of eyes. Detachment of the Descemet's membrane and false passage of the catheter were less frequent (Grieshaber et al. 2010).

11 MINIMALLY INVASIVE GLAUCOMA SURGERY (MIGS)

Since both topical medication and glaucoma surgical procedures opening the conjunctiva have their disadvantages, several methods and devices have been developed to achieve IOP lowering with fewer adverse effects. These are collectively termed minimally invasive glaucoma surgery (MIGS). MIGS procedures can be further divided into three categories based on the structure, or the site of the aqueous-outflow resistance they are designed to bypass. Current methods and devices allow us to bypass the aqueous into subconjunctival space, through the trabecular meshwork to Schlemm's canal or to the suprachoroidal space. All MIGS procedures are performed ab interno through a peripheral corneal incision with minimal direct conjunctival surgical damage.

The XEN Gel implant (Allergan, Dublin, Ireland) offers a novel method for glaucoma surgery. It is a small tube made of porcine collagen and is inserted with an injector through a corneal peripheral incision, through Schlemm's canal, perforating the sclera to the subconjunctival space. The function of the XEN gel implant is to increase aqueous outflow under the conjunctiva. Subconjunctival MMC can be used in conjunction with the XEN gel implant to lessen scar reaction postoperatively (Sheybani et al. 2016). In that study, 89% of patients had an IOP reduction of ≥ 20% and 40% of patients were free of glaucoma medication after 12 months of follow-up. Another study showed qualified success rates (IOP <18 mmHg) of 80% in stand-alone surgery and 77% in a combination procedure of XEN gel implant and phacoemulsification after one year follow-up (Mansouri et al. 2018). One retrospective study of 234 eyes showed a primary success rate of 66% with glaucoma medication allowed after mean follow-up of 8.5 months (Widder et al. 2018). However, to my present knowledge there are no long-term results of XEN gel implant available.

The Trabectome (NeoMedix Inc., Tustin, CA, USA) is a device which uses electrocautery to remove a strip of tissue from the inner wall of Schlemm's canal and trabecular meshwork (Minckler et al. 2005). The handpiece of the trabectome is inserted through a temporal corneal incision, and the trabecular meshwork is cauterized with the tip of the handpiece. During their procedure, a gonioscopic lens allows visualization of anterior chamber-angle structures. Mean IOP reduction after 2 years is 31% (Kaplowitz et al. 2016), and the use of glaucoma medications is reduced by 0.99 ±0.54. All bleb-related complications are avoided, since the

trabectome allows a bleb-free procedure. The most common complications are hyphema, peripheral anterior synechiae, corneal injuries, and transient IOP spikes (Kaplowitz et al. 2016).

Another alternative to remove tissue from the trabecular meshwork is with the Kahook dual blade (Greenwood et al. 2017). It is an instrument with a curved tip and two blades (one on each side) placed behind the tip. It allows sharp cuts of trabecular meshwork tissue with visualization by a gonioscopic lens. Mean IOP reduction after 6 months follow-up was 26%, with blood reflux from collector canals seen in 39% of cases (Greenwood et al. 2017).

Another option for bypassing the trabecular meshwork is the iStent (Glaukos Corporation, Laguna Hills, CA, USA), a titanium stent inserted with an injector through the peripheral corneal incision into Schlemm's canal. While in place, it allows aqueous to bypass the trabecular meshwork. Postoperative IOP after 2 years decreased from 20.3 to 13.6 mmHg, but the amount of glaucoma medication in use remained unchanged (Ferguson et al. 2016). Two or three iStents can even be injected during the same procedure (Katz et al. 2015).

Aqueous outflow from the anterior chamber directly to the suprachoroidal space can be achieved with a CyPass Micro-Stent (Alcon, Fort Worth, TX, USA), a 6.35mm long polyamide tube inserted through the corneal incision between the ciliary body and sclera with a gonioscopic lens and a guidewire. Postoperative IOP has been 16.4 mmHg after 12 months' follow-up with a mean of 1.4 glaucoma medications in use (Garcia-Feijoo et al. 2015). However, 17% needed additional glaucoma surgery during their first postoperative year.

12 COMPLICATIONS OF GLAUCOMA SURGERY

12.1 Common complications of surgical treatment

Hypotony, IOP falling too low postoperatively, results from postoperative filtration becoming too strong. It is usually transient, and its duration may be from a few days to many months. The definition of hypotony varies: IOP <4 to <6 mmHg is usual (Bissig et al. 2008, Palanca-Capistrano et al. 2009, Anand et al. 2011). After glaucoma surgery, prolonged hypotony usually refers to low IOP on repetitive measurements on different days or low IOP lasting for several weeks (Bissig et al. 2008, Cillino et al. 2008) or months (Anand et al. 2011). Hypotony is a serious complication of glaucoma surgery and can lead to problems in the fundus: hypotony maculopathy or choroidal detachment (Higashide et al. 2016); these can threaten vision.

If the postoperative aqueous outflow achieved is too strong compared to the aqueous production, the anterior chamber (AC) may become shallow. A shallow AC can dramatically reduce visual acuity in the immediate postoperative period and can lead to increased risk of hemorrhage into the anterior chamber.

The conjunctiva is opened during glaucoma surgery and then closed with sutures at the end of the operation. If these sutures are not closed carefully, aqueous may leak out of the surgical conjunctival wound, creating a possible migration route for extraocular bacteria. Later, the conjunctival filtration area may leak (bleb leak), which some surgeons consider a particular issue after trabeculectomy in conjunction with MMC.

With perforating glaucoma surgical procedures, the eye wall is penetrated. Some procedures may involve mechanical perforation of the peripheral iris: surgical iridotomy. Both of these may lead to postoperative bleeding into the anterior chamber (hyphema). Hyphemas can appear postoperatively even after non-perforating surgery. Blood in the anterior chamber and bloody aqueous flowing into the bleb may increase the risk of postoperative scarring of the conjunctiva and bleb by promoting fibroblast activity (Lama & Fechtner 2003).

Choroidal effusion is characterized by fluid accumulating in the suprachoroidal space postoperatively. The fluid can be serous or hemorrhagic; these conditions are clinically called (serous) choroidal detachment and suprachoroidal hemorrhage, respectively. Serous choroidal detachment results when, after glaucoma surgery, IOP falls and a subsequent increase in transmural pressure is achieved in capillaries (Schrieber & Liu 2015). Suprachoroidal hemorrhage occurs when the posterior

ciliary artery ruptures (Chu & Green 1999) during or after surgery. Mild serous choroidal detachment is usually painless, but suprachoroidal hemorrhage can be associated with severe pain in the affected eye.

Choroidal effusion is usually diagnosed with a fundus examination: one to four convex areas of choroidal detachment can be seen, delineated by vortex veins. With ultrasonography, serous and hemorrhagic fluid can be evaluated; echo density is thicker when blood is present in the suprachoroidal space (Schrieber & Liu 2015). Treatment can be with topical steroids and cycloplegics when conjunctival leakage has been ruled out. Serous detachment usually resolves if hypotony is treated, with visual acuity increasing to its preoperative level. Suprachoroidal hemorrhage has a worse prognosis compared to serous choroidal detachment, and visual acuity usually decreases severely (Reynolds et al. 1993).

Hypotony can lead to folds in the posterior retina and macula. Folding may lead to distortion of photoreceptor cells, collapse of the scleral wall, shortening of axial length, and relative hyperopia. In hypotony, irregular astigmatism may increase, which may affect visual acuity of the affected eye even more (Costa & Arcieri 2007). Cystoid macular edema may be present because of alterations in vascular permeability (Kokame et al. 2001), but this is assumed to be less important to decrease in visual acuity (Costa & Arcieri 2007). Changes in lamina cribrosa structures may lead to papilloedema in association with hypotony maculopathy (Minckler & Bunt 1977). B-scan ultrasound and especially OCT are helpful in diagnosing hypotony maculopathy. In trabeculectomy, use of MMC may elevate risk of hypotony maculopathy, the incidence of which has been reported between 0 and 20% (Costa & Arcieri 2007). Treatment of hypotony maculopathy is essentially the same as treatment of hypotony; the focus is upon an increase in IOP in order to reverse the inward bowing of the sclera. Treatment of hypotony and related complications includes suturing the conjunctiva or bleb if leakage occurs (Haynes & Alward 1999), injection of blood under the conjunctiva (Wise 1993), or closing the scleral flap tightly with sutures (Eha et al. 2008).

A functioning filtering bleb is essential for the success of penetrating and non-penetrating glaucoma surgery. Usually a larger, diffuse bleb with limited vasculature is considered ideal postoperatively. The presentation of an encapsulated bleb (Tenons cyst) is different: it is localized, usually highly vascular and dome-shaped with a thick wall. The subconjunctival tenons capsule forms a cyst-like cavity. An encapsulated bleb may lead to elevated IOP. After limbal surgery, an encapsulated bleb may cause discomfort, or dellen formation. Encapsulated blebs can be treated conservatively (Costa et al. 1997), but sometimes needling is required (Ewing & Stamper 1990).

Aqueous misdirection after intraocular surgery is characterized by elevation of IOP with subsequent anterior displacement of the iris and lens diaphragm. Its mechanism is not completely known, but the ciliary body, anterior hyaloid, and lens are involved (Ruben et al. 1997). As a result, aqueous produced by the ciliary body is directed posteriorly, with elevated or even low IOP (Greenfield et al. 1999). Symptoms may include decrease in vision, eye pain, and eye redness. Suprachoroidal hemorrhage, pupillary block glaucoma, and choroidal detachment need to be ruled out. Medical treatment includes mydriatics, lessening of aqueous production, and hyperosmotics (Simmons 1972). Surgically, anterior vitrectomy or pars plana vitrectomy with zonulectomy and iridotomy (Debrouwere et al. 2012) can be performed to re-establish a normal aqueous flow direction.

After glaucoma surgery, cataract progression is faster. This is especially true with trabeculectomy (AGIS (Advanced Glaucoma Intervention Study) Investigators 2001, Bindlish et al. 2002, Lim & Cha 2017), but also after tube surgery, cataract progresses at the same rate as after trabeculectomy (Gedde et al. 2012a). Postoperative inflammation and other complications are associated with cataract growth (AGIS (Advanced Glaucoma Intervention Study) Investigators 2001).

Astigmatic changes may occur after trabeculectomy (Hugkulstone 1991). The reason for these changes is unknown. Placement of the corneal flap and tight sutures (Hugkulstone 1991) and cautery (Rosen et al. 1992) have been proposed as the explanation. Use of MMC may induce less with-the-rule astigmatism after trabeculectomy (Hong et al. 1998).

12.2 Intraoperative complications of deep sclerectomy

Intraoperatively, a tear in the TDM may occur. If it is small, and the anterior chamber is maintained, it is referred to as a microperforation and may go unnoticed during the operation. Even though microperforations are small, they can lead to hypotony during the first postoperative weeks. If a larger tear in the TDM occurs intraoperatively, aqueous flows rapidly through it, IOP decreases instantly, the anterior chamber becomes shallow, and even a flat anterior chamber may occur. When a large perforation of the TDM occurs, a surgical iridotomy will be needed in order to avoid iris incarceration into the large TDM opening. Alternatively, the procedure can be transformed to trabeculectomy (Karlen et al. 1999, Ollikainen et al. 2011).

The incidence of TDM perforations has been 1.4 to 5.7% (Karlen et al. 1999, Ollikainen et al. 2011), but this incidence seems to become lower with more experienced surgeons (Karlen et al. 1999). The incidence of intraoperative microperforation has been 13% (Ollikainen et al. 2011).

12.3 Early postoperative complications of deep sclerectomy

Deep sclerectomy, even though it is a non-penetrating technique, may lead to inflammation of the anterior chamber during the first postoperative days; this can be detectable in laser flare-cell measurement (Chiou et al. 1998a). One week postoperatively, inflammation settles into its preoperative state after deep sclerectomy, as opposed to four weeks after trabeculectomy (Chiou et al. 1998a). Postoperative inflammation promotes release of cytokines and fibroblast activity in the wound area. These can lead to granulation-tissue formation and eventually scarring and fibrosis of the wound area (Seibold et al. 2012).

Incidence of macular edema related to hypotony after deep sclerectomy has been reported at between 0 and 3.5% (Dahan & Drusedau 2000, Bissig et al. 2008).

During the first day or a few days after DS, the eye is very commonly hypotonous, but this is normally transient, and the IOP rises during the first weeks (Shaarawy et al. 2001). If the eye remains hypotonous after DS, a perforation or microperforation to the anterior chamber may have occurred during the operation. Ways to treat postoperative hypotony are several. Autologous blood can be injected under the conjunctiva near the flap to achieve stronger scar formation and a subsequent rise in IOP. The scleral flap can be partially or completely closed by sutures. Such closure can be achieved by suturing through conjunctiva (Shirato et al. 2004) or by first opening the conjunctiva and then suturing the scleral flap.

Prolonged hypotony can lead to choroidal detachment, but that usually resolves by itself if the hypotony is treated. Choroidal detachment is rare after DS, the incidence having been 0.5 to 7.6% (Bissig et al. 2008, Anand et al. 2011) in studies with larger patient populations.

Detachment of the Descemet's membrane after DS is a very rare complication. It has been reported a few times, with its highest incidence being 1.5% (Kozobolis et al. 2001, Ravinet et al. 2002, Anand et al. 2011). It occurs when the Descemet's membrane detaches from the underlying corneal stroma, and fluid accumulates in this new space. Postoperatively, it can be diagnosed by a decrease in visual acuity and corneal opacification (Ravinet et al. 2002), if detachment progresses centrally to the pupillary area. The underlying reason has been suggested to be high intrableb pressure with a tenons cyst or trauma (Ravinet et al. 2002). Hemorrhagic Descemet's membrane has also been reported (Kozobolis et al. 2001). Treatment is with intracameral injection of sulfur hexafluoride gas (Ravinet et al. 2002) or, if visual acuity remains good, with follow-up only (Kozobolis et al. 2001, Ravinet et al. 2002). After follow-up, visual acuity usually returns to its preoperative level (Kozobolis et al. 2001, Ravinet et al. 2002).

Hyphema, one of the major complications after trabeculectomy (Edmunds et al. 2002, Stalmans et al. 2006), usually resolves by itself but can raise postoperative IOP and possibly worsen postoperative fibrosis. For this reason, hyphema is

considered a significant complication of glaucoma surgery. Incidence of hyphema after DS has been reported as between 2.6% and 21% (Kozobolis et al. 2002, Bissig et al. 2008, Cillino et al. 2008, Anand et al. 2011). A low incidence of hyphema can be explained by DS being initially a non-perforating technique, with the wall of the eye not being perforated during the procedure. Normally, no iridotomy is performed, as opposed to the procedure in trabeculectomy. Hyphema after DS can result from perforation of Descemet's membrane and subsequent bleeding under the conjunctiva or blood flow from iris vessels or ciliary processes (Mendrinos et al. 2008).

A postoperative wound leak results from inadequate closure of the conjunctiva after DS, with its incidence being 3.3 to 8.6% (Kozobolis et al. 2002, Bissig et al. 2008, Anand et al. 2011). A postoperative wound leak is diagnosed by a positive Seidel test. Wound leaks after DS offer a possible route for bacterial invasion of the surgical bleb and subsequent blebitis or possibly endophthalmitis. A wound leak can be treated with a therapeutic contact lens, surgical resuturation of the conjunctiva (with possible patching with a conjunctival autograft) (Ollikainen et al. 2011), or with observation only.

Blebitis is a bacterial infection of the filtration area under the conjunctiva; the cause is microbial invasion, possibly after a wound leak. Postoperative blebitis is rare after DS with incidence of only 0 to 1% (Bissig et al. 2008, Anand et al. 2011).

Endophthalmitis is a bacterial infection inside the globe: in the anterior chamber, posterior chamber, or vitreous cavity.

The Descemet's membrane, during DS, is left intact. This forms an anatomical barrier between subconjunctival and intraocular spaces. One reported endophthalmitis after DS showed an intraoperative Descemet's membrane tear (Anand et al. 2011), but to the best of my knowledge no other study has reported postoperative endophthalmitis (Kozobolis et al. 2002, Bissig et al. 2008, Ollikainen et al. 2011). Although postoperative endophthalmitis is rare after DS, no statistical difference in endophthalmitis incidence can be found between DS and penetrating glaucoma surgery (Ang et al. 2010).

Postoperatively, the iris can adhere to the Descemet's window. This can lead to a dramatic rise in IOP, sometimes to higher than the preoperative level. It is considered to occur because of an unnoticed microperforation or perforation of Descemet's membrane during the primary surgery. Another time of occurrence is after GP, when a YAG laser hole is made in the Descemet's membrane to increase the ouflow of anterior chamber fluid.

On both of these occasions, ouflow of anterior chamber fluid draws part of the iris into the hole in the Descemet's membrane. The iris closes the hole in the Descemet's membrane and IOP begins to rise because outflow decreases.

12.4 Late postoperative complications of deep sclerectomy

Conjunctival and episcleral scarring postoperatively can lead to fibrosis of the surgical bleb. Signs are elevated IOP with diffuse conjunctival injection in the early phase (Mendrinos et al. 2008). Later, the bleb can appear encapsulated, and the wall can be thickened. These changes lead to a decrease in filtration under the conjunctiva with a subsequent rise in IOP, and, if continued, lead to surgical failure if filtration stops.

Intraoperative antimetabolites may prevent or lessen bleb fibrosis. Bleb fibrosis after DS has been 11.4 to 16.7% (Kozobolis et al. 2002, Bissig et al. 2008).

Cataract progression has also been reported after DS. After DS, 23% of eyes needed a cataract operation after 3 years of follow-up (Ollikainen et al. 2011) and rate of cataract progression appears to be lower compared to that with trabeculectomy, with 20% needing a cataract operation during first postoperative year (Edmunds et al. 2002). This is thought to occur because DS is an initially non-perforating procedure, the anterior chamber is not entered with surgical instruments, and no iridectomy is made.

DS seems to have only a small effect on corneal curvature. After the combination procedure of DS and phacoemulsification, the average amount of keratometric astigmatism change has been 0.18D (Corcostegui et al. 2004). Non-penetrating glaucoma surgery seems to induce fewer corneal astigmatic changes than does trabeculectomy (Egrilmez et al. 2004).

DS induces loss of corneal endothelial cells postoperatively. There is only one comparative study concerning endothelial cell loss after DS and trabeculectomy without MMC (Arnavielle et al. 2007). In that study endothelial cell loss was 4.5% during the first postoperative year after DS, compared to 9.6% after trabeculectomy.

Effect of DS on axial length (AL) is not known. AL is decreased after trabeculectomy by 0.26 to 0.32 mm when IOP is lowered (Saeedi et al. 2014, Usui et al. 2013). The choroidea is thickened when IOP is lowered with trabeculectomy; half of the optically measured AL decrease was actually due to an increase in choroideal thickness (Saeedi et al. 2014). Reported postoperative complications of two DS studies (Bissig et al. 2008, Anand et al. 2011) and Tube versus trabeculectomy study (Gedde et al. 2012a) are summarized in Tables 1. and 2.

Table 1. Early postoperative complications in two DS studies (Anand et al 2011 and Bissig et al.2016) and Tube versus trabe study (Gedde et al. 2012). Numbers in percentage of eyes affected.

	Anand et al.	Bissig et al.	Tube	Trabe + MMC
Choroidal effusion	0.5	7.6	14	13
Shallow or flat anterior chamber	0	0	10	10
Wound leak	5.7	0	1	11
Hyphema	2.6	8.6	2	8
Aqueous misdirection	0	0.9	3	1
Suprachoroidal hemorrhage	0	0	2	3
Vitreous hemorrhage	0	0	1	1
Decompression retinopathy	0	0	0	1
Cystoid macular edema	0	0	0	1

Tube = subgroup of Baerveldt shunt in Tube versus trabeculectomy study; Trabe + MMC = subgroup of Trabeculectomy with MMC in Tube versus trabeculectomy study

Table 2. Late postoperative complications in two DS studies (Anand et al 2011 and Bissig et al. 2008) and Tube versus trabe study (Gedde et al. 2012). Definitions of bleb configuration and ocular fundus changes may exist between studies. Numbers in percentage of eyes affected.

	Anand et al.	Bissig et al.	Tube	Trabe + MMC
Persistent corneal edema	NA	NA	16	9
Dysesthesia	NA	NA	1	8
Persistent diplopia	NA	NA	6	2
Encapsulated /cystic bleb	44	22.8	2	6
Bleb leak	4.1	8.6	0	6
Choroidal effusion	NA	7.6	2	4
Cystoid macular edema	NA	0	5	2
Hypotony maculopathy	1.5	0	1	5
Tube erosion	-	-	5	-
Endophthalmitis /Blebitis	1.5	0	1	5
Chronic or recurrent iritis	0	0	2	1
Tube obstruction	-	-	3	-
Retinal detachment	0	0	1	1
Corneal ulcer	0	0	0	1
Shallow or flat anterior chamber	0	0	1	0

Tube = subgroup of Baerveldt shunt in Tube versus trabeculectomy study; Trabe + MMC = subgroup of Trabeculectomy with MMC in Tube versus trabeculectomy study

13 ANTIFIBROTICS

Postoperative bleb fibrosis is one of the most important reasons for failure of glaucoma surgery during the postoperative period. Antifibrotics can be useful in avoiding excessive postoperative fibrosis. The most commonly used are Mitomycin-C (MMC) and 5-Fluorouracil (5-FU).

13.1 Mitomycin-C

Mitomycin-C (MMC) is an antibiotic agent with an antiproliferative function affecting both fibroblasts and endothelial cells (Smith et al. 1994). It cross-links DNA, inhibits protein synthesis, and affects all phases of the cell cycle (Lama & Fechtner 2003). In glaucoma surgery, MMC prevents scar formation and enhances bleb survival. MMC is a much more potent agent than 5-Fluorouracil (5-FU) (Smith et al. 1994) and can be instilled intraoperatively or during the postoperative period (Liu et al. 2016). MMC use in trabeculectomy was published in 1990 (Chen et al. 1990), and it has become widely used in glaucoma filtration surgery.

Intraoperatively, polyvinylalcohol sponges are soaked in MMC and inserted under the conjunctiva and scleral flap for 1 to 4 minutes. Then the sponges are removed, and the MMC is carefully washed away with balanced salt solution (BSS). The concentration of MMC can vary, with concentrations usually being 0.02 mg/ml to 0.4 mg/ml (Anand 2011, Mansouri et al. 2011).

Postoperatively MMC can be injected under the conjunctiva with needling performed subsequently when needed.

MMC has been widely used in deep sclerectomy, achieving good IOP control postoperatively (Kozobolis et al. 2002, Anand et al. 2011, Guedes et al. 2011, Ollikainen et al. 2011, Mercieca et al. 2015).

The number of studies comparing DS with and without MMC are limited. In one study (Kozobolis et al. 2002), MMC was found to enhance the IOP-lowering effect of DS with a rate of adverse effects comparable to that in DS without MMC. Postoperative IOP was 15.96 mmHg with MMC, compared to 18.71 without. MMC did not raise the risk of postoperative complications.

In another study, MMC used in DS did not affect the qualified success rate postoperatively: 72.4%, compared to 61.4% without MMC (Mercieca et al. 2015).

When comparing trabeculectomy with and without intraoperative MMC, results have been controversial. In two studies (Cohen et al. 1996, Carlson et al. 1997), MMC use resulted in better IOP control postoperatively. However, in another study, no difference in surgical success appeared when comparing surgical results after trabeculectomy with or without use of MMC (Shin et al. 1998).

Since MMC has a potent wound healing inhibition effect, adverse effects have also emerged.

Late-onset infections after trabeculectomy have been more common after MMC use (Jampel et al. 2001). In one study analyzing eyes with postoperative endophthalmitis, 67% had been operated on with MMC (Song et al. 2002). Hypotony maculopathy has also been associated with MMC use in trabeculectomy (Costa et al. 1993, Suner et al. 1997). Endothelial-cell loss after trabeculectomy with MMC has been 9.5% during the first three months postoperatively, but after that, further cell loss did not occur (Storr-Paulsen et al. 2008). Reports also involve scleritis (Fourman 1995) and scleromalacia (Akova et al. 1999) after trabeculectomy augmented with MMC.

13.2 5-fluorouracil

5-fluorouracil (5-FU) functions as an antimetabolite by competitively inhibiting further synthesis of thymine nucleotides. This leads to cessation of DNA synthesis, which leads to cell death (Lama & Fechtner 2003). Exposure to 5-FU leads to inhibition of tenon capsule fibroblast proliferation (Gressel et al. 1984, Khaw et al. 1992) and to inhibition of the contraction of collagen (Occleston et al. 1994).

In conjunction with deep sclerectomy, 5-FU is normally administered in one or several postoperative injections when IOP is elevated and postoperative scarring or vascularisation of conjunctiva is present (Ambresin et al. 2002, Khairy et al. 2006, Bissig et al. 2008). In one study's postoperative period after DS, 24.5% of eyes needed at least one subconjunctival 5-FU injection, with 4.9% of eyes having a needling procedure with 5-FU (Bissig et al. 2008). Alternatively, sponges soaked with 5-FU can be instilled under the conjunctiva for up to 5 minutes, after which they are removed and the 5-FU washed away (Singh et al. 2000, Joshi et al. 2005).

No randomized studies concern the IOP-lowering effect of 5-FU with DS. With trabeculectomy, postoperative IOP has been lower after 5-FU use: 12.0 vs. 16.8 mmHg, after 20 month's follow-up (Goldenfeld et al. 1994). Side-effects were the same as with the non-5-FU group, except that corneal punctate keratopathy was more common.

Side-effects of 5-FU with trabeculectomy have included corneal toxicity (Shapiro et al. 1985) and increased risk of endophthalmitis (Wolner et al. 1991).

AIMS OF THE STUDY

(I)
To study retrospectively the pressure-lowering effect of DS in NTG patients (I). How low an IOP can be reached by DS with or without MMC. To find possible complications of DS when low IOP is targeted.

(II)
To study prospectively the intraocular pressure-lowering effect of DS in NTG patients (II) until one year postoperatively.
To compare the effect of DS with and without MMC on postoperative IOP, on surgical success, and on adverse effects during the first postoperative year.

(III)
To study the long-term IOP-lowering effect of DS with and without MMC in NTG patients.
To compare DS with and without MMC on surgical success and adverse effects after long-term follow-up.

(IV)
To study and compare, retrospectively, the pressure-lowering effect of DS in POAG and EXG patients (IV).
To find any preoperative, intraoperative, or early postoperative factors related to surgical success.

(V)
To study prospectively the effect of IOP-lowering with DS on visual acuity in the early postoperative period (V).
To study the effect of DS on macular structures, and on corneal curvature, and corneal-shape indices in the early postoperative period.

MATERIAL AND METHODS

All patients were operated on in Helsinki University Central Hospital by glaucoma surgeons. Deep sclerectomy was performed as follows: the flap of the conjunctiva was performed superiorly, superolaterally, or superotemporally with its base in fornix. Superficial flap was rectangular with a thickness of one-third of the sclera. The scleral flap was cut anteriorly until the cornea was reached. If MMC was used, polyvinyl alcohol sponges were impregnated in it and then were introduced under the conjunctiva. The MMC was washed away with a balanced salt solution. A rectangular deep flap was created with its anterior edge reaching the cornea in order to achieve a trabeculo-Descemet's window of adequate size while separating the corneal stroma and the Descemet's membrane. The central wall of Schlemm's canal was carefully removed and the deep flap was completely excised. The collagen implant in use was Aquaflow® (Staar Surgical, Nidau, Switzerland), fixed to the stromal bed with one 10-0 polyamide (Ethilon®, Ethicon Inc, Somerville, NJ, USA) suture in order to keep the scleral pocket open during the first postoperative months. The superficial flap was loosely closed with 10-0 nylon sutures. Closure of the conjunctiva was performed by continuous or interrupted sutures or both, with 9-0 polyglactin (Vicryl®, Johnson & Johnson, St-Stevens-Woluwe, Belgium). A triamcinolone injection was given subconjunctivally.

The definition of glaucoma was optic neuropathy with visual field defect and optic nerve head presenting with common glaucomatous morphologic changes in the absence of other ocular or congenital diseases. Open-angle glaucoma was considered when glaucoma patients had open angles in examination with a gonioscopic lens.

POAG was defined when open-angle glaucoma patients had IOP ≥ 22 mmHg, and no signs of secondary glaucoma. EXG was considered, if exfoliation material was seen in open-angle glaucoma patients in the anterior capsule or pupil border after pupil dilatation. NTG was considered when patients with open-angle glaucoma always had an IOP of 21 mmHg or lower (one to two measurements between 22 and 24 mmHg allowed) and no signs of secondary glaucoma (such as exfoliation material or pigment deposits). IOP was measured with Goldmann applanation tonometer.

Normal distribution of samples was tested with Shapiro-Wilk or Kolmogorov-Smirnov tests. Summary statistics were presented as mean (±standard deviation, SD) when normal distribution was found. When normality assumption did not hold, median and range were used as summary statistics. The Wilcoxon signed ranks test was used to test comparisons in paired samples. The Mann-Whitney test was used to test non-paired samples. When samples were normally distributed,

Student's t-test was used to compare equality of means. Chi-squared test and Fisher's exact test (Study III) were used to test equality of the proportions. Survival analysis in Study III was performed with the Mantel-Cox test when comparing MMC and non-MMC groups. Success probabilities in Study IV were assessed with Kaplan-Meier estimators. The relative effect of fixed and time-varying explanatory variables on hazard of failing was modeled with an extended Cox-model (Study IV). Statistical significance level was set at p= 0.05. In studies II and III, sample size was calculated with alpha error of 5% and beta error 50%. In Study IV sample size was calculated with alpha error 5% and beta error 10%.

(I)

I analyzed 21 eyes of 18 consecutive NTG patients (16 women, two men). Patients underwent DS in Helsinki University Central Hospital between 2004 and 2007. Indication for surgery was progression of visual field loss, an IOP considered too high despite medication or intolerance to topical glaucoma medication. DS was performed superiorly, superonasally, or superotemporally. All but one patient received MMC (0.4mg/ml) soaked polyvinylalcohol sponges for 3 minutes under the conjunctiva. In three eyes DS was combined with phacoemulsification from a temporal wound and implantation of an intraocular lens. Follow-up visits were scheduled for 1 day, 1 week, 2 weeks, and 4 weeks postoperatively. After 4 weeks, follow-up was carried out either in our hospital or by local ophthalmologists. If IOP was considered too high during follow-up, GP was performed. I reported success rates at three IOP levels: 20%, 25%, and 30% reduction. Success was considered complete if IOP reduction was achieved without glaucoma medication, and a qualified success if glaucoma medication was needed

(II and III)

We studied 37 eyes of 37 patients (29 women, 8 men) in these prospective randomized controlled studies. Patients were consecutive NTG patients scheduled for DS in Helsinki University Central Hospital between 2007 and 2009. DS was performed superiorly in all patients. Patients were randomized with respect to the use of intraoperative MMC. The group operated on with intraoperative MMC had 15 patients and 22 patients were operated on without MMC (Table 3).

Table 3. Baseline characteristics of patients. Data are presented as mean ± SD.

	MMC (n=15)	non-MMC (n=22)	P
Age [years]	65 ± 5	62 ± 8	0.22
Follow-up [months]	12.3 ± 0.5	12.2 ± 0.4	0.31
Sex	13 women	16 women	0.31
IOP [mmHg]	15.2 ± 2.8	15.1 ± 2.9	0.92
CCT [µm]	516 ± 33	515 ± 47	0.94
Number of glaucoma medications	2.2 ± 0.8	2.6 ± 1.0	0.27
MD [dB]	9.4 ± 7.3	9.9 ± 5.5	0.80
CDR	0.84 ± 0.13	0.80 ± 0.10	0.37
Previous phacoemulsification	1	3	0.42
Previous LTP	4	1	0.053
Previous SLT	2	1	0.336

MMC = mitomycin-C used with operation, non-MMC = mitomycin-C not used, P = p-value, IOP = intra-ocular pressure, CCT = central corneal thickness, MD = mean defect in visual field, CDR = cup-to-disc ratio, LTP = lasertrabeculoplasty, SLT = selective laser trabeculoplasty.

MMC was used intraoperatively in the same way as in study (I). All patients received a collagen implant during the operation. The indication for surgery was progression of visual field loss (32 eyes) and IOP considered too high (5 eyes).

During the follow-up period, if IOP was considered too high, GP was performed at least one month postoperatively. Topical glaucoma medication was begun if GP had been performed and IOP remained too high. Needling with or without antimetabolites was performed when necessary.

Follow-up visits were scheduled 1 day, 1, 2, and 4 weeks, and 3, 6, and 12 months postoperatively (Study II). Additional follow-up visits 3, 5, and 6 to 9 years postoperatively were included (Study III). The outcome was considered a complete success if IOP was lowered by 25%, IOP was >4 mmHg, and no glaucoma medication was required. If medication was necessary to achieve the same limits, the operation was considered a qualified success.

(IV)

I analyzed retrospectively 235 eyes of 198 patients (138 women), who were the first consecutive patients operated on in Helsinki University Central Hospital with DS for either POAG or EXG between 2004 and 2006. I included only eyes with untreated IOP ≥ 22 mm Hg and an open angle in gonioscopy. If exfoliation material was present during examination, the eye was included in the EXG group (108 eyes). If no exfoliation material was present, the eye went into the POAG group (127 eyes). All other glaucoma subtypes were excluded. Follow-up visits were initially scheduled for 1 day, 1 week, 2 weeks, and 4 weeks postoperatively. After that, follow-up was carried out in our hospital or by local independent ophthalmologists.

Complete success was defined as an IOP between 4 and 17 mmHg without medication, and qualified success as an IOP between 4 and 17 mmHg with glaucoma medication allowed. 1-week success was defined as an IOP between 2 and 14 mmHg one week postoperatively without medication. We studied different factors affecting the outcome of surgery by a Cox regression model in which we included as explanatory variables patient age, glaucoma subtype, preoperative IOP, number of preoperative glaucoma medications, any previous ocular surgery, surgeon's experience, use of intraoperative MMC, and 1-week success. The effect of the surgeon's experience on surgery outcome was examined by giving the patient a number indicating the number of DSs performed by that surgeon during his/her career (the number "4" for the surgeon's fourth operation, "21" for the 21st operation).

(V)

I analyzed 35 eyes of 35 patients who underwent surgery with DS for POAG, EXG, or NTG. Each was examined preoperatively, one week, two weeks, and four weeks postoperatively. With every examination, I performed subjective refraction, IOP measurement by Goldmann applanation tonometer, and an ophthalmologic examination. Anterior chamber depth (ACD) and axial length (AL) were measured by IOL-master (Carl-Zeiss Meditec AG, Jena, Germany). Corneal shape was evaluated by a corneal Galilei Dual Scheimpflug Analyzer (SIS Surgical Instrument Systems AG, Biel, Switzerland). The corneal Scheimpflug was analyzed by a cornea specialist. I measured macular volume and foveal thickness using Stratus OCT (Optical Coherence Tomography, Stratus OCT Model 3000, Carl Zeiss Meditec Inc., Dublin, CA, USA). OCT measurements were analyzed by a retina specialist without knowledge of the clinical situation of the eyes concerned.

RESULTS

(I)

After a median 13 months' follow-up, IOP was significantly decreased to 10.5 mmHg (4-15). Median IOP reduction was 37% (12-78). Complete success at a 20%, 25%, and 30% reduction in IOP was achieved in 67%, 62%, and 52% of eyes. Qualified success was achieved in 71%, 67%, and 52% respectively. One patient needed a re-operation after 5 months, and was included in the success analysis as a failure.

Median glaucoma medication was reduced from 3 (0-4) preoperatively to 0 (0-3, $p<0.001$) postoperatively. By the last follow-up visit, GP had been performed on 10 eyes (48%). Among these eyes, IOP decreased from 16 mmHg (12-19) prior to GP to 12 mmHg (6-19) after GP. Intraoperative complications were tearing of the conjunctiva (three eyes) and microperforation (one eye). Postoperative complications were loss of two or more Snellen lines of visual acuity in three eyes and resuturing of the conjunctiva in three eyes. Hypotony (IOP <4 mmHg) was found in nine eyes (43%) one week, and in two eyes (10%) 4 weeks postoperatively. No eyes showed choroidal detachment, shallow anterior chamber, or hypotony maculopathy.

(II and III)

Initially 37 patients were included in the study and continued follow-up until one year (Study II, Table 3). After that, 3 patients (8%) dropped out; 13 patients in the MMC group and 21 in the non-MMC group had complete follow-up of 6 to 9 years (Study III). IOP decreased significantly in the MMC group from 15.2 mmHg (2.8) to 5.9 (3.1), $p<0.001$ one month postoperatively. Postoperatively, after 3, 6, and 12 months, IOP decreased to a respective 7.6 mmHg (3.7), $p<0.001$; 8.0 (3.1), $p<0.001$; and 9.3 (2.7), $p<0.001$. IOP was 9 mmHg (2-13), $p=0.002$, at the last follow-up visit 6 to 9 years postoperatively (Table 4).

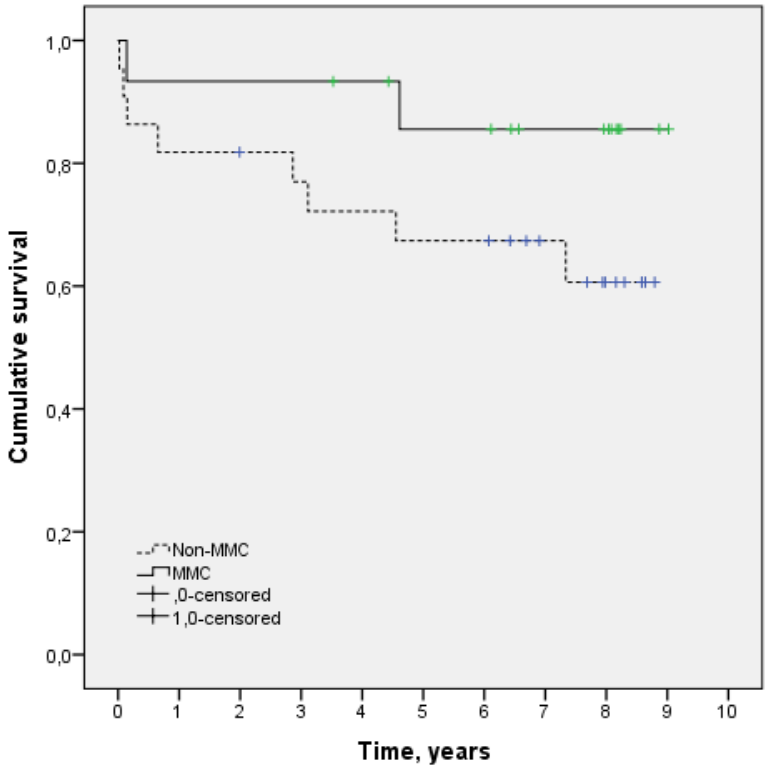
Table 4. Results of deep sclerectomy with and without intraoperative mitomycin-C (MMC) in normal tension glaucoma patients

		Baseline	1 Years		3 Years		5 Years		6-9 Years			
				p*		p*		p*		p*	CSucc	QSucc
IOP (mmHg)	MMC	15 (11-21)	10 (5-13)	0.001	11.5 (5-14)	0.002	10 (6-17)	0.002	9 (2-13)	0.002	8/13 62%	11/13 85%
	non-MMC	15 (10-19)	11 (7.5-16)	<0.001	12 (7-16)	0.001	13 (7-16)	0.002	10 (5-13)	<0.001	9/21 43%	13/21 62%
	p	0.99	0.006		0.45		0.032		0.36		0.48	0.25
Medication (N)	MMC	3 (1-4)	0 (0-2)	<0.001	0 (0-3)	<0.001	1 (0-3)	<0.001	0 (0-3)	<0.001		
	non-MMC	2 (1-3)	0 (0-3)	<0.001	0 (0-3)	<0.001	0 (0-3)	<0.001	0 (0-3)	<0.001		
	p	0.32	0.99		0.45		0.58		0.86			
Goniopuncture	MMC	-	7/15 47%		9/15 60%		11/14 79%		11/13 87%			
	non-MMC	-	16/22 73%		17/22 77%		17/19 89%		21/21 100%			
	p		0.11		0.26		0.63		0.14			
Needling	MMC	-	2/15 13%		2/15 13%		3/14 20%		4/13 31%			
	non-MMC	-	3/22 14%		4/21 18%		6/19 32%		12/21 57%			
	p		>0.99		>0.99		0.70		0.17			
Re-operation	MMC	-	0/15		1/15 7%		1/14 7%		1/13 8%			
	non-MMC	-	0/22		0/21		1/19 5%		4/21 20%			
	p								0.63			

Data as median (range). IOP=intraocular pressure, medication=median number of medications for glaucoma, MMC = deep sclerectomy done with MMC, non-MMC = deep sclerectomy without MMC, needling = cumulative number of eyes needled, with or without MMC, re-operation=cumulative number of eyes re-operated on, CSucc = Complete success, QSucc = Qualified success

p=statistical significance between groups, p* = statistical significance within groups, compared with baseline

In the non-MMC group, IOP decreased from 15.1 mmHg (2.9) to 11.0 (3.6), p<0.001 one month postoperatively; 3, 6 and 12 months postoperatively IOP was a respective 13.1 (4.3), p=0.10; 10.8 (3.3), p<0.001; and 11.8 (2.0), p<0.001. IOP was 10 mmHg (5-13), p<0.001, at the last follow-up visit. IOP was lower in the MMC group until 5 years postoperatively, with no difference in IOP thereafter between groups. 95% confidence interval of IOP one year postoperatively was 7.8 to 10.8 mmHg in the MMC group and 10.9 to 12.7 mmHg in the non-MMC group. After 3, 5 and 6-9 years, the 95% confidence intervals of IOP were 9.5 to 12.5, 9.0 to 12.3, and 6.3 to 10.6 mmHg in the MMC group and 10.8 to 13.2, 11.6 to 14.0, and 8.7 to 10.8 mmHg in the non-MMC group (unpublished). As for surgical success, we found no difference between groups at any point in time. Total success was achieved in the MMC-group in 10 of the 15 eyes (67%), and in the non-MMC group in 9 of the 22 eyes (41%) in (p=0.12) after 12 months (Study II). After 6 to 9 years of follow-up, complete success in both groups combined was 50%, and qualified success was 71% (Study III, Figure 1).



GP was performed in 47% of eyes in the MMC group and 73% in the non-MMC group during the first postoperative year (Study II), and GP rate increased to 87% and 100% after 6 to 9 years follow-up (Study III) with no difference between groups. Iris incarceration was encountered equally, 27% of eyes in the MMC group and 36% in the non-MMC group (p=0.64), all but one were treated with laser iridoplasty.

One month postoperatively, 4 eyes (27%) in the MMC group had hypotony (IOP < 4mmHg); 3 and 6 months postoperatively, three and two eyes had hypotony. After 12 months, none of the eyes had hypotony (Table 5).

Table 5. Intra- or postoperative complications

	MMC (n=15)	non-MMC (n=22)	p-value
Hypotony 1 months	4	0	0.010
3 months	3	0	0.029
6 months	2	0	0.078
12 months	0	0	
Cystoid maculopathy	1	0	0.22
Loss of ≥ 3 lines of visual acuity	2	1	0.34
Microperforation	1	0	0.22
Dellen	1	1	0.78
Needling	2	4	0.69
Resuturation of conjunctiva	1	5	0.19

The non-MMC group showed no postoperative hypotony. Two eyes in the MMC group had IOP between 2 to 4 mmHg, both with visual acuity of 1.0 in Snellen after 6 to 9 years of follow-up.

Four eyes had a BCVA reduction of 2 or more Snellen lines after 6 to 9 years of follow-up. Two eyes developed cataracts, one eye had macular degeneration, and one eye developed diabetic maculopathy.

Twelve months postoperatively, 12 eyes (80%) in the MMC group and 15 (68%) in the non-MMC group needed no glaucoma medication (p=0.427), the number of glaucoma medications in use was reduced in both groups throughout follow-up, and no difference existed between groups. Conjunctival resuturation was necessary for one eye in the MMC group and five eyes (23%) in the non-MMC group.

Needling was performed in two eyes (13%) in the MMC group and four eyes (18%) in the non-MMC group during the first year. This trend continued, the median number of needlings in the MMC group being 0 (0-2) compared to the non-MMC group's one (0-5, p=0.08) until the end of follow-up. When needling was necessary, the trend was towards more repetitions in the non-MMC group.

Initially 14 phakic eyes were in MMC group and 19 in the non-MMC group, with a cataract operation performed in six (43%) and in six (32%, p=0.42) respectively.

The rate of serious postoperative complications was low, with no cases of choroidal effusion, hypotony maculopathy, shallow anterior chamber, hyphema, endophthalmitis, late bleb leakage, blebitis or malignant glaucoma encountered.

(IV)

A total of 56 eyes had a follow-up of less than 12 months. These were included in the Cox regression model, but were excluded from other analysis of results. A total of 179 eyes (97 POAG and 82 EXG) had a follow-up of at least 12 months; mean follow-up was 38 (18) months, and between groups no difference emerged in duration of follow-up (p=0.303). MMC was used in 32 eyes (33%) with POAG, and in 22 eyes (27%) with EXG (p=0.37).

Preoperatively, IOP was lower in the POAG group, 22.6 mmHg (SD 5.1), than in the EXG group, 25.5 (6.5) (p=0.001). In the POAG group, IOP decreased to 16.8 mmHg (7.5) (p<0.001) and in the EXG group to 16.5 (7.8) (p<0.001) (Table 6).

Table 6. IOP, qualified and complete success, GP, and medication after the last visit of patients with at least 12 months` follow-up presented as mean (SD)

	n	IOP		Qualified Success	Complete Success	GP	GP time	Medication	
		PRE	POST					PRE	POST
POAG	97	22.6 (5.1)	16.8 (7.5)	70%	46%	64%	6.5 (10.8)	3.0 (1.1)	1.1 (1.5)
EXG	82	25.5 (6.5)	16.5 (7.8)	66%	43%	82%	5.2 (9.7)	3.1 (1.0)	1.3 (1.5)
p (between groups)		0.001	0.80	0.54	0.62	0.011	0.48	0.31	0.48

n, number of eyes; IOP, intraocular pressure; PRE, preoperatively; POST, postoperatively; GP, goniopuncture; GP time, time between surgery and postoperative goniopuncture in months; Medication, number of glaucoma medications

Postoperative IOP was the same between groups (p=0.80), but IOP reduction was greater in the EXG group than in the POAG group (9.0 mmHg vs. 5.8 mmHg) (p=0.023).

Complete success was achieved in 46% of eyes in the POAG group and in 43% in the EXG group (p=0.62), and qualified success in 70% in the POAG and 66% of eyes in the EXG groups (p=0.54). GP was more commonly performed in the EXG group (82%), than in POAG group (64%) (p=0.011). Reoperations were more common in the EXG group (24%), than in POAG group (12%) (p=0.037).

We studied the effect of explanatory variables on the complete and qualified success with Cox regression modeling. A one-week success lowered the hazard rate of losing complete success by 34% (p=0.031) and losing qualified success by 54% (p=0.004). We found no other factors to be related significantly to complete or qualified success. Surgeons' experience in DS had no effect on achieving complete or qualified success. Patients were operated on by eight surgeons; the median number of operations was 32, with the range from 1 to 96 (unpublished).

(V)

IOP decreased from a preoperative 20.8 mmHg (5.1) to 8.8 (7.3) (p<0.001) after one week, to 9.9 (6.5) (p<0.001) after 2 weeks, and 12.8 (5.8) (p<0.001) after 4 weeks following the operation. BCVA changed from a preoperative 0.14 Logmar (0.12) to 0.22 (0.20) (p=0.006) in one week, and to 0.19 (0.15) (p=0.011) in 2 weeks after the operation. BCVA returned to 0.17 (0.18) (p=0.28) 4 weeks postoperatively. Axial length decreased from 24.12 mm (1.81) preoperatively to 23.96 (1.81) (p<0.001) at one week, to 23.96 (1.82) (p<0.001) at 2 weeks, and to 24.02 (1.81) at 4 weeks postoperatively (Table 7).

TABLE 7. Parameters before and after deep sclerectomy. Results as mean (SD). P as compared to pre-operative values.

	PRE	1 WEEK	P	2 WEEKS	P	4 WEEKS	P
IOP	20.8 (5.1)	8.8 (7.3)	<0.001	9.9 (6.5)	<0.001	12.8 (5.8)	<0.001
BCVA	0.14 (0.12)	0.22 (0.20)	0.006	0.19 (0.15)	0.011	0.17 (0.18)	0.28
AL	24.12 (1.81)	23.96 (1.81)	<0.001	23.96 (1.82)	<0.001	24.04 (1.81)	<0.001
ACD	3.37 (0.61)	3.27 (0.63)	0.22	3.31 (0.57)	0.56	3.36 (0.61)	0.69
SPH EQUIV	-1.02 (2.62)	-1.15 (2.69)	0.14	-1.01 (2.64)	0.50	-1.18 (2.62)	0.14
SIM K MAX	44.6 (1.6)	44.9 (1.5)	0.007	44.8 (1.7)	0.06	44.9 (1.5)	0.022
SIM K MIN	43.7 (1.6)	43.7 (1.5)	0.58	43.7 (1.5)	0.50	43.9 (1.4)	0.08
SIM K MIN AXIS	94 (49)	94 (51)	0.81	99 (56)	0.77	101 (45)	0.33
ACP	44.3 (1.6)	44.4 (1.5)	0.029	44.3 (1.5)	0.41	44.5 (1.5)	0.014
CCT	547 (25)	540 (29)	0.003	540 (27)	0.002	541 (24)	0.001
MAC VOL	6.31 (0.54)	6.28 (0.64)	0.71	6.39 (0.56)	0.19	6.32 (0.59)	0.49
FOV THICK	214 (24)	218 (33)	0.60	222 (31)	0.17	219 (29)	0.34
MACULAR FOLDS (%)	0/33, (0)	3/33, (9)	0.25	4/32, (13)	0.13	2/34, (6)	0.50
MACULAR EDEMA (%)	3/33, (9)	2/31, (7)	>0.99	3/31, (10)	>0.99	3/34, (9)	>0.99

PRE = Pre-operative values; IOP = Intraocular pressure; BCVA = Best corrected visual acuity; AL = Axial length in mm; ACD = Anterior chamber depth in mm; SPH EQUIV = Spherical equivalence; SIM K MAX = Steeper simulated K-value in diopters; SIM K MIN = Flatter simulated K-value in diopters; SIM K MIN AXIS = Axis of flatter axis in degrees; ACP = Average corneal power in diopters; CCT = Central corneal thickness in µm; MAC VOL = Central macular volume in mm^3; FOV THICK = Foveal thickness in µm

A steeper corneal meridian changed from 44.6 D (1.6) preoperatively to 44.9 (1.5) (p=0.007) at one week, and to 44.9 (1.5) (p=0.022) 4 weeks postoperatively. The postoperative 95% confidence interval of steeper meridian varied between 44.23 D to 45.47 D (unpublished). Average corneal power changed from 44.3 D (1.6) preoperatively to 44.4 (1.5) (p=0.029) at one week, and to 44.5 (1.5) (p=0.014) at 4 weeks postoperatively. Central corneal thickness decreased from 547 um (25) preoperatively to 540 (29) (p=0.003) at one week, to 540 (27) (p=0.002) at 2 weeks, and to 541 (24) (p=0.001) at 4 weeks postoperatively. The postoperative 95% confidence interval of central corneal thickness varied between 530 and 550 um (unpublished). Macular volume, foveal thickness, macular folds, and macular edema showed no change postoperatively. Four patients had macular folds in OCT measurement in association with hypotony after 2 weeks and two of these persisted until 4 weeks with visual acuities of 0.9 in Snellen lines.

DISCUSSION

1 PATIENTS AND METHODS

Study I was retrospective, conducted to gain information as to how low an IOP can be reached with DS, which was a relatively new method in our hospital in 2007. I had only 18 patients and 21 eyes in this study, and follow-up was 12 months. These were the first patients operated on with DS in our hospital. Experience with Study I helped us in planning Study II.

Study II was prospective and randomized. This type of study was ideal for comparing two treatment methods: DS with or without MMC. We included only patients with low preoperative IOP, and our number of patients was relatively low, only 37. Few patients fulfill our criteria. We included, however, all eligible patients in our hospital's department of glaucoma surgery over two and half years. The follow-up time was one year.

Study III was a follow-up for the patients of Study II. It carried on until 6 to 9 years postoperatively. Our dropout rate in Study III was low, only three patients were lost to follow-up; two discontinued study visits, and one died. In other studies, dropout rates have been higher (Bissig et al. 2008, Anand et al. 2011).

Definition of NTG was based on IOP measurements without consideration of vascular or systemic factors. One or two measurements of IOP between 22 and 24 were allowed if all other IOP measurements were 21 mmHg or below (11 eyes). Although NTG features include peak IOP under 21 mmHg without treatment, these patients were included in the study. This definition may be challenged, but purpose was to find the IOP-lowering effect of DS when preoperative IOP is already low.

The aim of the study was to find the IOP-lowering effect of DS when aiming for low postoperative IOP. Another aim was to find possible additional benefits of MMC use. No visual field measurements were studied and direct conclusions on preventing visual field loss on these patients cannot be made on the basis of my study. In order to be able to find differences in visual field defect progression, the study design would have to have been different, and a control group of non-operated patients would have been needed. More frequent postoperative control visits with visual field testing would have been needed. My study aimed in studying IOP lowering with DS, since it has been beneficial in NTG patients.

Study IV was retrospective, with POAG and EXG patients. These were the first POAG and EXG patients operated on with DS in our hospital. Being retrospective, its follow-up time varied. We included all patients in the Cox regression model, but we excluded patients with less than one year follow-up from final results concerning IOP. When patients with shorter follow-up were excluded, mean follow-up time was 38 months. After exclusion, I had 97 eyes in the POAG and 82 in the EXG groups, which is, to my knowledge, the largest number of EXG eyes in any peer-reviewed study.

Study V was prospective, with 35 patients and 35 eyes and a 3-month follow-up. An OCT analysis of the macula was carried out by a retina specialist in a masked fashion. During the immediate postoperative period, patients had difficulties focusing during OCT measurement, which may have been affected by their glaucomatous visual field defect. I had no equipment to study the thickness of the choroid, which would have been a very interesting topic. Corneal topographic measurements were sometimes difficult to perform and analyze when IOP decreased after surgery. Sometimes the repeatability of corneal measurements was poor. Unfortunately, measurements of the anterior chamber volume and angle were not reliable with Scheimpflug analyzer.

That we had no predetermined target IOP may have affected our results, especially concerning retrospective Studies I and IV. In these studies, follow-up was in part performed by local ophthalmologists, and the role of GP during the postoperative period was not fully realized, since many times medication was initiated before performance of GP. Sometimes the treating ophthalmologist may have been satisfied with the IOP lowering achieved by surgery, despite it not achieving a decrease of 25%. Performing GP was more controlled in prospective Studies II and III.

2 THE EFFECT OF DS IN NTG (I, II, III)

DSCI reduces IOP efficiently even when target pressure is low. Its IOP-lowering effect is both clinically and statistically significant until 6 to 9 years postoperatively.

In the prospective study, mean IOP after one year was 9 to 12 mmHg. This IOP-lowering effect was maintained during our follow-up with an IOP of 9 to 10 mmHg after 6 to 9 years.

Performing GP is mandatory for good IOP control postoperatively. The GP rate was almost 90% during our follow-up even with intraoperative MMC. Without MMC, all patients needed GP during our 6-to 9-year follow-up.

Trabeculectomy in NTG has been studied only in retrospective fashion. One recent study investigated the Moorfields Safe Surgery method with MMC in NTG with good results. IOP was lowered from 14.7 mmHg to 10.2 mmHg and IOP was >25% lower in 63.6% of eyes (Jayaram et al. 2016), with immediate postoperative hypotony in 2.3% and late hypotony in 0.8% of eyes. That study was retrospective, however, with only 24% of eyes, 31 out of 131, having a 4-year follow-up.

Another study reported good IOP-lowering results after traditional trabeculectomy with MMC: preoperative IOP of 13.3 mmHg decreased to 7.2 mmHg (Schultz et al. 2016). In their study, hypotony occurred in 20%, and hypotony maculopathy in 6% of eyes, and of 18 eyes, cataract surgery was needed for 8 (44%) during a follow-up of 4 years. That study was retrospective, and 50% of operated eyes had a 4-year follow-up.

A third study with 39 eyes had a preoperative IOP of 15.9 mmHg and after 3 years of follow-up, this was decreased to 12 mmHg (Jongsareejit et al. 2005), with hypotony maculopathy noticed in 18% of the eyes.

Postoperative IOP has been 7.2 to 12 mmHg after trabeculectomy with MMC in NTG patients after 3 to 4 years' follow-up (Jongsareejit et al. 2005, Jayaram et al. 2016, Schultz et al. 2016). The IOP-lowering effect in our study after DS was similar: 9 to 10 mmHg after 6 to 9 years' follow-up.

3 THE EFFECT OF DS IN POAG AND EXG (IV)

IOP can be significantly lowered with DS among POAG and EXG patients. This effect in IOP was apparent throughout our follow-up of 3 years. The preoperative IOP of 22.6 and 25.5 mmHg was lowered to 16.8 and 16.5 mmHg in the POAG and EXG groups at the last follow-up visit. Between POAG and EXG groups no difference emerged in postoperative IOP, but EXG patients needed more GP. Success rates showed no difference between EXG and POAG eyes.

My results are in concordance with previous findings (Drolsum 2006, Mendrinos et al. 2009, Ollikainen et al. 2011).

The largest prospective study had 37 EXG eyes operated on by DSCI with MMC. After 3 years, IOP was significantly reduced from 25 to 11 mmHg (Ollikainen et al. 2011). Complete or qualified success was achieved in 73% of eyes, with GP needed in 87%.

In another study of 22 eyes, the IOP-lowering result was of the same magnitude; preoperative 29.9 mmHg decreased to 13.2 mmHg 4 years postoperatively (Mendrinos et al. 2009). In their study, MMC was used in 23%, complete success was achieved in 54.5% and GP was performed in 63.6% of eyes.

A third study with 28 EXG eyes and 45 months' follow-up showed good results as well concerning IOP lowering: preoperative 28.3 mmHg decreased to 15.5 mmHg after follow-up (Drolsum 2006). In that study, MMC was used in 18%, and GP was performed in 32%, with complete success for 50%.

The postoperative IOP achieved in my study of EXG was higher than in other studies (11 to 15.5 mmHg). That I analyzed the first consecutive eyes operated on with DS in our hospital, may have affected my results. MMC was used in only 26.8% in EXG group, but today, MMC is used for a larger proportion. My success definition was an IOP between 4 and 17 mmHg, which was hard to achieve. My study was retrospective, and I had no target IOP determined before the operation. The follow-up of some of the patients was performed by private ophthalmologists who may have been satisfied with an IOP higher than 17 mmHg. The complete success rate in my study and in these other studies after 3 to 4 years' follow-up has been from 43 to 54.5% (Drolsum 2006, Mendrinos et al. 2009, Ollikainen et al. 2011).

4 THE EFFECT OF DS ON OCULAR STRUCTURES (V)

I tried to find possible effect of DSCI on corneal topography, ocular dimensions and macular structures in a prospective study. Visual acuity decreased immediately after DSCI, but then increased back to preoperative level between two and 4 weeks postoperatively. Previously, even faster recovery of visual acuity after DS has been reported (Shaarawy et al. 2004).

AL decreased after DSCI, and this change persisted for up to 4 weeks postoperatively and was related to a decrease in IOP. Decrease in AL has occurred after trabeculectomy (Cashwell & Martin 1999, Karasheva et al. 2003, Usui et al. 2013). Our ACD was unchanged. Some amount of decrease in AL while ACD remains constant may be explained by changes in choroideal thickness. In one study of trabeculectomy, when IOP was lowered, AL decreased postoperatively (Saeedi et al. 2014). In their study, half the reduction in AL was explainable by thickening of the choroid. Unfortunately, when this study was made, I had no equipment to measure its thickness. Possible changes in choroideal thickness after DSCI would be an interesting study topic.

After DSCI, corneal dimensions showed changes. A steeper meridian of the cornea was further steepened one to 4 weeks postoperatively, and average corneal power increased one and 4 weeks postoperatively. The preoperative mean of steeper meridian is within 95% confidence intervals of postoperative measurements, indicating small actual change. Although differences in steeper meridian and average corneal power were statistically significant when compared to preoperative values, the amount of change was low, only 0.3D in steeper corneal curvature, and the clinical meaning of this change is doubtful. At the same time, spherical equivalence and subjective refraction remained unchanged, and 4 weeks postoperatively, visual acuity had already increased to preoperative level. The scleral flap was sutured loosely and did not affect the direction of corneal astigmatism.

Postoperatively, the central cornea became 6 to 7 um thinner. A similar finding has been made after trabeculectomy (Moschos et al. 2017). However, the preoperative mean thickness of central cornea is within 95% confidence intervals of postoperative measurements. Lowering IOP could theoretically alter endothelial function and lead to less fluid accumulating into the corneal stroma. An iatrogenic change in corneal structures can be achieved when creating a Descemet's window; even detachment of the Descemet's membrane with subsequent hemorrhage has been reported (Kozobolis et al. 2001).

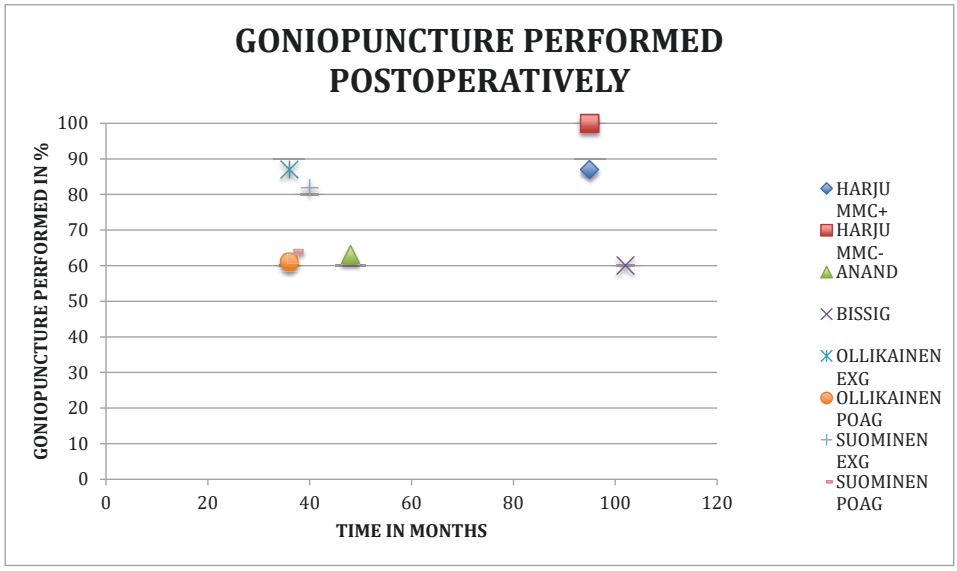
Normal diurnal variation of corneal measurements in my patients was unknown, and I had no control group in this study. In one study of glaucoma patients, up to 12 um diurnal change in corneal thickness was measured (Villas-Boas et al. 2009).

OCT analysis showed four patients having macular folds in association with hypotony 2 weeks postoperatively, and at 4 weeks, two of these persisted with good visual acuities. I found no signs of macular edema, and no change in macular volume or in foveal thickness. Macular edema has been found in 0 to 3.5% of eyes after DS (Dahan & Drusedau 2000, Bissig et al. 2008) and choroideal detachment in 0.5% to 7.6% (Bissig et al. 2008, Anand et al. 2011). My small sample size may explain why I found no signs of these adverse effects postoperatively. However, my findings support the view that after DS fewer changes in the ocular fundus occur postoperatively, compared to the situation after trabeculectomy (Cillino et al. 2004), and with DS, irreversible macular changes affecting visual acuity are uncommon.

5 MITOMYCIN IN DS (I, II, III, IV)

In our prospective study, eyes having surgery with MMC had lower IOP until 5 years postoperatively, but after 5 years, the difference in IOP was no longer statistically significant. Confidence intervals of MMC and non-MMC groups` postoperative IOP overlap after one year. The difference between these groups may have been diminished because of more frequent GPs and needlings in the non-MMC group. Moreover, the eyes in the non-MMC group also received MMC injections when needled. A larger study group with more power may have made our results statistically significant. Study groups with NTG patients, however, tend to be small. We included all eligible NTG eyes in this prospective study for over 2 years, between 2007 and 2009, at Helsinki University Central Hospital.

Eyes having surgery without MMC were more likely to need GP in the postoperative period, at 100% vs. 87%. Both of these groups had large amount of GP performed, but our follow-up period was as long as from 6 to 9 years. Rates of GP have ranged from 6 to 29% per follow-up year (Figure 2).



It is therefore possible that when follow-up is continued until 10 years or longer, MMC eyes will also show a GP rate close to 100%.

A tendency toward more needling procedures appeared in our non-MMC group, but this difference was not statistically significant.

Adverse effects from MMC are sometimes feared since it is a potent agent affecting fibroblast activity. In our studies, MMC did not increase the number of adverse effects. After application, MMC was carefully washed away with balanced salt solution (BSS). Our method with MMC use is essentially the same as the Moorfields Safer Surgery technique (Dhingra & Khaw 2009). Polyvinylalcohol sponges soaked with MMC are inserted posteriorly under the conjunctiva to avoid contact with the limbal conjunctival margin. Sponges allow a constant amount of MMC to be released, and the contact time was 3 minutes. MMC was then carefully washed away with BSS. This method may allow a relatively standard amount of MMC to be in contact with ocular tissues.

MMC concentration was 0.4 mg/ml. Use of MMC with DS varies: good IOP control has been achieved without MMC in other glaucoma subtypes (Bissig et al. 2008), but many surgeons prefer MMC with DS at concentrations of 0.2 mg/ml (Anand et al. 2011, Mansouri et al. 2011) to 0.4 mg/ml (Ollikainen et al. 2011). MMC at a concentration of 0.4 mg/ml has been used with trabeculectomy in NTG (Hagiwara et al. 2000, Jongsareejit et al. 2005, Shigeeda et al. 2002, Jayaram et al. 2016). Use of higher concentrations of MMC can be justified when treating NTG patients, since target IOP is low.

6 PREDICTION OF SURGICAL OUTCOME AND LEARNING-CURVE EFFECT

Success rates were better when IOP one week postoperatively was between 2 and 14 mmHg in the Cox regression analysis of Study II. This finding is interesting, since postoperative follow-up could theoretically be adjusted accordingly. The reason for a too-high one-week IOP may be an incorrect dissection plane or a too-small filtration through the Descemet's window. Later, these eyes may show a rise in IOP, when the scarring process lessens filtration. One-week IOP lower than 2 mmHg may be an indication of microperforation. In eyes with early microperforation of the Descemet's window, a risk may occur for iris incarceration with subsequent problems in aqueous filtration. One-day IOP was found to be prognostic of postoperative IOP control in one study (Shaarawy et al. 2004), but another found it had no prognostic value (Guedes et al. 2011). Considering the results of my study, one-week IOP may have more prognostic value.

Previously it became clear that in viscocanalostomy, the effect of the learning curve is clear, with a better success rate achieved after the first ten cases (Jonescu-Cuypers et al. 2001, Luke et al. 2002). In DS, achieving the correct dissection plane in the first cases has been difficult (Dietlein et al. 2000). We analyzed the effect of the learning curve on success rates with a Cox regression model, but in this small series, we failed to show any effect. This is in contrast to previous findings. My study consisted of first cases of POAG and EXG operated on with DS in our hospital. Today, MMC is more widely used, and GP is performed when IOP rises before initiation of topical glaucoma medication. Three eyes were reported having a perforation to the anterior chamber intraoperatively, and these were excluded from the study of 235 eyes. It is unlikely that excluding these affected my results concerning the learning curve effect.

7 DS COMPLICATIONS

GP was common in our studies with longer follow-up (Studies III and IV), reaching 87 to 100% in NTG patients after 6 to 9 years. Our results are in line with previous results (Figure 2). Target pressure in NTG patients is low, which may explain GP rates up to 100% with longer follow-up.

In EXG patients, GP was more common than in POAG patients. EXG eyes needed more GP than did POAG eyes, 81% vs 64%, but this may indicate that EXG is a more aggressive disease than is POAG, and IOP tends to increase more easily. Explanation may be that exfoliation material accumulates into, and possibly changes the function of, the trabecular meshwork (Morrison & Green 1988).

Another explanation may be the effect of exfoliation syndrome on the blood-aqueous barrier, with possibly altered postoperative inflammation (Nguyen et al. 1999). Another study had a similar result, with more GP performed on EXG (87%) than on POAG (61%) eyes during 3 years of follow-up (Ollikainen et al. 2011). In their study, all eyes were operated on in conjunction with MMC.

During GP, the non-penetrating DS procedure is essentially transformed to penetrating procedure, when the trabeculo-Descemet's membrane is perforated with a YAG laser. Because of its high incidence after DS, GP is mainly considered an enhancement to a DS procedure rather than failure. After GP is performed, however, DS is no longer a non-penetrating procedure.

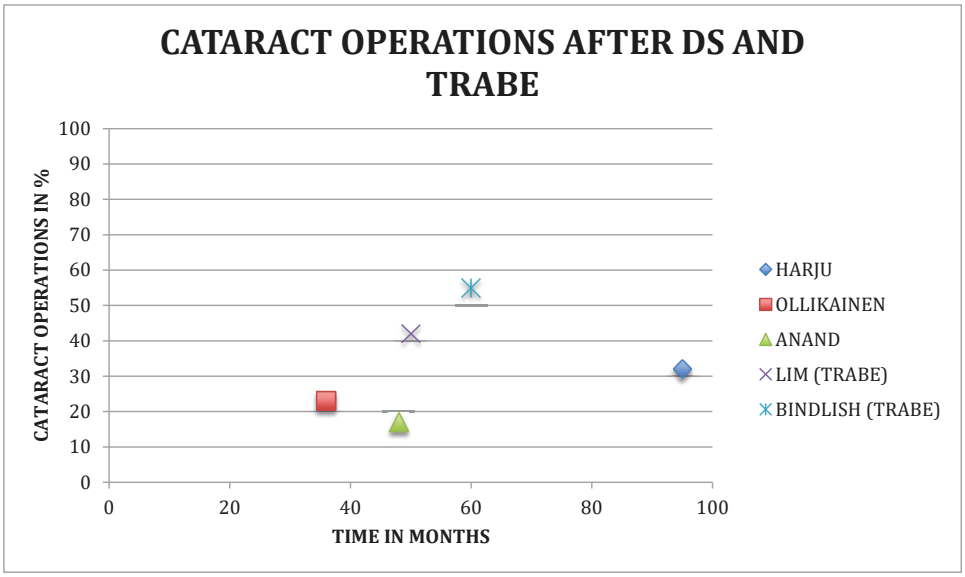
GP is not free of risks. Its main complications are iris incarceration to the opening in the trabeculo-Descemet's membrane and hypotony.

In Study III, iris incarceration to the Descemet's window occurred, when groups were combined, in 32% of eyes, MMC use had no effect. Reported incidence of iris incarceration after GP has been 13.2% with 3 years' follow-up (Anand & Pilling 2010). In a more recent study, when Argon laser peripheral iridoplasty (ALPI) and laser iridotomy were performed on peripheral iris before GP (Di Matteo et al. 2016), iris incarceration rate was efficiently reduced to 3%. Risk of hypotony after GP has been 4% (Anand & Pilling 2010). Hypotony after GP has a high risk for development of hypotony maculopathy.

In POAG and EXG eyes, needling was required in 14 to 15%. The needling rate in these patients was as expected, as a needling rate of 14% has been usual in primary DS procedures (Anand et al. 2011).

In NTG eyes with longer follow-up, needling was required for 13.5% of eyes during the first postoperative year. This increased to 26% after 5 years and to 47% after 6 to 9 years. Preoperative use of MMC had no effect on needling rate. Needling rate in these NTG eyes was higher than in POAG or EXG. A possible explanation could be low target IOP in these eyes. In one study of DS after failed trabeculectomy, the needling rate was 32% after 5 years' follow-up (Anand & Wechsler 2012), similar to our NTG patients. Episcleral and subconjunctival fibrotic processes seem to continue for at least 6 years postoperatively after DS.

The need for a cataract operation was 4.0 to 7.7 %/ year after DS in our study and in others' studies (Anand et al. 2011, Ollikainen et al. 2011). Cataract surgery is more common after trabeculectomy with an annual incidence of 10.1 - 11.0% (Bindlish et al. 2002, Lim & Cha 2017), (Figure 3).



This can be clinically important, since besides transient loss of BCVA, the cataract operation itself may compromise the function of filtering surgery (Klink et al. 2005). In prospective studies II and III no combination procedures were included. In a recent study of DS and phacoemulsification combination procedures, good IOP lowering result was achieved, with a success (IOP <16 or 30% reduction, with or without medication) rate of 68.3% after three years' follow-up (Mercieca et al. 2015).

My prospective study (II) with NTG, had three eyes with hypotony (IOP <4 mmHg) after 3 months, and two eyes after 6 months. All hypotonic eyes were in the MMC group. One of these eyes developed cystic maculopathy but was diagnosed as diabetic maculopathy with need of subsequent vitrectomy and anti-vascular endothelial growth-factor injections. The non-MMC group had no cases of hypotony. After a follow-up of 6 to 9 years (Study III), one eye had an IOP of 2 to 3 mmHg and one had 4 mmHg, both with visual acuities of 1.0 in Snellen.

In my retrospective study (IV) of EXG and POAG patients, no cases of hypotony were found. In these patients preoperative IOP was higher than in NTG patients, and MMC was used in only 30% of the eyes. No postoperative hypotony maculopathy was found.

The incidence of hypotony has been 0 to 4% in other studies concerning DS with MMC (Cillino et al. 2008, Anand et al. 2011, Mesci et al. 2012). Incidence of hypotony maculopathy has been 0 to 3.5% (Dahan & Drusedau 2000, Bissig et al. 2008).

In our prospective studies, four eyes lost two or more lines in best corrected visual acuity (BCVA). Three of these were in the MMC group; one eye had cataract, one had macular degeneration, and one had diabetic maculopathy. In the non-MMC group, BCVA decreased from 1.0 to 0.63 in one eye, and some cataract formation was visible.

CONCLUSIONS

(I)

DS was safe and effective in reducing IOP in the one-year retrospective study. Nearly half of the eyes needed GP during the first postoperative year. Intraoperative complications consisted of tearing of conjunctiva and microperforation. Postoperatively, loss of BCVA was found but could be explained by cataract growth. Hypotony was common during the first postoperative week but diminished during the first month. No severe complications, such as endophthalmitis, blebitis or suprachoroidal hemorrhage were found.

(II)

In the prospective study DS reduced IOP effectively during the first postoperative year in both MMC and non-MMC groups. IOP was lower when MMC was used. However, in surgical success no benefit was found with MMC use. More than half of the eyes needed GP during first postoperative year. More hypotony was present during first three months when MMC was used, but none of the eyes was hypotonous one year postoperatively. MMC use was not related to other intra- or postoperative complications.

(III)

In the long-term IOP was effectively lowered throughout the 6 to 9 year follow-up. Postoperative IOP was lower in MMC group until 5 years postoperatively, thereafter no difference was found. In surgical success MMC use showed no additional benefit. Almost all eyes needed GP during follow-up. No difference between groups was found in postoperative complications or interventions.

(IV)

In EXG and POAG eyes, DS reduced IOP effectively, with postoperative IOP being the same between groups. EXG eyes needed more reoperations. GP was more common among EXG eyes. IOP between 2 and 14 mmHg one week postoperatively was found to have prognostic value considering surgical success. No other factor with prognostic value for surgical success was found.

(V)

Lowering IOP with DS resulted in a decrease of BCVA in the early postoperative period. BCVA returned to the preoperative level between 2 and 4 weeks postoperatively. Macular dimensions showed no change after DS. Two eyes had macular folds until 4 weeks postoperatively, but their visual acuities were unaffected. IOP lowering with DS shortened the eye as measured with an IOL-master. Corneal curvature of steeper meridian increased and corneal thickness decreased after DS. These changes were relatively small, and these changes may not explain the lower visual acuity during first two postoperative weeks.

Several topics concerning DS remain to be resolved. It would be interesting to compare the effects and complications of DS and safe surgery trabeculectomy in a prospective and randomized study. Studying choroidal changes after DS could also be helpful in explaining changes observed in the immediate postoperative period. To find the effect of IOP lowering with DS on NTG patients concerning visual field deterioration would be important during a long follow-up of over 10 years.

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