SAFETY AND EFFICACY OF INTRACAMERAL MYDRIATICS IN CATARACT SURGERY

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Who would believe that so small a space could contain the images of all the universe? Oh mighty process!

Leonardo da Vinci (1452-1519)
Codice Atlantico

To my family
ABSTRACT
Safety and efficacy of intracameral mydriatics in cataract surgery
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Background: In order to perform cataract surgery, adequate dilatation of the pupil is essential. This is traditionally achieved by preoperative topical mydriatic eye-drops, commonly cyclopentolate and phenylephrine. This routine has several disadvantages. First, the slow penetration through the cornea delays the onset of mydriasis. Second, the limited bioavailability of topically administered substances with significant systemic absorption may increase the risk for systemic side effects. Third, even if good mydriasis is achieved initially with topical mydriatics (TM), the effect tends to wear off during surgery. In relation to cataract surgery a transient postoperative corneal oedema is sometimes noted, indicating effects on the corneal endothelial pump function. These effects have been ascribed to ultrasonic or mechanical trauma from the phacoemulsification procedure. Corneal endothelial cell loss (ECL) is a commonly studied variable, not least because it is associated with the long-term risk for corneal decompensation. But, there has been a debate whether postoperative corneal swelling after phacoemulsification cataract surgery correlates to ECL.

Aims: To evaluate an alternative mydriatic regimen for phacoemulsification cataract surgery: intracameral injection of mydriatics mixed with lidocaine (ICM). Additionally, to determine the correlation between early transient postoperative corneal oedema and permanent ECL after phacoemulsification cataract surgery.

Methods: Pupil dilatation with ICM (150 µl of lidocaine 1%, phenylephrine 1.5%, and cyclopentolate 0.1%) was compared to TM (phenylephrine 10% and cyclopentolate 1%) prior to cataract surgery. Additionally, two ICM-groups were randomized to receive either 0.6 µg/ml epinephrine added to the irrigating balanced salt solution or no epinephrine in the irrigation solution. Furthermore, two randomized ICM-groups, with or without cyclopentolate, were analyzed. The patients planned for cataract surgery were examined with ultrasonic pachymetry, specular microscope endothelial photography and Orbscan II slit-scan tomography pre- and postoperatively.

Results: With ICM, mydriasis reached 95 ± 3% of its final value within 20 seconds. In the ICM-group, the pupils were smaller than in the TM-group (mean 6.7 ± 1.0 mm versus 7.7 ± 1.0 mm, P<.001), but did not contract intraoperatively as the TM pupils did. Conversely, with ICM the pupil sizes generally increased during the cataract procedures. This increase was significantly greater without epinephrine in the irrigating solution (13 ± 19% versus 4 ± 14%; p = 0.02). No significant differences in pupil sizes were observed between the patients who were given ICM with or without cyclopentolate. The central corneal swelling at the first postoperative day was strongly correlated to the central ECL at 3 months, R² = 0.785, P < 0.001.

Conclusions: ICM is a rapid and safe alternative to TM in phacoemulsification cataract surgery. An irrigating solution without epinephrine can safely be used with ICM. Cyclopentolate, administrated intracameraly, has no immediate additive mydriatic effect to intracameral lidocaine combined with phenylephrine. The degree of permanent corneal endothelial damage in cataract surgery is reflected in the degree of early postoperative corneal swelling.

Key words: intracameral - mydriatics - pupil - cataract - phacoemulsification - lidocaine – phenylephrine - cyclopentolate - epinephrine - endothelial cell loss.
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1. ABBREVIATIONS

BCVA  best corrected visual acuity
CDE   cumulative delivered energy
CV    coefficient of variation
DE    degree of elongation
ECCE  extracapsular cataract extraction
ECL   corneal endothelial cell loss
ETDRS Early Treatment Diabetic Retinopathy Study
HSF   hexagon shape factor
ICCE  intracapsular cataract extraction
ICM   intracameral mydriatics
IFIS  intraoperative floppy iris syndrome
IOL   intraocular lens
IOP   intraocular pressure
LOCS  Lens Opacities Classification System
MAP   mean blood pressure
NSAID non-steroidal anti-inflammatory drug
OVD   ophthalmic viscosurgical device
TM    topical mydriatics
VA    visual acuity
2. ORIGINAL PAPERS

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals.


IV. Lundberg B, Behndig A. Separate and additive mydriatic effects of lidocaine hydrochloride, phenylephrine and cyclopentolate after intracameral injection. Accepted for publication in *J Cataract Refract Surg.*
3. INTRODUCTION

3.1 Definition of cataract

A cataract is any opacity of the lens, whether it is a small local opacity or a diffuse general loss of transparency. To be clinically significant, however, the cataract must cause significant reduction in visual acuity (VA) or functional impairment. Symptoms of cataract include reduced visual acuity, photophobia, glare, myopisation and monocular diplopia.

3.2 History of cataract surgery

Ancient surgeons did not know that the cataract was an obscurity of the lens. They considered it a “suffusion” that formed between the pupil and the lens. The term cataract was introduced by Constantinus Africanus (AD 1010-1087), a Carthaginian monk and ocularist, who translated the Arabic term for suffusion into the Latin “cataracta”, meaning “waterfall” or “blockage of flow”, such as the cataracts that hindered travellers on the Nile River.

The known history of cataract surgery starts as early as 800 BC. At this time Susruta and other surgeons in India practiced “couching”. This method was carried out with a lancet and a blunt needle and the opaque lens was pushed backwards and downwards into the vitreous cavity “or dislodged into another place where it was less disturbing” (Galenos, 130-200 AD). This method was also used in many of the European countries during the 18th and 19th centuries.
A next step in the development of cataract surgery was taken when Jacques Daviel (1696-1762) on April 8, 1745 failed in performing a couching procedure. He then made an inferior corneal incision and inserted a needle behind the lens and delivered it with some loss of vitreous. Daviel published this method in an article where he reported 115 cataract extractions with 100 successes. Since Daviel opened the capsule, these were the first extracapsular operations (ECCE), i.e. the lens capsule was left in place. This method was further developed by others e.g. Albrecht von Graefe (1828-1870) and gained increased acceptance.

During the same period Samuel Sharp (1753) and George de la Faye (1752) came up with the intracapsular cataract operation (ICCE), where both the lens and the capsule was taken out. Sharp expelled the lens from the eye by pressure of his thumb. ICCE was improved during the 19th and 20th centuries through the use of different instruments e.g. spoon, curette and strabismus hook. In 1957 Joaquin Barraquer discovered that the enzyme α-chymotrypsin could cause zonulolysis and thereby made it easier to remove the lens. In 1961 cryoextraction of the lens was introduced by Tadeusz Krwawicz.

ICCE was the most accepted method and by 1944 85% of the patients had a postoperative best corrected visual acuity (BCVA) of 20/30 or better. However, there still was a 5% rate of potentially blinding complications. Additionally, there were difficulties in the optical correction of the aphakic patient, i.e. to use aphakic glasses, which were heavy and induced substantial aberrations in the periphery. A shift from ICCE to new methods of ECCE evolved in an effort to reduce complications and to facilitate the placement of intraocular lenses.

The first attempt to insert a lens implant was reported in Leipzig 1795, when Casaamata inserted a glass lens. It was not successful and the next development of intraocular lenses (IOLs) began in 1949. Harold Ridley, an English ophthalmologist, observed that polymethylmethacrylat (PMMA) fragments from cockpit windshields were well tolerated in the anterior segment of the eyes of war pilots, who had experienced plane accidents. He then started to place disc-shaped PMMA lenses in a biconvex design behind the iris after ECCE. Although he had to abandon his lens design due to the high complication rates, his idea started the development of IOLs. A number of surgeons continued to develop the IOLs and the ECCE technique despite the rather widespread scepticism.

In 1967 another mile-stone in cataract surgery was launched when Charles Kelman presented the phacoemulsification technique, which is a development of ECCE. This method is based on ultrasound, generated via an intraocular probe, which is introduced through a small corneal incision. The ultrasound fragments the lens into smaller pieces, which are removed through the probe by vacuum
suction. In developed countries, a further development of this technique is the most commonly used method today.\textsuperscript{10,11}

The history of mydriatics starts more than 500 years ago. Anticholinergic drug-extracts from leaves of the deadly nightshade plant were installed into the eye to induce mydriasis. During the 1500s large pupils were considered beautiful and therefore the name “belladonna”, or “beautiful woman”, was established. The primary active ingredient of belladonna is atropine, which is still used today. In the 1950s shorter acting anticholinergic drugs like cyclopentolate and tropicamide were introduced. These drugs are still frequently utilized in ophthalmology nowadays. In 1897 epinephrine was isolated from the adrenal gland, establishing a new class of mydriatic drugs, adrenergic agonists, of which phenylephrine is one commonly used in ophthalmologic practice today.\textsuperscript{12}

3.3 The cataract operation

The cataract removal procedure used in this thesis and in most developed countries today comprises (with some variations) the following 10 steps:

1. A main incision usually localized temporally at the limbal region and one or two side ports.

2. Injection of intracameral lidocaine for anaesthesia.

3. Injection of an ophthalmic viscosurgical device (OVD) into the anterior chamber to create a space and to protect the corneal endothelial cells.

4. Formation of a capsulorhexis, i.e. to tear a rounded hole in the anterior part of the lens capsule. The created “lid” of the capsule is removed.

5. Hydrodissection of the lens by injecting fluid under the lens capsule in order to separate the lens from the capsule.
6. Lens removal through phacoemulsification (partition of the lens) and aspiration of the lens substance.

7. Aspiration of the remaining lens cortex with an irrigation/aspiration instrument.

8. Injection of OVD into the anterior chamber and the capsular bag in order to implant a foldable IOL, which unfolds in the capsular bag.

9. Removal of the OVD, which if left in place will lead to a high postoperative pressure peak.

10. Injection of an antibiotic in the anterior chamber to reduce the risk for postoperative intraocular infection. Suturing of the wounds is usually not required.

Most cataract surgeons of today would probably concur in the following statement that was made by DW Green already in 1905 at the American Academy meeting; “A well conceived and properly executed extraction is probably the acme of surgical skill. No other surgery approaches it in definiteness of conception, delicacy, of execution in the nicety with which the different steps are carried out, the object to attained, and lastly, the contentment and joy it has brought to humanity. Other surgeries relieve suffering, some prolong life, and some correct deformity, but the extraction of the opaque lens does all of these and more.”

3.4 Epidemiology, health economics and risk factors

Cataract is one of the commonest causes of vision loss and the worldwide leading cause of blindness. WHO has estimated that 40-45 million people worldwide have a non useful vision (i.e. they are unable to walk about unaided or have a VA <3/60) and that cataract accounts for 48 % of these cases. Population based studies in the USA has shown that the prevalence of cataract, causing loss of vision to 20/30 or worse in persons 75 years or older, is about 39 % for men and 46 % for women. For all ages the prevalence is 16 % and for those older than 75 years 42 %. Without consideration of VA, the prevalence for senile lens opacities are for ages 52-64 years 21%, 65-74 years 53% and 75-85 years 80%. In 2006, approximately 72 500 cataract operations were performed in Sweden and 62% of these were carried out in women. Approximately 84 % of all operated patients achieve VA ≥ 0.5 in the operated eye and for patients with no ocular co-morbidity the corresponding figure is 95 %. Additionally, there is a benefit of second eye surgery and there are several studies that have pointed out that the cataract operation is a highly cost effective surgery. Also for less
developed countries, cataract surgery is ranked as one of the most cost-effective public-health measures.\textsuperscript{26}

A variety of risk factors for developing cataract have been studied. Personal factors such as age, gender, ethnic group and genetic factors are well accepted risk factors for cataract. Environmental risk factors such as cigarette smoking, ultraviolet B exposure, diabetes and low socioeconomic status are of public health interest because preventive strategies can be targeted to these groups. Direct eye trauma is a known risk factor and there is also robust evidence that long-term use of high doses of steroids is a risk factor for cataract.\textsuperscript{14,27}

### 3.5 Anatomy and physiology (cornea, iris and lens)

The cornea, the iris and the lens are situated in anterior part of the eye. The main function of the \textit{cornea} is to refract the incoming light and it contributes to approximately 2/3 of the total refractive power (the lens refracts the remaining part). The cornea is made up of three major structures. The \textit{epithelium} consists of 4-6 cell layers that form 5-10 \% of the total corneal thickness of about 540 \( \mu \text{m} \).\textsuperscript{28-30} The superficial epithelial cells have tight junctions that prevent penetration of tear fluid into the stroma. The \textit{stroma} mainly consists of collagen lamellae with interleaved keratocytes and constitutes about 90\% of the corneal thickness. Its water content differs in different parts of the structure and the transparency is dependent on its dehydrated state, which in turn is maintained by the endothelial pump. The \textit{endothelium} is a 5 \( \mu \text{m} \) thick monolayer of closely joined hexagonal cells. From what we know today, these cells are not likely to proliferate in humans and the loss of cells is therefore compensated by sliding and thinning of adjacent cells to cover the defect.\textsuperscript{31-33}
This lack of cell division results in a gradual corneal endothelial cell loss (ECL) throughout life, with an average cell loss of 0.3-0.6% per year. At birth the endothelial cell density is 3500-4000 cells/mm² and decreases in adulthood to 1500-2500 cells/mm². Apart from the ECL in the normal aging process a reduction in cell number can also occur due to trauma, intraocular surgery, and ocular diseases.

The endothelial cells have a potential of ion transport and hence the term “fluid pump” has been used in order to explain the capability of the endothelium to dehydrate the stroma. If there is a disturbance in the endothelial cell layer that diminishes the capability of the fluid pump, it can result in a corneal oedema or decompensation. The structure of the corneal endothelium can be depicted by a specular microscope and assessed by imaging programs (Figure 1).

Figure 1. A. Specular microscopy showing the corneal endothelial cell layer. B. Measurements of the individual cells.
The iris works as the eye’s aperture and adjusts to the amount of incoming light. It consists of two main layers. The posterior leaf contains the dilator muscle, the sphincter muscle, and the posterior pigmented epithelium. The more superficial anterior leaf consists of a connective tissue stroma with melanocytes, blood vessels, and nerve endings that supplies the sphincter and dilator. From a front view of the iris, the dilator muscle is located circumferentially, in the midperiphery of the iris. The dilator muscle activation that leads to pupil dilatation (mydriasis) is mediated by norepinephrine that stimulates the $\alpha_1$-adrenergic receptors of the iris (see page 21).

The circumferential sphincter muscle is located just inside the pupillary border. The sphincter muscle contraction, which leads to pupil size reduction (miosis) is mediated by acetylcholine interaction with the muscarinic receptors of the iris (see page 21).

The colour of the iris is determined by the number and size of the melanin pigment granules in the stromal melanocytes.$^{43}$

The lens functions are to refract light onto the retina and to provide accommodation and it principally consists of a capsule, cortex and nucleus.
The lens capsule is an elastic, transparent collagen basement membrane. It contains the lens cells and is capable of moulding the lens during accommodative changes. The lens is supported by zonular fibres that is inserted to the equatorial region of the capsule and attach to the ciliary body. Behind the lens capsule is a layer of lens epithelial cells. These cells migrate toward the equator, where they transform into lens fibres. Within the lens, the fibres form different optical zones with different densities, i.e. the cortex and nucleus.

The pathogenesis of age related cataracts is not completely understood. With increasing age, the lens enlarges and decreases in accommodative power. The lens nucleus undergoes compression and hardening as new layers of cortical fibres are formed. Changes in lens proteins and increasing hydration are also of importance. These changes lead to fluctuations in the refractive index, scattering of light rays and reduced transparency which gives the patient the cataract symptoms mentioned above. The three main types of age-related cataracts are nuclear, cortical and posterior or subcapsular cataracts.\textsuperscript{44,45}

3.6 Pharmacology and drug transport

In order to understand the papers of this thesis, one has to gain some basal knowledge about the pharmacology of the eye. The (dilating) pharmacological agents in eye drops are applied on to the ocular surface, but the intended site of action is within the eye, i.e. the iris. Very little of topical eye drops is maintained in the eye. Only about 20% of a drop is retained in the cul-de-sac because there is only a limited raise in the volume of the lacrimal fluid. The rapid turnover of the fluid in the tear reservoir of 16% per minute, also reduces the amount of the drug.\textsuperscript{46,47}

The main penetration route for ocular pharmacological agents is through the cornea.\textsuperscript{48,49} To traverse the cornea the drug must pass through the lipid-rich (hydrophobic) environment of the epithelial cell membranes, since the epithelial
cells have tight junctions. Furthermore, it must cross the water-rich (hydrophilic) milieu of the stroma and another hydrophobic lipid barrier at the endothelium. Studies of the corneal permeability show that lipid solubility is more important than water solubility to facilitate penetration.\textsuperscript{46,47,50}

When the drug has reached its target it often interacts with a receptor. If the interaction stimulates the receptor’s natural function, the drug is named an \textit{agonist}. If the interaction results in an opposing effect the drug is named an \textit{antagonist}.

The main traditional dilating substances in the papers are cyclopentolate, phenylephrine, and epinephrine. These drugs initiate different courses of events in the eye, but the following refers to the actions on the iris. Cyclopentolate is an anticholinergic drug and it is an antagonist, i.e. blocks the action of the neurotransmitter acetylcholine at the muscarinic receptors of the iris sphincter. The result is paralysis of the sphincter and therefore leads to (a passive) pupil dilatation.

Phenylephrine and epinephrine are both adrenergic agonists. There are different types of adrenergic receptors ($\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$) and the distribution of adrenergic receptors in the human iris muscles shows mainly $\alpha$- and few $\beta$-receptors in the dilator. The iris sphincter has both $\alpha$- and $\beta$-receptors and stimulation of both types induces a relaxation of the sphincter.\textsuperscript{49} The transmitter for these receptors in the eye is norepinephrine. Phenylephrine is an adrenergic agonist acting specifically on the $\alpha_1$-receptors of the iris dilatator, resulting in a (active) pupil dilatation. Epinephrine is also an agonist that dilates the pupil but acts on both the $\alpha$- and $\beta$-receptors in the iris.

As described above, the iris colour differs due to the composition of the melanin pigment granules. The degree of melanin pigment can affect the onset and duration of an intraocular drug. The melanin pigment binds the drug and in a dark pigmented iris is therefore the onset of dilatation slower and the maximum pupil dilatation is limited. Since there is a slow release from the melanin-bound drug reservoir, the effect of the drug can be prolonged.\textsuperscript{51}

In addition, lidocaine, a local anaesthetic drug is studied in this thesis. It obstructs the nerve conduction by blocking the sodium channels in the cell membranes, leading to an increased threshold for electrical excitability. Lidocaine can be injected into the anterior chamber of the eye and provides sufficient anaesthesia to perform the cataract procedure.\textsuperscript{52} The anesthetizing effect also offers some pupil dilating capacity through its mechanism of action, i.e. to anesthetize and paralyze the muscles of the iris.\textsuperscript{53}

When different drugs are used topically on the eye, there is a substantial systemic absorption, mainly through the nasal mucosa but also through the conjunctiva.\textsuperscript{54} Since the receptors described above are located also in other parts
of the body, there is a risk for systemic side-effects, also with doses used in ophthalmology. Cyclopentolate can produce systemic effects such as flushing, tachycardia, constipation, urinary retention and confusion.\textsuperscript{55} Topically applied adrenergic drugs can cause hypertension, tachycardia, bradycardia, headaches, tremor, hyperglycaemia, sweating and weakness.\textsuperscript{55}

### 3.7 Introduction to the papers

When a cataract becomes visually significant or the patient has symptoms that interfere with their daily life, treatment is justified. Today, there is no known protective agent that can delay the onset or progression of cataract and surgery is the only treatment available.\textsuperscript{14}

Cataract surgery has, as described above, undergone significant developments and over the past decades it has improved further. Phacoemulsification offers faster visual rehabilitation,\textsuperscript{56} less induced astigmatism,\textsuperscript{11} and a more predictable postoperative refraction\textsuperscript{11} than large incision extracapsular cataract extraction (ECCE). Progress in surgical techniques with smaller incisions\textsuperscript{47}, continuous circular capsulorhexis\textsuperscript{58}, better OVD’s\textsuperscript{59}, advanced phacoemulsifiers and techniques\textsuperscript{60} and foldable IOL’s\textsuperscript{61,62} has improved the postoperative results further. The developments has also enabled less extensive anesthesia\textsuperscript{63} and a decrease in the need for hospitalization\textsuperscript{64,65} and postoperative controls.\textsuperscript{56} Still, some perioperative routines have changed little, including the routine for preoperative pupil dilatation.

In order to be able to perform cataract surgery adequate mydriasis is required. This is usually achieved by topical administration of anticholinergic and sympathomimetic mydriatic agents, commonly cyclopentolate and phenylephrine. However, this regimen has disadvantages. Firstly, the slow penetration through the cornea delays the onset of mydriasis,\textsuperscript{66,67} with a maximum mydriatic effect at 30 minutes for cyclopentolate\textsuperscript{68} and 75 minutes for phenylephrine.\textsuperscript{69} In practice, this means that the waiting time for the pupil to dilate is often several-fold longer than the surgical procedure. A 45 minute preoperative preparation time for administrating the preoperative dilatation eye drops, (cyclopentolate and phenylephrine administered three times with a 15 minute interval) results in an accumulated total waiting time of about 6 years for the cataract procedures during one year in Sweden only.

Secondly, the limited bioavailability of topically administered substances\textsuperscript{48} with significant systemic absorption\textsuperscript{68,70} may increase the risk for cardiovascular side effects,\textsuperscript{71,72} especially in high-risk groups such as patients with hypertension\textsuperscript{73} or cardiovascular diseases\textsuperscript{74} and children.\textsuperscript{75,76}

Thirdly, even if good mydriasis is achieved initially, the mydriatic effect tends to wear off during surgery, especially in patients with diabetes mellitus\textsuperscript{77,78} and intraoperative floppy iris syndrome (IFIS).\textsuperscript{79-82}
IFIS is a perioperative manifestation that has attracted much attention recently. It is defined by one or several intraoperative characteristics of the iris; iris billowing, iris prolapse and pupillary miosis, which can compromise the cataract surgery. It has been demonstrated that IFIS is associated with tamsulosin, a systemic sympathetic α_A-receptor blocker that is used for treating the symptoms of benign prostatic hypertrophy (BPH). In these studies 43 to 90% of the patients taking tamsulosin showed signs of IFIS during cataract surgery. Between 0.7 (England) to 3% (USA) of the patients operated for cataract are taking tamsulosin. Several strategies have been proposed to manage the iris in IFIS; preoperative treatment with topical atropine, iris retractors or pupil expansion ring, OVD techniques with reduced fluidic parameters and intracameral phenylephrine.

Pupillary constriction during cataract surgery may increase the risk for complications, including iris damage, incomplete cortex removal, posterior capsule rupture, vitreous loss and dislocation of lens material. Maintenance of mydriasis during the whole procedure is therefore crucial. Several complementary treatments to preoperative dilating eye drops have been suggested in order to maintain a good mydriasis; mechanically, e.g. with iris retractors, pharmacologically, e.g. with topical non-steroidal anti-inflammatory drugs (NSAIDs), viscous metaxedrine 10%, or with intraoperative intracameral epinephrine.

Nowadays, preservative-free epinephrine in low concentrations is commonly used in the irrigating solution during cataract surgery to maintain mydriasis. This routine circumvents the problems encountered previously with epinephrine with a low pH and toxic preservatives, and no apparent side-effects have been noted. However, as epinephrine is unstable in a solution with physiological pH, time-consuming repeated blending procedures are needed, which complicates the perioperative routines.

Today, several substances are given into the anterior chamber during the cataract procedure, e.g. acetylcholine, cefuroxime, trypan blue, lidocaine, and epinephrine. If using an intracameral mydriatic regimen given at the start of the procedure, one may avoid a disadvantage of topical mydriatics (TM) as there would be a reduced preoperative waiting time. An intracameral mydriatic procedure may also lower the risk for systemic side effects since the dose of the mydriatic agents could be reduced and because the drugs would not enter the system through the nasal mucosa pathway. In order to evaluate this intracameral mydriatic regimen, and as well as to investigate the need for epinephrine in the irrigating solution when using this approach, three of the aims for this thesis on page 25 were formulated.

Despite the improvements of the cataract surgery a more or less pronounced, transient postoperative corneal edema is sometimes noted after
phacoemulsification surgery.\textsuperscript{59,104} The induced oedema indicates effects on the corneal endothelial pump function.\textsuperscript{105} These effects have been ascribed to ultrasonic or mechanical trauma from the phacoemulsification procedure,\textsuperscript{106,107} as opposed to in large-incision techniques where the effects on the cornea mainly result from the incision and the lens expression.\textsuperscript{108} Whether postoperative corneal swelling after phacoemulsification surgery correlates to ECL has been a matter of debate for several years.\textsuperscript{105,108-111} ECL is a commonly studied, highly relevant postoperative variable, not least because it is associated with the long-term risk for corneal decompensation (pseudophakic bullous keratopathy).\textsuperscript{112} Quantification of the ECL, however, requires specular microscopy with comparison of pre- and postoperative photographs\textsuperscript{113} and is not often performed in routine clinical practice. Evaluation of the postoperative corneal oedema, however, is easily done on the first postoperative day with ultrasonic or optical pachymetry or even with a simple slit lamp examination. The evaluation of the postoperative corneal oedema has relevance also in that the oedema limits fast visual rehabilitation. The assumption that postoperative corneal oedema after cataract surgery correlates to ECL added an additional aim to this thesis.
4. AIMS

Paper I
To evaluate the efficacy and safety of an alternative intracameral mydriatic regimen (ICM): intracameral injection of lidocaine 1%, phenylephrine 1.5% and cyclopentolate 0.1%, and to compare it with traditional preoperative topical mydriatic eye-drops (TM).

Paper II
To determine the correlation between early, postoperative corneal oedema and permanent corneal endothelial cell loss after standardized phacoemulsification cataract procedures and to evaluate other possible risk factors for postoperative corneal endothelial cell loss.

Paper III
To evaluate whether it is necessary to include epinephrine in the irrigating solution to maintain an adequate pupil size during phacoemulsification cataract surgery when using ICM.

Paper IV
To evaluate if intracameral lidocaine 1% and phenylephrine 1.5% alone give sufficient pupil dilatation for an entire cataract operation and to clarify the individual mydriatic effects of lidocaine 1%, phenylephrine 1.5% and cyclopentolate 0.1% after intracameral injection.
5. MATERIALS AND METHODS

5.1 Ethics
All studies were approved by the Research Ethics Committee of Umeå University and the patients were included after providing informed consent.

5.2 Inclusion criteria
Patients with age-related cataracts.

5.3 Exclusion criteria
Patients with diabetic retinopathy with proliferative changes, glaucoma medication with pilocarpine, a history of uveitis, previous intraocular surgery, previous eye trauma, malformations of the anterior segment, conditions where mechanical pupil dilatation was considered, only one functioning eye, signs of corneal disease, scheduled bilateral operations, “serious general disease” or cognitive insufficiency were not included.

5.4 Surgical technique
All surgeries involved a temporal corneoscleral incision, a Series 20.000 Legacy® phacoemulsifier with standardized settings, and sodium hyaluronate 3%–chondroitin sulfate 4% with sodium hyaluronate 1% (DuoVisc®) as OVD. The nucleus was emulsified with the stop and chop technique. An AcrySof® foldable IOL was implanted in all cases. Balanced salt solution (BSS®) with 0.6 µg/ml of epinephrine where applicable, was used as the irrigating solution.

5.5 General design for all studies
Prospective randomized double-masked study design. All the studied drugs and placebo drops were coded so that neither the operating surgeon nor the patient was aware of which treatment was given. For topical anaesthesia, all patients were given 3 drops of tetracaine 1% at 15-minute intervals before surgery. Postoperatively, dexamethasone 0.1% was given 3 times daily for 3 weeks. No agents to reduce the intraocular pressure (IOP) were given postoperatively.

The sterile intracameral mydriatic solution used (ICM) contained 150 µl of a preservative-free mixture of lidocaine 1%, phenylephrine 1.5% and cyclopentolate 0.1%. The cocktail was prepared by the Product and Laboratory Department of the Swedish Pharmacy (Apoteksbolaget AB). ICM was administrated intracamerally through the side port via a syringe with a blunt cannula. The volume of each injection was 150 µl and prior to each injection approximately the same amount of aqueous was withdrawn.
During the cataract surgery, balanced salt solution (BSS\textsuperscript{®}) with 0.6 \(\mu\)g/ml of epinephrine was used as the irrigating solution, except for when the study protocol was planned to not include epinephrine addition. The cataract operations were video taped so that the pupil size could be registered throughout the procedure. The pupil size measurements were performed as follows: Firstly, the width of the blade of a 2.75 mm slit knife held over the incision site was measured directly on the monitor screen. Secondly, two perpendicular pupil diameters were measured (on the same still picture) in order to calculate the mean pupil diameter. The pupil diameter in mm could then be calculated as the mean pupil diameter/blade width x 2.75.

5.6 Specific study design

5.6.1 Paper I

Sixty patients were included and randomized. One group (30 patients) was given TM comprising 3 drops each of cyclopentolate 1% and phenylephrine 10% at 15-minute intervals before surgery. They also received 150 \(\mu\)l of preservative-free lidocaine 1% intracameraly at the beginning of the procedure. The other group (30 patients) was given placebo eye drops at the same intervals as in the topical group and ICM at the start of the operation. Pupil measurements were made every 5 seconds after the ICM injection. The pupil diameter was also measured after OVD injection before capsulorhexis and before and after OVD injection prior to the IOL insertion. Two surgeons performed each operation, so that one could start the procedure and give the intracameral injection; thus, neither the subsequent operating surgeon nor the patient was aware of which treatment was given in each case.

Preoperatively and 1 day and 1 month postoperatively, the pupil size and the central, nasal, and temporal corneal thicknesses (pachymetry) were measured with the Orbscan II and central corneal endothelial photographs were taken with the Topcon SP-2000P specular microscope. Corneal endothelial morphology was calculated from a central cluster of 50 cells from each photograph using the Image J program (developed at the U.S. National Institute of Health and available on the Internet at http://rsb.info.nih.gov/ij/). In addition to the endothelial cell count, the hexagonal shape factor (HSF), the degree of cell elongation (DE), and the coefficient of variation in cell size (CV) were calculated and the preoperative and postoperative values compared. The BCVA was measured preoperatively and 1 month postoperatively using the ETDRS-Fast protocol and the IOP was measured preoperatively and 1 day and 1 month postoperatively by Goldmann applanation tonometry. Aqueous cells were graded on a scale from 0 to 5 and flare from 0 to 4 preoperatively and 1 day and 1 month postoperatively. Additionally, the nuclear, anterior cortical, or posterior cortical cataract was graded preoperatively using the LOCS III protocol and pseudoexfoliations, iris colour (blue, mixed, or brown), age and sex of the patients were recorded. Intraoperatively, cumulative delivered energy (CDE =
phaco power × phaco time), total surgical time, amount of BSS® used, and complications were noted. The blood pressure and pulse immediately preoperatively and postoperatively were measured. Finally, all patients graded their subjective sensation of pain and glare during the procedure using a visual analogue scale (VAS) from 0 to 10.

5.6.2 Paper II

Thirty patients planned for cataract operation were examined in the same way, as described in paper I, except for pupil size, blood pressure, pulse and VAS, which was not performed in this study. Additionally, the same measurements were made after 2 and 3 months. The thirty cases were chosen for follow-up based on the increase in their corneal thickness at the centre of the cornea at the first postoperative day; these included the first 10 patients with a <5% increase, the first 10 with a 6 to 20% increase, and the first 10 with a >20% increase. Raw data were extracted from the Orbscan II measurements and used for calculation of the corneal thickness at a central 1-mm zone and at a 1-mm zone 2 mm nasally from the corneal centre. Corneal endothelial photos were taken from the central and nasal locations of the cornea preoperatively, at 1 day and after 1, 2 and 3 months. At the first postoperative day, photos with the specular microscope could be obtained from only 19 cases because of postoperative corneal swelling with haze in the remaining 11 corneas. When a corneal endothelial photograph could be obtained, the cornea was defined as “clear,” and when a photograph could not be obtained, it was defined as “not clear.” The corneal thickness was also obtained from the SP-2000P measurements and was also measured, centrally and nasally, with an ultrasonic pachymeter at all visits.

5.6.3 Paper III

A total of one hundred and forty patients were included in this study. The first sample of 90 patients was randomized into two groups. Group 1 (45 patients) was given 150 µl ICM at the beginning of the cataract operation, which was performed using BSS® containing 0.6 µg/ml epinephrine as irrigating solution. Group 2 (45 patients) underwent the same procedure, but without epinephrine in the irrigating solution. The second sample of 50 patients, randomized into two groups, was given TM in all cases. Group 1 (25 patients) was given irrigating solution with epinephrine and group 2 (25 patients) received irrigating solution without epinephrine. In both the ICM and TM settings, the first 15 + 15 cases in each group (with and without epinephrine in the irrigating solution, respectively) were analysed as described in paper I.
5.6.4 Paper IV

This study included fifty six patients. Firstly, 16 patients received lidocaine 1%, phenylephrine 1.5% and cyclopentolate 0.1% intracamerally at the beginning of the procedure. The substances were injected separately, one after the other. Lidocaine was always injected first and the order of cyclopentolate and phenylephrine was randomized as the second and third injection, thus creating two study groups.
Secondly, 40 patients were randomly assigned to either receiving 150 µl of ICM containing lidocaine 1%, phenylephrine 1.5% and cyclopentolate 0.1%, (group A; 20 cases), or 150 µl of ICM with lidocaine 1% and phenylephrine 1.5% only (group B; 20 cases). The pupil sizes were measured as described in paper I. No epinephrine was added to the irrigation solution. At the first postoperative day, the pupil sizes and corneal thickness were measured with the Orbscan II.

5.7 Statistics

The SPSS and Microsoft Office Excel software were used for statistical calculations. A binary logistic regression model was used to evaluate whether preoperative differences existed between the groups in BCVA, IOP, pseudoexfoliation, iris color, cataract classification, corneal endothelial cell count, pupil size, corneal thickness, pulse, mean blood pressure (MAP), age, or sex. The Mann-Whitney U test was used to evaluate pain, glare, and cell and flare data, and the Student 2-tailed t test was used for all other statistical comparisons. A P value < 0.05 was considered statistically significant. Mean values were given with standard deviations for numeric data and medians and ranges or inter quartile range for ordinal data.
The univariate associations of the different variables with the percentage of ECL at 3 months were evaluated using correlation analysis. A backward stepwise multiple regression analysis was performed to identify the variables independently contributing to the ECL, employing the variables associated with the cell loss on univariate analysis (P < 0.1).
Pearson’s bivariate correlation was used to test the correlations between all numerical variables. Spearman’s Rho was used in the correlation tests involving nucleus colour, an ordinal variable. Hotelling’s formula was used to compare two correlations with a common variable.
6. RESULTS

6.1 Paper I

In the group which received ICM, the pupils reached 95 ± 3 % of their maximum size after 20 seconds (Figure 1). The mean pupil size after OVD injection was smaller in the ICM group (6.7 ± 1.0 mm) than in the TM group (7.7 ± 1.0 mm) (P < 0.001), but the pupils in the ICM group often continued to enlarge throughout the cataract procedure (+4.5 ± 8.1%). Conversely, in the TM group the pupils tended to contract (−2.1% ± 7.8%) (P = 0.002). The difference in pupil size before IOL implantation was therefore smaller (7.0 ± 0.9 mm vs. 7.5 ± 0.9 mm) between the groups, but still significant (P = 0.04) (Figure 2). At 1 day, the pupils in the ICM group were significantly larger than in the topical group (5.7 ± 1.1 mm versus 3.7 ± 0.8 mm) (P < 0.001).

Figure 1. Pupil size (mean ± SD) after injection of ICM (s = seconds), n=30.

Figure 2. Pupil size at capsulorhexis (Rhexis) and before IOL implantation (IOL). White bars – TM (n=30). Grey bars – ICM (n=30).
The mean ECL at 1 month was 2.3 ± 6.1% in the ICM group and 4.1 ± 6.0% in the TM group (P = 0.25) (Table 1), but the postoperative cell counts were not significantly different from the preoperative values (P = 0.2 and P = 0.2, respectively). In contrast, cells were more irregular and elongated postoperatively in both the ICM group and the TM group as assessed by HSF (P = 0.009 and P = 0.001, respectively) and by DE (P = 0.004 and P < 0.001, respectively). Again, there were no significant differences between the two groups (Table 1).

A significant decrease in pulse rate occurred in the TM group (P = 0.0055) but not in the ICM group (P = 0.15). The difference in pulse deceleration was significant between the groups (P = 0.009) (Table 1). The slightly increased postoperative MAP did not differ significantly from the preoperative values in either the ICM group or the TM group (P = 0.07 and P = 0.1, respectively) (Table 1).

Table 1. Selected perioperative parameters.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>INTRACAMERAL MYDRIATICS</th>
<th>TOPICAL MYDRIATICS</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>30</td>
<td>30</td>
<td>.92</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>72±7</td>
<td>72±10</td>
<td></td>
</tr>
<tr>
<td>Mean surgical time (min)</td>
<td>9.1±2.7</td>
<td>9.1±1.7</td>
<td>.92</td>
</tr>
<tr>
<td>Phaco CDE (% min)</td>
<td>4.2±2.5</td>
<td>9.6±10.2</td>
<td>.0084</td>
</tr>
<tr>
<td>BSS used (mL)</td>
<td>137±39</td>
<td>141±55</td>
<td>.70</td>
</tr>
<tr>
<td>Change in BCVA (log mar)</td>
<td>.50±.26</td>
<td>.65±.53</td>
<td>.17</td>
</tr>
<tr>
<td>Pupil size after viscoelastic injection (mm)</td>
<td>6.7±1.0</td>
<td>7.7±1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pupil size at lens implantation (mm)</td>
<td>7.0±.9</td>
<td>7.5±.9</td>
<td>.040</td>
</tr>
<tr>
<td>Change in mean blood pressure (mm Hg)</td>
<td>6.1±.76</td>
<td>6.4±9.1</td>
<td>.88</td>
</tr>
<tr>
<td>Change in pulse rate (min−1)</td>
<td>−4.0±5.5</td>
<td>−8.2±6.6</td>
<td>.0091</td>
</tr>
<tr>
<td>Subjective discomfort from eyedrops (0-10)</td>
<td>1(0;1.4)</td>
<td>.5(1.1)</td>
<td>.41</td>
</tr>
<tr>
<td>Subjective pain, start of procedure (0-10)</td>
<td>3(0;1.5)</td>
<td>0(0.1;1.1)</td>
<td>.22</td>
</tr>
<tr>
<td>Subjective pain, rest of procedure (0-10)</td>
<td>.5(0.2.2)</td>
<td>0(0.1.3)</td>
<td>.19</td>
</tr>
<tr>
<td>Subjective sensation of glare (0-10)</td>
<td>.6(0.1;7)</td>
<td>2.6(1.8;3.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Flare at day 1 (0-5)</td>
<td>2.0(1.3;2.0)</td>
<td>2.0(1.0;2.0)</td>
<td>.065</td>
</tr>
<tr>
<td>Cells at day 1 (0-4)</td>
<td>1.0(1.0;1.0)</td>
<td>1.0(1.0;1.0)</td>
<td>.40</td>
</tr>
<tr>
<td>Change in central corneal thickness at day 1 (%)</td>
<td>9.0±6.1</td>
<td>11.8±7.2</td>
<td>.11</td>
</tr>
<tr>
<td>Endothelial cell loss (%)</td>
<td>2.3±6.1</td>
<td>4.1±6.0</td>
<td>.25</td>
</tr>
<tr>
<td>Change in endothelial cell hexagonality (HSF)</td>
<td>.22±.33</td>
<td>.31±.35</td>
<td>.32</td>
</tr>
<tr>
<td>Change in endothelial cell elongation (DE)</td>
<td>.014±.021</td>
<td>.025±.022</td>
<td>.054</td>
</tr>
<tr>
<td>Change in endothelial cell polymegethism (CV)</td>
<td>.0052±.0093</td>
<td>.0071±.015</td>
<td>.57</td>
</tr>
</tbody>
</table>

Means±SD, except †, Means and interquartile range.
P-values calculated with Student’s unpaired t test, except *, Mann-Whitney U-test

When comparing the intraoperative parameters between the ICM and TM groups, we found no significant differences in surgical time and irrigating solution used but the mean phaco CDE was significantly lower in the ICM group (4.2 ± 2.5% vs. 9.6 ± 10.2%) (P = 0.008) (Table 1).
Complications in the ICM group were 1 case of slight damage to the capsulorhexis and in the TM group, 1 case each of iris prolapse and posterior capsule rupture without vitreous loss. Mechanical pupil dilatation was performed in 3 eyes in the ICM group and 1 eye in the TM group.

6.2 Paper II

The main finding of this paper was that the increase in central corneal thickness seen on the first postoperative day was strongly correlated with the central ECL at 3 months postoperatively. For Orbscan II pachymetry, $R^2 = 0.785$, $P < 0.001$ (Table 1, Figure 1A). Corneas defined as clear on the first postoperative day had significantly less central and nasal ECL at 3 months, than corneas defined as not clear (central: $8.0 \pm 8.2\%$ and $31.5 \pm 14.8\%$, respectively, $P < 0.001$, and nasal: $3.3 \pm 5.2\%$ and $16.4 \pm 10.5\%$, respectively, $P = 0.0033$) (Figure 2).

Table 1. Correlations between selected perioperative variables and corneal endothelial cell loss after phacoemulsification surgery.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CENTRAL CELL LOSS</th>
<th>NASAL CELL LOSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Univariate</td>
</tr>
<tr>
<td>Age (years)</td>
<td>76 ± 7</td>
<td>0.09</td>
</tr>
<tr>
<td>Surgical time (min)</td>
<td>7.7 ± 1.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Phaco time (min)</td>
<td>0.32 ± 0.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Phaco EPT (% min)</td>
<td>4.2 ± 2.5</td>
<td>0.08</td>
</tr>
<tr>
<td>BSS used (ml)</td>
<td>125 ± 38</td>
<td>0.20</td>
</tr>
<tr>
<td>Preoperative BCVA (logMAR)</td>
<td>0.47 ± 0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pupil size during phaco (mm)</td>
<td>2.5 ± 0.46</td>
<td>0.08</td>
</tr>
<tr>
<td>Preoperative IOP (mm Hg)</td>
<td>17.0 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IOP change to day 1 (mm Hg)</td>
<td>−0.17 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nucleus color (a.u.)</td>
<td>3.2 ± 1.1</td>
<td>−0.60*</td>
</tr>
<tr>
<td>Preoperative cell count (l/mm³)</td>
<td>2.752 ± 681</td>
<td>0.04</td>
</tr>
<tr>
<td>Preoperative HSF (a.u.)</td>
<td>0.82 ± 0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>Preoperative DE (a.u.)</td>
<td>0.109 ± 0.020</td>
<td>0.04</td>
</tr>
<tr>
<td>Preoperative CV (a.u.)</td>
<td>0.063 ± 0.011</td>
<td>0.02</td>
</tr>
<tr>
<td>Pachymetry change to day 1 (Orbscan) (%)</td>
<td>15.2 ± 17.6</td>
<td>0.78</td>
</tr>
<tr>
<td>Pachymetry change to day 1 (PachPen) (%)</td>
<td>11.2 ± 10.4</td>
<td>0.40</td>
</tr>
<tr>
<td>Pachymetry change to day 1 (SP2000-P) (%)</td>
<td>5.4 ± 4.3</td>
<td>0.15</td>
</tr>
</tbody>
</table>

BSS = balanced salt solution; BCVA = best-corrected visual acuity; CV = coefficient of variation in cell size; DE = degree of elongation; EPT = effective phaco time; HSF = hexagon shape factor; IOP = intraocular pressure; logMAR = logarithm of the minimal angle of resolution; SD = standard deviation.

Correlations between selected perioperative variables and ECL 3 months after phacoemulsification surgery ($n = 30$). Multiple regression analysis shows that nucleus color is the only pre- or intraoperative variable independently correlated with the central ECL in this study. No such variable was independently correlated to the nasal cell loss. * Spearman’s correlation coefficient. Note that the SP2000-P pachymetry change only includes the patients with clear corneas on day 1.
Figure 1. (A) The relationship between the increase in central corneal thickness at the first postoperative day, obtained with Orbscan II (x-axis) and the central ECL at 3 months (y-axis; $R^2 = 0.785$, $P < .001$). The formula of the regression line is \{central cell loss\} = 0.926 * \{central edema\}. (B) The same relationship for the nasal cornea ($R^2 = 0.656$; $P < .001$). The formula of the regression line is \{peripheral cell loss\} = 0.674 * \{peripheral edema\}.

Figure 2. The central ECL at 3 months postoperatively in patients whose corneas were clear at the first postoperative day (patients 1 to 19; clarity defined by the ability to obtain an SP 2000-P photograph and for those whose corneas were not clear (patients 20 to 30). Note the higher ECL in the latter group ($P < .001$).

The increase in corneal thickness at day 1 was more pronounced centrally than nasally (15.2 ± 17.6% and 11.2 ± 12.7%, respectively, $P = 0.027$). The same also applied to ECL at 3 months (16.6 ± 15.8% and 8.8 ± 10.3%, respectively, $P < 0.001$) (Figure 1, B). The central and peripheral cell losses were moderately correlated ($R^2 = 0.393$, $P < 0.001$). In the central cornea, the cell loss in relation to the oedema was larger than in the nasal cornea Figure 1, A and B).
The nasal ECL at 3 months correlated more strongly with the nasal increase in corneal thickness seen at day 1 than to the central increase in corneal thickness, for Orbscan II: $R^2 = 0.656; P < 0.001$ and $R^2 = 0.428; P < 0.001$, respectively. A significant central cell loss was seen from 1 to 2 months postoperatively ($P = 0.034$) but not from 2 to 3 months ($P = 0.80$). A large cell loss from 1 to 2 months was not associated with a large total cell loss ($R^2 = 0.015, P = 0.55$). In the nasal part of the endothelium, no additional cell loss was noted after 1 month.

Lens nucleus colour (medians and ranges) was 2.5 (1–3) for group 1 (<5% increase in corneal thickness), 3 (2–4) for group 2 (6-20% increase in corneal thickness), and 4 (3–5) for group 3 (>20% increase in corneal thickness). All four lenses with nucleus colour grade 5 were within group 3. The nucleus color was the only pre- or intraoperative variable independently associated with the central ECL on multiple regression analysis ($P = 0.024$) (Table 1).

### 6.3 Paper III

When using ICM, the pupil was significantly larger at the end of the operation than at the beginning in the non-epinephrine group (Table 1, Figure 1). The increase in pupil size from T1 to T3 in the epinephrine group was also statistically significant (Table 1, Figure 1), but the increase in pupil size in the ICM cases was significantly larger without than with epinephrine ($P = 0.02$) (Table 2). When comparing the pupil size after OVD injection in the non-epinephrine group, there was a significant increase in contrast to the epinephrine group, where there was no significant pupil changes noticed (Table 1).

On the contrary to when using ICM, the TM pupil sizes decreased significantly in both groups (Table 1, Fig. 2), but significantly more in the non-epinephrine group ($p < 0.001$) (Table 2).

![Figure 1](pupil_sizes.png)

**Figure 1.** Pupil sizes at different surgical time points with intracameral mydriatics without (ICM 0, n=45), and with (ICM E, n=45) 0.0006 mg/ml epinephrine in the irrigating solution. The pupil sizes were determined before the first injection of the ophthalmic viscosurgical device (OVD); T1, after the first OVD injection (immediately before performing the capsulorhexis); T2, before the second OVD injection (after phacoemulsification); T3, and after the second OVD injection (immediately before inserting the IOL); T4. Note that the increase in pupil size is significantly larger without, than with epinephrine.
Table 1. The pupil sizes at different surgical time points.

<table>
<thead>
<tr>
<th></th>
<th>Pupil size (mm) at T1</th>
<th>Pupil size (mm) at T3</th>
<th>P =</th>
<th>Change in pupil size (%)</th>
<th>Pupil size (mm) at T2</th>
<th>Pupil size (mm) at T4</th>
<th>P =</th>
<th>Change in pupil size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICM 0</td>
<td>5.6±1.3</td>
<td>6.2±1.1</td>
<td>&lt;0.001</td>
<td>+13±19</td>
<td>6.2±1.3</td>
<td>6.5±1.1</td>
<td>0.007</td>
<td>+6±16</td>
</tr>
<tr>
<td>ICM E</td>
<td>5.7±1.0</td>
<td>5.9±1.2</td>
<td>0.049</td>
<td>+4±14</td>
<td>6.2±1.0</td>
<td>6.2±1.0</td>
<td>0.8</td>
<td>+0±10</td>
</tr>
<tr>
<td>TM 0</td>
<td>7.7±1.0</td>
<td>6.8±1.2</td>
<td>&lt;0.001</td>
<td>-12±7</td>
<td>7.9±1.0</td>
<td>7.1±1.1</td>
<td>&lt;0.001</td>
<td>-11±5</td>
</tr>
<tr>
<td>TM E</td>
<td>7.9±0.8</td>
<td>7.5±0.8</td>
<td>&lt;0.001</td>
<td>-5±4</td>
<td>8.1±0.8</td>
<td>7.7±0.9</td>
<td>&lt;0.001</td>
<td>-4±5</td>
</tr>
</tbody>
</table>

ICM 0 = intracameral mydriatics, no epinephrine (n = 45); ICM E = intracameral mydriatics, with epinephrine (n = 45); TM 0 = topical mydriatics, no epinephrine (n = 25); TM E = topical mydriatics, with epinephrine, (n = 25). The pupil sizes were determined before the first injection of the ophthalmic viscosurgical device (OVD); T1, after the first OVD injection (immediately before performing the capsulorhexis); T2, before the second OVD injection (after phacoemulsification); T3, and after the second OVD injection (immediately before inserting the IOL); T4. The columns “Change in pupil size” represent the change from T1 to T3 and from T2 to T4, respectively.

Table 2. The change in pupil size between different surgical time points.

<table>
<thead>
<tr>
<th>Difference in pupil size</th>
<th>Mean difference (mm) without epinephrine</th>
<th>Mean difference (mm) with epinephrine</th>
<th>P =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in pupil size T1/T3 with ICM</td>
<td>0.6±0.6</td>
<td>0.2±0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Difference in pupil size T2/T4 with ICM</td>
<td>0.3±0.7</td>
<td>0.6±0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Difference in pupil size T1/T3 with TM</td>
<td>-0.9±0.4</td>
<td>-0.4±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference in pupil size T2/T4 with TM</td>
<td>-0.9±0.4</td>
<td>-0.3±0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ICM 0 = intracameral mydriatics, no epinephrine (n = 45); ICM E = intracameral mydriatics, with epinephrine (n = 45); TM 0 = topical mydriatics, no epinephrine (n = 25); TM E = topical mydriatics, with epinephrine, (n = 25). The pupil sizes were determined before the first injection of the ophthalmic viscosurgical device (OVD); T1, after the first OVD injection (immediately before performing the capsulorhexis); T2, before the second OVD injection (after phacoemulsification); T3, and after the second OVD injection (immediately before inserting the IOL); T4. Note that the pupils are significantly smaller without than with epinephrine at T3 and T4.

Figure 2. Pupil sizes at different surgical time points with topical mydriatics, without (TM 0, n = 25), and with (TM E, n = 25) 0.0006 mg/ml epinephrine in the irrigating solution. The pupil sizes were determined before the first injection of the ophthalmic viscosurgical device (OVD); T1, after the first OVD injection (immediately before performing the capsulorhexis); T2, before the second OVD injection (after phacoemulsification); T3, and after the second OVD injection (immediately before inserting the IOL); T4.
6.4 Paper IV

In the first 16 patients (the two groups with the stepwise injections) lidocaine gave a pupil dilatation to \(4.9 \pm 0.6\) mm and \(4.9 \pm 0.5\) mm respectively \((P = 0.9)\). After injection of cyclopentolate an additional \(1.3 \pm 0.6\) mm was reached \((P < 0.001)\). In the other group, where phenylephrine was given as the second injection, the pupils dilated \(2.1 \pm 0.5\) mm \((P < 0.001)\). The difference in pupil enlargement between the groups was significant \((P = 0.02)\). After the third injection, cyclopentolate did not give any further significant pupil changes, \(-0.1 \pm 0.1\) mm \((P = 0.1)\). Phenylephrine, however, provided a further dilatation of \(0.7 \pm 0.4\) mm \((P = 0.003)\). The difference in dilatation between the groups was also significant after the third injection \((P = 0.001)\). There was no significant difference in the final pupil size after dilatation, \(6.9 \pm 0.8\) mm vs. \(7.0 \pm 0.9\) mm \((P = 0.7)\) (Figure 1).

![Figure 1](image.png)

**Figure 1.** Pupil sizes after stepwise intracameral injections of lidocaine 1% (LID), phenylephrine 1.5% (PHE) and cyclopentolate 0.1% (CYC), 150µl each, the order of the latter two injections being randomized. Black circles: phenylephrine first; \(n=7\), white circles: cyclopentolate first; \(n=8\). Note that the addition of phenylephrine has a pronounced mydriatic effect, as opposed to cyclopentolate.

In the additional 40 patients, where 20 were given ICM with cyclopentolate (group A) and 20 ICM without cyclopentolate (group B), we found no significant differences in pupil size at any time point up to 30 seconds (Figure 2). The pupil size at 30 seconds, before OVD was \(5.8 \pm 0.7\) mm in group A and \(5.9 \pm 1.0\) mm in group B \((P = 0.7)\) and after OVD, \(6.5 \pm 0.8\) mm vs. \(6.7 \pm 1.2\) mm \((P = 0.5)\).
The pupil size after phacoemulsification, before injecting OVD, was $6.0 \pm 0.8$ mm in group A and $6.1 \pm 1.1$ mm in group B ($P = 0.8$). After OVD injection, the pupil size reached $6.4 \pm 0.8$ mm in group A and $6.4 \pm 1.3$ mm in group B ($P = 1.0$). At 1 day the pupils were significantly smaller in group B, $2.9 \pm 0.8$ mm vs. $4.7 \pm 1.1$ mm ($P < 0.001$).

**Figure 2.** Pupil sizes after intracameral injection of ICM (intracameral mydriatics). A= ICM, 150 µl with lidocaine 1%, phenylephrine 1.5% and cyclopentolate 0.1% (n=19). B= ICM, 150 µl with lidocaine 1% and phenylephrine 1.5% (n=20). Note that there are no significant differences between the pupil sizes.
7. DISCUSSION

7.1 Safety and efficacy of ICM (I)

The studies I, III and IV show that ICM can be safely used in routine phacoemulsification cataract surgery. The applied doses are sufficient to produce a satisfactory pupil dilatation without causing measurable side effects on the eye. The ECL in our studies is in accordance with those reported in modern phacoemulsification surgery.\textsuperscript{114-116} Peri- and postoperative parameters such as surgical time, amount of irrigation fluids, cells and flare in the anterior chamber, IOP and VA are not different compared with traditional TM. Patients in the intracameral group also reported less discomfort from glare. This is probably due to that a normal-sized pupil at the initiation of the procedure allows a more gradual adaptation to the microscope light. Because of the design of study I, the mydriatics and lidocaine were often left in the anterior chamber for several minutes before surgery. From this we indirectly conclude that leaving ICM in the anterior chamber for a few minutes is unlikely to have detectable adverse effects on the eye.

One of our initial concerns was how long it would take for the pupil to dilate with ICM. Since the pupil reaches 95\% of its maximum within 20 seconds, the surgeon can proceed with the surgery almost immediately after injecting ICM. This was demonstrated in study I, but could also be confirmed in study IV (see Figure 2, page 37); 95\% of the pupils maximum is reached at 19 seconds in group A and at 18 seconds in group B). A possible advantage with ICM, is that the preoperative time to prepare the patient is shortened and the flexibility, i.e. to switch orders of the patients, is improved. This is helpful both for the preparing staff and the doctor and may lead to better working conditions and expanded operation schedules.

The phaco CDE was significantly lower in the ICM group in study I. This could mean that the lenses were softer in this group, although the grade of cataracts was similar between the groups. A lower phaco CDE and an equal operation time could also indicate that the surgical performance is as good with ICM as with TM, even though in general, the pupils were slightly smaller in the intracameral group. Furthermore, the pupils dilated with ICM often continued to enlarge during the cataract operation. Therefore, clinically with ICM, if the pupil is sufficiently large at the beginning of the procedure, it is likely to remain sufficiently large throughout the procedure. A pupil that enlarges during surgery, even if it is smaller, may even be more comfortable to work with than a larger pupil that is contracting. A clinical ICM study on 198 consecutive cases confirmed the safety of the surgical performance with short operation times and few complications and the study also showed good postoperative results.\textsuperscript{117}
An additional study has also established the safety of ICM compared to TM concerning postoperative macular oedema, with no statistical significant differences.\textsuperscript{118}

The doses of cyclopentolate and phenylephrine in the TM group of study I were 6.2 and 4.3 times higher, respectively, than in the ICM group (calculations based on a drop size of 37 \(\mu\text{L}\)).\textsuperscript{65} The lower dose and the intracamer al distribution may reduce the risk for cardiovascular side effects in certain groups of patients.\textsuperscript{71-74}

Pulse deceleration has been reported with phenylephrine\textsuperscript{119-121} and was less in the ICM group than in the TM group. The lower doses of mydriatics with ICM may therefore make it especially suitable in certain cases such as patients with heart conditions.

### 7.2 ICM and epinephrine in the irrigating solution (III)

As noted in the introduction, pupillary constriction during the cataract operation may increase the risk for complications.\textsuperscript{88} In order to avoid this, preservative-free epinephrine in low concentrations is nowadays commonly used in the irrigating solution to maintain mydriasis. But since epinephrine is unstable in a solution with physiological pH,\textsuperscript{55} time-consuming blending procedures occupy the operating staff.

In contrast to the mean pupil contraction when using TM, the pupil size increases throughout the cataract procedure with ICM, as stated in study I. Study III was therefore conducted to evaluate whether it is really necessary to include epinephrine in the irrigating solution when using ICM.

Adding epinephrine to the irrigating solution does not contribute to preserving the pupil size during phacoemulsification cataract surgery when using ICM. On the contrary, a greater pupil enlargement is achieved with ICM without epinephrine in the irrigating solution than with epinephrine. The exact mechanisms behind this finding are not known, but the dilator muscle in the iris has mainly \(\alpha\)-adrenergic and few \(\beta\)-adrenergic receptors. Phenylephrine is more potent in stimulating \(\alpha\)-receptors than epinephrine. The response occurs in reverse order for \(\beta\)-receptors.\textsuperscript{49} When phenylephrine is injected into the anterior chamber, the adrenergic receptors become occupied, but when epinephrine enters the eye it may gradually compete with phenylephrine and take over some of the receptors. Being a weaker dilator, epinephrine may thus lead to a smaller pupil.

The difference in pupil size when using ICM with or without epinephrine in the irrigating solution, become less pronounced after injection of OVD as the OVD acts as an unspecific pupil dilator.

An irrigating solution without epinephrine can consequently be used, when operating with ICM. This could simplify and make the perioperative procedure safer since the repeated blending processes are obviated.
The current study confirmed that epinephrine is needed when using TM. The pupil sizes generally decreased when using TM, with or without epinephrine, but the difference between the epinephrine and non-epinephrine groups was clearly significant, with greater constriction without epinephrine. It has been suggested that the well known phenomenon of intraoperative pupil constriction is mediated via the release of prostaglandins by mechanical stimulation of the iris. This is likely since prostaglandins have been proved to induce miosis. The exact mechanism is still unclear, but prostaglandin receptors have been demonstrated in the iris and also in ocular sympathetic nerves, modulating the neurotransmitter release. Therefore the use of topical NSAIDs has been suggested. However, the benefit of NSAIDs in reducing pupil constriction during cataract surgery remains somewhat elusive.

7.3 The separate effects of the ICM components (IV)

As shown in study I, the duration of mydriasis is longer with ICM compared to TM, which results in a larger pupil at the first postoperative day. A larger pupil the day after surgery may allow an easier examination of the eye’s posterior segment and the VA at the first postoperative day is as good with ICM as with TM, but some patients are a bit concerned with the larger pupil. The ICM cocktail contains cyclopentolate 0.1% and phenylephrine 1.5%. Cyclopentolate is an anticholinergic (passive) agent, which performs its effect through inhibition of the acetylcholine receptors of the iris and it has a rather long mydriatic effect, up to 24 h. The sympathomimetic (active) agent phenylephrine acts mainly through stimulation of the α-receptors in the iris dilator and it has a shorter duration with an effect up to 5-7 h. Since a modern cataract removal is a rapid procedure in most cases, our aim with study IV was to evaluate if intracameral lidocaine and phenylephrine alone give sufficient pupil dilatation for the whole operation.

ICM without cyclopentolate gave the same pupil dilatation as ICM containing cyclopentolate. This was demonstrated by the stepwise injections of the substances and confirmed by the masked, randomized comparison of the additional 40 cases. A plausible explanation to this phenomenon may be that cyclopentolate, being passive, may be a weaker dilator compared to phenylephrine, at least momentarily. Cyclopentolate may be more effective over time since it has a longer duration and perhaps it has its place when the operation times are longer than in routine phacoemulsification surgery. The pupils at 1 day were significantly larger in the cyclopentolate group, likely owing to the longer action of the substance. Hence, removing cyclopentolate from the ICM solution, a more rapid reversal of the dilatation occurs resulting in a faster normalization of the pupil to the first postoperative day.
ICM also contains lidocaine 1% that, as stated in the introduction, offers some pupil dilating capacity by anesthetizing the iris muscles. The pupil size is regulated by a co-operation of the pupil sphincter and dilator. It is stated that the iris sphincter is stronger than the dilator,\textsuperscript{43} and will largely determine the pupil size for example under a bright microscope light. Anesthetizing both muscles under such conditions will therefore result in a pupil dilatation. Lidocaine has also been used as the sole mydriatic agent in cataract surgery.\textsuperscript{53,135} The present study confirms that lidocaine, apart from its anesthetizing effect, also has a dilating capacity. The effect, however, may be a bit weak for many routine cases, based on the present data, especially since the trauma of the operation release prostaglandins, causing miosis.\textsuperscript{123} Therefore, phenylephrine 1.5% appears to be a good complement to lidocaine 1%.

In reference to this, there has also been shown that preoperative topical cyclopentolate can be omitted when using intracameral lidocaine together with preoperative topical phenylephrine.\textsuperscript{136}

Considering the different duration of the ICM solutions – with or without cyclopentolate – the surgeon may possibly have an option to choose the one that suits the actual operation.

7.4 The relationship between postoperative corneal oedema and endothelial cell loss (II)

During the process of this thesis, we noticed a tendency towards that the degree of the postoperative corneal oedema correlated to the ECL. An extended study was therefore conducted.

Through its design study II contained large variations in the corneal swelling at the first postoperative day and a clear correlation was found between the early postoperative swelling and the ECL at 3 months. Literature offers relatively little information about the range of ECL after phacoemulsification surgery, but cases with more than 50% cell loss have been reported.\textsuperscript{137} (Mean + 2 * SD) values ranging from 11\%\textsuperscript{114} to 34\%\textsuperscript{138} have been reported, meaning that 2.5\% of the patients would exceed that level of cell loss, assuming a normal distribution of the cell loss. It could also be that in other studies of ECL after cataract surgery, patients with very dense nuclei, high levels of ultrasonic energy and a severe postoperative corneal oedema comprise a small part of the total material, making this relationship less evident. Also, patients with too dense nuclei are often not included in studies.\textsuperscript{137,138}

When analyzing other possible risk factors for ECL after phacoemulsification cataract surgery the nucleus colour was the only pre- or intraoperative variable independently associated with the central ECL. A dense nucleus has also been identified as a risk factor in other studies,\textsuperscript{106,137,138} whereas some studies report successful results with phacoemulsification surgery, even in cases with very dense nuclei.\textsuperscript{104,114} Previous studies have also found infusion volume, type of IOL, complications of surgery, age, axial length, phacoemulsification time and
ultrasound power to be risk factors associated with postoperative ECL,\textsuperscript{106,107,137,138} even if the some studies have shown contradictory results concerning the latter four parameters.\textsuperscript{106,107,137,139}

In study I, we had no significant ECL after the phacoemulsification cataract surgery. The sixty patients were followed up to one month. However, it may be difficult to demonstrate a significant cell loss without a larger number of patients. On the other hand, we observed a greater cell irregularity postoperatively that may indicate that the endothelial cells had not “come to rest” completely and that a follow-up of 1 month is too short to make conclusions. But, Elvira et al.\textsuperscript{140} report little change in the cell count from 1 to 3 months postoperatively and we proposed that perhaps parameters such as HSF and DE are more sensitive to the minute endothelial changes induced by modern phacoemulsification surgery than the traditional cell count.

An ECL of 7.9 ± 4.1\% at 2 to 5 days postoperatively and thereafter no further ECL up to 1 year, has been reported.\textsuperscript{141} The authors stated that measuring the early ECL proved to be an indication of ECL at 12 months. Others have reported an ECL that was significantly higher than the physiological rate up to two years and asserted that even this follow up time was not sufficient to establish the total ECL after cataract surgery.\textsuperscript{142} However, several studies have found stabilization of the corneal endothelium 3 months after cataract surgery,\textsuperscript{108,143,144} and many have a chosen a follow up time for 1 to 3 months.\textsuperscript{107,145-147} Considering that the endothelial morphology had returned to baseline values at 3 months postoperatively, the cell loss at this time point is likely to have stabilized or at least to have entered a slower phase. Three months appeared to be a suitable end point in our setting, considering that essentially the same results could have been obtained with a follow-up of 1 month.

In the current study, the cell loss at the nasal part of the cornea more strongly correlated with the corneal swelling at that location than to the central swelling. This may indicate a correlation between the local swelling and the local cell loss within the same cornea, meaning that a central spot of corneal oedema is likely to be associated with a smaller overall cell loss than a generalized oedema. Confirmation of this hypothesis, however, will require further studies.

Orbscan II has been reported to give highly reproducible pachymetric values\textsuperscript{148,149} but slightly higher than ultrasonic or conventional optical pachymetry.\textsuperscript{150} Therefore the option of an acoustic correction factor is available in the Orbscan II.\textsuperscript{151,152} In corneas with haze, such as in the edematous corneas in our study, Orbscan II has been reported to underestimate the corneal thickness slightly,\textsuperscript{153,154} and central and peripheral values may also not be entirely comparable to the Orbscan II.\textsuperscript{155} Also, the corneal thickness in normal corneas affect the validity of the measurements.\textsuperscript{156} Hence, different derived equations for corrections have been proposed.\textsuperscript{155,156} This may have a less significant
consequence in our study, since we focused on pachymetrical differences rather than absolute values. Therefore reproducibility is of greater importance than measurement calibration in this type of setting. Our impression is that the Orbscan II pachymetry gives more relevant information than ultrasonic pachymetry after phacoemulsification surgery, because it correlates better with the ECL. Possibly, this may be due to better reproducibility of the Orbscan II measurements.

The results of the present study indicate that a clinically significant postoperative corneal oedema is strongly associated with a clinically significant ECL. The increase in pachymetry at the first postoperative day compared with the preoperative value should be a useful indicator of the effects on the corneal endothelium exerted by the phacoemulsification procedure. There was a significant difference in postoperative ECL between patients whose corneas were defined as “clear” and those defined as “not clear”. Therefore, even the simple examination in the slit lamp with clinical assessment of the cornea at 1 day could roughly estimate which patients are at risk for a large ECL and consequently may be scheduled for a more careful follow up. Future refinements of the phacoemulsification techniques should aim to minimize early postoperative corneal swelling to allow for more rapid visual rehabilitation, as well as to minimize permanent corneal endothelial damage.

7.5 Future considerations and studies

With ICM, the pupil is in average 1.0 mm smaller in the beginning of the operation, when compared to TM. Even if it has been demonstrated that this does not affect the safety of the cataract procedure, it could sometimes be helpful to have a larger pupil. It may therefore be a future consideration to add a single mydriatic drop during the preoperative preparations in order to overcome this drawback. Evaluation of this will demand further investigations.

Cholinergic agonists such as acetylcholine (Miochol®) is sometimes used intracamerally during the cataract procedure to contract the pupil in order to stabilize the IOL, avoid vitreous in the anterior camber and reduce elevated postoperative IOP. One reflection is how cholinergic agonists would function when used together with ICM. We have not noticed any problems concerning this, but theoretically more muscarinic receptors could be occupied when using ICM with cyclopentolate since it is administered intracamerally. This might impede the action of acetylcholine. However, this theoretical problem should not be an issue when cyclopentolate is removed from the ICM cocktail. It has also been demonstrated that the use of dilating preoperative phenylephrine drops do not interfere with the effect of acetylcholine. We will continue with a study in order to confirm the safety with ICM and acetylcholine.
ICM could have advantages in managing IFIS since the phenylephrine concentration in ICM is higher than the suggested treatment with intracameral phenylephrine for IFIS.\textsuperscript{86} The use of ICM could also possibly obviate the need for preoperative atropine, which is suggested to be administered topically 3 times daily for 2 days before surgery.\textsuperscript{87} Especially since atropine might lead to urinary retention and thereby abate the effect of tamsulosin. ICM in combination with a cohesive, high molecular OVD such as Healon\textsuperscript{®} 5 can be an appropriate solution to reduce the problems associated with IFIS.
8. CONCLUSIONS

Paper I
ICM with lidocaine 1%, phenylephrine 1.5% and cyclopentolate 0.1% is a new method of dilating the pupil before cataract surgery. It is a safe and effective way to achieve an adequate pupil size in order to carry out the cataract procedure.

Paper II
The degree of postoperative corneal oedema at the first postoperative day is strongly correlated to the degree of corneal endothelial cell loss after phacoemulsification cataract surgery.

Paper III
When ICM is used the need for epinephrine in the irrigating solution during cataract surgery is obviated. The study confirms that epinephrine in the irrigating solution reduces the intraoperative pupil constriction when using TM.

Paper IV
ICM without cyclopentolate 0.1% renders sufficient dilatation of the pupil for routine phacoemulsification cataract surgery. By eliminating cyclopentolate, a more rapid postoperative normalization of the pupil size is accomplished.
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