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Intracameral Mydriatics in Cataract Surgery

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1. Introduction

The routines for cataract surgery have undergone a remarkable development over the past two to three decades (Lundstrom, Stenevi et al. 2002). Surgical techniques have improved constantly, and now require less extensive anesthesia (Behndig and Linden 1998), decreased need for hospitalization (Oshika, Amano et al. 2001; Yi, Flanagan et al. 2001) and fewer postoperative controls (Edwards, Rehman et al. 1997). Still, it is remarkable that some perioperative routines have undergone very little change, despite the general improvement. One of those more or less unchanged routines have been the routine for preoperative pupil dilatation.

In a phacoemulsification cataract procedure, a large proportion of the work is done within the eye, and sufficient mydriasis is a prerequisite to allow for visualization of the capsulorhexis and the lens. Conversely, poor mydriasis during cataract surgery increases the risk of intraoperative complications such as posterior capsule rupture (Artzen, Lundstrom et al. 2009), A small pupil can make instrument maneuvering within the eye more difficult, make the capsulorhexis hydrodissection and phacoemulsification more difficult to perform of the lens nucleus can lead to an increased risk of iris damage, and increases the risk also for other complications, including sphincter tear, bleeding and dropped nucleus. Iris damage due to a small pupil can result in an irregular and atonic pupil with photophobia and other types of discomfort.

Traditionally, topical administration of a combination of anticholinergic (passive) mydriatic agents such as cyclopentolate 1%, tropicamide 1%, homatropine 5% or scopolamine 0.25% and sympathomimetic (active) mydriatic agents such as phenylephrine 2.5% to 10% has been the preferred way to achieve mydriasis. Often, topical nonsteroidal antiinflammatory drops such as indomethacin 1%, flurbiprofen 0.03%, or suprofen 1% are also added, to enhance and prolong the mydriatic effect. The administration of the eye drops is typically started 45 minutes to 1 hour before the surgical procedure. It is clear that this regimen has some disadvantages. First, it is well known that the slow penetration of mydriatic substances through the cornea renders a slow pupil enlargement (Lovasik 1986; Chien and Schoenwald 1990) with a maximum mydriatic effect at 30 minutes for cyclopentolate (Haaga, Kaila et al. 1998) and as much as 75 minutes for phenylephrine. (Matsumoto, Tsuru et al. 1982) In practice, this means that the waiting time for the pupil to dilate often is several-fold longer than the surgical procedure itself. Second, limited bioavailability of topically administered substances means a significant systemic absorption (Doane, Jensen et al. 1978; Kaila, Huupponen et al. 1989; Haaga, Kaila et al. 1998) which in turn may increase the risk

for cardiovascular side-effects, (Fraunfelder and Scafidi 1978; Fraunfelder and Meyer 1985) especially in high-risk groups such as persons with hypertension, (Hakim, Orton et al. 1990) or cardiovascular diseases, (Meyer and Fraunfelder 1980) and in children. (Ogut, Bozkurt et al. 1996; Elibol, Alcelik et al. 1997), Third, even if a good mydriasis is achieved initially, the mydriatic effect often tends to diminish during the operation, and especially when the procedure takes longer than expected. Different solutions have been suggested to prolong the mydriatic effect from topical mydriatics such as preoperative treatment with diclofenac (Antcliff and Trew 1997), viscous 10% phenylephrine, (Duffin, Pettit et al. 1983) or intraoperative intracameral epinephrine. (Duffin, Pettit et al. 1983; Liou and Yang 1998). In 2003, we first introduced the concept of intracamerally injected mydriatics, in which mydriatic substances were mixed with the intracameral lidocaine given at the start of the phacoemulsification cataract procedure. As we will see below, a local anesthetic will also have an additive, passive mydriatic effect when injected intracamerally (Cionni, Barros et al. 2003). We early found that when using a regimen involving intracameral mydriatics, some of the disadvantages with topical mydriatics are avoided, since the method means no preoperative waiting time and also reduced doses of the mydriatic substances - and thereby likely lowers the risk for systemic side-effects (Lundberg and Behndig 2003) (Morgado, Barros et al. 2010). In our own current setting, a preservative-free mixture of phenylephrine 1.5% and lidocaine 1% is used, but other solutions have been proposed and used clinically, mainly preservative-free epinephrine 0.025% with lidocaine 0.75%, or lidocaine 1% only. Other substances have been tried experimentally and proven efficient, such as epinine 0.3% - 3.0% and isoprenaline 0.3%. An interesting consequence of the concept of intracameral mydriatics in intraocular surgery is also that is provides us with a possibility to use other mydriatic substances than the traditional anticholinergics and α_1-adrenergics (Cionni, Barros et al. 2003; Lundberg and Behndig 2009; Myers and Shugar 2009), since the doses of potentially cardiotoxic drugs can be reduced, and we no longer have to consider limitations in bioavailability because of the corneal barrier. Cyclopentolate, whether given topically or intracamerally, has been demonstrated not to contribute to increased mydriasis when using intracameral mydriatics (Lundberg and Behndig 2008), and neither has epinephrine added to the intraoperative infusion (Lundberg and Behndig 2007). Cyclopentolate and similar substances are therefore often abandoned in intracameral mydriatics regimens today, and accordingly, intraoperative epinephrine infusion is more seldom used today by surgeons using intracameral mydriatics. With intracameral mydriatics, the mydriasis generally reaches 95% its final value within 20-30 seconds. Intracameral mydriatics render slightly smaller pupils than topical mydriatics at a maximum dosage, but with intracameral mydriatics, the pupils do not contract intraoperatively, as with topical mydriatics. As insufficient adrenergic stimulation of the pupil dilator appears to be a major factor causing intraoperative pupil contraction during phacoemulsification cataract surgery (Antcliff and Trew 1997; Liou and Yang 1998; Backstrom and Behndig 2006), intracameral mydriatics containing an adrenergic substance is effective in re-dilating the pupil (Backstrom and Behndig 2006; Mori, Miyai et al. 2010), and are also used to prevent intraoperative floppy iris syndrome (IFIS) (Gurbaxani and Packard 2007; Takmaz and Can 2007; Cantrell, Bream-Rouwenhorst et al. 2008). With intracameral mydriatics, the patients perceive less initial glare from the operation microscope light, as the pupil is small at the beginning of the procedure. The intracameral mydriatics concept has been extensively studied from a safety perspective by us and others, and is found to be safe with no increase in corneal endothelial

cell loss (Lundberg and Behndig 2003) (including at long-term follow-up), inflammatory reaction, postoperative corneal swelling (Lundberg and Behndig 2003) or macular edema (Johansson, Lundberg et al. 2007). Furthermore, in routine surgery, the surgical performance does not differ from when a standard topical mydriatic regimen is used (Behndig and Eriksson 2004). Intracameral mydriatics comprise a rapid, effective and safe alternative to topical mydriatics in phacoemulsification surgery. It has a potential to simplify the preoperative routines, and for certain high-risk groups, it may reduce the risk for cardiovascular side effects.

2. Intracameral mydriatics

2.1 Published studies

Several studies have been published suggesting different routines for the use of intracameral mydriatics, and evaluating the various regimens. This chapter aims to give a brief overview of the published studies.

2.1.1 Initial studies: Cyclopentolate/phenylephrine/lidocaine

In 2003 our group published a prospective, randomized, double-masked study (Lundberg and Behndig 2003) in which the patients were randomly assigned either of two treatments: traditional topical mydriatics with 3 drops each of cyclopentolate 1% and phenylephrine 10% with 15 minutes interval plus 150µl of preservative-free xylocaine 1% intracamerally at the beginning of the procedure, or intracameral mydriatics with placebo eye drops and 150 µl of a preservative-free mixture of cyclopentolate .1%, phenylephrine 1.5% and lidocaine 1% intracamerally. In this study, the intracameral injection was given by the other surgeon, and thus, neither the operating surgeon nor the patients were aware of which of the two treatments was given, allowing for the double-masked design. The pupil sizes were recorded during surgery using video recordings, and also at one day and one month postoperatively, using the Orbscan II®, (Marsich and Bullimore 2000) (Bausch & Lomb Surgical, Inc., San Dimas, CA). In addition, corneal endothelial morphometry, ETDRS visual acuity (Camparini, Cassinari et al. 2001) intraocular pressure (IOP) and intraoperative blood pressure and pulse were measured.

After injection of intracameral mydriatics, the pupils reached 95±3% of their maximum size after 20 seconds (Figure 1). In the intracameral mydriatics group, the pupil size after viscoelastic injection was 6.7±1.0 mm, which was about 1 mm smaller than with topical mydriatics, but when using intracameral mydriatics the pupils continued to enlarge throughout the procedure as opposed to when topical mydriatics were used. The corneal endothelial morphometry did not differ between intracameral and topical mydriatics. A significant pulse deceleration was seen with topical, but not with intracameral mydriatics. This likely resulted from the fact that the total dose of phenylephrine with intracameral mydriatics in this setting was only 23% of that with topical mydriatics. The results of this study were confirmed in a small pilot series of 10 patients published by Soong *et al* in 2006 (Soong, Soultanidis et al. 2006), where it was also concluded that the intracameral technique is a safe, rapid, and effective alternative to conventional topical mydriasis in phacoemulsification cataract surgery, and that it can reduce the duration of stay within the outpatient surgical units. The latter is not least important considering the high turnover of modern cataract surgery. The authors had also, at the time of publication, continued with another 280 uneventful routine cases using the same technique.

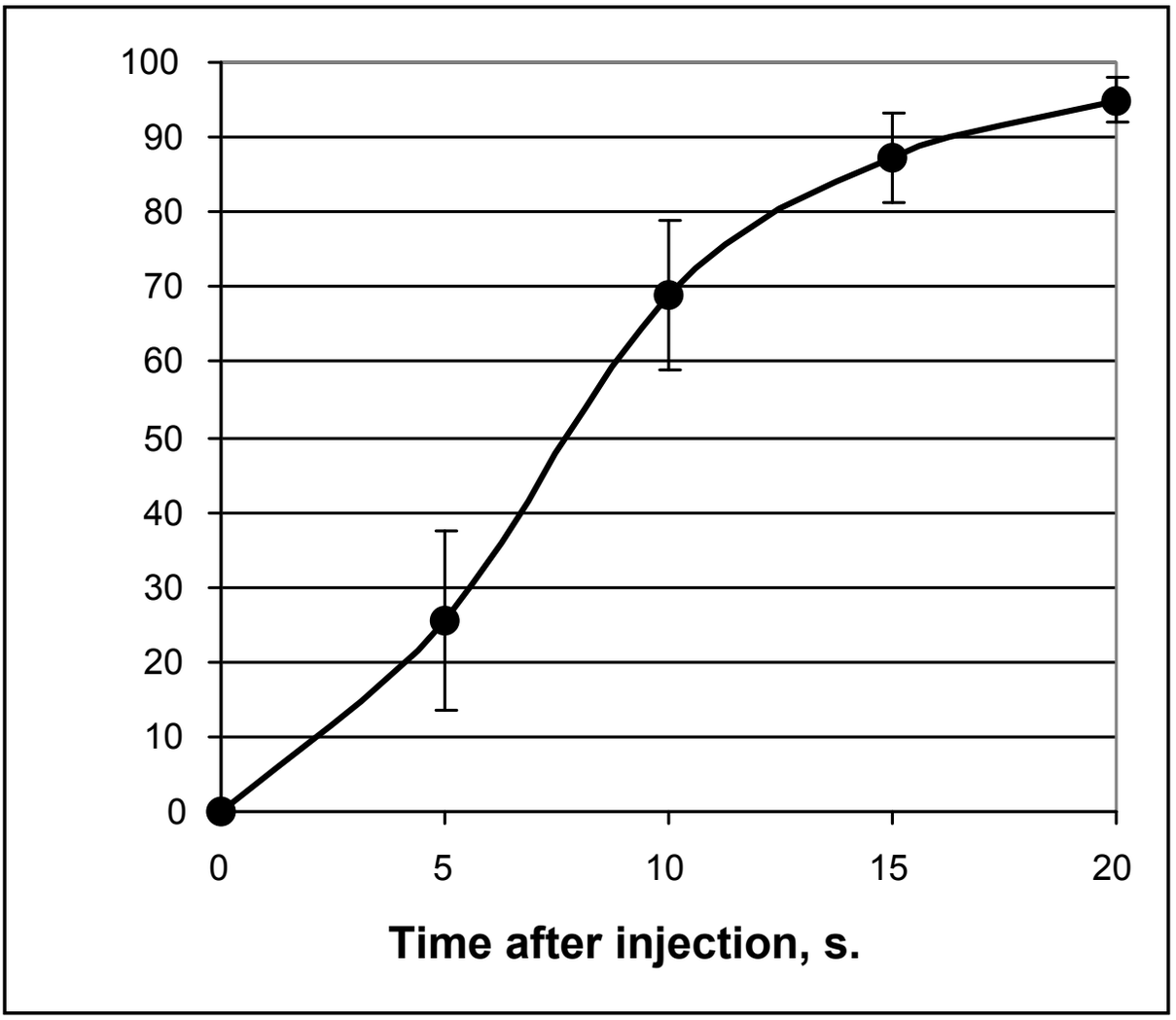


Fig. 1. Pupil size after injection of intracameral mydriatics. Pupils reached 95±3% of their maximum size after 20 seconds.

2.1.2 Initial studies: Lidocaine

At the same time as the above mentioned study (in fact in the same number of Journal of Cataract and Refractive Surgery) Robert J Cionni *et al* published an article describing the use of 300 to 500µl of Xylocaine-MPF 1% injected intracamerally as the sole mydriatic agent (Cionni, Barros et al. 2003). Epinephrine 0.3 cc of 1:1000 was also added to the infusion. The authors state that "Mydriasis begins immediately, enabling the surgeon to proceed within 90 seconds." In this study, the first 12 patients had adequate mydriasis, with a mean pupil size before dilation of 2.4 mm (range 1.5 to 3.1 mm) and after intracameral Xylocaine-MPF 1%, 6.5 mm (range 5.2 to 7.2 mm).

2.1.3 Further studies on lidocaine

The results from Cionni's study were confirmed in 2007 by Nikeghbali *et al* (Nikeghbali, Falavarjani et al. 2007) in a prospective comparative case series including 57 patients randomized to receive either topical mydriatics (30 eyes) or intracameral lidocaine (27 eyes) to dilate the pupil. The topical mydriatics given consisted of 3 drops of cyclopentolate 1%

and phenylephrine 5% given 5 minutes apart starting 60 minutes before surgery. The intracameral group received 0.2-0.3 ml of preservative-free lidocaine 1% intracamerally. Noteably, in this study, no epinephrine was added to the irrigating solution. The mean pupil dilation was 4.52±0.08mm in the intracameral group and 4.06±0.09 mm in the topical group, and no difference in the overall subjective surgical performance was noted. Similar results were also published the following year in the Indian Journal of Ophthalmology by the same group; in a case series of 31 consecutive cases the pupils dilated from 2.63±0.33 mm to 7.03±0.61 90 seconds after injection of 0.2 to 0.3 ml of preservative-free lidocaine 1%, and no negative effects on the surgical performance were noted (Nikeghbali, Falavarjani et al. 2008). Jayadev and Nayak also published a short report on this regimen in 2007 (Jayadev and Nayak 2007).

Noticeably, both the studies by Nikeghbali (Nikeghbali, Falavarjani et al. 2007; Nikeghbali, Falavarjani et al. 2008) and Jayadev (Jayadev and Nayak 2007) demonstrate significantly larger pupils after intracameral lidocaine without preoperative topical mydriatics, than we have seen in our investigations (Lundberg and Behndig 2008). This difference in effect from intracameral lidocaine may be due to population differences, differences in lidocaine dosage, or the fact that the pupil size was measured 90 seconds after the intracameral lidocaine injection in the studies in question. Generally, the onset of mydriasis from a passive dilator such as lidocaine, administered intracamerally will be a bit slower than from the combination of an active and a passive dilator.

2.1.4 Surgical performance

In 2004, a series of 198 consecutive cases operated with intracameral mydriatics was compared to the previous 198 cases operated with traditional topical mydriatics (Behndig and Eriksson 2004). Several pre- intra- and postoperative parameters were registered, the subjective surgical performance was graded after each procedure, and the change in pulse and oxygen saturation induced by the ICM injection was registered. Despite the smaller pupils at the initiation of the procedures, no increase in operation time or complication rates was seen with with intracameral mydriatics, compared to when standard topical mydriatics were used. Furthermore, the subjective surgical performance was ranked as equally good for both groups. The studies from Nikeghbali *et al* (Nikeghbali, Falavarjani et al. 2008) confirmed the results of a surgical performance similar to when using topical mydriatics.

2.1.5 Handling intraoperative pupil constriction

In 2006, a prospective, randomized, placebo-controlled, double-masked study study involving 80 patients was published, aiming to determine whether intracameral mydriatics can redilate pupils that contract during phacoemulsification cataract surgery (Backstrom and Behndig 2006). Patients were randomized to receive or not receive an addition of 0.6 μg/ml of epinephrine to the irrigation solution, and further randomized to have an injection of our original intracameral mydriatics mixture or placebo after the phacoemulsification and cortex cleaning. The pupil sizes were registered at different time points during surgery and the day after surgery. There was a greater degree of pupil contraction in the absence of epinephrine in the irrigation solution compared to in the presence of epinephrine. In cases where no epinephrine was added to the irrigation solution, the intracameral mydriatics solution given significantly redilated the pupils at 30 seconds ($p<0.001$ compared with placebo) as well as at 2 mins ($p = 0.015$ compared with placebo). These findings are also well

in accordance with the later findings of Mori *et al*, demonstrating a satisfactory pupil ditatation with an intracameral solution containing phenylephrine and tropicamide in cases with insufficient pupil dilatation from topical mydriatics (Mori, Miyai et al. 2010). The findings of the 2006 study also confirms earlier reports that insufficient adrenergic stimulation of the pupil dilator is a major factor causing intraoperative pupil contraction during phacoemulsification cataract surgery (Antcliff and Trew 1997; Liou and Yang 1998). Likely, this factor also contributes to the absence of pupil contraction seen when using a large bolus dose of an adrenergic substance at the beginning of a surgical procedure (as with intracameral mydriatics), as opposed to when topical mydriatics are employed (Lundberg and Behndig 2003; Lundberg and Behndig 2007).

2.1.6 Omitting epinephrine infusion

It has long been known that addition of epinephrine to the irrigating solution prevents intraoperative pupil constriction in phacoemulsification surgery with topical mydriatics (Antcliff and Trew 1997; Liou and Yang 1998; Backstrom and Behndig 2006). To investigate whether this holds true also with intracameral mydriatics, we performed a study in 2007 to evaluate the possibility of removing epinephrine from the irrigating solution in phacoemulsification surgery when using intracameral mydriatics (Lundberg and Behndig 2007). In this prospective, randomized, double-masked study involving a total of 140 cataract patients, the first part of the study included 90 patients divided into two groups. Patients in both groups were given 150 µl of the intracameral mydriatic solution at the beginning of the procedure. In the first group, 0.6 µg/ml epinephrine was added to the irrigating solution; no epinephrine was added to the irrigation solution used in the second group. The second part of the study involved 50 patients, all of whom were given topical mydriatics and then similarly divided into two groups and treated as in the first part of the study. As noted in our initial studies (Lundberg and Behndig 2003), the pupil sizes generally increased during the procedures with intracameral mydriatics. Interestingly, this increase was significantly greater without epinephrine (13 +/- 19% versus 4 +/- 14%; $p = 0.02$). In the topical mydriatics setting, pupil sizes decreased intraoperatively in both groups; significantly more without epinephrine (- 5 +/- 4% versus - 12 +/- 7%; $p < 0.001$). We concluded that an irrigating solution without epinephrine can safely be used with intracameral mydriatics. The increase in pupil size during the procedure was even shown to be greater without epinephrine. As epinephrine is unstable in a solution with physiological pH, time-consuming repeated blending procedures are needed, which can be avoided if intracameral mydriatics are used. The study also confirms earlier findings that epinephrine is beneficial when using topical mydriatics (Antcliff and Trew 1997; Liou and Yang 1998; Backstrom and Behndig 2006).

2.1.7 Omitting cyclopentolate

Since we suspected that the onset of mydriasis from intracameral cyclopentolate was too slow for the substance to be meaningful as an intracameral mydriatic, and that the passive dilating effect of lidocaine would be quite sufficient together with an adrenergic substance such as phenylephrine, we decided to assess the separate mydriatic effects of intracameral cyclopentolate hydrochloride, lidocaine hydrochloride and phenylephrine hydrochloride in another prospective randomized double-masked study published in 2008 (Lundberg and Behndig 2008). The study involved a total of 56 cataract patients: in 16 patients, lidocaine 1%, phenylephrine 1.5%, and cyclopentolate 0.1% were injected sequentially one after the other.

Phenylephrine and cyclopentolate were randomized to switch in order, creating 2 study groups with 8 patients in each. In part two of the study, an additional 40 patients were randomized to receive either all three substances intracamerally (lidocaine 1%, phenylephrine 1.5%, and cyclopentolate 0.1%) or intracameral lidocaine 1% and phenylephrine 1.5% only.
Lidocaine alone gave a significant pupil dilation to 4.9±0.6 mm. When cyclopentolate was injected next, the pupil size increased further by 1.3±0.6 mm. When phenylephrine was added, the pupil increased an additional 0.7±0.4 mm. In the second group, in which phenylephrine was given directly after lidocaine, the pupil size increased by 2.1±0.5 mm. When cyclopentolate was added as the third substance, no significant change in the pupil size could be seen (Figure 2). Accordingly, no statistically significant differences in pupil size were observed between the 20+20 patients who were given intracameral mydriatics with or without cyclopentolate. Noteably, though, the day after surgery, the pupils were significantly larger in the cyclopentolate group (4.7±1.1mm) than in the group without cyclopentolate 2.9±0.8 mm. We concluded that cyclopentolate administrated intracamerally has no immediate additive mydriatic effect to intracameral lidocaine plus phenylephrine, or to put it more precisely, intracameral cyclopentolate dilates the pupil after surgery, but not during surgery. After this study, cyclopentolate was omitted from our clinical routine preparation.

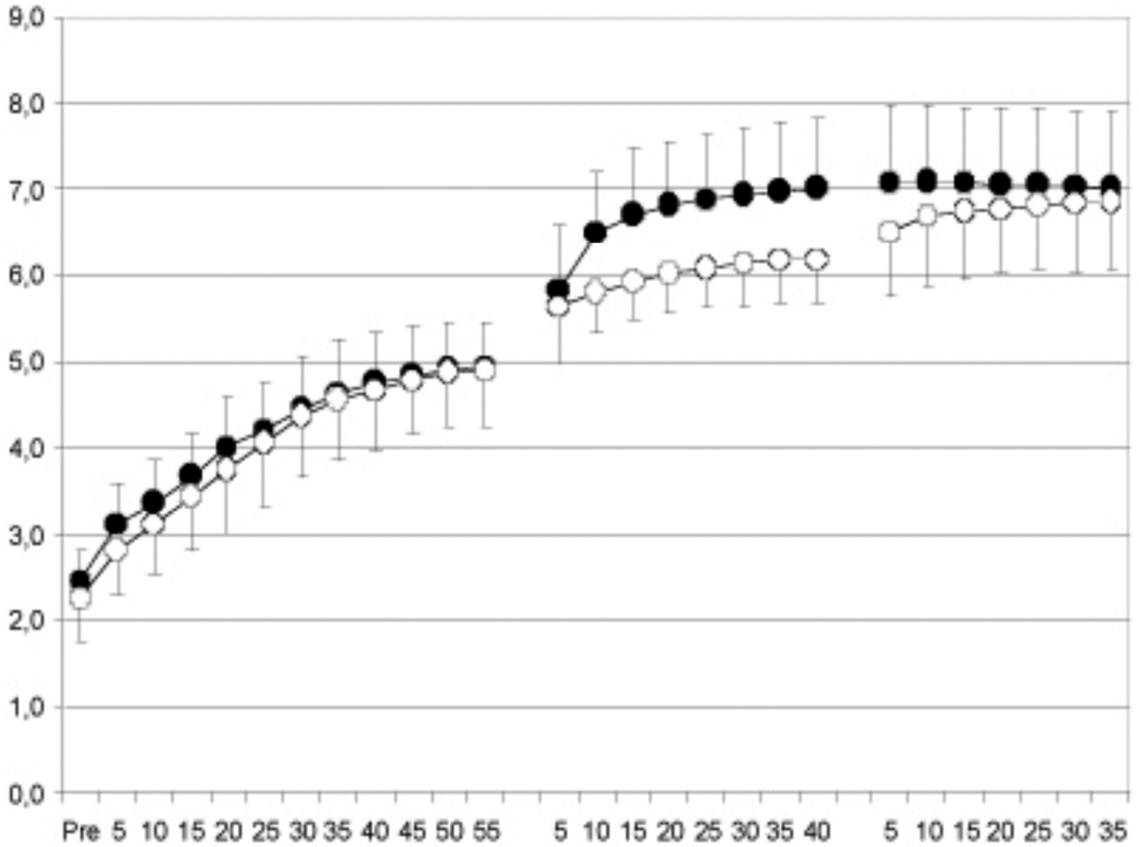


Fig. 2. The figure shows the pupil sizes (in mm, Y-axis) at different time points (in seconds, X-axis) after stepwise intracameral injections of lidocaine 1% (given first in both gruops, left part of the diagram), phenylephrine 1.5% and cyclopentolate 0.1%, 150 mL each. The order of the latter 2 injections was 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. Cyclopentolate given after phenylephrine has no detectable additive mydriatic effect.

A later study showed that when 2 drops of topical phenylephrine 10% combined with 150µl of intracameral lidocaine 1% is given at the beginning of a phacoemulsification procedure, no additive mydriatic effect can be seen from administrating preoperative topical cyclopentolate (Lundberg and Behndig 2009). The study was designed as a prospective, double-masked, randomized trial including 20 patients with age-related cataract. Initially, the pupil sizes were significantly smaller in the group where no topical cyclopentolate had been given - 4.8±1.2 mm compared to 6.5±1.4 mm, but the lidocaine injection increased the pupil sizes significantly in the absence of cyclopentolate, so that the pupil sizes were equalized throughout the surgical procedure for the both treatments. These findings show that the passive diating effect from intracameral lidocaine is sufficient, without topical passoive diating agents, and that preoperative topical cyclopentolate can be omitted when intracameral lidocaine is used.

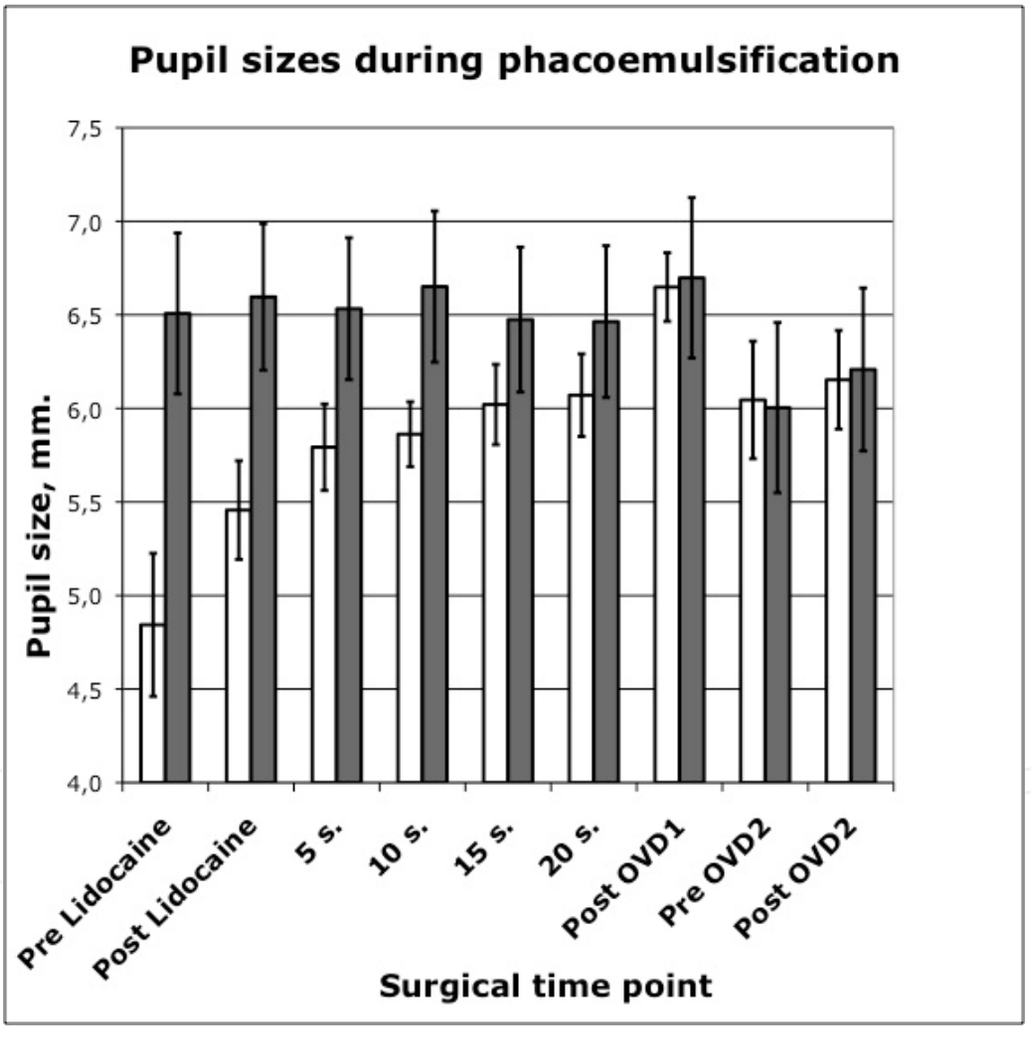


Fig. 3. The figure demonstrates the pupil sizes (in mm, Y-axis) at different time points during the phacoemulsification process (X-axis) before and after the intracameral injection of 150µl lidocaine 1% Both treatment groups were given 2 drops of topical phenylephrine 10%; group 2 (grey bars) were also given 2 drops of topical cyclopentoloate 1%. Note that intracameral lidocaine has a pronounced mydriatic effect, noticeable when preoperative cyclopentolate is not given, and that both groups have practically identical pupil sizes throughout the procedure from after the injection of the ophthalmic viscosurgical device (OVD) and on.

2.1.8 Epinephrine/lidocaine

In their paper "Optimizing the intracameral dilation regimen for cataract surgery: prospective randomized comparison of 2 solutions" from 2009, William G Myers and Joel K Shugar compared the efficacy of a solution of epinephrine 0.025% and lidocaine 0.75% in fortified balanced salt solution ("epi-Shugarcaine") and the original solution from our group (cyclopentolate 0.1%, phenylephrine 1.5%, and lidocaine 1%). The study was designed as a pair-eye single-masked prospective study involving 84 eyes of 42 patients. Topical tropicamide was given to both treatment groups. The pupils were statistically significantly larger with epi-Shugarcaine; 0.528 mm larger 1 minute after instillation and 0.34 mm larger at the end of the procedure (Myers and Shugar 2009). Since epinephrine is a much more unspecific adrenergic stimulator than the specific α_1-receptor phenylephrine, the findings of this important study indirectly indicate that adrenergic receptors other than the α_1-receptor stimulated by phenylephrine may be involved in the mydriatic response from intracamerally administered mydriatics. Subsequent studies have lent further support to this theory, as we will see below.

2.1.9 Tropicamide/phenylephrine

In a study from 2010, Mori *et al* investigated the efficacy and safety of intracameral injection of a commercially available eye drop containing 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mori, Miyai et al. 2010), demonstrating no increased damage to cultured human corneal endothelial cells, and a good mydriatic effect in cases with poor mydriasis after preoperative topical mydriatics.

2.1.10 Cardiovascular safety

Cardiovascular effects from topical mydriatic substances have been reported by many authors thoughout the years (Fraunfelder and Scafidi 1978; Meyer and Fraunfelder 1980; Fraunfelder and Meyer 1985; Hempel, Senn et al. 1999; Motta, Coblentz et al. 2009). A rapid absorption of anticholinergic and/or adrenergic substances via the nasal mucosa can render surprisingly high systemic levels of the substance. In our first two studies, we could se no signs of negative cardiovascular effects from intracameral myriatics (Lundberg and Behndig 2003; Behndig and Eriksson 2004), which is well in accordance with the facts that the doses of the adrenergic and anticholinergic substances are lower when the substance is administered intracamerally, and that there is likely to be a smaller proportion of the drug that enters the lacrimal drainage system with intracameral administration. Morgado *et al* confirmed in a study from 2010 involving 90 patients that topical mydriatics is more efficient from an initial mydriatic point of view, but intracameral mydriatics are safer from a cardiovascular point of view (Morgado, Barros et al. 2010). Taken together, the reports on cardiovascular safety combined with the widespread clinical routine use of intracameral mydriatics are reassuring – the risk of systemic side effects is not likely to be higher with the intracameral route of administration.

2.1.11 Macular safety

Many investigators have reported an association between the use of epinephrine and macular edema in glaucoma patients (Kolker and Becker 1968; Thomas, Gragoudas et al. 1978; Classe 1980; Mehelas, Kollarits et al. 1982), particularly in aphakia, but also in pseudophakia, a condition known as epinephrine maculopathy (Miyake, Shirasawa et al.

1989). It has been hypothesized that epinephrine maculopathy is induced by a mechanism involving prostaglandins or other eicosanoids and not directly by epinephrine (Miyake, Shirasawa et al. 1989). Whatever the exact mechanisms behind epinephrine maculopathy may be, it is particularly important to rule out negative effects on the macula from the rather large doses on adrenergics given in intracameral mydriatics. Therefore, in 2007, an investigation aiming to quantify the macular edema induced by intracameral phenylephrine and lidocaine in phacoemulsification surgery was undertaken (Johansson, Lundberg et al. 2007). Optical coherence tomography (OCT) has been used in several studies to assess the macular thickness after cataract surgery (Sourdille and Santiago 1999; Biro, Balla et al. 2006; Ching, Wong et al. 2006), including randomized trials to evaluate intraoperative treatments (Ball and Barrett 2006). With this highly sensitive instrument, minute postoperative macular thickness increases can be detected in a high proportion of cataract patients, also after uneventful surgery (Sourdille and Santiago 1999; Biro, Balla et al. 2006). Such changes, although subtle, can have a clinical relevance, being associated with decreased contrast sensitivity (Ball and Barrett 2006) or visual acuity (Sourdille and Santiago 1999). In a randomized study of 22 patients, 11 patients were given 150 µl of a mixture of phenylephrine 1.5% and lidocaine 1% intracamerally for mydriasis and anesthesia. The control group (n = 11) was given conventional topical mydriatics and intracameral lidocaine. No differences in macular edema between the 2 treatments could be noted on optical coherence tomography. The degree of foveal thickness increase found in the study, with a thickness increase exceeding 15µm in about 20% of the cases, is in the same range as previously reports from other reports with topical mydriatics (Sourdille and Santiago 1999; Ball and Barrett 2006).

Similar results have later been reported also for intracameral epinephrine from Bozkurt *et al*. In a consecutive, randiomized case series of a total of 158 uneventful cataract procedures half of the eyes were given 0.2 ml of 0.02% epinephrine as an intracameral injection. No difference was seen in central macular thickness with optical coherence tomography at any time point up to 6 months after surgery. In both treatment groups, the increase in macular thickness from preoperatively to 1, 3, and 6 months postoperatively was significant. In this rather large series, clinically significant macular edema was noted in 3 eyes in the epinephrine group and 3 eyes in the control group. The authors concluded that intracameral injection of 0.2 ml of 0.02% epinephrine did not increase the risk for macular edema after uneventful phacoemulsification.

2.1.12 Long term follow-up

The results from 40 of the cases from the original 2003 study on intracameral mydriatics were evaluated after 6 years, to assess if any long term complications such as posterior capsule opacification would be more frequent in patients operated with intracameral mydriatics. In the study, the visual acuity was measured using the ETDRS-fast protocol (Klein, Klein et al. 1983; Camparini, Cassinari et al. 2001), and the intraocular pressure, the grade of inflammation inflammation, the corneal thickness and the corneal endothelial cell loss were evaluated. The degree of posterior capsule opacification was assessed from standardized photographs using a digital camera. The grading of the posterior capsule opacifiaction (fraction and severity) was done with the POCOman program (Accessed from James Boyce, PhD (Bender, Spalton et al. 2004; Ronbeck, Zetterstrom et al. 2009)). The same masked observer performed the measurements twice for every image and the mean of the 2 measurements was calculated.

At 6 years, no statistically significant differences could be observed in visual acuity, intraoucular pressure and pupil size. The corneal thickness and endothelial cell loss did not differ significantly between the two treatment groups. At the 6 year follow up the total endothelial cell loss was 16.5 ± 14.6% in the TM group vs. 15.0 ± 15.4 % in the intracameral mydriatics group (P=0.73). Furthermore, the endothelial cell morphology showed no statistical differences between the cases where intracameral mydriatics had been used and the control cases with traditional topical dilatation at surgery. The median posterior capsule opacification fraction was 9 % in the TM group vs. 7.5 % in the intracameral mydriatics group (P=0.8). Similarly, the median severity grade of the posterior capsule opacification was 0.12 vs. 0.10 (P=0.7). Two patients in each group had YAG laser capsulotomy (P=1.0). A hydrophobic acrylic intraocular lens (MA60BM, Alcon Laboratories, Fort Worth, TX) was implanted in all cases in this study. The posterior capsule opacification scorings are in accordance with the results of other studies using the POCOman program, hydrophobic acrylic intraocular lenses and similar or shorter time for follow up (Kang, Choi et al. 2009; Ronbeck, Zetterstrom et al. 2009). Also, the rate of YAG capsulotomy in the present study was similar to reported rates from previous studies done with a comparable follow up times and acrylic hydrophobic lenses (Boureau, Lafuma et al. 2009; Boureau, Lafuma et al. 2009; Ronbeck, Zetterstrom et al. 2009).

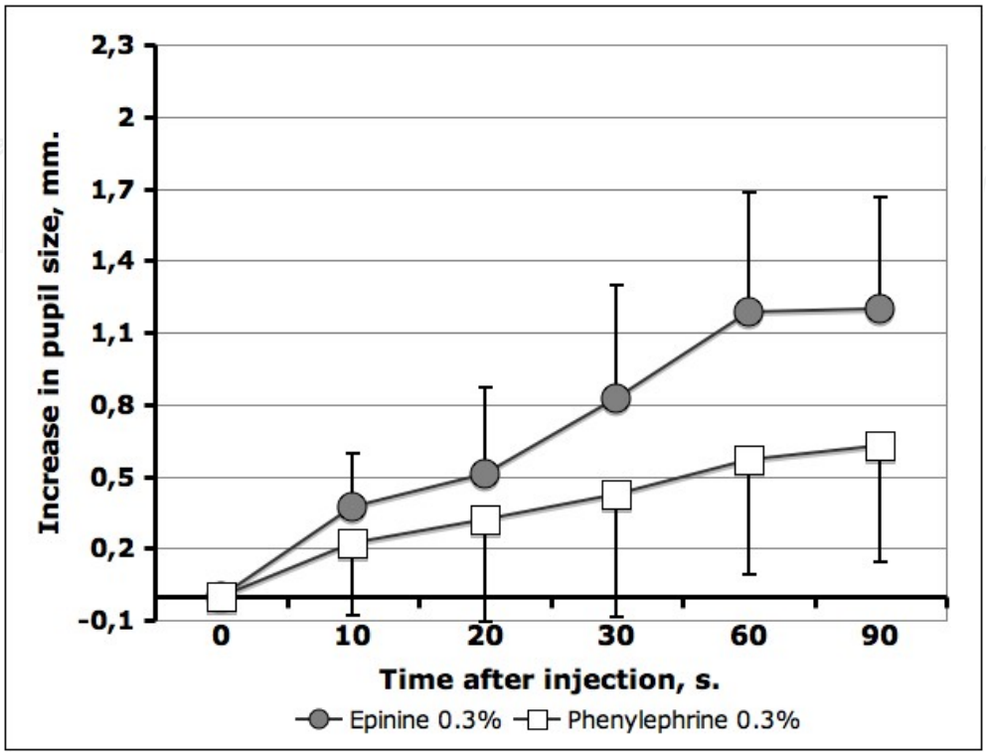
Studies concerning corneal endothelial cell loss predominantly have follow up times of a year or less and there is a wide range in reported corneal endothelial cell loss after cataract surgery (Werblin 1993; Dick, Kohnen et al. 1996; Mathys, Cohen et al. 2007). However, it is stated that there is a progressive corneal endothelial cell loss after cataract surgery that exceeds the physiological cell loss (Lesiewska-Junk, Kaluzny et al. 2002). In the present study, the 6 year corneal endothelial cell loss appears to be comparable with other studies with longer follow up times] (Werblin 1993; Dick, Kohnen et al. 1996) (Lesiewska-Junk, Kaluzny et al. 2002).

In summary, the study showed that the concept of using intracameral mydriatics in phacoemulsification cataract surgery is safe, also in a long perspective.

2.1.13 Epinine

Other candidate substances for intracamral use have also been evaluated. In 2009, we performed a study of intracamerally injected N-methyl-3,4-dihydroxyphenylamine (epinine) to phenylephrine in a porcine eye model involving 112 eyes from newly slaughtered pigs (Lundberg and Behndig 2009). Epinine is an adrenergic substanse that also shows dopaminergic properties (Pyman 1909) (Barger and Dale 1910). Epinine is known to stimulate all six known receptors in cardiovascular tissues: α_1, α_2, β_1, β_2, DA_1 and DA_2 (Itoh 1991), and can be regarded as one of the most unspecific adrenergic/dopaminergic stimulators in this respect. In the study, after contracting the pupils with acetylcholine, 0.15 mL epinine or phenylephrine 0.3%, 1.5%, or 3.0% was given as an intracameral injection. Interestingly, epinine was significantly more potent than phenylephrine at equal concentrations. Similar results have also been demonstrated for related topical substances: ibopamine, an ester of epinine, is hydrolyzed to epinine during its passage through the cornea and exerts its pharmacological effects within the eye as epinine (Soldati, Gianesello et al. 1993). Topical ibopamine is routinely used as a mydriatic in some countries due to its interesting pharmacological profile: 2% ibopamine is a more potent mydriatic than 10% phenylephrine (Marchini, Babighian et al. 2003), and the mydriatic effect is reversed within 4 hours (Gelmi, Palazzuolo et al. 1989), making ibopamine the most short-acting and most

effective topical mydriatic agent studied this far. Given these circumstances, we think epinine cold be a promising candidate substance for intracameral injection to achieve mydriasis in cataract surgery.



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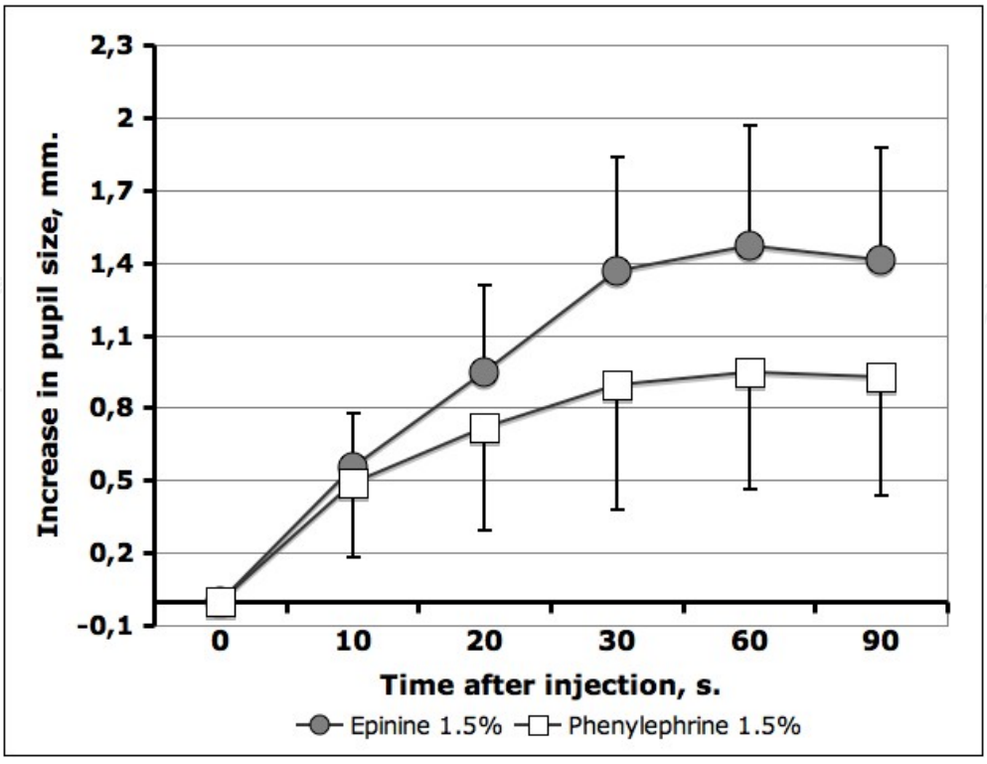

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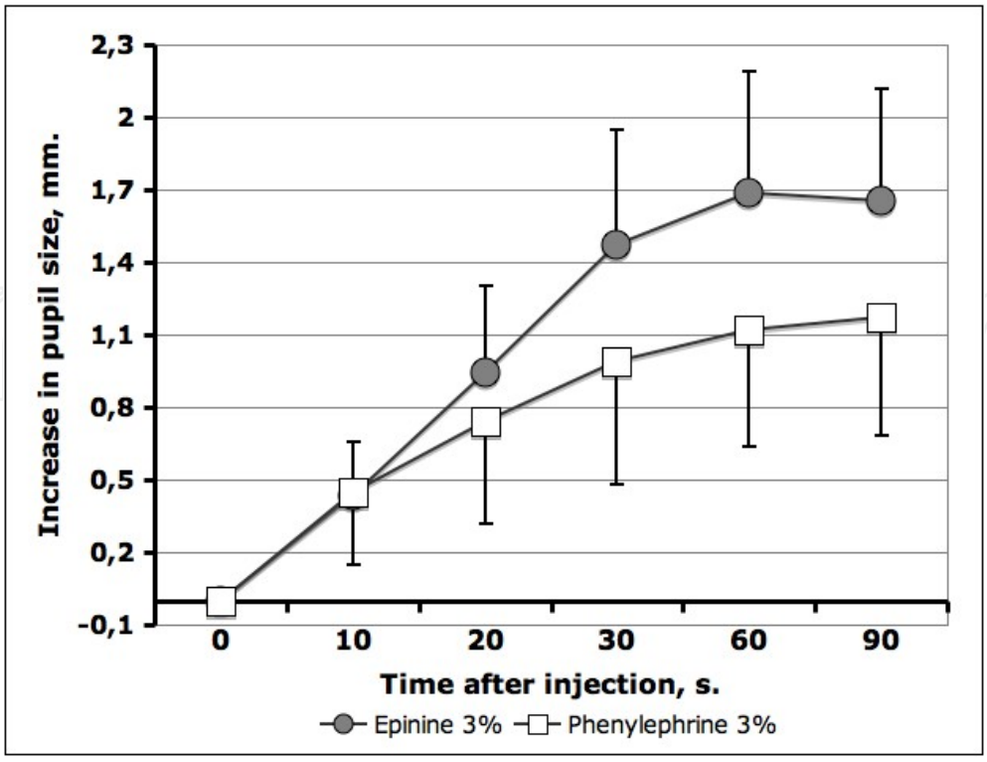

C

Fig. 4. The figure shows the increase in pupil size in porcine eyes after an intracameral injection of 150µl epinine hydrochloride (grey circles) or phenylephrine hydrochloride (white squares): 0.3% (4A) 1.5% (4B) and 3% (4C). Epinine has a more pronounced mydriatic effect at all concentrations.

2.1.14 Isoprenaline

In 2011, we compared the mydriatic effect of intracamerally injected isoprenaline (a β-receptor stimulator) plus phenylephrine to phenylephrine alone and to epinephrine in a porcine eye model with 89 intact porcine eyes; 0.3% isoprenaline and 0.15 ml 3.0% phenylephrine were injected sequentially in the mentioned or the reverse order. The control groups were treated with 0.025% epinephrine intracamerally or placebo. Phenylephrine injected after isoprenaline had a larger mydriatic effect than epinephrine, but without isoprenaline pretreatment, the mydriatic effect of phenylephrine was significantly smaller than that of epinephrine. Isoprenaline also showed a small mydriatic effect of its own. The β-receptor stimulator isoprenaline enhances the mydriatic effect of intracameral phenylephrine, indicating a role for the β-receptor in the mydriatic response. Mydriasis mediated by β-receptors may explain why non-specific adrenergic stimulators such as epinine and epinephrine can have larger mydriatic effects than the specific α_1-receptor stimulator phenylephrine (Janbaz, Lundberg et al. 2011).

2.2 Adrenergic receptors

Phenylephrine, commonly used as an intracameral mydriatic, is characterized as a specific α_1-receptor agonist. In rats and rabbits, it has been shown that the alpha(1A)-adrenoceptor is the chief mediator of the adrenergic mydriatic effects of the iris dilator muscle (Yu and Koss 2002; Yu and Koss 2003), but the mydriatic effect from an adrenergic substance may still be a

bit more complex; as an example, stimulation of iris β-receptors can cause a relaxation of the pupil sphincter (Toda, Okamura et al. 1999). The study of Myers and Shugar indicates that epinephrine may be a more potent mydriatic agent than phenylephrine when injected intracamerally (Myers and Shugar 2009), and indeed, epinephrine has a larger affinity for the β-receptor than phenylephrine (Mishima 1982). Accordingly, we have shown in a porcine eye model that the β-receptor stimulator isoprenaline fortifies mydriasis from intracameral phenylephrine (Janbaz, Lundberg et al. 2011), which further suggests a role for the β-receptor in the mydriatic response. Mydriasis mediated by β-receptors may explain why non-specific adrenergic stimulators such as epinephrine can have larger mydriatic effects than the specific α_1-receptor stimulator phenylephrine.
Epinine has a broad spectrum of adrenergic and dopaminergic effects (Itoh 1991), and the fact that epinine stimulates all adrenergic receptors, including the β_1-receptor (Itoh 1991) may contribute to a mydriatic effect superior to that of phenylephrine.

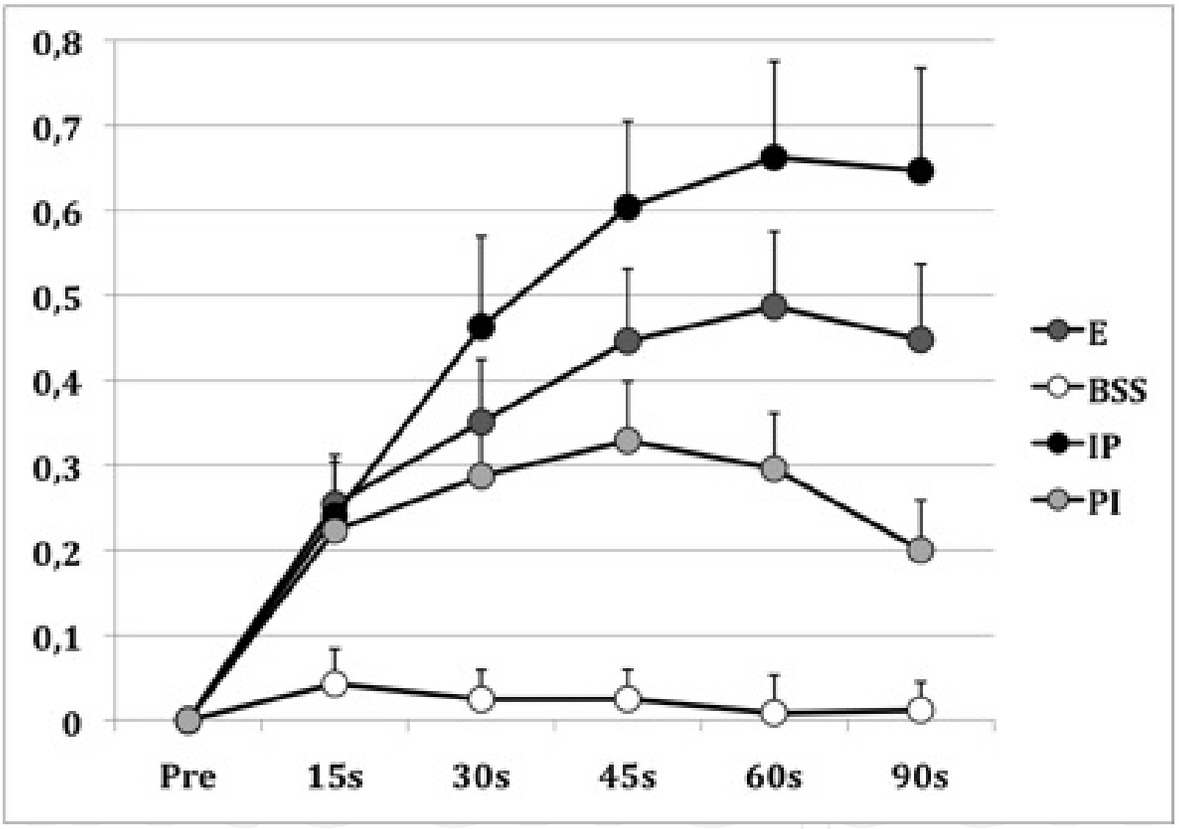

Fig. 5. The increase in pupil size in porcine eyes after an intracameral injection of 0.15 ml 0.025% epinephrine (E; n=20), Balanced Salt Solution (BSS; n=26), 0.3% isoprenaline followed by 3.0% phenylephrine (IP; n=21) or the latter two in the reversed order (PI; n=22), means and standard errors of the mean. The mydriatic effect of phenylephrine is significantly enhanced after pretreatment with isoprenaline ($p<0.05$ from 30-60 s), making it even larger than that of epinephrine ($p<0.05$ at 30 s; $p<0.01$ at 45-90 s).
(It is worth noting that due to logistic reasons, we were unable to receive the porcine eyes within 24 hours in this study, as opposed to in the epinine material (see 2.1.8) Therefore, the mydriatic responses in this study were generally smaller, but still fully measurable and possible to quantify and compare between the groups.)

2.3 Using intracameral mydriatics in intraoperative floppy iris syndrome (IFIS)

Intraoperative floppy iris syndrome (IFIS) is a condition often associated with systemic medication with α_1 adrenergic receptor antagonists for benign prostatic hyperplasia. The substances most often discussed are tamsulosin, terazosin, doxazosin and alfuzosin. Of these, tamsulosin predominates in the literature. IFIS was first described and defined in 2005 as a clinically observed triad: fluttering and billowing of the iris stroma, tendency for iris prolapse, and pupil constriction. As any cataract surgeon will realize, such conditions will make the surgical procedure more difficult and increase the risk for complications. The presumed mechanism by which tamsulosin causes IFIS is by blocking α_1 receptors in the iris dilator muscle, and thereby preventing mydriasis during cataract surgery. Certain measures can be taken to reduce the risk of surgical complications in patients with IFIS, including iris hooks, preoperative topical atropine (Masket and Belani 2007), and – perhaps most interesting in this context - intracameral phenylephrine or epinephrine (Gurbaxani and Packard 2007; Masket and Belani 2007). Manvikar *et al* first described the use of intracameral phenylephrine to enhance mydriasis in patients with IFIS (Manvikar and Allen 2006). In their series of 32 cases on tamsulosin medication, the degree of IFIS varied among cases: 53% eyes had good mydriasis preoperatively from topical mydriatics but of these 43% showed intraoperative pupil constriction. Thirty- eight percent had semi-dilated pupils, and 9% had poor preoperative dilation. Intracameral phenylephrine, when needed, was efficient in dilating the insufficiently dilated pupils. It is well known that pupil sizes get generally smaller with age. It has been demonstrated, however, that there is no difference in α_1-adrenoceptor sensitivity in the elderly and the young, and thus, age related miosis is not attributable to an alteration in the iris α_1-receptors with age (Buckley, Curtin et al. 1987). Takmaz and Can published a large material in 2007, where the incidence of IFIS was determined to be 1.6% in the whole material of 858 eyes, and in no less than 14 of the 18 eyes of patients using tamsulosin (77.8%). Intracameral epinephrine was effective in preventing intraoperative miosis in the IFIS cases (Takmaz and Can 2007). A similar frequency of IFIS - just above 1% - has been reported also by other groups (Oshika, Ohashi et al. 2007; Keklikci, Isen et al. 2009). Gurbaxani and Packard showed in 2007 in a series of seven cases who were on systemic tamsulosin for benign prostatic hyperplasia that intracameral phenylephrine gave a significant reduction in iris mobility and fluttering, as well as a sustained mydriasis, in accordance with most other reports on intracameral mydriatics (Lundberg and Behndig 2003; Behndig and Eriksson 2004; Lundberg and Behndig 2007; Myers and Shugar 2009). In a retrospective material by Chen *et al* (Chen, Kelly et al. 2010), the incidence of IFIS among patients operated by resident physiciancs was 29.6% among patients taking tamsulosin, and more common among patients with a preoperative dilated pupil diameter of less than 6.5 mm. The authors concluded from their findings that the use of intracameral lidocaine-epinephrine did not reduce the incidence of IFIS.

To conclude, most authors agree that although intracameral adrenergics may not affect the incidence of IFIS *per se*, the enlargement of the pupils obtained in these difficult cases is still of benefit for the surgical handling and outcome. The published data support the intuitive impression that adrenergic substances at high doses should be beneficial in cases where the iris has an insufficient muscle tone, as in IFIS.

2.4 Pharmacokinetics of intracameral mydriatics

Generally, diffusion through the cornea is considered to be the main penetration route for topically applied drugs (Mishima 1981; Grass and Robinson 1988), and the corneal

epithelium is considered to be the main barrier (Sieg and Robinson 1976; Mishima 1981; Grass and Robinson 1988). Topically applied drugs generally penetrate the cornea slowly, with aqueous peak times ranging from 0.7 hours to 2.2 hours for various substances (Mishima 1981; Grass and Robinson 1988). For topically applied mydriatics the slow penetration through the cornea means a slow mydriatic onset (Lovasik 1986; Chien and Schoenwald 1990). For example, the peak mydriatic effect for cyclopentolate is at 30 minutes (Haaga, Kaila et al. 1998) and for phenylephrine 75 minutes (Matsumoto, Tsuru et al. 1982). In addition the bioavailability is limited for topically administered substances, which means a significant proportion of the drug will be absorbed systemically (Doane, Jensen et al. 1978; Kaila, Huupponen et al. 1989; Haaga, Kaila et al. 1998). Injecting a substance directly intracamerally will increase its bioavailability substantially, and accordingly decrease the systemic absorption. The onset of the effect will generally be very rapid after intracameral injection. Below, the research fields of intracameral pharmacokinetics will be briefly exemplified by lidocaine and phenylephrine.

2.4.1 Lidocaine

In a study from 1998, we determined the intracameral concentrations of lidocine after topical administration or intracameral injection (Behndig and Linden 1998). After 3 drops of topical lidocaine, the aqueous humour lidocaine concentration was 1.4±0.5 µg/ml and with 6 drops, 4.3±1.5µg/ml. With an intracameral injection, a concentration of 341.8 +/- 152.6 µg/ml was reached. We concluded that measurable amounts of lidocaine entered the anterior chamber in topical anesthesia, and that more entered when more drops were given. It is likely that concentrations in this range could anesthetize the iris, but they are far lower than the concentrations after an intracameral injection. This is probably the reason why the mydriatic effect from topical anesthetics is very minute - although it is indeed detectable and quantifyable with sensitive methods (Behndig 2007). Thus, topically administered lidocaine is found in low, but likely pharmacologically effective levels in the aqueous humor (Behndig and Linden 1998), and it has a measurable direct mydriatic and cycloplegic effect, at least in eyes with pale (blue) irides and less pigment binding of the substance (Behndig 2007). Since anesthetic agents lack adrenergic or anticholinergic properties, these mydriatic and cycloplegic effects can be ascribed a paralytic effect on the iris, analogous to the marked pupil dilation seen after intracameral lidocaine (Cionni, Barros et al. 2003).

In the beforementioned study, the lidocaine measured concentrations after an intracameral injection were about 10 times lower than what could be expected from simple dilution of the aqueous humor, meaning that just below 10 % of the injected lidocaine was found in the aqueous after 2 minutes. The rapid increase in anterior chamber volume and pressure upon injecting a volume of 100 µl might lead to diffusion of aqueous (and lidocaine) into the posterior chamber. An unknown proportion of the drug may also bind to iris pigment, as has been shown to occur for the related substance cocaine, and also for other drugs.

2.4.2 Phenylephrine

A dose-response study for intracameral phenylephrine from 2010 (Behndig and Lundberg 2010) showed that phenylephrine when injected intracamerally in human subjects has a rather moderate mydriatic effect at low concentrations and that the effect is very similar in concentrations ranging from 0.015-0.5%. Higher concentrations, however, (1.5 or 3.0%) give significantly larger pupils. Noticeably, a similar lack of dose-response relationship has been

noted by several investigators for topical phenylephrine when comparing 2.5% to 10% (Weiss, Weiss et al. 1995; Tanner and Casswell 1996; Motta, Coblentz et al. 2009). Applying experimental bioavailability data (Mishima 1981) and assuming an aqueous humor volume of 160 µl (Jonsson, Markstrom et al. 2006) and a dose of three 37µl drops (Behndig and Linden 1998), three drops of 2.5 -10% would give intracameral doses of 0.14 and 0.57 mg phenylephrine, respectively, which is in the same range as the four lower concentrations in the dose-response study (0.02 mg – 0.73 mg). One point five and 3.0% would thus give 3.9 and 7.7 times higher intracameral phenylephrine doses, respectively, than a standard "maximum dilatation" regimen involving 3 drops of phenylephrine 10%. The effects of such high doses of phenylephrine have never been studied in humans, since the maximum recommendable topical dose is limited by potential systemic side effects (Hakim, Orton et al. 1990; Ogut, Bozkurt et al. 1996; Elibol, Alcelik et al. 1997; Lundberg and Behndig 2003), but it appears that increasing the dose of phenylephrine further would increase also the mydriatic effect beyond what can be reached with the standard topical "maximum dilatation". It may also be of interest to note that a lack of dose-response relationship similar to that of intracameral phenylephrine has been noted also for intracameral epinephrine in dilutions ranging from 0.00025% to 0.004% (Liou and Chen 2001).

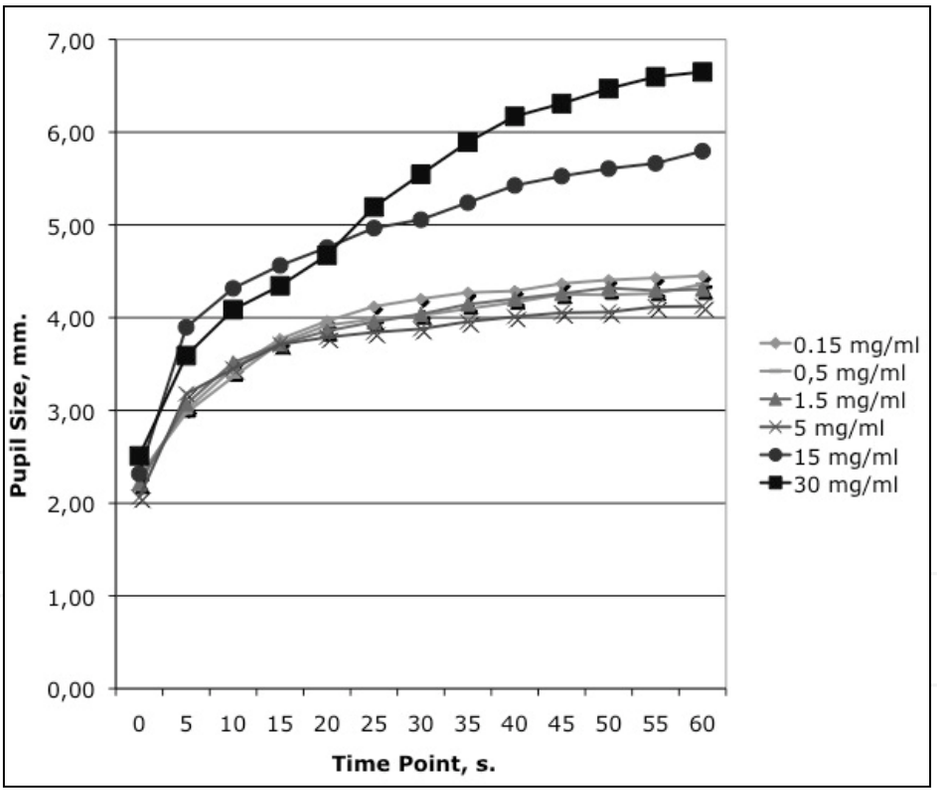

Fig. 6. The increase in pupil size after different concentrations of intracameral phenylephrine in cataract patients. Note that the mydriatic effect, including the time course, is very similar in concentrations ranging from 0.015-0.5% (0.15-5.0 mg/ml). At higher concentrations, 1.5 or 3.0%, a larger mydriatic effect is seen.

The rather weak effect of phenylephrine at low doses is a bit puzzling given that the α_1-receptors of the iris dilator are considered to be the most important mediators of the adrenergic mydriatic response (Yu and Koss 2002; Yu and Koss 2003). The binding of

phenylephrine to the α_1-receptor is rather weak - less than 1/5 of that for epinephrine (Besse and Furchgott 1976). This may in part - but not fully - explain why comparably high doses of phenylephrine are required to achieve mydriasis. Although phenylephrine has a high specificity for the α_1-receptor, it may not be 100% specific (Mishima 1982), and at very high concentrations such as when using intracameral mydriatics, stimulation of other receptors, for example the β-receptor, could also be speculated to contribute to the mydriatic effect.

2.5 Preparation of intracameral mydriatics

It was early noted that sodium bisulfite-containing solutions of epinephrine damaged the corneal endothelium (Hull, Chemotti et al. 1975). Solutions containing sodium bisulfite are therefore usually not recommended for intracameral use, although some authors claim they may be safe from an endothelial perspective if sufficiently diluted (Hull, Chemotti et al. 1975; Hull 1979). Epinephrine *per se* is not toxic to the corneal endothelium (Liou, Chiu et al. 2002), but bisulfite-free preparations of epinephrine may not always be easy to purchase in different countries (Myers and Edelhauser 2011). Another putative disadvantage of several adrenergic substances, including epinephrine, is their instability at a neutral pH, which often means they may need to be prepared freshly on a daily basis in clinical routine use. A commercially available eye drop containing 0.5% tropicamide and 0.5% phenylephrine hydrochloride, with addition of benzalkonium chloride, epsilon-amino capronic acid, boric acid, chlorbutanol and pH-adjusting reagents has recently been described as safe for intracameral use by a Japanese group (Mori, Miyai et al. 2010). Else, it is not advisable to try preparations for topical use intracamerally (Hull 1979), and *ex tempore* preparations are usually required for intracameral mydriatics, as we still lack commercially available preparations (Lundberg and Behndig 2003; Myers and Shugar 2009). Soong *et al*, in their publication from 2006 (Soong, Soultanidis et al. 2006), advocated the use of an intracameral cocktail prepared aseptically in the operating room from minims of cyclopentolate hydrochloride 1% phenylephrine hydrochloride 10% and 0.5 mL preservative-free lignocaine hydrochloride 2%. The substances were diluted to final concentrations of 0.1% cyclopentolate, 1.5% phenylephrine and 1.0% lignocaine.

In the studies from our group, as well as in our clinical routine, the sterile solutions of intracameral mydriatics are prepared by the Product and Laboratory Department of the Swedish Pharmacy (Apoteksbolaget AB) from sterile salts of the mydriatic and anesthetic substances. In our current routine this means phenylephrine hydrochloride 15 mg and lidocaine hydrochloride 10 mg, with addition of Sodium edetase 1 mg, boric acid 3,85 mg (for isotony) and *aqua injectabile* ad 1 ml. The sterile solution is supplied in 10 ml airtight glass containers with rubber membranes to allow for use in multiple patients during the same day of surgery. Unopened containers can be used for up to 3 months.

3. Conclusion

In the development of today's highly efficient routines for cataract surgery, the concept of intracameral mydriatics definitely has a place. From our calculations, the time a patient spends in an operating clinic during a visit for a routine cataract operation with traditional topical mydriatics for pupil dilatation consists of 82% waiting for the pupil to dilate and 18% being operated. Based on the available data, we can safely conclude that intracameral mydriatics comprise a safe and efficient alternative to traditional topical mydriatics, with time saving and simplifying potentials.

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