Intracameral Mydriasis:
The New Standard Route for Cataract Surgery

Laboratoires Théa Satellite Symposium
XXXIII Congress of the ESCRS

6 September 2015
Barcelona, Spain
Chairperson’s Introduction

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Beatrice Cochener MD, Professor and Chairperson of Brest University Hospital in France, chaired the Laboratoires Théa Satellite Symposium “Intracameral mydriasis: the new standard route for cataract surgery” held on 6 September at the XXXIII Congress of the ESCRIS in Barcelona, Spain.

“Keeping the pupil dilated during cataract and other lens replacement procedures is critical. Intraoperative miosis, which occurs more frequently in the new femtocataract procedure, increases the difficulty of these procedures and makes complications more likely,” said Prof Cochener.

While appropriate mydriasis is usually achieved by the administration of topical eye drops, their use has clear drawbacks in terms of the time needed to dilate the pupil and the risk of systemic side effects, she added.

“That is why ophthalmologists have been looking for alternatives to improve on current methods. Today’s symposium will give us the opportunity to hear about the possible benefits of a new intracameral approach to maintain stable intraoperative mydriasis and reduce side effects,” she said.

Mydrane™ is the first standardised ophthalmic combination of tropicamide 0.02 per cent, phenylephrine 0.31 per cent and lidocaine one per cent designed for intracameral administration just after the first incision during cataract surgery.

Prof Cochener announced that the symposium would focus on a number of key topics relevant to mydriasis during cataract surgery:

- Dr Paul Rosen would talk about practices across the European Union to manage mydriasis and discuss their related risks/benefits
- Dr Marc Labetoulle, as the main investigator, would present the latest clinical trial data for Mydrane™
- Dr Anders Behndig would conclude with a discussion of how intracameral administration of mydriasis may benefit cataract surgeons in daily practice
Pupillary dilation for cataract surgery is important for a number of reasons. Whilst enabling, clear visualisation of the intraocular structures, it also reduces the risk of iris, corneal, and capsule complications and enables accurate placement of the intraocular lens (IOL).

While “adequate dilation” is a subjective term, most surgeons would probably agree that it means more than 6.0mm and ideally 7.0mm or 8.0mm. Pupil constriction can occur intraoperatively for a variety of reasons. Surgical trauma, prostaglandin release, and intraoperative floppy iris syndrome, for example, can all generate periperaoperative complications. Surgically-induced miosis during cataract surgery is also associated with a higher risk of complications such as posterior capsule rupture, iris trauma and uveitis.

From a patient perspective, the ideal mydriatic should be easy to administer, offer pain-free surgery, be well tolerated in the eye and have low systemic side effects.

Another factor which is often forgotten, but which is important to bear in mind is the effect of any treatment on the health economy – in essence, we need a process that is simple to implement and which enables more efficient, cost-effective cataract surgery.

**PUPIL PHYSIOLOGY**

The size of the pupil is under the control of two types of muscle: the iris sphincter and the iris dilator. The former is innervated by the parasympathetic nervous system and the latter by the sympathetic nervous system. Dilating agents include parasympathetic antagonists such as tropicamide, cyclopentolate and atropine, which act by paralyzing the iris sphincter muscle, or sympathetic antagonists such as phenylephrine which work by stimulating the iris dilator muscle.

**In the operating room, drops were used in over half of cases in 2013 (56 per cent)...**

Of the more commonly used mydriatic agents, tropicamide has the fastest onset with maximum mydriasis in 20-30 minutes and duration of activity of approximately six to eight hours. Its anticholinergic action blocks the responses of the sphincter and ciliary muscles with side effects lasting four to five hours. Cyclopentolate’s onset of action is about 30-60 minutes, while atropine has an onset of 20-40 minutes but duration of seven to 12 days. The adrenergic receptor phenylephrine has an onset of 30 to 60 minutes and duration of about three hours. Known side effects of its use include tachycardia and hypertension.

Poor pupil dilation increases with age, darker iris colour, pseudoexfoliation syndrome, diabetes, previous iritis and ocular trauma.

From a surgeon’s perspective, the ideal mydriatic agent is one that dilates the pupil rapidly, ensures maximum comfort for the patient during the surgery and requires minimal intervention from healthcare personnel. It should ensure a pupil size of 6.0mm or more, have a duration effect of at least one to two hours and result in minimal side effects.

**EUROPEAN PRACTICE PATTERNS**

A recent European Observatory of Cataract Surgery study of practice patterns across the EU provided a timely snapshot of surgeon preference in terms of mydriatic use. Overall about 480 experienced ophthalmologists performing an average of about 500 cataract procedures a year were involved in the study.

The study showed that the vast majority of pupil dilations are carried out by the nurse in the outpatient setting prior to surgery. The main exception is Sweden where a significant number of dilations are self-administered at home by patients prior to surgery.

In terms of the mydriatic agent used, eye drops or drug-release inserts were most commonly used in the outpatient setting. In the operating room, drops were used in over half of cases in 2013 (56 per cent), with intracameral injection accounting for 22 per cent, inserts in 11 per cent and in the irrigation fluid in 10 per cent. Cyclopentolate and phenylephrine were the most popular compounds in both the outpatient setting and in the operating room.

The figures are particularly illuminating when we examine the percentage of dilation problems that led to a delay in operating prior to surgery: 10 per cent in Spain, 4.7 per cent in the United Kingdom, and two per cent in Sweden and The Netherlands. The extent of the delay involved is also revealing: in 2014, 21 per cent of the delays were less than one minute, nine per cent were one to four minutes, 17 per cent were five to nine minutes, and 36 per cent experienced a delay of 15 minutes and over.

This shows the clear impact on patient flows through the operating room due to poor dilation. This also accounts for the high percentages of cases that required additional mydriasis. In the UK, it was 37 per cent, which is probably related to the extensive use of adrenaline in the infusion bottles. Phenylephrine is the most commonly used additional mydriatic, accounting for 93 per cent of cases in the UK, for instance, and 94 per cent in Belgium.
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The New Standard Route for Cataract Surgery

Pros / cons Intracameral vs Drops

- Drug
  - lidocaine / phenylephrine / tropicamide
- Route of admin
  - Intracameral
- Efficacy
  - Rapid onset of mydriasis > 20sec
  - Stable dilation and sustained throughout surgery
  - Smaller pupil size
  - Less systemic absorption
- Systemic adverse events
  - No systemic absorption
  - No bacterial contamination
  - No corneal surface toxicity
  - No additional corneal endothelial damage or CMO
- oculocutaneous adverse events
  - No reaction
- Cost
  - Higher for drug
  - Lower for nursing time

In summary, preoperative mydriatic eye drops can be perceived cheaper, but they require greater nursing input for administration, entail greater patient discomfort and carry an increased risk of side effects. Ocular inserts are easier to use and have less associated side effects than eye drops, but despite its higher unit cost than mydriatic eye drops, inserts resulted in overall savings in health-care costs, mainly associated with reduced nursing time. Based on this evidence, the future undoubtedly lies in intracameral mydriasis with minimal toxicity, less nursing time, and greatly improved efficiency in the operating room.

Although the drugs are inexpensive, there is a significant cost to health services in terms of personnel time.

The concept of injecting mydriatics intracamerally at the start of the phacoemulsification cataract procedure was introduced by Lundberg and Behndig in 2003. Mydriatic drugs mixed with intracameral lidocaine were injected through the side port or principal port just after the incision and before the introduction of viscoelastic. The advantages of such an approach included reduced preoperative waiting time, reduced doses of the mydriatic substances and therefore a lower risk of systemic side effects.

Intracameral mydriasis was introduced in parallel with intracameral anaesthesia and antibiotics, with phenylephrine used on an ad hoc basis for rescue/secondary pupil dilation in cases of IFIS and intraoperative miosis. Up until recently, there had been no licensed or manufactured combination of phenylephrine and lidocaine available, but that is about to change with the introduction of Mydrane™ onto the market. Mydrane™ contains lidocaine, a neuronal membrane stabiliser, which has an anaesthetic effect on the iris stroma nerves and relaxes both sphincter and dilator muscles. The net effect is pupil dilation. Lidocaine has no cycloplegic effect, is synergistic with other mydriatics and has minimal systemic absorption and no demonstrable effect on the corneal endothelium. The other active ingredient in Mydrane™ is 1.5 per cent phenylephrine with minimal cycloplegic effect, a significant mydriatic effect, minimal systemic absorption and no demonstrable effect on the corneal endothelium.

The promise of intracameral mydriatics such as Mydrane™, and borne out by initial studies of the compound, are greater efficacy and enhanced safety. By significantly lowering the dose of the active agent needed to induce mydriasis the risk of systemic absorption and side effects is greatly reduced. Such an approach means rapid onset of mydriasis and stable dilation throughout the surgery with enhanced comfort and safety for the patient. There is also reduced risk of ocular adverse events with no bacterial contamination and no corneal surface toxicity or endothelial damage. The direct cost is higher than for topical mydriatic eye drops but lower in terms of nursing time and preparation of the patient.

The survey also questioned surgeons concerning the issues they considered most important in terms of mydriasis prior to and during cataract surgery. The surgeons highlighted concerns such as saving time for the nurses in administering drops, limiting adverse events, having a quick onset of mydriasis, saving time in the operating room, having a large pupil and the fact the mydriasis should be stable during surgery.

In terms of the preferred routes of administration and drug to be used, factors such as the medical history of the patient, comfort, convenience, safety and efficiency all play a part in determining the choice for the surgeon. For instance, adrenergic drugs are best avoided in patients with a history of cardiovascular disease. Preoperative eye drops are usually one or a combination of tropicamide, cyclopentolate and phenylephrine, a non-steroidal anti-inflammatory drug (NSAID) and/or a local anaesthetic such as lidocaine. Some surgeons prefer to use topical gels in the inferior fornix or an ocular sustained-release insert. These drugs can also be administered intracamerally for much faster onset of mydriasis.

EYE DROPS – CONVENIENT BUT WITH DRAWBACKS

Eye drops are usually administered four times every 15 minutes for 1 hour prior to surgery. The downside of using drops includes low bioavailability and high systemic absorption and a slow mydriatic onset, taking 30 to 40 minutes for full dilation to be achieved. The drugs’ duration can last up to 24 hours after surgery and intraoperative miosis may still occur even after their administration. Systemic adverse events also need to be borne in mind with topical mydriatics. Known side effects include tachycardia, hypertension, headache, and even myocardial infarction and stroke in very rare cases. Although the drugs are inexpensive, there is a significant cost to health services in terms of personnel time.

For the ocular sustained-release insert, which combines tropicamide and phenylephrine, the sustained-release device is placed into the conjunctival fornix one hour before surgery and removed prior to the start of surgery. Efficacy is slightly slower in terms of the onset of mydriasis, but it delivers stable dilation which is sustained throughout surgery and a larger pupil size than topical eye drops. Adverse events are also less problematic as the active agents are absorbed via the conjunctiva and the total dose delivered is five to 10 times less than with topical administration. So there is less systemic absorption, ocular adverse events are minimal, with reduced corneal toxicity and risk of bacterial contamination. While the cost is higher for the device compared to topical eye drops, it is nevertheless likely to be less expensive in terms of nursing time.

Eye drops and inserts have some known disadvantages including the slow penetration of mydriatic substances throughout the cornea with slow pupil enlargement. In practice this means that the waiting time for the pupil to dilate is often considerably longer than the surgical procedure itself. The limited bioavailability of topical substances also means there is significant systemic absorption, especially with eye drops. The mydriatic effect also tends to decrease during the operation, which is problematic if the procedure takes longer than expected and additional mydriatics may be required.
Intracameral Mydriasis: The New Standard Route for Cataract Surgery

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Cataract surgery is the most frequent procedure performed in ophthalmic surgery. Obtaining optimal stable mydriasis and anaesthesia remain fundamental to ensuring consistent outcomes. Topical eye drops have been the mainstay of mydriasis in the modern cataract era, but the drawbacks of this approach are well known: it requires considerable staff resources, is time consuming and carries the risk of systemic overdosing and, more frequently, toxicity for the corneal epithelium. Its efficacy is also limited, with secondary administration of mydriatics frequently required intraoperatively to avoid complications associated with constricted pupils.

The safety profile of topical mydriatics should also give ophthalmologists pause for thought. Phénylpéphrine, for instance, acts on the iris dilator muscles and its known side effects include hypertension, syncope, myocardial infarction, tachycardia and arrhythmia. The antimuscarinic drug tropicamide is associated with side effects such as dry mouth, tachycardia, headache and allergic reactions. Other drugs such as cyclopentolate and atropine are also available, but are less used today because the time to obtain cycloplegia and the duration of mydriasis are less than optimal. Elderly patients, the main candidates for cataract surgery, are at most risk of adverse events from systemic absorption of mydriatics.

Against this background, the rationale for an alternative delivery method to obtain mydriasis gathered momentum. The concept of intracameral injection of mydriatics seemed to address many of the known issues with topical eye drops: quicker onset of mydriasis, more stable mydriasis during surgery and reduced risk of ocular toxicity and systemic overdosing. However, the use of custom-blended or home-made intracameral formulations has brought its own problems including medical errors from incorrect dosing or dilution as well as the risk of infection.

To address the shortcomings of eye drops and custom-blended formulations, a ready-to-use standardized injectable mydriatic solution with industrial quality controls appears as a good solution. That product, Mydrane™, is now available on the market after successfully completing phase III clinical trials.

Combining a solution of two mydriatics, phénylpéphrine 0.31 per cent and tropicamide 0.02 per cent, and an anaesthetic (lidocaine one per cent), Mydrane™ is designed for single-use intracameral injection in cataract surgery in patients who have demonstrated, during the pre-operation visit, a satisfactory pupil dilatation following instillation of mydriatics (pre-op fundus examination)

At the beginning of the surgery, 200 μL of Mydrane™ is slowly injected by the surgeon, in the anterior chamber through the side port or principal port. The onset of action is extremely rapid, with 95 per cent of maximal dilation achieved in 30 seconds after administration of Mydrane.

SAFETY AND EFFICACY DATA
The safety and efficacy of Mydrane™ was demonstrated in a recently-completed phase III prospective, randomised, controlled study comparing intracameral Mydrane™ to standard topical regimen. Capsulorhexis was successfully performed without any other mydriatic treatment for patients...

The international, multicentre study enrolled patients undergoing phacoemulsification with intraocular lens (IOL) implantation under topical anaesthesia (2 tetracaine instillations). Of 609 patients screened initially, 593 were selected and 591 randomised. The final analysis included 266 patients in the Mydrane™ group and 277 in the group receiving topical mydriatics.

The selected eye of participating patients received either intracameral injection of 200 μL of Mydrane™ just after incision during cataract surgery (treatment group), or a standard topical regimen of 1 drop each of tropicamide 0.5 per cent and phénylpéphrine 10 per cent (reference group) repeated three times at 10 minute intervals, beginning 30 minutes preoperatively. The non-inferiority of Mydrane™ to the standard topical regimen was tested and the main outcome measures were pupil size, intraoperative ocular discomfort, and safety.

The primary endpoint was realisation of the capsulorhexis without the use of any additive mydriatic treatment. The main secondary endpoint was the response rate to treatment, defined as the realisation of the capsulorhexis without the use of any additive mydriatic treatment and a pupil size measured as being at least 6.0mm just before capsulorhexis. The other secondary criteria were pupil size at different time points throughout the surgery, ocular discomfort (anaesthesia) as reported by the patient at different time points during the surgery, surgeon satisfaction at each stage of surgery, use of additional anaesthetics intraoperatively, preoperative and surgical times; and safety/global tolerance.

In terms of results, capsulorhexis was successfully performed without any other mydriatic treatment for patients...
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The mean pupil size in the Mydrane™ group remained stable throughout surgery...

Cardiovascular and other safety data such as endothelial cell loss, corneal thickness, visual acuity and postoperative IOP, were similar between groups. There were also no issues of persistent mydriasis in any of the groups.

Comparing the use of additional drops in the study, analysis showed that patients in the reference group may have received up to 54.8-fold higher doses of phenylephrine than patients in the Mydrane™ group. As is well documented, the use of additional drops before surgery can lead to overdosing and systemic side effects.

ADVERSE EVENTS
There was no difference in the incidence of any adverse ocular events between the two groups. There was no difference between Mydrane™ and the reference regimen, particularly in terms of capsule rupture during surgery, retinal thickness and events of macular edema after the surgery, and loss of endothelial cells following phacoemulsification.

In terms of subjective ocular symptoms, patients reported less pain at day 8 in the Mydrane group. This suggests that the lack of multiple installations before the surgery may induce less epithelial toxicity preoperatively and better restoration of the ocular surface postoperatively for those patients that received intracameral mydriatics.

The global patient satisfaction was slightly higher for Mydrane™ (98.9 per cent) compared to the reference group (96.8 per cent). Surgeon satisfaction was also greater for Mydrane, with 24 surgeons defining the surgery as “somewhat difficult” in the reference group compared to 10 in the Mydrane™ group.

As one might expect, there was a longer overall surgery time in the reference group, related to the preoperative administration of the eye drops. Interestingly, however, focusing solely on the real time of intraocular surgery between capsulorhexis and cefuroxime injection, there was no difference at all between the two groups. This suggests that the injection of Mydrane™ does not lead to greater difficulty during surgery as a result of the rapid mydriasis achieved with intracameral administration.

In summary, the phase III trial demonstrated that Mydrane™ is an effective and safe alternative to standard mydriatic eye drops for initiating and maintaining intraoperative mydriasis. Rapid, stable and adequate mydriasis was triggered by the injection of Mydrane™ and one injection was sufficient for all patients. Those patients who received Mydrane™ were significantly more comfortable during the active intraocular phase of the surgery and spent less overall time in the surgical centre compared to patients who received a topical regimen. Surgeon satisfaction was also higher for Mydrane compared to topical mydriatics.
The impetus for my long-standing interest in mydriatics stemmed from the realisation in 2002 that we were spending about 80 per cent of surgery time in our clinic dilating the pupil and 20 per cent performing the surgery. Such a situation was clearly far from satisfactory, leading to an inefficient use of clinical resources and time.

That topical mydriatics have some disadvantages is not in dispute: they offer a slow onset, carry the risk of systemic side effects and offer no guarantee against intraoperative pupil constriction. This latter problem was solved to some degree in Sweden with the addition of epinephrine irrigation to the infusion bottle.

It was at the ASCRS meeting in 1996 that I heard Professor James Gills talk about the benefits of adjunctive intracameral lidocaine for the first time. I returned home to Sweden and started doing it immediately. Not only did the patients feel less pain but I also had the impression that the pupils were more stable during surgery when using intracameral lidocaine. This is when I started thinking it might be a good idea to add a mydriatic agent to the lidocaine solution and dilate the pupil at the same time. This would essentially kill two birds with one stone and enable us to cut down on the use of drops and dispense with some of these unpleasant side effects with topical mydriatics.

The initial formulations we used were lidocaine one per cent, cyclopentolate 0.1 per cent and phenylephrine 1.5 per cent. We soon realised, however, with cyclopentolate that the onset was too slow and the duration too long as the pupil remained dilated the day after surgery. This was confirmed by a clinical study that we carried out looking at the onset of various different intracameral mydriatic compounds which showed that lidocaine injected in the anterior chamber has a mild mydriatic effect but is not sufficient on its own for cataract surgery. With subsequent injection of phenylephrine, however, there was a substantial additional mydriatic effect. The effect was very slight, however, when cyclopentolate was injected as the second drug. Switching the order of the drugs and injecting cyclopentolate after phenylephrine had no effect.

We found that no statistically significant differences in pupil size were observed between the patients who were given intracameral mydriatics with or without cyclopentolate. The day after surgery, however, the pupils were found to be significantly larger in the cyclopentolate group than in the group without cyclopentolate. We concluded that cyclopentolate administrated intracameraly has no immediate additive mydriatic effect when added to intracameral lidocaine plus phenylephrine. After this study, cyclopentolate was omitted from our clinical routine preparation.

COMFORT LEVELS

As part of our clinical studies, we also questioned patients about their comfort levels during surgery. A point worth mentioning with intracameral mydriatics is that the patients perceive less initial glare from the operation microscope light as the pupil is small at the beginning of the procedure. This makes it easier to start the surgery as the patient is more comfortable under the bright light than if they had received topical mydriatics and had a larger pupil at the beginning of the procedure. While the pupils are initially slightly smaller with intracameral administration, they continue to enlarge throughout surgery. This is very beneficial because if the pupil is large enough for the creation of the capsulorhexis it will also be sufficiently large for the rest of the procedure.

One of the clear benefits of intracameral administration of mydriatics is the rapid onset effect after injection, with mydriasis generally attaining 95 per cent of its final value within 20-30 seconds. In terms of safety, intracameral mydriatics have been shown to be safe with no increase in corneal endothelial cell loss, inflammatory reaction, postoperative corneal swelling or macular oedema.

In summary, intracameral mydriatics comprise a rapid, effective and safe alternative to topical mydriatics in phacoemulsification surgery. It has the potential to simplify preoperative routines, and for certain high-risk groups, may reduce the risk for cardiovascular side effects.

Since introducing intracameral mydriatics in Sweden in the early 2000s, we have seen that 97 per cent of the overall operating time is now spent on surgery and just three per cent on pupil dilation. I think that represents a far more satisfactory statistic and suggests that intracameral mydriatics will continue to have a major role to play in safe and efficient modern cataract surgery.
MYDRANE 0.2 mg/ml + 3.1 mg/ml + 10 mg/ml solution for injection.

**Composition:** One dose of 0.2 ml solution contains 0.04 mg of tropicamide, 0.62 mg of phenylephrine hydrochloride and 2 mg of lidocaine hydrochloride. Excipient.

**Therapeutic indications:** MYDRANE is indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia during the surgical procedure. MYDRANE is indicated in adults only.

**Posology and method of administration:** Intracameral use. One ampoule for single eye use. Mydrane must be administered by an ophthalmic surgeon. Posology: MYDRANE should only be used in patients who have demonstrated, at a previous visit, a satisfactory pupil dilation with topical mydriatic therapy. Adults: Slowly inject, by intracameral route, 0.2 ml of MYDRANE in only one injection, at the start of the surgical procedure.

**Contraindications:** Hypersensitivity to the active substances (tropicamide, phenylephrine hydrochloride and lidocaine hydrochloride) or to any of the excipients. Known hypersensitivity to anaesthetics of the amide type. Known hypersensitivity to atropine derivatives.

**Undesirable effects:** Adverse reactions were reported with MYDRANE during clinical trials. Most were ocular and of mild to moderate intensity. Summary of the safety profile: Posterior capsule rupture and cystoid macular oedema are well known complications occurring during or after cataract surgery. They may occur uncommonly (less than 1 case per 100 patients). Adverse reactions, reported during clinical trials, are presented according to System Organ Class below in order of decreased seriousness within each frequency grouping: Nervous system disorders (uncommon, ≥1/1,000 to <1/100): Headache. Eye disorders (uncommon, ≥1/1,000 to <1/100): Keratitis, Cystoid macular oedema, Intraocular pressure increased, Posterior capsule rupture, Ocular hyperaemia. Vascular disorders (uncommon, ≥1/1,000 to <1/100): Hypertension. Nature and contents of container: One 1 ml sterile brown glass (type I) ampoule filled with 0.6 ml of solution for injection, per paper/PVC blister. Box of 1, 20 and 100 ampoules together with respectively 1, 20 and 100, 5-micron sterile filter needles. Not all pack sizes may be marketed. For further information, please contact Laboratoires THEA. MARKETING AUTHORISATION HOLDER: Laboratoires THEA - 12, Rue Louis Blériot - 63017 Clermont-Ferrand Cedex 2 – France – Tel: +334.73.98.14.36. DATE OF EUROPEAN AUTHORISATION: 02 JUL 2015. DATE OF REVISION OF THE TEXT: 02 JUL 2015.