Towards Less Drops in Cataract Surgery

Laboratoires Théa Satellite Symposium
XXXIV Congress of the ESCRS

11 September 2016
Copenhagen, Denmark
We are entering an era of almost drop-less cataract surgery and this is bringing with it numerous advantages to the patient and the surgeon. For the patient, it means that, together with an almost non-existing risk of systemic exposure of mydriatic drugs, there is no ocular surface toxicity, and this is a significant issue, especially in the older cataract population where the limitations of the ocular surface are more significant. For the surgeon, it provides many practical benefits in that it greatly reduces the demands on hospital personnel and the complexity of the preparation of the patient.

Laboratoires Théa’s recent launch across Europe of Mydrane® – the world’s first approved intracameral combination of anaesthetic-mydriatic preparation – brings us closer to that goal, as mydriatic drops make up the majority of the drops applied to the eye before surgery with the topical approach. Moreover, instead of being applied several times over the 30 minutes to one hour before surgery as with topical mydriatics, Mydrane® is injected exactly when needed in the operating room. That, in turn, leads to a more streamlined and less time-consuming model for the entire cataract surgery.

At the ESCRS Satellite Symposium, we had several distinguished presenters who shared their experience and insights on the efficacy and tolerability of Mydrane® and its potential to transform cataract surgery in Europe and we are pleased to share their expertise with our readers in this supplement.

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. Dosage: 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 single eye use only. For further information, please contact Laboratoires THEA. MARKETING AUTHORISATION HOLDER: Laboratoires THEA – 12, Rue Louis Blériot – 63317 Clermont-Ferrand Cedex 2 – France – Tel. +33 (0) 4 73 98 14 36. DATE OF EUROPEAN AUTHORISATION: 02 JUL 2015. DATE OF REVISION OF THE TEXT: 02 JUL 2015.
In the history of modern cataract surgery, there has been a gradual move towards a more localised therapy with a more rapid passage of the patient through the surgical process. In the case of anaesthesia that has meant moving from general anaesthesia to local anaesthesia, such as peribulbar and subtenons, to eye drops and more recently to intracameral anaesthesia. Such approaches yield the obvious benefit of delivering the agent directly to where it is needed to achieve the desired effect with minimal systemic toxicity while leaving other ocular structures unaffected. The launch of Mydrane® across Europe means that we may now apply this principle to mydriasis with a commercially manufactured product.

Current techniques for achieving mydriasis are in the main complicated and time-consuming. A review of European practice patterns in cataract surgery shows how a intracameral mydriasis may greatly reduce the complexity and costs of cataract surgery. In the Netherlands, we perform annual surveys on surgical practice styles. For our 2014 survey we had a 60% response rate, accounting for a total of 110,000 cataract procedures. It showed that 70% of our procedures are performed with topical and 23% with subtenons. However, the survey was somewhat deficient in that the questionnaire did not probe into the way the topical anaesthesia is delivered to the eye or how mydriasis was performed.

Some years ago, the European Observatory of cataract surgery (Eurobscat) was developed in order to get a better idea of the types of drugs used and their mode of administration. A total of 480 surgeons from nine countries are included in the survey, accounting for approximately 250,000 cataract surgeries throughout Europe. The surgeons involved all performed at least 150 operations per year and have at least five years of practice. They are represented in proportion to the number of cataract surgeons in each country.

A publication of the outcomes of the observatory survey in 2013 shows that local anaesthesia is used almost exclusively, with eye drops being by 67%. The surgeon's responses to the questionnaire revealed that in cataract procedures, drops are used alone by 39%, and are used in combination with intracameral anaesthesia by 21%, with peribulbar by 19% subtenons by 9 percent. Intracameral anaesthesia is used most commonly in the UK, Spain and Poland where 35-40% of surgeons reported its use. (Behndig JCRS 2015; 41:2635).

In terms of initial mydriasis, Eurobscat’s most recent survey show that 76% have the instillation of the mydriatic agents performed by the nurse outside the operating room and 13% of the patient doing at home and 11% do in the operating room including prep room or other closely related room.

Among patients who undergo initial mydriasis at home, 94% of respondents said that they had their patients use eye drops. Inserts are used in a couple of countries, notably Spain and France, where 11 percent and 16% of surgeons, respectively used the approach. In those cases, either their patient themselves or a visiting health assistant administered the inserts.

Among respondents whose patients' initial mydriasis is performed by a nurse outside of the operating room, 79% overall said that they use eye drops and 21% use inserts. The countries with the highest proportion using inserts were France (61%) and Belgium (63%). Among those whose patients undergo mydriasis in the operating room, 74% overall use eye drops, however 19% use intracameral mydriasis. The countries where surgeons reported using intracameral mydriatics most commonly were Sweden (62%), Poland (32%) and the UK (25%).

How Does Your Practice Compare with Others Around the EU for Mydriasis in Cataract Surgery?

Rudy M.M.A. Nuijts MD, PhD, University Hospital Maastricht, The Netherlands
rudy.nuijts@mumc.nl

In terms of initial mydriasis, Eurobscat’s most recent survey show that 76% have the instillation of the mydriatic agents performed by the nurse outside the operating room.
THE NEED FOR BETTER MYDRIASIS

If we asked the surgeons in the Netherlands which improvements are needed in cataract surgery, 50% respond that they are satisfied with their current way of doing things. However, 17% feel that there is a need for better and more innovative instrumentation, 12% a gain of time during surgery would be welcome. But 8% also say they would like to achieve better and longer lasting mydriasis and improve their mydriasis protocol. Moreover, when asked to weigh in importance on a scale of 1-10 the parameters of mydriasis, the European surgeons overall gave stable mydriasis a mean score of 9 and gave achieving the largest pupil size a mean score of 8.3. Other parameters in surgery rated as high in importance included having a very fast set up for mydriasis (6.1), also considering patients comfort) and a proper control of the mydriasis drug with limited adverse events (6.5). The surgeons considered the time which the nurse uses to set up mydriases was by as of importance, giving it a mean score of 6 (Figure 1).

Another important finding from the Eurobocat study was that failure of initial mydriasis strategy appeared to be fairly common, additional mydriatics were used in 14% of procedures. Furthermore, problems with pupil dilation leading to a delay in operating occurred in two% to 10% of cases depending on the country. The delays lasted 12.8 minutes on average, which is about the same amount of time it would otherwise have taken to perform the whole cataract procedure.

In my department, the current protocol is that we use three different kinds of mydriatic drops, phenylephrine HCl 25mg/ml, Tropicamide 5mg/ml and Cyclopentolate HCl 5mg/ml. The nurse starts instilling the drops 30 minutes before the procedure with repeated instillations 10 and 20 minutes later. Patients also simultaneously received a drop of antibiotic at each time point. For anaesthesia patients receive preferably topical anaesthesia and on indication a subtenons block.

By comparison, when we used Mydrane®, the only drops we used were an antibiotic as in our usual protocol. So the pathway and the input of labour is completely different. In addition, the eye is exposed to much less in the way of ocular surface toxicity, which can lead to mild punctate keratitis in many eyes (Figure 2). Regarding efficacy, we found that in 12 eyes of 12 patients maximum dilatation was achieved with Mydran® after a mean of 47.9 seconds with values ranging from 31 seconds to 81 seconds. The mean diameter of the pupil prior to the Mydrane® injection was 2.2 mm, following injection the mean pupil diameter increased to 6.4 mm, with values ranging from 5.5 mm to 8.1 mm. That equates to an average pupil dilatation of 4.2 mm.

The injection of a viscoelastic increased the mean pupillary diameter to 7.2 mm, equating to an additional 0.8 mm of dilatation. On the other hand, Mydrane® produced only an additional 1.1 mm of dilatation in six eyes that also underwent subtenons anaesthesia due to the subtenon effect and various ocular comorbidities. Because I did not wish to have to change my protocol more than necessary for different types of patients, I have ventured outside of the usual recommendations for Mydrane® and used it in patients using alpha blocker. However, I found that the agent was sufficiently effective in these patients and in my view the use of alpha blockers should not be a contradiction to its use. We also found that Mydrane® produced no visible side effects in corneas with Fuch’s endothelial dystrophy.

In summary, we found in our small trial that Mydrane® produces a rapid mydriasis, with a mean dilatation of 4.2 mm in 48 seconds which is stable throughout the cataract procedure. There were no comfort problems during injection and patients receiving Mydrane® had a better ocular surface postoperatively than our patients who undergo cataract surgery with topical mydriasis.

Among surgeons in the Netherlands, topical mydriasis with eye drops still predominates, and 90% of the survey’s respondents reported that their protocol was to have initial mydriasis administered by the nurse outside of the operating room. However, at our centre we have recently had the opportunity of using Mydrane® for the first time. Our experience demonstrated the substantial gain in time and reduction in personnel and overall increase in the simplicity of the cataract procedure the new mydriatic-anaesthetic preparation can afford, compared to current practice.
Towards Less Drops in Cataract Surgery

Achieving a stable and efficient mydriasis can still be a problem even by modern techniques of cataract surgery. That is a problem because a widened stable mydriasis is key to reducing the risk of complications and insuring that the eye remains in good condition. A large randomised trial has established that the new intracameral anaesthesia-mydriatic preparation Mydrane® from Laboratoires Théa can provide sufficient and stable mydriasis with considerable benefits in terms of patient’s comfort compared to topical drops. Mydrane® is a ready-made solution of two mydriatics, phenylephrine 0.31% and tropicamide 0.02%, and one anaesthetic, lidocaine 1%. It is prepared as a single-use ampoule and is designed for intracameral use in cataract surgery in patients who have demonstrated satisfactory pupil dilatation following installation of normal topical mydriatics during a preoperative visit. It is injected immediately through the side port or principal port incision just before the injection of the viscoelastic. The rapidity of the effect is amazing, sometimes less than 30 seconds 95% of maximum dilation is achieved. Moreover, the dilatation lasts till the end of surgery. The efficacy and safety of Mydrane® was demonstrated in a Phase III pivotal study. The multicentre randomised controlled trial analysed the outcomes in more than 600 patients undergoing cataract surgery. The patients were divided into two groups to receive either Mydrane® or topical mydriatics and anaesthetics. (Labetoulle M, et al. Br J Ophthalmol 2016;100: 976–985) The primary aim of our study was to evaluate the safety and efficacy of the anaesthetic and mydriatic effects of Mydrane® compared to standard topical therapy. The study’s secondary endpoint was the so-called response rate to treatment, that is, the realisation of the capsulorhexis without any additional mydriatic treatment with a pupil that is at least 6.0 mm diameter.

In the phase III study, the pupillary diameter was measured at five different stages of the cataract procedure. Namely, just before the first incision, just before injection of the viscoelastic, before the capsulorhexis, before the IOL injection and just before the intracameral injection of cefuroxime at the end of surgery. We also recorded the patients’ discomfort and the surgeon’s satisfaction at each stage of the procedure. Other parameters recorded included the requirement for additional anaesthetics or mydriatics, and the preoperative surgical times and the overall safety and tolerance profile. Preoperatively the Mydrane® group received only a few drops of lidocaine five minutes and one-minute prior to surgery, and nothing else apart from Mydrane®, in contrast, the reference group required three instillations of tropicamide and phenylephrine during the 30 minutes before the procedure as well as lidocaine.

I believe that Mydrane® adds a valuable tool to our cataract surgery armamentarium

We found that almost identical percentages of patients in the Mydrane® and the reference groups who underwent capsulorhexis without further mydriatics, 98.6% and 94.7%, respectively and in the percentages who maintained a pupil greater than 5.5 mm size at T3 just before capsulorhexis, 98.4% and 94.3%, respectively. In addition, the mean pupil size in the Mydrane® group remained stable throughout surgery, whereas the effects of the topical mydriatics began to diminish from the commencement of the procedure (Figure 1).

LESS PAIN AND PRESSURE

Moreover, in terms of patients’ comfort during surgery, there was a statistically significant difference between the groups in favour of Mydrane®. That is, 77.95% of patients in the Mydrane® group reported experiencing no pain or pressure at any time during surgery, compared to 67.8% in the reference group (p=0.034). In addition, the proportion of patients with no pain was higher in the Mydrane® group than in the reference group at two critical time points in the cataract procedure. Namely, just before the performing the capsulorhexis (81% vs 77.5%) and just before injection of the IOL (78% vs 68%). Therefore, I believe that Mydrane® adds a valuable tool to our cataract surgery armamentarium. Its key advantages are that one injection is sufficient to produce rapid mydriasis that remains stable throughout the cataract procedure. There are no safety concerns with the preparation regarding endothelial or macular toxicity and it also saves time and money in the operating room, providing patients with better comfort and surgeons with greater satisfaction than with topical mydriasis.
With every agent that is applied to the eye care must be taken to ensure that it will achieve its desired effect without causing damage to the tissues with which it comes into contact. In a preclinical tolerance and efficacy safety study, 60 pigmented rabbits underwent intracameral injection of either 100μL 200μL of Mydrane® or the same quantity of placebo (0.9% NaCl) either with or without post-administration rinsing. Animals were assessed at one to seven days postoperatively. They were euthanized on the eighth day and examined for signs of ocular toxicity. Following injection of Mydrane® into the anterior chamber, mydriasis was very rapid with the maximum dilation achieved one minute. In addition, this mydriasis lasts for at least 24 minutes and rinsing did not influence the preparation’s mydriatic effect. As expected, the placebo had no mydriatic effect at all. In addition, laser flare meter testing showed no significant signs of anterior chamber inflammation in eyes without rinsing. However, in both groups rinsing induced a slight increase in anterior chamber inflammation, which was detectable only by slit-lamp examination. Moreover, confocal microscopy showed that there was no endothelial cell loss in either group and pachymetry showed there was no corneal swelling in either group as well. These results therefore raised no concerns with Mydrane® regarding endothelial toxicity. The product was safe and well tolerated in rabbits’ eyes at the volumes and concentrations used, with no ocular adverse effects (Acta Ophthalmologica - Volume 94, Issue S256, October 2016, C. Olmiere and K. Viaud-Quentric - 14 SEP 2016, DOI: 10.1111/j.1755-3768.2016.0439).

The Phase III clinical trial yielded similar results regarding the safety and efficacy of Mydrane®. It also showed that patients receiving the new intracameral preparation did not differ in terms of corneal or macular toxicity and that mydriasis may have safety advantages over topical mydriasis in terms of systemic exposure. For example, there were no safety concerns regarding best corrected visual acuity and Intraocular Pressure (IOP) as both parameters were virtually equal in the two groups. There was also no significant difference between the groups in terms of endothelial cell loss, with mean reductions of 9.1% and 7.6% in endothelial cell density in the Mydrane® and reference group, respectively. Mean corneal thickness was unchanged in either group. There was also no difference between the two groups regarding clinically relevant macular toxicity. In the Mydrane® group, three eyes (1.2%) had subclinical macular oedema and one eye in each group had clinically significant macular oedema. There was no change in mean macular thickness in either group. Ocular adverse events were uncommon in either group. An increase in IOP being most common, occurring in three patients in the Mydrane® group (1.1%) and two in the reference group. There was also one case each (0.4%) of conjunctival hyperaemia, conjunctival hyperaemia, corneal disorder, corneal epitheliun defects, and corneal oedema in the reference group and none in the Mydrane® group. There was also one in each group of keratitis.

Among 15 patients whose blood was tested throughout following mydriatic administration, phenylephrine could be detected in the blood of only two patients receiving Mydrane®, compared to all of those in the reference group. In the Mydrane® group, plasma phenylephrine levels appeared to peak after two minutes, when it became detectable in 7% of patients. However, it was undetectable by four minutes after injection. In the reference group, phenylephrine became detectable in plasma after about two minutes and was detectable in 80% of eyes by four minutes into surgery. Furthermore, no tropicamide could be detected in the plasma in any patient at any time, but it could be detected in all patients in the reference group.

In conclusion, these preclinical and clinical studies raised no safety concerns regarding the cornea or retina. Furthermore, the lower systemic exposure compared to topical mydriasis represents an important safety advantage for patients with cardiovascular disease, since, as is well known, tropicamide and phenylephrine may have synergistic and possibly toxic side effects on a patient’s blood pressure and heart rate.

**Figure 1:**

**Figure 2:**
Towards Less Drops in Cataract Surgery

**Intracameral Mydriatics and Mydrane® in Routine Clinical Practice**

**Anders Behndig** MD, PhD Department of Clinical Sciences, Ophthalmology, Umeå University, Umeå, Sweden
anders.behndig@ophthal.umu.se

I have a relatively long experience in the use of intracameral mydriatics. My colleague Bjorn Lundberg MD, PhD and I first began investigating the concept in 2002 and I have been using intracameral mydriatics since 2003. They are now used in a large proportion of Swedish cataract procedures.

We had several factors motivating us to try this approach. There was the slow onset of topical mydriatics which we recognised as a problem. There was also some concern regarding systemic exposure with the topical mydriatics. Although that is mostly a theoretical in most patients, it can be something to consider in elderly patients and those with cardiovascular disease.

However, what annoyed us most about topical mydriatics was a problem that many surgeons see that intra-operative pupil constriction. Prior to adopting the use of intracameral mydriatics, we addressed that problem by mixing epinephrine in irrigating solution to maintain mydriasis throughout the entire cataract procedure. However, this approach required some toilsome effort as we needed to repeatedly blend the epinephrine with the irrigating solution throughout the day because epinephrine is unstable in solutions at neutral pH.

Our first step in developing an intracameral approach was to investigate the dose response of different mydriatics when injected in the anterior chamber. We found that the effect of phenylephrine was quite rapid. The difficulty was that a high concentration of the mydriatic is necessary to get a satisfactory effect. Therefore, we lowered the concentration to 1.5% and added cyclopentolate 0.1% and lidocaine 1%.

However, we discovered that cyclopentolate did not add to the mydriatic effect since most of it does not achieve its peak effect until long after surgery was completed. Therefore, our current formulation consists of phenylephrine as the sole mydriatic and lidocaine. They are composed by a local compounding pharmacy.

The key difference between our current formulation and Mydrane® is that Laboratoires Théa has reduced the concentration of phenylephrine even further, to 0.31%. That is probably one of the reasons that we can find almost none in systemic circulation and they also added tropicamide 0.02% which adds to the mydriatic effect, as opposed to cyclopentolate which is too slow for this type of pharmacology.

**Intracameral mydriatics adds safety and simplicity in routine clinical practice**

In our initial experience with the new mydriatic-anaesthetic combination, we have found that the onset of effect is very rapid following injection. In addition, in their responses to a questionnaire, patients who underwent intracameral mydriasis reported less light sensitivity at the beginning of surgery than did those who underwent topical mydriasis. As a result, the patients receiving intracameral mydriatics were more comfortable at the beginning of the surgery.

In a further investigation we compared the complication rate in two groups of 200 patients, one of which underwent intracameral mydriasis and topical mydriasis and aenesthesia in the other. We found that during phacoemulsification, cortex aspiration, and IOL implantation the number of eyes with and without complications was equal in the two groups, with no complications in almost 90% of eyes (Figure 1).

In conclusion, intracameral mydriatics adds safety and simplicity in routine clinical practice. And now after 13 years of using intracameral mydriatics, the availability of an approved product is most welcome from my perspective also.
Towards Less Drops in Cataract Surgery

How Can a Combination of Mydriatics and Anaesthetics Improve Your Daily Practice?

Beatrice Cochener MD, PhD, Professor and Chairperson of Brest University Hospital in France
beatrice.cochener@ophthalmologie-chu29.fr

There is an increasingly urgent need for improving our efficacy and skill in cataract surgery. Cataract surgery is already the most commonly performed procedure in the world and cataracts are definitely on the increase as shown in a WHO report estimate that there will be 3.2 million cataract surgeries in 2020. Average 40% of people over 70 years of age have cataracts. Moreover, patients today are demanding an earlier improvement in their vision and so the cataract procedures are being performed earlier than before.

The goal of greater efficiency in cataract surgery may be achieved through a fast track approach designed to improve the organization and equipment in order to optimize the efficacy and cost-effectiveness of the procedure without reducing safety. It is a new concept that extends beyond the simple ambulatory management of patients.

Ultimately the aim of the fast track approach is to enable patients to go directly to surgery without a lot of time-consuming and uncomfortable preoperative preparation. Once the procedure has been performed the patient leaves the theatre and goes home. In this way it should become possible to improve the outcomes and lower the healthcare costs.

It can be defined as a coordinated perioperative approach designed to reduce the stress on everybody starting from the patient, going to the nurse, and even of course the surgeon.

It combines various techniques used in the care of patients undergoing elective operations, it includes newer approaches to pain control and mydriasis, minimally invasive surgical techniques aggressive post operative rehabilitation.

The fast track process requires participation and commitment from a multidisciplinary team including the anaesthesiologists, the nursing staff, social services and the hospital administration. An important aspect of this approach is an improved communication between the welcome desk and outpatient service and between outpatient service and operating room. In short, the fast track approach involves making all modifications in the organisation of surgery that will reduce the time the patient has to spend at the hospital.

We are really saving time and energy and, at the same time, reducing the risks

The more time energy and personnel a procedure requires, the longer the waiting will be. Therefore, our key target is to optimise patient flow and reduce the amount of time patients need to be in the hospital lists. Intracameral Mydrane® in the form of a reliable and commercially available preparation perfectly fits the fast track model. Since it provides mydriasis exactly when you want it, it improves the organisation of the surgical theatre and streamlines the flow of patients without sacrificing safety.

In summary, we are entering a new era of dropless surgery where everything is done in a fast track manner so that patients will require less management preoperatively and everything done intraocularly. Besides improving the patient flow, we also may enhance the safety of cataract surgery in this way. We know that around 80% of the drugs applied topically enter the systemic circulation and there are also safety considerations for the ocular surface, since repeated instillations of drops there is a risk of keratitis. And although there is a lot of emphasis on trying to save time and money, we are also focusing on patient satisfaction and safety issue so we are really saving time and energy and, at the same time, reducing the risks.