PROGRESSES IN MANAGEMENT IN OCULAR SURFACE AND CATARACT SURGERY

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Moderated Laboratoires Théa’s Satellite Symposium PROGRESSES IN MANAGEMENT IN OCULAR SURFACE AND CATARACT SURGERY held on 15 September 2019 at the XXXVII Congress of the ESCRS in Paris, France.

The first part of the symposium is as an overview on the concept of dry eye pathophysiology and treatment since the first tear substitute available in 1902. Over the last century, dry eye understanding has evolved profoundly. Advances in diagnosis and treatments of the ocular surface, for instance new bioprotective options such as trehalose and hyaluronic acid (Thealoz® Duo*, laboratoires Théa, France), will be discussed. Now it is clear that inflammation is among the most important mechanisms in the pathogenesis of Dry Eye Disease, triggering the vicious circle of Dry Eye. That’s why decoding inflammation in dry eye disease is essential. Reducing inflammation is an important target in dry eye disease treatment. This symposium is the opportunity to have an overview of the new advances in patient management with preservative free, low-dose hydrocortisone.

The second part of the symposium will concentrate on the use of the intracameral mydriatic and anaesthetic during cataract surgery. Mydrane®** is the first standardised ophthalmic combination of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1%, designed for single-use intracameral injection in cataract surgery.

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*Thealoz®Duo, class IIb medical device: Trehalose 3% Sodium Hyaluronate 0.15%. Bioprotection, hydration and lubrication of the eye, for treatment of moderate to severe dry eye syndrome.

**Mydrane®: Solution for injection. Tropicamide 0.2 mg/mL, phenylephrine hydrochloride 3.1 mg/mL, lidocaine hydrochloride 10mg/mL. Indicated for cataract surgery to obtain mydriasis and intracocular anaesthesia during the surgical procedure in adults only. Mydrane® should only be used in patients who have already demonstrated, at pre-operative assessment, a satisfactory pupil dilatation with a topical mydriatic therapy.
FROM ARTIFICIAL TEARS TO TARGETED EYE DROPS
Professor Christina . GRUPCHEVA - Bulgaria

Since the first tear substitute marketed in 1902, the concept of dry eye pathophysiology and treatment has evolved profoundly. Today, powerful topical treatments are needed for faster results, adapted to diurnal and overnight dynamics of the ocular surface, and allowing a personalized treatment for efficient and lasting results. Such targeted treatments are made possible by the large choice of eye drops, from aqueous supplementation to various viscosity-enhancing agents and anti-inflammatory topical drugs.

Targeted treatment starts with acute diagnosis of dry eye syndrome. It must be reminded that patients may have no symptoms, despite the presence of inflammation at microstructural level. Greater inflammation generates visible symptoms and signs visible at clinical level, such as red eye, and becomes therefore destructive to the delicate ocular surface. Distinction must be done between evaporative dry eye and aqueous deficient dry eye. Then, the treatment is implemented by steps, which all include eye drops and particularly artificial tears.

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Focus on Artificial Tears: Improvement

Artificial tears may be preserved or preservative free. It is nowadays well known and documented that chronic exposure of the ocular surface to preservatives induces toxicity and adverse changes to the ocular surface.

Available preservative free tear substitutes include: hyaluronic acid (HA), hydroxypropyl methylcellulose (HPMC) and carboxy methylcellulose (CMC). HA is statistically superior to CMC on subjective symptom and on objective measurements, especially on the long term.

Ocular residence time is a crucial parameter of efficacy. Indeed, even during sleep, there are rapid eye movements under close eyelids, and the ocular surface needs to be lubricated. Ocular residence time not only depends on viscosity, but on several parameters: mucoadhesion, pH, surface tension, toxicity.

Normal tears viscosity ranges between 1.05 and 5.97 mPa.s. Further increases simply reflect reflex tearing and blinking in order to restore the original viscosity of tears (homeostasis). Increased viscosity in a product might feel cooler and can be preferred by some patients, especially before going to sleep.

Well known from food industry, trehalose is a natural bioprotectant/osmoprotectant, known from food industry, trehalose is a natural bioprotectant/osmoprotectant, known from food industry, trehalose is a natural bioprotectant/osmoprotectant, known from food industry...
decreasing the ocular inflammatory cycle. Lifitegrast was found to be a highly potent drug in various clinical trials as it alleviates both the signs and symptoms of DED. It protects the corneal surfaces and is well tolerated locally as well as systemically. Personalization of step 2 involves more attention to the eyelids and especially Demodex, with topical treatments such as tea tree oil and relevant terpen-4-ol products. This step also include moisture chambers, and systemic treatment including tetracyclines.

- **Step 3** adds several possibilities to the previous steps, including **serum drops**: autologous serum (AS), adult allogeneic serum, umbilical cord serum or platelet preparations. The use of AS is based on the assumption that AS contains biochemical components that may allow to mimic natural tears more closely than artificial tears. But a recent Cochrane review reported inconsistency in possible benefits of AS for improving participant-reported symptoms and other objective clinical measures. Thus, there might be some benefit in the short-term, but there is no evidence of an effect after two weeks of treatment.

- **In step 4**, the long term use of steroids is proposed, as well as various **surgical approaches**. Amniotic membranes may provide very good results in some patients.

Patients must understand from our explanations that the diagnosis and treatment of dry eye is a process taking time and requiring a gradual implementation following standardized steps and repeated evaluation. Subjective symptoms assessment may be more comparable if supported by standardized questionnaires such as OSDI. Signs are evaluated by a variety of non-invasive objective tests, likely to quantify the improvement. T-BUT, staining and osmolarity measurement are probably the most useful among them.

**CONCLUSIONS**

Publication numbers on dry eye are growing exponentially since the eighties. The more is known about dry eye pathophysiology, the more personalization of treatment is feasible. Personalised treatments are complex but they are crucial for the management of the patients.

**DECODING INFLAMMATION IN DRY EYE DISEASE: NEW ADVANCES IN PATIENT MANAGEMENT**

Professor Gerhard GARTHÖFER – Austria

Inflammation is among the most important mechanisms in the pathogenesis of Dry Eye Disease, triggering the vicious circle of Dry Eye. As such pro-inflammatory cytokines and other inflammatory markers can be found on the ocular surface of patients with Dry Eye Disease, even without prominent evident clinical signs.

From a pathophysiological point of view, inflammation induces two major consequences: tissue destruction and inflammatory cytokines released, which in turn fires the reflex tear response, leading to a reduction of corneal sensitivity and reflex tear secretion, with a final consequence of a compromised tear film.

Thus, reducing inflammation is an important target in dry eye disease treatment. This can be achieved by different treatment modalities. As a first step, topical lubricants are known to reduced inflammation by limiting the mechanics stress to the ocular surface. As such, it has been shown that a 30 days treatment with a lubricant eye drop solution reduces ocular symptoms and signs altogether with the inflammation marker HLA-DR.

If treatment with lubricants is not sufficient, international guidelines recommend the use of anti-inflammatory eye drops such as topical steroids or cyclosporine. Cyclosporin A is a powerful anti-inflammatory agent, with proved efficacy in dry eye. However, the benefit of cyclosporine A is rather slow to establish, with a full effect achieved after 3-6 months of treatment.

Corticosteroids block the whole inflammatory cascade of arachidonic acid. Their effects in dry eye have been well documented for decades, on symptoms as well as on inflammatory markers, and are achieved on a rather short time.

The downside of corticosteroids is the occurrence of adverse effects after long-term use, mainly cataract, with a considerably increased risk compared to people not using steroids. A further risk of topical therapy with corticosteroids is ocular hypertension, which increases with the relative anti-inflammatory activity of the preparation.
Inflammation is one of the key triggers of ocular surface diseases. Treatment with preservative-free, low-dose hydrocortisone reduced ocular redness and decreased OSDI in both study groups with no change in IOP. Because of its good safety profile, preservative-free, low-dose hydrocortisone may be an interesting alternative to standard corticosteroid treatment of ocular surface inflammation in dry eye.

TO STREAMLINE THE FLOW OF YOUR CATARACT SURGERY LIST

Professor Rudy NUIJTS - The Netherlands

Most cataract surgeons nowadays strive towards cataract surgery that is fast, efficient, and comfortable to the patient. Optimal mydriasis and anesthetics are crucial in improving efficiency of cataract surgery and preventing intraoperative complications: sufficient mydriasis is necessary for visualization of the capsulorhexis, lens implantation, and poor mydriasis during cataract surgery increases the risk of intraoperative complications.

With regards to anesthesia, we have already seen a shift from retrobulbar techniques to topical anesthesia in the Netherlands, which is more efficient and more comfortable to the patient.

A survey amongst 480 European cataract surgeons has shown that, when asked what they found most important about mydriasis, the stability and size of the mydriasis were valued highest (European Observatory of Cataract Surgery, 2015).

Topical mydriasis is still the most common method used. However, this method has several disadvantages. Firstly, it takes time to achieve proper mydriasis after instillation of the eye drops, which requires the patient to be present at the hospital well in advance of the surgery. Furthermore, multiple administrations are necessary, which is done by a nurse, to whom wages need to be paid. Topical mydriatics can have multiple systemic side effects, such as tachycardia and cardiac arrhythmia. Finally, they may reduce the integrity of the ocular surface, which may impair visualisation during cataract surgery.

Mydrane® is a solution for intracameral injection which contains phenylephrine and tropicamide, as well as lidocaine for additional anesthesia. It is designed for patients undergoing cataract surgery who have demonstrated sufficient pupil dilation following topical mydriatic administration during the preoperative visit.

The purpose of the current study was to compare the effectiveness and costs of Mydrane® to two alternatives: topical mydriatics and Mydriasert®*. The study was a single center study in the Zuyderland Medical Centre, Heerlen, the Netherlands, non-randomized and comparative with three study groups recruited consecutively. The main inclusion criterion was patients undergoing cataract surgery under topical anesthesia. The main exclusion criteria were the presence of ophthalmic disorders affecting visual acuity or potentially interfering with surgery, and patients with known incomplete mydriasis as determined during the preoperative visit.

The main outcome parameter of the study is incremental costs of the surgery.
Secondary outcomes were set as, pupil diameter, determined by the ratio between white-to-white distance and pupil diameter at various critical time points, just before the main incision, just before OVD injection, just before CCC, just before IOL insertion, and just before ceferoxime injection at the end of surgery. And satisfaction of the cataract surgeries with mydriasis and visualization during the case. Patients evaluation by the CatQuest questionnaire preoperatively and 4 weeks postoperatively, and by VAS pain scale, ranging from 0 to 10, directly postoperatively.

Davey et al. performed a model-based budget impact analysis in UK, evaluating the costs for one hospital over 1 year (3000 cataract operations). The direct costs of Mydrane® was £18,000, compared to £3,300 fot the other mydriatics. But the topical group had higher nurse costs (£19,400 vs £0), resulting in slightly higher total costs for topical group: £14,500 vs £10,900.

The current study was designed for the conditions in the Dutch - health system. In Netherlands, Mydrane® has a higher purchase price than topical mydriatics. But the price difference may be higher or lower depending on the country, and the extra cost may be compensated or not by savings on other costs components, especially if the intracameral injection is nurse time saving. Indeed, as the global patient flow remained the same during the study it has been difficult to assess this criteria.

An other important limitation of the current study was that the quality of the ocular surface was not investigated. Mydrane® being injected in the anterior chamber may preserve the ocular surface integrity, which may improve visualization during surgery and patient satisfaction as well as post-surgery ocular surface diseases, as shown in other studies.

Subjects received Mydrane® (plus oxybuprocain chloride 0.4% + tetracaine chlorhydrate 0.1% plus phenylephrine 10% and tropicamide 1% as mydriatics) in one eye and the standard eye-drops (oxybuprocain chloride hydroxide 0.4% + tetracaine chlorhydrate 0.1% plus phenylephrine 10% and tropicamide 1% as mydriatics) in the fellow eye.

Subjects were randomized (1:1) to receive the Mydrane® or standard eye drops for their first surgeries. Surgery of the fellow eye was performed within 7 days after the first surgery. Patients were evaluated before, immediately after, 1 day and 7 days after each surgery.

The mean OSI obtained from the double-pass point-spread function image (HD Analyzer) indicated no significant lower intraocular scattering in Mydrane®, but practical implication of better optical quality. The parameters of vBUT, obtained from the HD Analyzer, indicated no significant differences between eyes. The eyes operated with Mydrane® had lower OSI values than standard eye drops group. The difference was not statistically significant but was clinically meaningful.
Fewer epithelial alterations were detected in the eyes operated with Mydrane®.

30% of the eyes operated with eye drops had epithelial alterations meanwhile only 8% with Mydrane® group. There were fewer epithelial alterations detected in eyes that received Mydrane® 24h after surgery and no epithelial alterations 7 days after surgery. Corneal epithelial alterations persisted further than 7 days in some cases with standard eye-drops.

Conjunctival inflammation decreased faster in eyes that received Mydrane® than those with standard eye-drops.

Conjunctival staining scores increased just after the surgery in both groups. But it decreases faster in the eyes operated with Mydrane®. Hyperaemia assessment scores were clinically decreased faster in the Mydrane® group.

The percentage of the patients and surgeon who evaluated the surgery as very satisfactory were significantly higher in Mydrane® group than eye drops.

The understanding on dry eye is growing exponentially since the eighties. The more is known about dry eye pathophysiology, the more personalization of treatment is complex but also crucial. Treatment of Dry Eye is not just about lubricants. We need also combine strategy with lid hygiene, lubricants and preservative free anti-inflammatory therapy. Inflammation is recognized as having a prominent role in the development and progression of the pathogenesis of DED. Inflammation is both a cause and effect of DED. Although artificial tears, even those supplemented with osmoprotectants (e.g. trehalose), have been shown to decrease hyperosmolality and ocular surface inflammation, they might be not enough to address the underlying disease process. Anti-inflammatory eye drops like the new preservative free, low-dose hydrocortisone are thus a therapeutic option for breaking the vicious inflammatory cycle.

Mydrane® is a solution for intracameral injection which contains phenylephrine and tropicamide, as well as lidocaine for additional anesthesia. Mydrane® is effective and safe for initiating and maintaining large and stable mydriasis and analgesia during cataract surgery. Mydrane® will allow surgeons to save time and can help to optimise organisation of the fast track process through its efficacy. Mydrane® reduces the risk of systemic and local side effects seen with the topical drugs.

**CONCLUSIONS**

Mydrane® usage in routine cataract surgery reduces corneal epithelial toxicity and ocular surface damage. Faster recovery of ocular surface integrity is achieved with less intraocular scattering and better optical quality. Patient comfort and satisfaction is increased before, during and after surgery.
Indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia during the surgical procedure in adults only. Mydrane® should only be used in patients who have already demonstrated, at pre-operative assessment, a satisfactory pupil dilation with a topical mydriatic therapy.

**MYDRANE®** 0.2 mg/ml + 3.1 mg/ml + 10 mg/ml solution for injection.

**COMPOSITION:** 1 ml of solution for injection contains 0.2 mg of tropicamide, 3.1 mg of phenylephrine hydrochloride and 10 mg of lidocaine hydrochloride. 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 with a known effect: sodium (0.59 mg per dose). Excipients. Indications: MYDRANE® is indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia during the surgical procedure. MYDRANE® is indicated in adults only. Posology: MYDRANE® should only be used in patients who have already demonstrated, at pre-operative assessment, 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. Pregnancy: MYDRANE® should not be used during pregnancy. Breastfeeding: MYDRANE® should not be used during breast feeding. Undesirable effects: Nervous system disorders (uncommon): Headache. Eye disorders (uncommon): Keratitis, Cystoid macular oedema, Intraocular pressure increased, Posterior capsule rupture, Ocular hyperaemia. Vascular disorders (uncommon): Hypertension. Nature and contents of container: One paper/PVC blister containing 1 ml sterile brown glass (type I) ampoule filled with 0.6 ml of solution for injection. Separated 5-micron sterile filter needles packed in individual blisters are provided. Box of 1, 20 and 100 sterile ampoules together with respectively 1, 20 and 100 5-micron sterile filter needles. Kit of one paper/PVC blister containing one 1 ml sterile brown glass (type I) ampoule filled with 0.6 ml of solution for injection and one 5-micron sterile filter needle. Box of 1, 20 and 100 kits (i.e. blister containing a sterile ampoule and a sterile filter needle). Not all pack sizes may be marketed.

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