Valorization

Valorization is the application of academic knowledge to create societal, economic or commercial value

Cataract, a cloudiness of the natural intraocular lens, is the leading cause of preventable and treatable blindness.\(^1\) The prevalence of age-related cataract will keep rising, as the number of people aged 60 years and older will increase.\(^2\) Surgical intervention is the only available treatment for cataract. Each day, approximately 573 patients undergo cataract surgery in the Netherlands (working days only). Dutch hospitals account for 148 905 cataract surgeries a year, which corresponds to 872 cataract surgeries per 100 000 population.\(^3,4\) These numbers are even higher in some other countries, such as Austria, Denmark, Germany, Portugal and Sweden.\(^5\) Although reported success rates of modern cataract surgery are above 92%, surgical techniques and perioperative care continue to evolve and improve, in order to prevent the occurrence of complications and to optimize visual recovery.\(^6\) Pseudophakic cystoid macular edema (PCME), is one of the most important complications after regular cataract surgery.\(^7,8\) PCME may cause suboptimal visual acuity and contrast sensitivity during the immediate postoperative period, and may have a significant impact on daily routines, postoperative visual rehabilitation and quality of life.\(^9\)

From a scientific perspective

PCME results from a postoperative inflammatory response.\(^10\) Although corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been used for almost fifty years to prevent the occurrence of PCME, there remained a lack of high quality evidence with regard to their efficacy. As a result, remarkable contrasts can be seen between the clinical recommendations of leading authorities.\(^6,11-13\) The PREvention of Macular EDema after cataract surgery (PREMED) study, funded by the European Society of Cataract and Refractive Surgeons (ESCRS), is currently the largest multicenter study directly comparing the efficacy of a corticosteroid eye drop, NSAID eye drop and the combination of both. The incidence of clinically significant macular edema (CSME) was 5.1% in patients treated with dexamethasone eye drops, 3.6% in patients treated with bromfenac eye drops and 1.5% in patients treated with a combination of both drugs.

Previous studies have shown that patients with diabetes mellitus have an increased risk of developing cystoid macular edema (CME) after cataract surgery, especially if they are also diagnosed with diabetic retinopathy.\(^7\) ESCRs PREMED study report 2 shows that a single subconjunctival injection with 40 mg triamcinolone acetonide (TA) can effectively prevent the occurrence of CME after cataract surgery in these high-risk patients.
From a patient perspective

Cataract surgery has evolved into one of the most frequently performed surgical procedures in the world and can significantly improve quality of life in patients with mild to severe visual impairment. The high success rate of modern phacoemulsification techniques raises high expectations for postoperative visual recovery, based on the patient’s previous experiences with family, friends or neighbors. Optimal prevention of postoperative complications is of utmost importance, especially in a demanding population such as the modern Western society. The ESCRS PREMED study found that the odds of developing CSME are 2.6-3.7 times higher if a patient uses only bromfenac or dexamethasone eye drops, as compared to patients using a combination of both. Patients using a combination of NSAID and corticosteroid eye drops will benefit from optimization of postoperative care with a faster visual rehabilitation.

Another point of interest from a patient perspective is the ease of drug administration. Combination treatment with a corticosteroid and NSAID, as recommended from the ESCRS PREMED study, involves frequent eye drop administration. While once-daily NSAID preparations can be used to prevent PCME, most corticosteroids require three to four administrations a day. Eye drops containing more than one active substance are frequently used in ophthalmology, in order to reduce the frequency of eye drop administration. Although fixed combinations of a corticosteroid and antibiotic have been used for many years, there are currently no available preparations containing a corticosteroid and NSAID. Further research is needed to investigate whether it is feasible to produce such fixed preparations with comparable drug efficacy, since intraocular bioavailability might be reduced in fixed preparations. If pharmaceutical companies are able to produce a new eye drop containing a fixed corticosteroid and NSAID combination, preferably with a once- or twice-daily administration scheme, this eye drop will have a large target audience. Fixed combinations of a corticosteroid and NSAID will reduce the frequency of eye drop administration after cataract surgery, improve patient compliance and reduce corneal exposure to preservatives. Furthermore, less frequent drug dosing will reduce the burden for home care services, who are frequently involved in postoperative care.

From a health care perspective

In recent years, cataract surgery has evolved into one of the most cost-effective of all health care interventions. According to recent studies, the costs of postoperative anti-inflammatory eye drops are likely to be minimal compared to the overall cost savings resulting from fewer cases of PCME. Previous research has shown that annual health care claims are 15% higher in patients who developed CME after cataract surgery between 1997-2001, as compared to patients who did not. When considering ophthalmic care only,
total claims were 41% higher in patients who developed CME. An update found that the relative and absolute costs of CME after cataract surgery were even higher in 2011-2013. According to the results of the ESCRS PREMED study, the incidence of PCME can be further decreased if patients are treated with both corticosteroid and NSAID eye drops. A single perioperative subconjunctival injection with 40 mg TA could effectively prevent the occurrence of CME in high risk-patients with diabetes mellitus. Future research from our group will investigate the cost-effectiveness of these prophylactic treatments and their effect on vision-related quality of life, within the scope of the ESCRS PREMED study.

Although corticosteroid eye drops can be used at low costs, the use of NSAID eye drops involves widely differing prices among countries. While one bottle of bromfenac costs only €7.99 in the Netherlands, prices are more than 10-25 fold higher in other countries. Especially in the United States of America, the high costs of NSAID eye drops are a major problem, since average costs for a 30-day supply of bromfenac are €184.04 ($226.89) for brand medication and €125.18 ($154.32) for generic medication. Although NSAID eye drops significantly reduce the incidence of CME after cataract surgery, prophylactic NSAID treatment may not be cost-effective in countries where prices are very high. Therefore, government, health insurance companies and patients will benefit from lower market prices of NSAID eye drops.

Although previous studies have indicated that the costs of postoperative anti-inflammatory eye drops are minimal compared to the overall cost savings resulting from fewer cases of PCME, this is only applicable if patients are able to apply the eye drops themselves. If homecare services are involved to administer the eye drops four times daily for one week and one drop less per day every following week, the additional costs are approximately €1700, assuming that a homecare worker needs 20 minutes per administration at an hourly rate of €73. These additional costs for postoperative care are even higher than the costs of the cataract surgery itself, i.e. €1070 according to the Dutch healthcare authority (Nederlandse zorgautoriteit). This is one of the major reasons why ‘dropless cataract surgery’ is an important current research topic in cataract surgery. This thesis showed that a subconjunctival injection of 40 mg TA can effectively prevent the occurrence of CME after cataract surgery in diabetics who also used bromfenac and dexamethasone eye drops. Future studies should investigate whether TA is equally effective in case of dropless cataract surgery, in patients with and without diabetes mellitus. Other routes of dropless corticosteroid and NSAID treatment are under investigation.
Recommendations for clinical practice

The most recent Dutch guideline on cataract surgery, dated 2013, states that it is unlikely that topical NSAIDs provide a supplementary effect in prevention of inflammation after cataract surgery. However, based on the results of this thesis, we recommend treating all cataract surgery patients with a combination of corticosteroid and NSAID eye drops. Anti-inflammatory treatments can be initiated before or after cataract surgery. In 2014, approximately 29% of patients in Europe (49% in the Netherlands) received prophylactic anti-inflammatory eye drops before cataract surgery. These numbers will likely increase, now that recent studies have shown a significant effect of preoperative NSAID treatment. Topical treatment should start one to three days preoperatively in order to achieve optimal prevention of inflammation and PCME.

Currently, no specific preparation is preferred over others, based on their efficacy to prevent the occurrence of PCME. At this point, the optimal treatment should be chosen based on patient satisfaction, simplicity of drug administration, ocular comfort, and health care costs. Once-daily NSAID preparations are preferred, in order to improve patient satisfaction and compliance. In the Netherlands, nepafenac 3 mg/ml is the only NSAID eye drop registered for once-daily application. However, recent studies have shown that once-daily bromfenac 0.9 mg/ml can also effectively prevent inflammation after cataract surgery. Although bromfenac is not registered for once-daily application in the Netherlands, this could be an interesting alternative to nepafenac, given the lower costs involved with bromfenac treatment (see table 1).

<table>
<thead>
<tr>
<th>Table 1. Registered treatment regimens and costs in the Netherlands</th>
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<tbody>
<tr>
<td>Frequency of administration (drops/day)</td>
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<tr>
<td>------------------------------------------</td>
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<tr>
<td><strong>Corticosteroid</strong></td>
</tr>
<tr>
<td>Dexamethasone 1 mg/ml 4-6</td>
</tr>
<tr>
<td>Fluorometholone 1 mg/ml 2-4</td>
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<tr>
<td>Prednisolone 10 mg/ml 2-4</td>
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<tr>
<td><strong>NSAID</strong></td>
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<tr>
<td>Bromfenac 0.9 mg/ml 2</td>
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<tr>
<td>Diclofenac 1 mg/ml 3-5</td>
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<tr>
<td>Indomethacin 1 mg/ml 4</td>
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<tr>
<td>Ketorolac 5 mg/ml 3</td>
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<td>Nepafenac 3 mg/ml 1</td>
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NSAID: non-steroidal anti-inflammatory drug; wks: weeks
The Dutch national health care institute (Zorginstituut Nederland) does not provide recommendations regarding the optimal duration of topical corticosteroid treatment.\textsuperscript{39} In patients without diabetes or other risk factors, dexamethasone or prednisolone eye drops are generally used for approximately one month postoperatively.\textsuperscript{40} The frequency of topical corticosteroid administration is often reduced with one drop less per day every following week. In the Netherlands, the costs of dexamethasone eye drops are slightly lower than the costs involved with topical prednisolone treatment.

In conclusion, we recommend using topical nepafenac 3 mg/ml once daily for one to three days preoperatively and two weeks postoperatively; in combination with topical dexamethasone 1 mg/ml four times daily for one to three days preoperatively, one week postoperatively and one drop less per day every following week, in all patients undergoing cataract surgery with no increased risk of developing PCME. A personalized risk assessment should be made for all other patients, including patients with a history of diabetes mellitus, uveitis, epiretinal membrane or patients who underwent complicated cataract surgery. Ongoing research from our group will further explore these risk factors and will enable cataract surgeons to perform an adequate pre- and perioperative risk assessment.\textsuperscript{41} Pre- and postoperative treatment should be tailored to the needs of the individual patient. As shown in ESCRS PREMED study report 2, a single subconjunctival injection of 40 mg TA can effectively prevent the occurrence of CME after cataract surgery in diabetics, although this treatment also involves higher incidence rates of postoperative complications, such as an increased intraocular pressure. Appropriate strategies may also include high frequency topical corticosteroid administration, longer duration of topical corticosteroid treatment, or intravitreal corticosteroid or anti-vascular endothelial growth factor injections.\textsuperscript{27, 30, 42}

**Audience**

A key factor in optimizing prevention of CME after cataract surgery is to disseminate the results of the ESCRS PREMED study to other cataract surgeons. In the first instance, the ESCRS PREMED study results were presented at the annual congress of the ESCRS in October 2017. The presentation had the highest ratings on ESCRS On Demand.\textsuperscript{43} The same day, the ESCRS distributed a press release to all members. Afterwards, the results will be published in a peer-reviewed journal and other journals without referee system (e.g. EuroTimes, Ophthalmology News). Furthermore, the results have been presented at several national meetings throughout Europe and elsewhere (e.g. the Netherlands, Belgium, Switzerland, Greece and the USA). Ultimately, it is our goal to include the recommendations of the ESCRS PREMED study in our national guidelines, provided by the Dutch ophthalmological society (Nederlands oogheelkundig gezelschap, NOG) and international guidelines.\textsuperscript{32}
Patients will be informed about the results of the study via an article in the thrice yearly magazine of the Maastricht University Medical Center+ *Gezond Idee*. 
References


3. www.opendisdata.nl. Nederlandse zorgautoriteit, 2018


6. www.opendisdata.nl. Nederlandse zorgautoriteit, 2018


29 Donnenfeld E, Holland E. Dexamethasone Intracameral Drug-Delivery Suspension for Inflammation Associated with Cataract Surgery: A Randomized, Placebo-Controlled, Phase III Trial. Ophthalmology 2018
37 Cable M. Comparison of bromfenac 0.09% QD to nepafenac 0.1% TID after cataract surgery: pilot evaluation of visual acuity, macular volume, and retinal thickness at a single site. Clin Ophthalmol 2012; 6: 997-1004
39 Farmacotherapeutisch Kompas. https://www.farmacotherapeutischkompas.nl, Zorginstituut Nederland, 2018
41 Veldhuizen CA, Wielders LHP, Schouten JAG, van den Biggelaar FJHM, Winkens B, Nuijts RMMA. Perioperative risk factors for the development of cystoid macular edema after cataract surgery: a report from the ESCRS PREMED study. XXXV Congress of the ESCRS. Lisbon, 2017
43 ESCRS On Demand. https://escrs.conference2web.com/. ESCRS On Demand hosts recorded sessions from ESCR congresses and winter meeting, including conference presentations.