

Prevention and treatment of cystoid macular edema after cataract surgery

Citation for published version (APA):

Wielders, L. (2018). *Prevention and treatment of cystoid macular edema after cataract surgery*. [Doctoral Thesis, Maastricht University]. Gildeprint Drukkerijen. <https://doi.org/10.26481/dis.20180830lw>

Document status and date:

Published: 01/01/2018

DOI:

[10.26481/dis.20180830lw](https://doi.org/10.26481/dis.20180830lw)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

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.¹⁴ 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.^{8,15} 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.¹⁶ 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.¹⁷ 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.^{9,14} 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.⁹ An update found that the relative and absolute costs of CME after cataract surgery were even higher in 2011-2013.¹⁴ 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.¹⁸

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.^{11, 19, 20} 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.²⁰⁻²² 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 €73.²³ 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).³ 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.²⁴⁻³¹

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.³² 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.¹³ 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.^{33, 34}

Currently, no specific preparation is preferred over others, based on their efficacy to prevent the occurrence of PCME.³⁵⁻³⁷ 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.³⁸ 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).¹⁹

Table 1. Registered treatment regimens and costs in the Netherlands

| | Frequency of administration (drops/day) ³⁹ | Duration of postoperative treatment (wks) ³⁹ | Price per bottle (3-5 ml) ¹⁹ | Minims ¹⁹ |
|-------------------------|---|---|---|----------------------|
| Corticosteroid | | | | |
| Dexamethasone 1 mg/ml | 4-6 | | €2.46 | €0.36 |
| Fluorometholone 1 mg/ml | 2-4 | | €2.71 | |
| Prednisolone 10 mg/ml | 2-4 | | €2.71 | €0.82 |
| NSAID | | | | |
| Bromfenac 0.9 mg/ml | 2 | 2 | €7.99 | |
| Diclofenac 1 mg/ml | 3-5 | ≤ 4 | €5.54 | €0.60 |
| Indomethacin 1 mg/ml | 4 | 2-3 | €3.39 | |
| Ketorolac 5 mg/ml | 3 | 3 | €4.10 | |
| Nepafenac 3 mg/ml | 1 | 2-3 | €18.17 | |

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.³⁹ In patients without diabetes or other risk factors, dexamethasone or prednisolone eye drops are generally used for approximately one month postoperatively.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.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.^{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*.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 oogheekkundig gezelschap, NOG) and international guidelines.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

- 1 Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, Jonas JB, Keeffe J, Leasher J, Naidoo K, Pesudovs K, Resnikoff S, Taylor HR, Vision Loss Expert G. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *Lancet Glob Health* 2013; 1: e339-349
- 2 World report on ageing and health. World Health Organization, 2015
- 3 www.opendisdata.nl. Nederlandse zorgautoriteit, 2018
- 4 Bevolking en bevolkingsontwikkeling; per maand, kwartaal en jaar. <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37943ned/table?ts=1520764839747>, StatLine, 2017
- 5 Health Care Utilisation: Surgical procedures. <http://stats.oecd.org/index.aspx?queryid=30167>, OECD.Stat, 2018
- 6 Cataracts in adults: management. National Institute for Health and Care Excellence: Clinical Guidelines 2017
- 7 Chu CJ, Johnston RL, Buscombe C, Sallam AB, Mohamed Q, Yang YC, United Kingdom Pseudophakic Macular Edema Study G. Risk Factors and Incidence of Macular Edema after Cataract Surgery: A Database Study of 81984 Eyes. *Ophthalmology* 2016; 123: 316-323
- 8 McCafferty S, Harris A, Kew C, Kassm T, Lane L, Levine J, Raven M. Pseudophakic cystoid macular edema prevention and risk factors; prospective study with adjunctive once daily topical nepafenac 0.3% versus placebo. *BMC Ophthalmol* 2017; 17: 16
- 9 Schmier JK, Halpern MT, Covert DW, Matthews GP. Evaluation of costs for cystoid macular edema among patients after cataract surgery. *Retina* 2007; 27: 621-628
- 10 Rossetti L, Chaudhuri J, Dickersin K. Medical prophylaxis and treatment of cystoid macular edema after cataract surgery. The results of a meta-analysis. *Ophthalmology* 1998; 105: 397-405
- 11 Kim SJ, Schoenberger SD, Thorne JE, Ehlers JP, Yeh S, Bakri SJ. Topical Nonsteroidal Anti-inflammatory Drugs and Cataract Surgery: A Report by the American Academy of Ophthalmology. *Ophthalmology* 2015; 122: 2159-2168
- 12 Hoffman RS, Braga-Mele R, Donaldson K, Emerick G, Henderson B, Kahook M, Mamalis N, Miller KM, Realini T, Shorstein NH, Stiverson RK, Wirostko B, Committee ACC, the American Glaucoma S. Cataract surgery and nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg* 2016; 42: 1368-1379
- 13 Behndig A, Cochener-Lamard B, Güell JL, Kodjikian L, Mencucci R, Nuijts R, Pleyer U, Szaflik JP, Tassignon MJ, Rosen P. Surgical, Antiseptic and Antibiotic Practice in Cataract Surgery: Update from the European Observatory in 2014. Submitted 2018
- 14 Schmier JK, Covert DW, Hulme-Lowe CK, Mullins A, Mahlis EM. Treatment costs of cystoid macular edema among patients following cataract surgery. *Clin Ophthalmol* 2016; 10: 477-483
- 15 Singh RP, Lehmann R, Martel J, Jong K, Pollack A, Tsoibatzoglou A, Staurengi G, Cervantes-Coste Cervantes G, Alpern L, Modi S, Svoboda L, Adewale A, Jaffe GJ. Nepafenac 0.3% after Cataract Surgery in Patients with Diabetic Retinopathy: Results of 2 Randomized Phase 3 Studies. *Ophthalmology* 2017; 124: 776-785
- 16 Leibowitz HM, Kupferman A. Drug interaction in the eye. Concurrent corticosteroid-antibiotic therapy for inflammatory keratitis. *Arch Ophthalmol* 1977; 95: 682-685
- 17 Vandenbroeck S, De Geest S, Dobbels F, Fieuws S, Stalmans I, Zeyen T. Prevalence and correlates of self-reported nonadherence with eye drop treatment: the Belgian Compliance Study in Ophthalmology (BCSO). *J Glaucoma* 2011; 20: 414-421
- 18 Simons RWP, Wielders LHP, Schouten JSAG, van den Biggelaar FJHM, Winkens B, Veldhuizen CA, Nuijts RMM. Economic evaluation of pharmaceutical strategies to prevent cystoid macular edema after cataract surgery in nondiabetic and diabetic patients. XXXV Congress of the ESCRS. Lisbon, 2017
- 19 Medicijnkosten. www.medicijnkosten.nl, Zorginstituut Nederland, 2017
- 20 Drugs.com price guide. <https://www.drugs.com/price-guide/>, 2018
- 21 Newman-Casey PA, Woodward MA, Niziol LM, Lee PP, De Lott LB. Brand Medications and Medicare Part D: How Eye Care Providers' Prescribing Patterns Influence Costs. *Ophthalmology* 2018; 125: 332-339
- 22 Kim SJ, Patel SN, Sternberg P, Jr. Routine Use of Nonsteroidal Anti-inflammatory Drugs with Corticosteroids in Cataract Surgery: Beneficial or Redundant? *Ophthalmology* 2016; 123: 444-446
- 23 Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, S. ST. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Nederland, 2015
- 24 Margalit E, Boysen JL, Zastrocky JP, Katz A. Use of intraocular ketorolac tromethamine for the treatment of chronic cystoid macular edema. *Can J Ophthalmol* 2010; 45: 409-410

- 25 Omidria. Assessment report. European Medicines Agency (EMA), 2015
- 26 Tyson SL, Bailey R, Roman JS, Zhan T, Hark LA, Haller JA. Clinical outcomes after injection of a compounded pharmaceutical for prophylaxis after cataract surgery: a large-scale review. *Curr Opin Ophthalmol* 2017; 28: 73-80
- 27 Ahmadabadi HF, Mohammadi M, Beheshtnejad H, Mirshahi A. Effect of intravitreal triamcinolone acetonide injection on central macular thickness in diabetic patients having phacoemulsification. *Journal of Cataract and Refractive Surgery* 2010; 36: 917-922
- 28 Gills JP, Gills P. Effect of intracameral triamcinolone to control inflammation following cataract surgery. *J Cataract Refract Surg* 2005; 31: 1670-1671
- 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
- 30 Takata C, Messias A, Folgosa MS, Lucena LR, Lucena DR, Scott IU, Jorge R. Intravitreal injection versus subtenon infusion of triamcinolone acetonide during cataract surgery in patients with refractory diabetic macular edema. *Retina* 2010; 30: 562-569
- 31 Stringham JD, Flynn HW, Jr., Schimel AM, Banta JT. Dropleess Cataract Surgery: What Are the Potential Downsides? *Am J Ophthalmol* 2016; 164: viii-x
- 32 Bartels M, Henry Y, van Hecke M, Maatman M, Nuijts R, Reus N, Rulo A, Schuurhuis A, Tigchelaar-Besling O, Tjia K, Trap N. Richtlijn cataract. Nederlands Oogheelkundig Gezelschap, 2013
- 33 Donnenfeld ED, Perry HD, Wittpenn JR, Solomon R, Nattis A, Chou T. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: Pharmacokinetic-response curve. *Journal of Cataract and Refractive Surgery* 2006; 32: 1474-1482
- 34 Yavas GF, Ozturk F, Kusbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. *J Cataract Refract Surg* 2007; 33: 804-807
- 35 Zhao X, Xia S, Wang E, Chen Y. Comparison of the efficacy and patients' tolerability of Nepafenac and Ketorolac in the treatment of ocular inflammation following cataract surgery: A meta-analysis of randomized controlled trials. *PLoS One* 2017; 12: e0173254
- 36 Duan P, Liu Y, Li J. The comparative efficacy and safety of topical non-steroidal anti-inflammatory drugs for the treatment of anterior chamber inflammation after cataract surgery: a systematic review and network meta-analysis. *Graefes Arch Clin Exp Ophthalmol* 2017; 255: 639-649
- 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
- 38 Silverstein SM, Cable MG, Sadri E, Peace JH, Fong R, Chandler SP, Gow JA, Klier SM, McNamara TR, Bromfenac Ophthalmic Solution Once Daily Study G. Once daily dosing of bromfenac ophthalmic solution 0.09% for postoperative ocular inflammation and pain. *Curr Med Res Opin* 2011; 27: 1693-1703
- 39 Farmacotherapeutisch Kompas. <https://www.farmacotherapeutischkompas.nl>, Zorginstituut Nederland, 2018
- 40 Wielders LH, Lambermont VA, Schouten JS, van den Biggelaar FJ, Worthy G, Simons RW, Winkens B, Nuijts RM. Prevention of Cystoid Macular Edema After Cataract Surgery in Nondiabetic and Diabetic Patients: A Systematic Review and Meta-Analysis. *Am J Ophthalmol* 2015; 160: 968-981 e933
- 41 Veldhuizen CA, Wielders LHP, Schouten JSAG, 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 PREMEDI study. XXXV Congress of the ESCRS. Lisbon, 2017
- 42 Campochiaro PA, Han YS, Mir TA, Kherani S, Hafiz G, Krispel C, Liu TYA, Wang J, Scott AW, Zimmer-Galler I. Increased Frequency of Topical Steroids Provides Benefit in Patients With Recalcitrant Postsurgical Macular Edema. *Am J Ophthalmol* 2017; 178: 163-175
- 43 ESCRS On Demand. <https://escrs.conference2web.com/>; ESCRS On Demand hosts recorded sessions from ESCR congresses and winter meeting, including conference presentations.

