PREVENTION AND TREATMENT OF CYSTOID MACULAR EDEMA AFTER CATARACT SURGERY

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General introduction

Global estimates of the World Health Organization (WHO) indicate that there will be 76 million blind people in 2020.[1] There are many causes of blindness, including age-related macular degeneration, cataract, diabetic retinopathy, glaucoma and trachoma. Cataract blindness affects approximately 18 million people around the world.[1] Although cataract is the single most important cause of blindness on a worldwide scale, the proportion of blindness due to cataract is only 5-14% in Western Europe.[1, 2] Visually disabling cataracts occur less often in regions where healthcare services are easily available to most people, but this low prevalence of cataract blindness requires large numbers of cataract surgeries to be performed on a daily basis.

Cataract

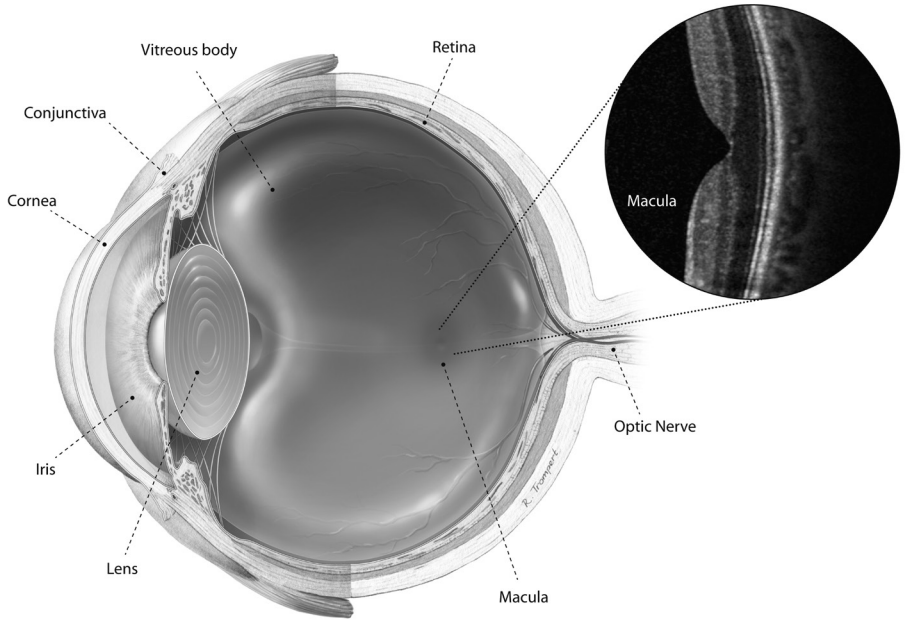
Cataract is a cloudiness of the natural crystalline lens. The lens is located posterior to the iris and anterior to the vitreous body (figure 1). The lens cooperates with the ocular tear film and the cornea to refract the light entering the eye. Furthermore, the crystalline lens provides accommodation, enabling young people to read without glasses. With increasing age, the rigidity, thickness and weight of the lens increase, while the transparency decreases.[3] The development of cataract is usually a natural process related to aging, and therefore most cases cannot be prevented. Some patient characteristics are recognized as risk factors for developing cataract, of which diabetes mellitus is the most well-known. The prevalence of cataract under the age of 65 is three to four times higher in diabetics, as compared to non-diabetics.[4]

Patients with cataract may complain of blurry vision and may experience monocular double vision and glare or halos around light sources. A myopic shift may lead to a renewed ability to read without reading glasses, which is also known as 'second sight of the aged'.[5] If left untreated, cataract will cause a gradual decline in quality of vision and may even interfere with quality of life.

Cataract surgery

Surgical intervention to remove the cloudy crystalline lens is the only available treatment for cataract. Surgery for cataract has been reported for many years, with its first description, called 'couching', dating from about the fifth century before Christ.[3] During the past century, cataract surgery techniques have evolved from intracapsular cataract extraction (ICCE), to extracapsular cataract extraction (ECCE), modern phacoemulsification cataract surgery and femtosecond laser assisted cataract surgery (FLACS).[6] Phacoemulsification cataract surgery has developed into one of the most commonly performed surgical proce-

Figure 1. Anatomy of the eye with a cross section of a normal macula lutea



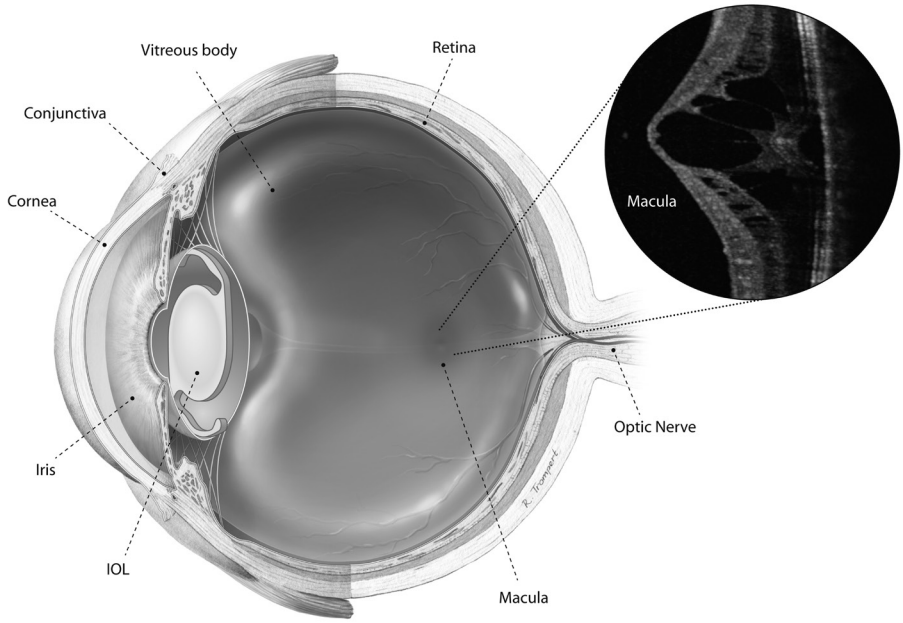
dures around the world and is considered one of the most cost-effective of all health-care interventions.[1, 7] Modern cataract surgery has a success rate of 92% or higher, and yet cataract surgery techniques continue to evolve and improve.[8]

Advanced surgical techniques have also decreased the incidence of postoperative complications. Endophthalmitis, which is reported in 0.036-0.050% of patients after cataract surgery, is considered the most dreaded complication of all.[9, 10] Other complications related to cataract surgery include cystoid macular edema (CME), intraocular inflammation, posterior capsule opacification and retinal detachment.[8] A major current focus in cataract surgery is how to optimize pre- and postoperative care in order to prevent the occurrence of complications and to optimize visual recovery.

Cystoid macular edema

CME after cataract surgery, also known as the Irvine-Gass syndrome, was first reported in 1953.[11, 12] CME involves the accumulation of fluid in the central part of the retina, also known as the macula lutea. It usually occurs within twelve weeks after cataract surgery, with a peak incidence at four to six weeks postoperatively.[13] Patients with CME will experience a reduced central visual acuity and reduced contrast sensitivity, and may complain of metamorphopsia.

Figure 2. Cystoid macular edema is an accumulation of fluid in the macula lutea



IOL: intraocular lens

Due to improvements in cataract surgery techniques, the incidence of CME after cataract surgery has significantly decreased.[14] Incidence rates as high as 50-60% were reported after ICCE in 1975, but gradually decreased to approximately 30% after ECCE, and further to 9% after phacoemulsification cataract surgery in 2003.[15-17] Currently, the incidence of CME after cataract surgery is estimated between 1-2% in patients without risk factors for developing CME after cataract surgery.[18, 19]

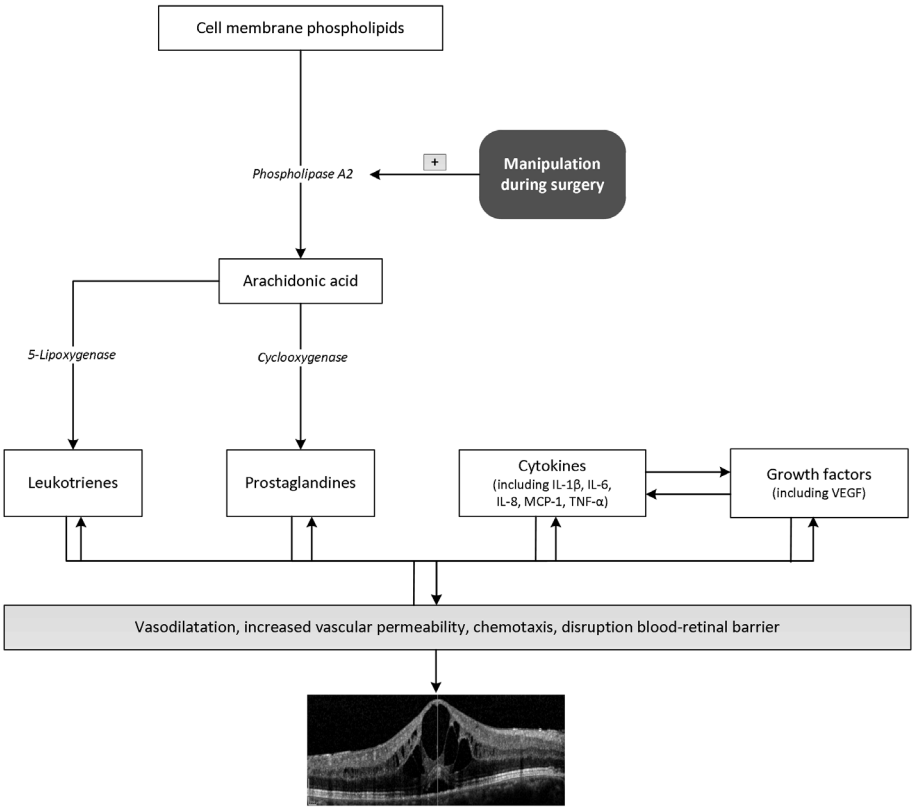
Pathophysiology of cystoid macular edema

CME after cataract surgery is the result of a postoperative inflammatory response. Inflammatory mediators are released into the anterior chamber during cataract surgery and diffuse to the posterior segment of the eye.[20] These inflammatory mediators cause vasodilatation, increased vascular permeability and disruption of the blood-aqueous and blood-retinal barrier (BRB). CME develops when transudate accumulates in the outer plexiform and inner nuclear layers of the retina.

Manipulation during cataract surgery causes activation of phospholipase A2, which in turn deliberates arachidonic acid from cell membranes.[14] Cyclo-oxygenase (COX) and 5-lipoxygenase catalyze the conversion of arachidonic acid into eicosanoids, such as prostaglandins and leukotrienes.[21] COX is expressed in the anterior segment of the healthy

eye, including the ciliary body and the iris stroma, predominantly in the pupillary and iris root areas.[22] Furthermore, COX is expressed in the posterior segment, including the retinal endothelial cells, ganglion cells, Müller cells and retinal pigment epithelium cells.[23] Historically, prostaglandins were considered the main inflammatory mediators involved in the development of CME after cataract surgery. It is also reported that aqueous prostaglandin concentrations increase after femtosecond laser treatment as part of FLACS.[24] Prostaglandins modulate intraocular pressure, induce miosis, and disrupt the blood-ocular barrier.

Figure 3. Pathophysiology of cystoid macular edema after cataract surgery



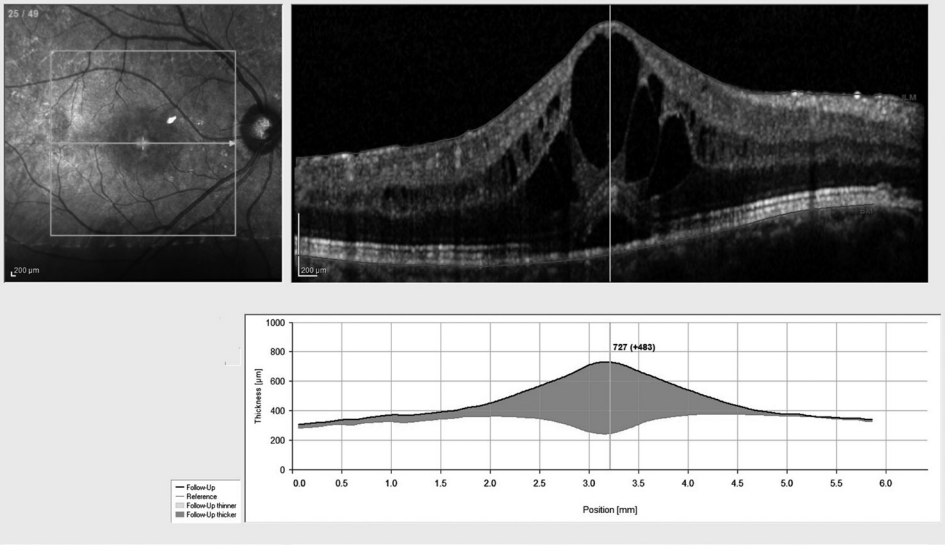
IL: interleukin; MCP: monocyte chemotactic protein; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor

Disruption of the blood-ocular barrier also results in leukocyte migration and production of other inflammatory mediators.[21, 23] Several studies report increased postoperative aqueous concentrations of interleukin 6 (IL-6), IL-8, monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α), when compared to preoperative levels.[25, 26] Other studies report increased perioperative aqueous humor concentrations of IL-1β, IL-6, IL-8, MCP-1, TNF-α and vascular endothelial growth factor (VEGF) in patients that went on to develop CME after surgery, as compared to patients who did not.[27, 28]

Optical coherence tomography

In the past, a clinical diagnosis of CME was confirmed using fluorescein angiography, which shows a petaloid pattern of fluid leakage surrounding the fovea. Nowadays, fluorescein angiography is mainly used to differentiate between various causes of CME. Since the 1990s, the primary diagnosis is made using optical coherence tomography (OCT), which provides high resolution cross-sections of the macula (see figure 4).[29, 30] The scanning speed of 20,000-50,000 A-scans per second makes this non-invasive technology very user-friendly.[31] Modern spectral domain (SD) OCT technology has a resolution of 10 µm in the lateral dimension and 5-7 µm in the axial direction.[31] Although macular thickness and volume measurements are considered reliable and reproducible, it should be noted that differences in software algorithms between SD-OCT devices may cause considerable variation in macular thickness calculations.[30, 31]

Figure 4. Optical coherence tomography image of cystoid macular edema after cataract surgery



Anti-inflammatory drugs

Although CME after cataract surgery may resolve spontaneously in the majority of cases, prevention of inflammation and CME is considered an essential step in postoperative care.[17, 32-35] Since CME is thought to be the result of a postoperative inflammatory response, anti-inflammatory drugs have long been used to prevent and treat CME after cataract surgery.[13] Novel anti-inflammatory agents, such as brimapitide (XG-102), have recently been studied in prevention of inflammation after cataract surgery, but have not been adopted to general practice yet.[36] By contrast, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been used for many years. The efficacy of anti-inflammatory eye drops depends on various pharmacological characteristics, including their ocular contact time; their ability to penetrate the cornea and diffuse into the aqueous humor, vitreous cavity and ocular tissues; as well as their ability to inhibit the production of inflammatory mediators.

Corticosteroids

Corticosteroids have traditionally been used to control and treat inflammation in the eye and other parts of the body. They inhibit a multiplicity of inflammatory mediators through inhibition of the enzyme phospholipase A2.[32] By inhibiting phospholipase, corticosteroids inhibit the COX pathway, as well as the lipoxygenase pathway.[14] Unfortunately, corticosteroids are also known for their potential complications, notably the development of an increased intraocular pressure.

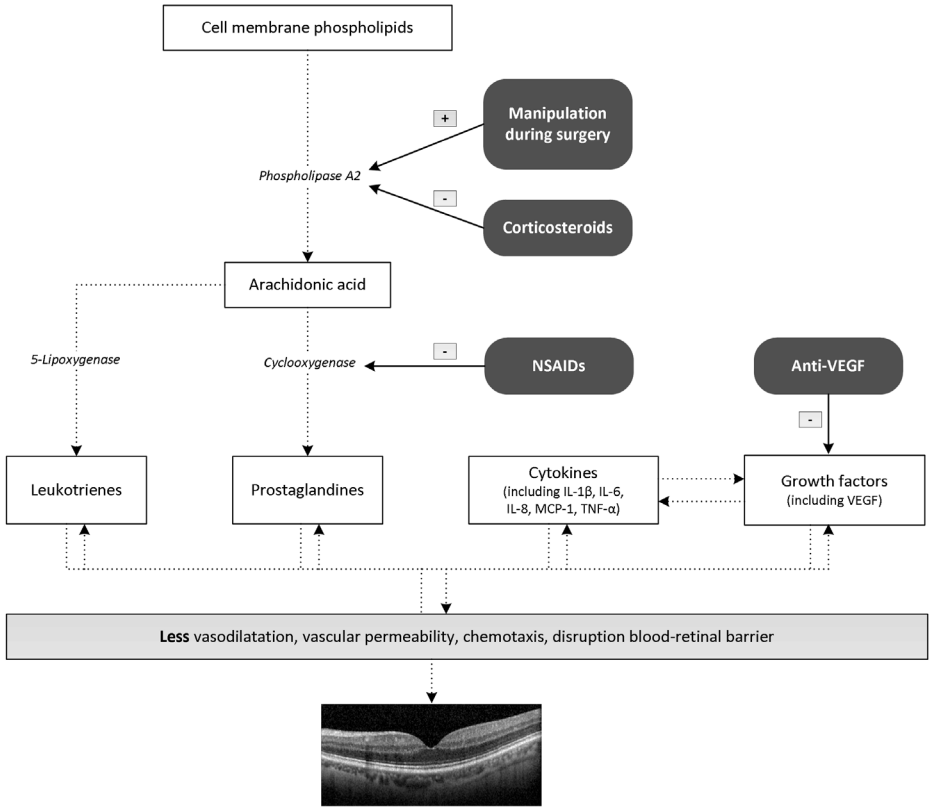
Corticosteroid eye drops, such as betamethasone, dexamethasone, fluorometholone, loteprednol and prednisolone, have been used in ophthalmology for many years. Most topical corticosteroids penetrate the eye through the cornea.[37] The ocular contact time of a corticosteroid can be increased by preparing the corticosteroid in a gel, microsuspension or viscous formulation.[38] Moreover, single drug administration is preferred over combination preparations such as tobramycin-dexamethasone, since previous studies report a reduced aqueous bioavailability of the corticosteroid, in case of concomitant application of an antibiotic drug.[39] Aqueous concentrations of topically applied fluorometholone are very low, when compared to other corticosteroid eye drops.[37] Although prednisolone eye drops result in the highest aqueous levels, dexamethasone and betamethasone are more potent anti-inflammatory corticosteroids with a greater binding affinity for the glucocorticoid receptors. The optimal corticosteroid concentration in treatment of ocular inflammatory diseases has to be investigated.[37, 38]

Non-steroidal anti-inflammatory drugs

More recently, NSAIDs have been used to treat ocular inflammation. NSAIDs inhibit the enzyme COX and thereby reduce prostaglandin synthesis during cataract surgery and

FLACS.[24] They inhibit prostaglandin synthesis in the anterior segment, vitreous and retina, and also reduce intraocular concentrations of other inflammatory mediators, such as VEGF and IL-12.[21, 40] NSAIDs are found to inhibit miosis during cataract surgery, reduce postoperative pain, and prevent the occurrence of inflammation and CME.[14, 21, 23, 40, 41]

Figure 5. Effects of anti-inflammatory drugs to prevent inflammation and cystoid macular edema after cataract surgery



IL: interleukin; MCP: monocyte chemotactic protein; NSAID: non-steroidal anti-inflammatory drug; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor

In the 1970s, indomethacin was the first NSAID to become available as an eye drop. Nowadays, many topical NSAIDs are available, such as bromfenac, diclofenac, flurbiprofen, ketorolac and nepafenac. Nepafenac is a prodrug that penetrates the cornea and is subsequently converted to amfenac by intraocular hydrolases.[42] It is approved by the European Medicines Agency (EMA) to prevent and treat pain and inflammation after cataract surgery

and to reduce the risk of developing CME after cataract surgery in diabetics.[43] The chemical structure of amfenac is identical to bromfenac, with the exception of one bromine atom. The EMA approved bromfenac eye drops for treatment of intraocular inflammation after cataract surgery.[44] Small studies compared the pharmacological characteristics of various topical NSAIDs, but were unable to report consistent results. The aqueous penetration of ketorolac is reported to be higher than the penetration of nepafenac and bromfenac.[42, 45] Topical bromfenac, nepafenac and ketorolac all diffuse into the vitreous humor to a measurable degree.[46] The availability in ocular tissues is reported to be highest after topical administration of bromfenac.[47] Bromfenac and amfenac are the most potent inhibitors of COX-2, which is considered the most important isoform of COX involved in inflammatory responses.[23, 47] By contrast, inhibition of vitreous prostaglandin production was lower after topical administration of ketorolac, when compared to nepafenac or bromfenac.[46, 48]

Anti-vascular endothelial growth factor

Intravitreal injection of anti-VEGFs, such as aflibercept, bevacizumab and ranibizumab, has become a powerful tool in prevention and treatment of retinal diseases. Previous studies have shown that VEGF causes a breakdown of the BRB and may play an important role in the development of CME after cataract surgery.[15] Monoclonal antibodies block VEGF production and are thought to reduce the risk of developing CME after cataract surgery. However, the use of intravitreal anti-VEGF injections to prevent and treat CME after cataract surgery remains controversial, given that the inhibition of other inflammatory mediators might be more effective.[15, 49]

Aim and outline of this thesis

CME is one of the most prevalent causes of suboptimal visual acuity after otherwise uncomplicated cataract surgery. For many years, ophthalmologists have tried to identify the optimal strategy to prevent the occurrence of postoperative CME, but guidelines vary between organizations and countries.[8, 34, 35] The current practice in prevention and treatment of CME after cataract surgery is discussed in more detail in **chapter 2**. This review describes the current evidence-based recommendations in preventing sustained visual impairment caused by CME after cataract surgery.

Chapter 3 reports the results of a systematic review, designed to systematically collect and summarize the current knowledge on the prevention of CME after cataract surgery. The study was performed according to the guidelines of the Cochrane collaboration and includes a structured meta-analysis to integrate the results of previous randomized controlled trials.[50] The review compares the efficacy of various pharmacological strategies to prevent CME within three months after cataract surgery, in diabetic and non-diabetic patients without CME preoperatively.

The PREvention of cystoid Macular EDema after cataract surgery (PREMED) study is a European multicenter trial, funded by the European Society of Cataract and Refractive Surgeons (ESCRS). The results of this study are presented in **chapters 4 and 5** of this thesis. The aim of the ESCRS PREMED study was to provide evidence-based recommendations that could be used for clinical guidelines on the prevention of CME after cataract surgery. ESCRS PREMED study report 1 compares the efficacy of topical bromfenac 0.09%, topical dexamethasone 0.1% and a combination of both in non-diabetic patients undergoing regular, uncomplicated phacoemulsification cataract surgery. ESCRS PREMED study report 2 aims to identify the optimal treatment in patients with diabetes mellitus. It is generally known that diabetics have a significantly increased risk of developing CME after cataract surgery, due to an increased permeability of the BRB.[18] ESCRS PREMED study report 2 compares the efficacy of a single subconjunctival injection with 40 mg triamcinolone acetonide, a single intravitreal injection with 1.25 mg bevacizumab, and a combination of both to prevent the occurrence of CME in these high risk patients.

Although CME after cataract surgery tends to resolve spontaneously in the majority of cases, chronic CME may produce anatomic alterations, causing sustained visual impairment.[51] Therefore, patients with CME after cataract surgery should be treated appropriately. The optimal treatment of CME after cataract surgery is explored in **chapter 6**, which describes the results of a systematic review. In accordance with the guidelines of the Cochrane collaboration, this systematic review summarizes the results of previous randomized controlled clinical trials on the treatment of CME after cataract surgery.

References

1 Global Initiative for the Elimination of Avoidable Blindness: action plan 2006-2011. World Health Organization, 2007
2 Lee CM, Afshari NA. The global state of cataract blindness. Curr Opin Ophthalmol 2017; 28: 98-103
3 Basic and Clinical Science Course™. American Academy of Ophthalmology
4 Pollreisz A, Schmidt-Erfurth U. Diabetic cataract-pathogenesis, epidemiology and treatment. J Ophthalmol 2010; 2010: 608751
5 Kanski JJ, Bowling B. Clinical Ophthalmology: A Systematic Approach,. Elsevier Health Sciences 2011
6 Webers VS, Visser N, Nuijts RM. [Development and future prospects of cataract surgery]. Ned Tijdschr Geneeskd 2015; 160: A9832
7 Wang W, Yan W, Fotis K, Prasad NM, Lansingh VC, Taylor HR, Finger RP, Facciolo D, He M. Cataract Surgical Rate and Socioeconomics: A Global Study. Invest Ophthalmol Vis Sci 2016; 57: 5872-5881
8 Cataracts in adults: management. National Institute for Health and Care Excellence: Clinical Guidelines 2017
9 Lundstrom M, Barry P, Henry Y, Rosen P, Stenevi U. Evidence-based guidelines for cataract surgery: guidelines based on data in the European Registry of Quality Outcomes for Cataract and Refractive Surgery database. J Cataract Refract Surg 2012; 38: 1086-1093
10 Endophthalmitis Study Group ESoC, Refractive S. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. J Cataract Refract Surg 2007; 33: 978-988
11 Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol 1953; 36: 599-619
12 Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. Arch Ophthalmol 1966; 76: 646-661
13 Shoss BL, Tsai LM. Postoperative care in cataract surgery. Curr Opin Ophthalmol 2013; 24: 66-73
14 Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. Drugs 2007; 67: 1291-1308
15 Ghasemi Falavarjani K, Parvaresh MM, Modarres M, Hashemi M, Samiy N. Intravitreal bevacizumab for pseudophakic cystoid macular edema; a systematic review. J Ophthalmic Vis Res 2012; 7: 235-239
16 Mentes J, Erakgun T, Afrashi F, Kerci G. Incidence of cystoid macular edema after uncomplicated phacoemulsification. Ophthalmologica 2003; 217: 408-412
17 Bradford JD, Wilkinson CP, Bradford RH, Jr. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. Retina 1988; 8: 161-164
18 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
19 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
20 Ersoy L, Caramoy A, Ristau T, Kirchhof B, Fauser S. Aqueous flare is increased in patients with clinically significant cystoid macular oedema after cataract surgery. Br J Ophthalmol 2013; 97: 862-865
21 Kim SJ, Toma HS, Barnett JM, Penn JS. Ketorolac inhibits choroidal neovascularization by suppression of retinal VEGF. Exp Eye Res 2010; 91: 537-543
22 Maihofner C, Schlotzer-Schrehardt U, Guhring H, Zeilhofer HU, Naumann GO, Pahl A, Mardin C, Tamm ER, Brune K. Expression of cyclooxygenase-1 and -2 in normal and glaucomatous human eyes. Invest Ophthalmol Vis Sci 2001; 42: 2616-2624
23 Semeraro F, Russo A, Gambicorti E, Duse S, Morescalchi F, Vezzoli S, Costagliola C. Efficacy and vitreous levels of topical NSAIDs. Expert Opin Drug Deliv 2015; 12: 1767-1782
24 Kiss HJ, Takacs AI, Kranitz K, Sandor GL, Toth G, Gilanyi B, Nagy ZZ. One-Day Use of Preoperative Topical Nonsteroidal Anti-Inflammatory Drug Prevents Intraoperative Prostaglandin Level Elevation During Femtosecond Laser-Assisted Cataract Surgery. Curr Eye Res 2016; 41: 1064-1067
25 Malecaze F, Chollet P, Cavrois E, Vita N, Arne JL, Ferrara P. Role of interleukin 6 in the inflammatory response after cataract surgery. An experimental and clinical study. Arch Ophthalmol 1991; 109: 1681-1683

26 Kawai M, Inoue T, Inatani M, Tsuboi N, Shobayashi K, Matsukawa A, Yoshida A, Tanihara H. Elevated levels of monocyte chemoattractant protein-1 in the aqueous humor after phacoemulsification. Invest Ophthalmol Vis Sci 2012; 53: 7951-7960

27 Dong N, Xu B, Wang B, Chu L, Tang X. Aqueous cytokines as predictors of macular edema in patients with diabetes following uncomplicated phacoemulsification cataract surgery. Biomed Res Int 2015; 2015: 126984

28 Funatsu H, Yamashita H, Noma H, Shimizu E, Mimura T, Hori S. Prediction of macular edema exacerbation after phacoemulsification in patients with nonproliferative diabetic retinopathy. J Cataract Refract Surg 2002; 28: 1355

29 Kim SJ, Bressler NM. Optical coherence tomography and cataract surgery. Curr Opin Ophthalmol 2009; 20: 46-51

30 Wolf-Schnurrbusch UE, Ceklic L, Brinkmann CK, Iliev ME, Frey M, Rothenbuehler SP, Enzmann V, Wolf S. Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. Invest Ophthalmol Vis Sci 2009; 50: 3432-3437

31 Sander B, Al-Abiji HA, Kofod M, Jorgensen TM. Do different spectral domain OCT hardwares measure the same? Comparison of retinal thickness using third-party software. Graefes Arch Clin Exp Ophthalmol 2015; 253: 1915-1921

32 Kessel L, Tendal B, Jorgensen KJ, Erngaard D, Flesner P, Andresen JL, Hjortdal J. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. Ophthalmology 2014; 121: 1915-1924

33 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

34 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

35 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

36 Chiquet C, Aptel F, Creuzot-Garcher C, Berrod JP, Kodjikian L, Massin P, Deloche C, Perino J, Kirwan BA, de Brouwer S, Combette JM, Behar-Cohen F. Postoperative Ocular Inflammation: A Single Subconjunctival Injection of XG-102 Compared to Dexamethasone Drops in a Randomized Trial. Am J Ophthalmol 2017; 174: 76-84

37 Awan MA, Agarwal PK, Watson DG, McGhee CN, Dutton GN. Penetration of topical and subconjunctival corticosteroids into human aqueous humour and its therapeutic significance. Br J Ophthalmol 2009; 93: 708-713

38 McGhee CN. Pharmacokinetics of ophthalmic corticosteroids. Br J Ophthalmol 1992; 76: 681-684

39 Leibowitz HM, Kupferman A. Drug interaction in the eye. Concurrent corticosteroid-antibiotic therapy for inflammatory keratitis. Arch Ophthalmol 1977; 95: 682-685

40 Medic A, Jukic T, Matas A, Vukojevic K, Sapunar A, Znaor L. Effect of preoperative topical diclofenac on intraocular interleukin-12 concentration and macular edema after cataract surgery in patients with diabetic retinopathy: a randomized controlled trial. Croat Med J 2017; 58: 49-55

41 Lim BX, Lim CH, Lim DK, Evans JR, Bunce C, Wormald R. Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery. Cochrane Database Syst Rev 2016; 11: CD006683

42 Bucci FA, Jr., Waterbury LD. A randomized comparison of to-aqueous penetration of ketorolac 0.45%, bromfenac 0.09% and nepafenac 0.1% in cataract patients undergoing phacoemulsification. Curr Med Res Opin 2011; 27: 2235-2239

43 Nepafenac. European public assessment report, summary for the public. European Medicines Agency (EMA), 2016

44 Bromfenac. European public assessment report, summary for the public. European Medicines Agency (EMA), 2017

45 Bucci FA, Jr., Waterbury LD. Aqueous prostaglandin E(2) of cataract patients at trough ketorolac and bromfenac levels after 2 days dosing. Adv Ther 2009; 26: 645-650

46 Heier JS, Awh CC, Busbee BG, Waterbury LD, Daniel P, Stoller GL, Cleary TS. Vitreous nonsteroidal antiinflammatory drug concentrations and prostaglandin E2 levels in vitrectomy patients treated with ketorolac 0.4%, bromfenac 0.09%, and nepafenac 0.1%. Retina 2009; 29: 1310-1313

47 Carreno E, Portero A, Galarreta DJ, Herreras JM. Update on twice-daily bromfenac sodium sesquihydrate to treat postoperative ocular inflammation following cataract extraction. Clin Ophthalmol 2012; 6: 637-644
48 Bucci FA, Jr., Waterbury LD. Prostaglandin E2 inhibition of ketorolac 0.45%, bromfenac 0.09%, and nepafenac 0.1% in patients undergoing phacoemulsification. Adv Ther 2011; 28: 1089-1095
49 Roh MI, Kim HS, Song JH, Lim JB, Kwon OW. Effect of intravitreal bevacizumab injection on aqueous humor cytokine levels in clinically significant macular edema. Ophthalmology 2009; 116: 80-86
50 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration, 2011
51 Hunter AA, Modjtahedi SP, Long K, Zawadzki R, Chin EK, Caspar JJ, Morse LS, Telander DG. Improving visual outcomes by preserving outer retina morphology in eyes with resolved pseudophakic cystoid macular edema. J Cataract Refract Surg 2014; 40: 626-631

Chapter 2

Introduction part 2:
Prevention of macular edema after cataract surgery

Laura H.P. Wielders, Jan S.A.G. Schouten, Rudy M.M.A. Nuijts

Curr Opin Ophthalmol. 2018 Jan;29(1):48-53

Abstract

Purpose of review: Although cataract surgery can effectively restore visual function in many patients with cataract, pseudophakic cystoid macular edema (PCME) remains an important cause of suboptimal visual acuity. The present review provides an overview of the current literature on the prevention and treatment of PCME.

Recent findings: Optimal prevention of PCME starts preoperatively with a personalized risk assessment. Diabetes mellitus, retinal vein occlusion, epiretinal membrane, macular hole and uveitis are the most important risk factors for developing cystoid macular edema after cataract surgery. Topical non-steroidal anti-inflammatory drugs (NSAIDs) either in addition to, or instead of, topical corticosteroids reduce the risk of developing PCME. Additional intravitreal corticosteroid and anti-vascular endothelial growth factor injections have been studied in diabetics. Timely diagnosis and treatment of PCME is essential. Topical NSAIDs solely, or in addition to corticosteroids, improve visual acuity in patients with PCME. Oral acetazolamide and intravitreal dexamethasone implants have been used in refractory cases.

Summary: Topical NSAIDs can be used solely, or in combination with topical corticosteroids, to prevent and treat PCME. Further research is needed to compare the efficacy of various NSAIDs, and to investigate the cost-effectiveness and long-term benefit of anti-inflammatory treatments on visual acuity, contrast sensitivity and quality of life.

Introduction on prevention of PCME

Worldwide, cataract remains an important cause of visual impairment and blindness. Severe cataract resulted in moderate to severe visual impairment in 35.2 million people in 2010, and caused blindness in 10.8 million people.[1] Cataract surgery is one of the most commonly performed surgical procedures and can effectively restore visual function.[2] Although recent advances in cataract surgery techniques have significantly decreased the incidence of postoperative complications, cystoid macular edema (CME) remains an important cause of suboptimal visual acuity.[3] Optical coherence tomography is considered the most sensitive method to detect and monitor CME, but this technique cannot distinguish between various underlying causes of the edema. Optic nerve staining on fluorescein angiography is a typical sign that can help to distinguish pseudophakic cystoid macular edema (PCME) from other causes of CME, such as diabetic macular edema.[3, 4] PCME, also known as the Irvine-Gass syndrome, is reported in 1.17-4.2% of cases, depending on the diagnostics and definitions used.[5-10] Most cases of PCME develop within three months after cataract surgery, with a peak incidence at four to six weeks postoperatively.[3, 5]

The present review summarizes recent literature on the prevention and treatment of CME after uncomplicated phacoemulsification cataract surgery in adult patients.

Pathophysiology

PCME is thought to be the result of a postoperative inflammatory response. Most research on the pathogenesis of PCME has focused on the role of prostaglandins, but other inflammatory mediators, such as vascular endothelial growth factor (VEGF) and various cytokines, have recently generated widespread interest.[11-13] Surgical manipulation during cataract surgery is thought to stimulate the production of inflammatory mediators from uveal tissue in the anterior segment, causing a disruption of the blood-aqueous and blood-retinal barrier (BRB). Subsequently, transudate accumulates in the outer plexiform and inner nuclear layers of the retina, and PCME develops.[14]

Risk factors

Prevention of CME after cataract surgery should ideally begin with a personalized preoperative risk assessment for each individual patient. The risk of developing CME after cataract surgery is influenced by many patient characteristics, notably diabetes mellitus, which remains the most well-known. A recent cohort study of Chu *et al*. has shown that the incidence of CME after cataract surgery is four times higher in diabetics, with an incidence rate of 4.04%. Moreover, this study reported a near linear trend between the severity of diabetic retinopathy and the risk of developing CME after cataract surgery. The study found an overall relative risk (RR) of 6.23 (95% confidence interval [95% CI]: 5.12-

7.58) when comparing patients with any diabetic retinopathy to non-diabetics. However, even diabetic patients without diabetic retinopathy had a significantly increased risk of developing CME. Preexisting impaired BRB function has been implicated as one of the main reasons for this. Previous panretinal photocoagulation did not reduce the risk of developing CME after cataract surgery.[7] As shown in table 1, longer duration of diabetes mellitus and insulin dependence were identified as additional risk factors.[15]

Retinal vein occlusion (RVO) is the second major risk factor for developing CME after cataract surgery, especially in patients who previously required treatment for RVO-associated CME.[16] Large cohort studies have also shown an increased risk in the presence of an epiretinal membrane, macular hole and uveitis.[5-7, 17] Moreover, patients who previously developed PCME in the contralateral eye demonstrate an increased risk.[6]

Contradicting statements have been made as to whether age, male gender, ethnicity or the use of prostaglandin analogues should be considered a risk factor.[5-7, 17-20] Dry age-related macular degeneration, glaucoma, retinitis pigmentosa, status of the posterior vitreous and high myopia were not identified as significant risk factors, nor were systemic factors, such as hypertension and ischemic heart disease.[5-8, 17, 20]

Complicated cataract surgery increases the risk of developing PCME. Moreover, significantly higher cumulative dissipated energy levels were found in patients who developed PCME.[8] Femtosecond laser assisted cataract surgery has not been implicated as an important risk factor, as were surgeon experience, pupil size and the use of 1 mg/0.1 ml intracameral cefuroxime.[7, 21, 22]

Table 1. Key risk factors for developing CME after cataract surgery

Ophthalmic comorbidity	Diabetic patients
Retinal vein occlusion	Higher grade of DR
Uveitis	Insulin dependence
PCME in the contralateral eye	Longer duration of DM
Epiretinal membrane	
Macular hole	

CME: cystoid macular edema; DM: diabetes mellitus; DR: diabetic retinopathy; PCME: pseudophakic cystoid macular edema

Prevention

Shortly after the first clinical description of PCME, ophthalmologists investigated the use of anti-inflammatory agents to prevent its occurrence.[23] As early as 1998, the results of a systematic review confirmed that prophylactic anti-inflammatory interventions are effective in reducing the risk of developing PCME.[24] Since then, ophthalmologists aim to identify

the optimal anti-inflammatory strategy before and after cataract surgery. Although topical corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in clinical practice, there still remains a lack of high quality evidence as to which treatment is the most effective. As a result, standard practice varies between organizations and countries, and remarkable contrasts can be seen between clinical recommendations of leading authorities, such as the American Society of Cataract and Refractive Surgery (ASCRS) and the American Academy of Ophthalmology (AAO).[25, 26]

A recent Cochrane review has investigated whether prophylactic use of topical NSAIDs either in addition to, or instead of, topical corticosteroids reduces the incidence of CME after cataract surgery. The results of this systematic review and meta-analysis suggest that topical NSAIDs are more effective than topical corticosteroids in reducing the risk of developing CME after cataract surgery (RR 0.27, 95% CI: 0.18-0.41). The authors also found evidence supporting the use of topical NSAIDs in addition to topical corticosteroids, but the quality of evidence was low. At three months postoperatively, the authors found a lower risk of developing poor vision due to CME in patients treated with a combination of both drugs, as compared to patients receiving only a topical corticosteroid (RR 0.41, 95%CI: 0.23-0.76). There were no significant differences with regard to mean visual acuity at three months after cataract surgery, consequently it remains unclear whether the use of topical NSAIDs improves visual function and quality of life.[27] Other meta-analyses found similar results, suggesting that topical NSAIDs either in addition to, or instead of, topical corticosteroids reduce the risk of developing CME after cataract surgery, whereas the effect on visual acuity remains unclear.[28-30] Only few studies have directly compared the efficacy of topical NSAIDs versus combination treatment with a topical NSAID and corticosteroid. Based on the results of an indirect treatment comparison, it remains unclear whether the use of corticosteroid eye drops can be avoided.[28]

Topical NSAIDs decrease the production of prostaglandins by inhibiting the enzyme cyclooxygenase (COX). Consequently, the efficiency of COX inhibition can be improved if NSAIDs are applied before the surgical trauma occurs. Two studies demonstrated less inflammation and a significant reduction in the incidence of PCME if patients started topical NSAIDs three days preoperatively.[31, 32]

Now that numerous studies and meta-analyses have established the benefit of NSAID eye drops before and after cataract surgery, ophthalmologists aim to identify the most effective NSAID preparation. A recent network analysis suggests that diclofenac is the most effective NSAID to reduce inflammation and flare after cataract surgery, followed by nepafenac, ketorolac, bromfenac and flurbiprofen. However, the authors report that most of the network comparisons were based on low-quality evidence and caution should

be taken interpreting the results.[33] Furthermore, the review did not investigate the efficacy of various NSAID preparations on postoperative CME. A pilot study including only twenty patients, suggests that bromfenac is more effective than nepafenac in preventing PCME.[34] A recent study by Lee *et al*. suggests that topical ketorolac was more effective than diclofenac in preventing macular thickening after cataract surgery.[35] Other studies could not find statistically significant differences between ketorolac and nepafenac, ketorolac and bromfenac or between ketorolac and indomethacin.[36-41]

Prevention in diabetics

Diabetes mellitus is a widely accepted risk factor for developing CME after cataract surgery and has been an important subject of investigation. Analogous to the non-diabetic population, topical NSAIDs seem to be useful in preventing CME after cataract surgery in diabetic patients. A combination of topical NSAIDs and corticosteroids significantly reduced the odds of developing CME and improved visual acuity, as compared to topical corticosteroid treatment.[28, 42-44] Several studies found that the risk of developing CME in diabetics can be further reduced if topical NSAID and corticosteroid treatment is continued for three months postoperatively.[5, 43]

While topical treatments are commonly used after standard phacoemulsification cataract surgery, recent studies have evaluated the efficacy of additional intravitreal treatments in diabetic patients. Ahmadabadi *et al*. investigated the efficacy of intravitreal 2 mg triamcinolone acetonide, in addition to topical corticosteroids, to further reduce the risk of developing CME after cataract surgery in patients with moderate non-proliferative diabetic retinopathy. No eyes in the triamcinolone acetonide group developed CME after cataract surgery, as compared to four eyes (19%) in the control group. Central subfield macular thickness remained significantly lower in the triamcinolone acetonide group until six months postoperatively.[45]

Because recent studies suggest a key role for VEGF in the pathogenesis of CME after cataract surgery, intravitreal anti-VEGF injections have generated considerable clinical interest. Udaondo *et al*. evaluated the efficacy of 0.5 ml ranibizumab, in addition to topical dexamethasone eye drops, in 54 eyes with mild to moderate diabetic retinopathy, but no diabetic macular edema, undergoing regular phacoemulsification cataract surgery. This study demonstrated a reduction in the incidence of CME in patients treated with ranibizumab. Only one patient (3.7%) in the ranibizumab group developed clinically significant CME at three months postoperatively, as compared to six patients (22.2%) in the control group.[46]

Treatment

Although acute CME resolves spontaneously in the majority of cases, timely diagnosis and adequate treatment are necessary to prevent anatomic alterations and sustained visual impairment.[4] Visual acuity may improve after resolution of PCME as long as septas of healthy retinal tissue persist between the cystic spaces, and if the photoreceptor inner segment/outer segment (IS/OS) layer of the retina remains intact.[47] Unfortunately, little is known about the natural course of PCME after modern phacoemulsification cataract surgery. Previous studies have shown that a longer duration of PCME decreases final visual acuity.[48] Nevertheless, there are no evidence-based recommendations as to which patients should be treated, nor about the optimum postoperative timing of treatment initiation.

Flach *et al*. showed that, in patients with chronic PCME, topical NSAIDs improve visual acuity within 30-90 days. Although visual acuity may decrease after cessation of treatment, visual acuity recovered in most patients after retreatment with NSAID eye drops.[49, 50] Moreover, small studies suggest that a combination treatment with a topical corticosteroid and NSAID is more effective than a topical corticosteroid alone. The time to resolution of PCME was significantly shorter in patients treated with a combination of topical corticosteroids and NSAIDs.[5, 51] Recently, it was shown that an increased frequency of topical corticosteroid administration, in addition to topical NSAIDs, improves the resolution of PCME. Patients using topical prednisolone every hour while awake had superior results regarding retinal thickness and visual acuity, as compared to patients using prednisolone only four times daily.[52] No significant differences were identified between various NSAID preparations.[53, 54] Furthermore, various systemic and intraocular treatments have been used in patients with refractive PCME, unresponsive to topical NSAIDs and corticosteroids. Oral acetazolamide, in addition to topical anti-inflammatory treatment, supports the resolution of PCME.[55] Promising results are also shown with regard to intravitreal corticosteroid implants.[56] A single intravitreal dexamethasone implant produced a larger decrease in retinal thickness, as compared to repeated intravitreal triamcinolone acetonide injections. However, there were no significant differences with regard to final visual acuity.[57] The effect of intravitreal anti-VEGF injections, such as bevacizumab and aflibercept, remains controversial as recent case series have shown variable results in treatment of PCME.[58-61] A recent case report on the use of intravitreal ketorolac, found no significant effect of visual acuity and macular thickness.[62]

Conclusions

Approximately 1-4% of patients develop CME after modern phacoemulsification cataract surgery, which is why PCME remains an important cause of suboptimal postoperative visual acuity. Diabetes mellitus is the most important risk factor for developing CME after cataract surgery. The severity of diabetic retinopathy, a longer duration of diabetes mellitus and insulin dependence were identified as additional risk factors. Other important risk factors include the presence of an epiretinal membrane, macular hole, RVO, uveitis or the development of PCME in the contralateral eye.

Previous studies have shown that topical NSAIDs either in addition to, or instead of, topical corticosteroids reduce the risk of developing PCME. Prophylactic treatment should ideally start a few days before surgery and should be continued for at least three months postoperatively in high-risk patients, including diabetics. Further research is needed to determine the long-term benefit of topical NSAIDs and corticosteroids on visual acuity, contrast-sensitivity and patient-related quality of life.

Whereas PCME resolves spontaneously in the majority of patients, previous studies have also shown that final visual acuity decreases if PCME exists for a longer period of time. The optimum postoperative moment for treatment initiation remains to be identified. Topical NSAIDs, with or without corticosteroids, improve visual acuity in patients with acute and chronic PCME. Oral acetazolamide and intravitreal dexamethasone implants can be used in refractory cases, whereas the effect of intravitreal anti-VEGF injections remains controversial.

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 Wang W, Yan W, Fotis K, Prasad NM, Lansingh VC, Taylor HR, Finger RP, Facciolo D, He M. Cataract Surgical Rate and Socioeconomics: A Global Study. Invest Ophthalmol Vis Sci 2016; 57: 5872-5881

3 Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol 2012; 23: 26-32

4 Shelsta HN, Jampol LM. Pharmacologic therapy of pseudophakic cystoid macular edema: 2010 update. Retina 2011; 31: 4-12

5 Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg 2007; 33: 1550-1558

6 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

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 Anastasilakis K, Mourgela A, Symeonidis C, Dimitrakos SA, Ekonomidis P, Tsinopoulos I. Macular edema after uncomplicated cataract surgery: a role for phacoemulsification energy and vitreoretinal interface status? Eur J Ophthalmol 2015; 25: 192-197

9 Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol 1953; 36: 599-619

10 Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. Arch Ophthalmol 1966; 76: 646-661

11 Funatsu H, Yamashita H, Noma H, Shimizu E, Mimura T, Hori S. Prediction of macular edema exacerbation after phacoemulsification in patients with nonproliferative diabetic retinopathy. J Cataract Refract Surg 2002; 28: 1355

12 Dong N, Xu B, Wang B, Chu L, Tang X. Aqueous cytokines as predictors of macular edema in patients with diabetes following uncomplicated phacoemulsification cataract surgery. Biomed Res Int 2015; 2015: 126984

13 Malecaze F, Chollet P, Cavrois E, Vita N, Arne JL, Ferrara P. Role of interleukin 6 in the inflammatory response after cataract surgery. An experimental and clinical study. Arch Ophthalmol 1991; 109: 1681-1683

14 Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. Drugs 2007; 67: 1291-1308

15 Yang J, Cai L, Sun Z, Ye H, Fan Q, Zhang K, Lu W, Lu Y. Risk factors for and diagnosis of pseudophakic cystoid macular edema after cataract surgery in diabetic patients. J Cataract Refract Surg 2017; 43: 207-214

16 Cho HJ, Hwang HJ, Kim HS, Lee DW, Kim CG, Kim BY, Kim JW. Macular Edema after Cataract Surgery in Eyes with Preoperative Retinal Vein Occlusion. Retina 2017

17 Shorstein NH, Liu L, Waxman MD, Herrinton LJ. Comparative Effectiveness of Three Prophylactic Strategies to Prevent Clinical Macular Edema after Phacoemulsification Surgery. Ophthalmology 2015; 122: 2450-2456

18 Lee KM, Lee EJ, Kim TW, Kim H. Pseudophakic Macular Edema in Primary Open-Angle Glaucoma: A Prospective Study Using Spectral-Domain Optical Coherence Tomography. Am J Ophthalmol 2017; 179: 97-109

19 Hernstadt DJ, Husain R. Effect of prostaglandin analogue use on the development of cystoid macular edema after phacoemulsification using STROBE statement methodology. J Cataract Refract Surg 2017; 43: 564-569

20 Oyewole K, Tsogkas F, Westcott M, Patra S. Benchmarking cataract surgery outcomes in an ethnically diverse and diabetic population: final post-operative visual acuity and rates of post-operative cystoid macular oedema. Eye (Lond) 2017

21 Ma B, Liu Y, Liu S, Luo M. Evaluation of the effect of intracameral cefuroxime on macular and subfoveal choroidal thickness and macular sensitivity in diabetic patients after cataract surgery. J Cataract Refract Surg 2017; 43: 201-206

22 Ye Z, Li Z, He S. A Meta-Analysis Comparing Postoperative Complications and Outcomes of Femtosecond Laser-Assisted Cataract Surgery versus Conventional Phacoemulsification for Cataract. J Ophthalmol 2017; 2017: 3849152

23 Waitzman MB. Topical indomethacin in treatment and prevention of intraocular inflammation--with special reference to lens extraction and cystoid macular edema. Ann Ophthalmol 1979; 11: 489-491
24 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
25 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
26 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
27 Lim BX, Lim CH, Lim DK, Evans JR, Bunce C, Wormald R. Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery. Cochrane Database Syst Rev 2016; 11: CD006683
28 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
29 Kessel L, Tendal B, Jorgensen KJ, Erngaard D, Flesner P, Andresen JL, Hjortdal J. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. Ophthalmology 2014; 121: 1915-1924
30 Juthani VV, Clearfield E, Chuck RS. Non-steroidal anti-inflammatory drugs versus corticosteroids for controlling inflammation after uncomplicated cataract surgery. Cochrane Database Syst Rev 2017; 7: CD010516
31 Donnenfeld ED, Perry HD, Wittpenn JR, Solomon R, Nattis A, Chou T. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: pharmacokinetic-response curve. J Cataract Refract Surg 2006; 32: 1474-1482
32 Yavas GF, Ozturk F, Kusbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. J Cataract Refract Surg 2007; 33: 804-807
33 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
34 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
35 Lee TH, Choi W, Ji YS, Yoon KC. Comparison of ketorolac 0.45% versus diclofenac 0.1% for macular thickness and volume after uncomplicated cataract surgery. Acta Ophthalmol 2016; 94: e177-182
36 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
37 Almeida DR, Khan Z, Xing L, Bakar SN, Rahim K, Urton T, El-Defrawy SR. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. J Cataract Refract Surg 2012; 38: 1537-1543
38 Weber M, Kodjikian L, Kruse FE, Zagorski Z, Allaire CM. Efficacy and safety of indomethacin 0.1% eye drops compared with ketorolac 0.5% eye drops in the management of ocular inflammation after cataract surgery. Acta Ophthalmol 2013; 91: e15-21
39 Tzelikis PF, Vieira M, Hida WT, Motta AF, Nakano CT, Nakano EM, Alves MR. Comparison of ketorolac 0.4% and nepafenac 0.1% for the prevention of cystoid macular oedema after phacoemulsification: prospective placebo-controlled randomised study. Br J Ophthalmol 2015; 99: 654-658
40 Jung JW, Chung BH, Kim EK, Seo KY, Kim TI. The Effects of Two Non-Steroidal Anti-Inflammatory Drugs, Bromfenac 0.1% and Ketorolac 0.45%, on Cataract Surgery. Yonsei Med J 2015; 56: 1671-1677
41 Ramakrishnan S, Baskaran P, Talwar B, Venkatesh R. Prospective, Randomized Study Comparing the Effect of 0.1% Nepafenac and 0.4% Ketorolac Tromethamine on Macular Thickness in Cataract Surgery Patients With Low Risk for Cystoid Macular Edema. Asia Pac J Ophthalmol (Phila) 2015; 4: 216-220
42 Pollack A, Staurenghi G, Sager D, Mukesh B, Reiser H, Singh RP. Prospective randomised clinical trial to evaluate the safety and efficacy of nepafenac 0.1% treatment for the prevention of macular oedema associated with cataract surgery in patients with diabetic retinopathy. Br J Ophthalmol 2017; 101: 423-427
43 Singh RP, Staurenghi G, Pollack A, Adewale A, Walker TM, Sager D, Lehmann R. Efficacy of nepafenac ophthalmic suspension 0.1% in improving clinical outcomes following cataract surgery in patients with diabetes: an analysis of two randomized studies. Clin Ophthalmol 2017; 11: 1021-1029

44 Singh RP, Lehmann R, Martel J, Jong K, Pollack A, Tsorbatzoglou A, Staurenghi 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
45 Ahmadabadi HF, Mohammadi M, Beheshtnejad H, Mirshahi A. Effect of intravitreal triamcinolone acetonide injection on central macular thickness in diabetic patients having phacoemulsification. J Cataract Refract Surg 2010; 36: 917-922
46 Udaondo P, Garcia-Pous M, Garcia-Delpech S, Salom D, Diaz-Llopis M. Prophylaxis of macular edema with intravitreal ranibizumab in patients with diabetic retinopathy after cataract surgery: a pilot study. J Ophthalmol 2011; 2011: 159436
47 Yuksel B, Uzunel UD, Kerci SG, Sagban L, Kusbeci T, Orsel T. Comparison of Subtenon Triamcinolone Acetonide Injection with Topical Nepafenac for the Treatment of Pseudophakic Cystoid Macular Edema. Ocul Immunol Inflamm 2016: 1-7
48 Wielders LH, Schouten JS, Aberle MR, Lambermont VA, van den Biggelaar FJ, Winkens B, Simons RW, Nuijts RM. Treatment of cystoid macular edema after cataract surgery. J Cataract Refract Surg 2017; 43: 276-284
49 Flach AJ, Dolan BJ, Irvine AR. Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. Am J Ophthalmol 1987; 103: 479-486
50 Flach AJ, Jampol LM, Weinberg D, Kraff MC, Yannuzzi LA, Campo RV, Neumann AC, Cupples HP, Lefler WH, Pulido JS, *et al*. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. Am J Ophthalmol 1991; 112: 514-519
51 Heier JS, Topping TM, Baumann W, Dirks MS, Chern S. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. Ophthalmology 2000; 107: 2034-2038;discussion 2039
52 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
53 Warren KA, Bahrani H, Fox JE. NSAIDs in combination therapy for the treatment of chronic pseudophakic cystoid macular edema. Retina 2010; 30: 260-266
54 Rho DS. Treatment of acute pseudophakic cystoid macular edema: Diclofenac versus ketorolac. J Cataract Refract Surg 2003; 29: 2378-2384
55 Curkovic T, Vukojevic N, Bucan K. Treatment of pseudophakic cystoid macular oedema. Coll Antropol 2005; 29 Suppl 1: 103-105
56 Sacchi M, Villani E, Gilardoni F, Nucci P. Efficacy of intravitreal dexamethasone implant for prostaglandin-induced refractory pseudophakic cystoid macular edema: case report and review of the literature. Clin Ophthalmol 2014; 8: 1253-1257
57 Dang Y, Mu Y, Li L, Mu Y, Liu S, Zhang C, Zhu Y, Xu Y. Comparison of dexamethasone intravitreal implant and intravitreal triamcinolone acetonide for the treatment of pseudophakic cystoid macular edema in diabetic patients. Drug Des Devel Ther 2014; 8: 1441-1449
58 Lin CJ, Tsai YY. Use of Aflibercept for the Management of Refractory Pseudophakic Macular Edema in Irvine-Gass Syndrome and Literature Review. Retin Cases Brief Rep 2016
59 Barone A, Russo V, Prascina F, Delle Noci N. Short-term safety and efficacy of intravitreal bevacizumab for pseudophakic cystoid macular edema. Retina 2009; 29: 33-37
60 Arevalo JF, Maia M, Garcia-Amaris RA, Roca JA, Sanchez JG, Berrocal MH, Wu L, Pan-American Collaborative Retina Study G. Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. Ophthalmology 2009; 116: 1481-1487, 1487 e1481
61 Spitzer MS, Ziemssen F, Yoeruek E, Petermeier K, Aisenbrey S, Szurman P. Efficacy of intravitreal bevacizumab in treating postoperative pseudophakic cystoid macular edema. J Cataract Refract Surg 2008; 34: 70-75
62 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

Chapter 3

Prevention of cystoid macular edema after cataract surgery in non-diabetic and diabetic patients: a systematic review and meta-analysis

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Abstract

Purpose: To evaluate the optimum medical strategy to prevent cystoid macular edema (CME) after cataract surgery.

Design: Systematic review and meta-analysis.

Methods: *Setting:* Cochrane, MEDLINE and EMBASE databases were searched to identify eligible randomized controlled trials (RCTs). *Study population:* RCTs comparing medical strategies to prevent CME after uncomplicated cataract surgery in non-diabetic and diabetic patients. *Observation procedures:* Data was extracted by two authors independently. Quality of individual RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias and Delphi criteria. *Main outcome measures:* Odds of developing CME within three months postoperatively and foveal thickness, macular volume and corrected distance visual acuity change within three months postoperatively, as compared to baseline.

Results: Seventeen trials reported incidence rates. Topical non-steroidal anti-inflammatory drugs (NSAIDs) significantly reduced the odds of developing CME as compared to topical corticosteroids in non-diabetic (odds ratio (OR) 0.11; 95% confidence interval (95% CI) 0.03-0.37) and mixed populations (OR 0.05; 95% CI 0.02-0.11). A combination of topical corticosteroids and NSAIDs significantly reduced the odds of developing CME as compared to topical corticosteroids in non-diabetic (OR 0.21; 95% CI 0.10-0.44) and diabetic patients (OR 0.17; 95% CI 0.05-0.50). Intravitreal corticosteroid or anti-vascular endothelial growth factor injections did not show any additional benefit in diabetics.

Conclusions: Topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids in non-diabetic and mixed populations. A combination of topical NSAIDs and corticosteroids reduced the odds of developing CME in non-diabetic and diabetic patients, as compared to topical corticosteroids.

Introduction

For many decades, cataract has been the leading cause of blindness in the world. A major current focus in cataract surgery is how to minimize complications and improve postoperative visual recovery. Over the years, the incidence of complications has significantly decreased owing to more advanced surgical techniques. Nowadays, cystoid macular edema (CME) is one of the most prevalent postoperative complications after otherwise uncomplicated cataract surgery.

CME after cataract surgery was first reported in 1953 and is also known as the Irvine-Gass syndrome.[1,2] It usually develops within three months postoperatively, with a peak incidence at four to six weeks after surgery.[3,4] It is considered the most important cause of suboptimal visual acuity within the first weeks postoperatively and strongly affects early recovery. Although CME has been reported in up to 23% of non-diabetic subjects after regular uncomplicated cataract surgery, most cases are self-limiting and patients experience no or only minimal reduction in visual acuity.[5-8] Approximately 0-6% of non-diabetic subjects develops visual complaints and suffer from clinically significant macular edema (CSME).[5,7,9] In contrast, incidence rates of CSME are up to 56% in diabetic patients with mild to moderate non-proliferative diabetic retinopathy (NPDR) and no CME preoperatively.[5,10-12]

In 1998, a review by Rossetti and associates reported that prophylactic anti-inflammatory interventions are effective in reducing the incidence of CME after cataract surgery.[8] Since then, many treatments have been studied in order to identify the optimal preventive treatment. Recently, Kessel and associates compared the efficacy of topical corticosteroids and topical non-steroidal anti-inflammatory drugs (NSAIDs) in controlling postoperative inflammation and preventing CME after uncomplicated cataract surgery in non-diabetic patients.[13] The systematic review showed less postoperative inflammation and less CME in the NSAID group. This study, however, did not compare any other intervention and did not address the efficacy in diabetic patients.

This systematic review was designed to collect and summarize the results of randomized controlled trials (RCTs) on the prevention of CME after cataract surgery. The current study compares the efficacy of preventive strategies on the odds of developing CME within three months after uncomplicated phacoemulsification cataract surgery with posterior chamber intraocular lens implantation in non-diabetic and diabetic patients with age-related cataract, without CME preoperatively and with no predisposing factors for developing CME. A meta-analysis and indirect treatment comparison was performed to compare the efficacy of various preventive treatments.

Methods

The systematic review and meta-analysis was designed using the guidelines of the Cochrane Handbook and result were reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[14,15] In accordance with Dutch guidelines, the medical ethics committee of the University Hospital Maastricht and Maastricht University decided that no institutional review board approval was required for this study.

Systematic review process

The Cochrane Library (1992 to present), MEDLINE (OVID, 1946 to present) and EMBASE (1947 to present) databases were searched in June 2013 and an update was conducted in July 2014. All search strategies included a combination of text words, including text words for cataract extraction (cataract extr*, phaco*), macular edema (irvine gass, edema, oedema) and study design (random*). The complete search strategy for the MEDLINE database is shown in appendix 1. Similar search strategies were used for the Cochrane Library and EMBASE databases. To prevent exclusion of eligible articles, there were no language, publication status or date restrictions. Reference lists of all included trials and previously published reviews were searched for additional RCTs by two review authors (L.W. and V.L.) independently. No trial registries were searched for unpublished trials and no study authors were contacted to identify additional studies. All records identified were managed using Endnote X7.

Titles and abstracts were scanned for eligibility by two review authors (L.W. and V.L.) independently. Discrepancies were resolved by discussion between the two authors. Full articles were obtained for all relevant abstracts and were reviewed by the two authors for eligibility. Both were unmasked to authors, journal, institution and trial results during the assessment. In order to provide a complete overview of the available evidence, all RCTs comparing at least two preventive strategies of any type, dosage or form, were included in this systematic review. The authors excluded trials investigating the prevention of CME after intracapsular or extracapsular cataract extraction, and trials including patients with preoperative CME or a high risk of developing CME postoperatively. Trials investigating the treatment of CME were also excluded.

Data extraction

All data were extracted in duplicate by two authors (L.W. and V.L.) independently. A standard data extraction form was used, including the following items: study size, funding sources, eligibility criteria, type of participants, type of interventions, follow-up period, outcome definition, retinal thickness classified according to the Early Treatment Diabetic

Retinopathy Study (ETDRS) retinal thickness map, macular volume (MV) and corrected distance visual acuity (CDVA).

All preventive strategies were classified into predefined treatment groups based on type of intervention and mode of administration (e.g. topical corticosteroids or subconjunctival corticosteroids). All preoperative, intraoperative and postoperative treatments were taken into account, except for once-only intraoperative eye drops that were thought not to influence the effect of additional preventive strategies. If an article included multiple study arms within the same treatment group, these arms were combined by adding the total number of participants in each group.

Risk of bias and quality of the included trials were assessed on study level by two reviewers independently of each other, using the Cochrane Collaboration's tool for assessing risk of bias and Delphi criteria. The Delphi list assesses the quality of RCTs based on treatment allocation (randomization and allocation concealment); baseline prognostic factors; eligibility criteria; masking of outcome assessors, care providers and patients; presentation of point estimates and measures of variability; and inclusion of an intention to treat-analysis.[16] The Cochrane Collaboration's tool for assessing risk of bias assesses various types of bias, including selection bias (sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); and other sources of bias.[14]

Meta-analysis

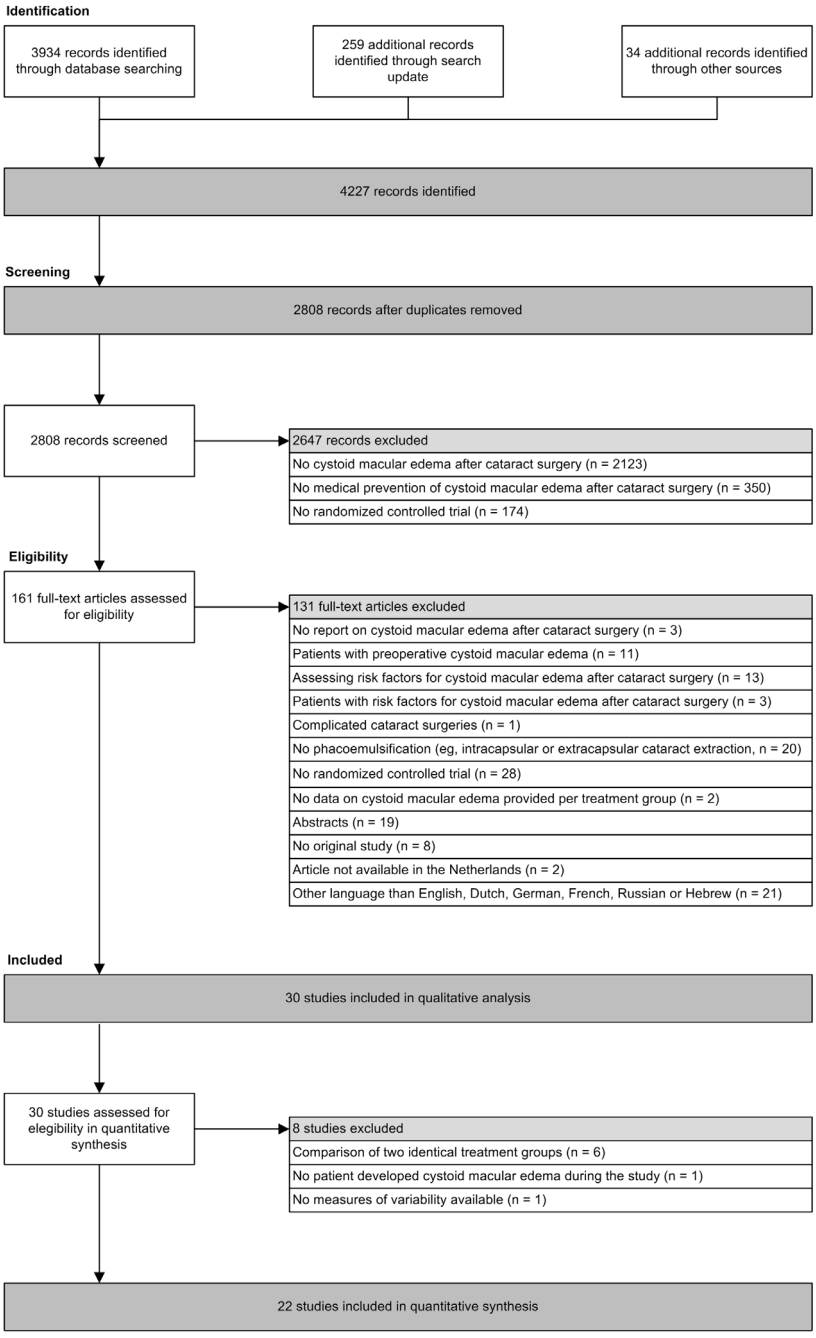
Subgroup analyses were performed for patients with and without diabetes mellitus (DM). An additional subgroup analysis was performed for all mixed populations, to compare data of studies that included both non-diabetic and diabetic patients. Trials comparing two identical treatment groups (e.g. two corticosteroid eye drops) were excluded from the meta-analysis, as were data from trials that did not provide any measures of variability.

The primary outcome was the incidence of CME within 3 months after cataract surgery, using the diagnostic tools and definitions of the included trials. In case an article used separate definitions for CME and CSME, the occurrence of CSME was used in the meta-analysis, as this is the most clinically relevant outcome. Secondary outcome measures were the difference in optical coherence tomography (OCT)-measured central foveal thickness (FT) in the central 1 mm area of the macula and MV in the central 6 mm area of the macula within 3 months postoperatively, as compared to baseline. Moreover, this study describes the difference between treatment groups in CDVA change within 3 months postoperatively, as compared to baseline. CDVA data were converted to logMAR scale if necessary. If articles reported only absolute values of baseline and postoperative FT, MV or CDVA, mean

changes were calculated from the available information. The standard deviation (SD) for FT, MV or CDVA change was imputed from the baseline and postoperative SD, using the methods described in the Cochrane Handbook.[14] If an outcome was measured more than once within 3 months postoperatively, the latest follow-up moment was selected for inclusion in the meta-analysis, with the intention of comparing the most long-term outcome.

Analyses were performed using Review Manager. Odds ratios (ORs) and accompanying 95% confidence intervals (95% CIs) were calculated for all dichotomous outcomes, whereas mean differences with 95% CI were analyzed for all continuous outcome measures. As described in the Cochrane Handbook, statistical heterogeneity was assessed using the χ^2 test. I^2 was used to describe the percentage of variability in effect estimate thought to be a result of heterogeneity.[14] Whenever possible, treatment groups were compared directly using a classical pairwise meta-analysis. Some indirect comparisons could be performed using the Bucher method. This method can be used if no RCT compared two treatment groups directly, while both treatments have been compared to placebo or standard treatment in other trials.[17]

Figure 1. Flow chart visualizing the selection of randomized controlled trials



Results

The literature search retrieved 2808 titles and abstracts. Thirty trials were included in this systematic review. Reasons for exclusion in each stage of the article selection process are shown in detail in the flow chart in figure 1. Characteristics of included studies are listed in appendix 2. Eleven trials included only patients without DM and seven trials included only diabetic patients. Twelve other trials included patients with and without DM or did not report the incidence of DM in the study population. These trials were clustered and referred to as "mixed populations". In the non-diabetic and mixed populations, most trials compared the effect of topical corticosteroids, topical NSAIDs or a combination of both.[18-35] By contrast, many different treatments have been compared in diabetic subjects, including subtenon corticosteroids,[36] intravitreal corticosteroids[37] and intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections.[38-40] A complete overview of the studied treatment groups and definitions used in the included trials are given in table 1-3 for non-diabetic, mixed and diabetic populations, respectively.

Eight trials could not be included in the meta-analysis, since ORs and 95% CIs could not be calculated for the reported treatment comparisons. Quantitative measures could not be calculated because no patient developed CME in either treatment group,[41] because there were no measures of variability given by the authors[31] or because the study compared two identical treatment groups as defined in this study (e.g. comparing two different types of corticosteroid eye drops).[18,19,21,34,35,42] A complete overview of all meta-analyses is provided in appendix 3 and a summary of all treatment comparisons is provided in table 4.

Quality of evidence

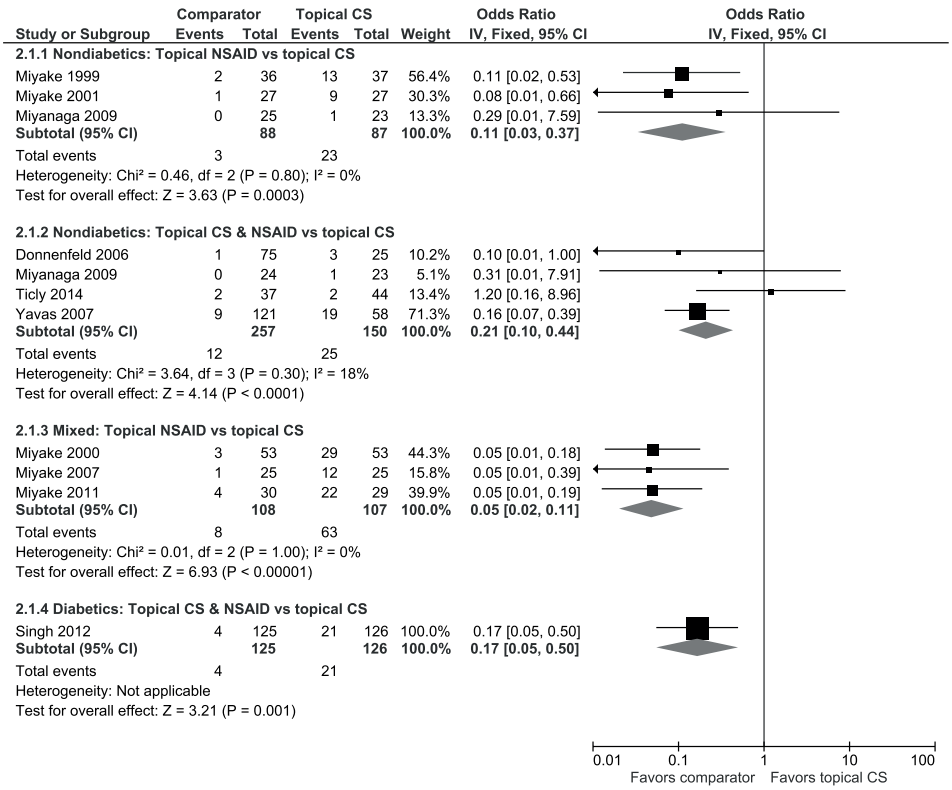
Only RCTs were selected for inclusion in this study. Appendix 2 contains an assessment of the risk of bias within studies and the quality of the included RCTs. As evident from appendix 3, the overall quality of evidence of the included studies was low to moderate. Eleven trials used a table of random numbers to randomize the included patients,[18-21,29,34-38,43] one trial used centralized randomization by the pharmacy[32] and three trials used envelopes.[25,29,44] The method of treatment allocation was unclear in fifteen other trials. Six trials stated that the treatment allocation was concealed from the investigators.[18,19,29,32,45,46] Six trials were open-label studies.[22,23,31,43,44,46]

Non-diabetic patients

As shown in table 1, nine trials reporting the incidence of CME after cataract surgery in non-diabetic patients could be included in this meta-analysis. The meta-analysis in figure 2 shows that topical NSAIDs significantly reduced the odds of developing CME after cataract surgery, as compared to topical corticosteroids. The OR was 0.11 (95% CI 0.03-0.37;

I^2 0%).[22,24,27] The difference in efficacy between topical corticosteroids and NSAIDs was not statistically significant if patients also received oral prednisolone for seven days postoperatively (OR 0.06; 95% CI 0.00-1.10).[43] A combination of topical corticosteroids and topical NSAIDs reduced the odds of developing CME as compared to topical corticosteroids as a single-drug treatment, with an OR of 0.21 (95% CI 0.10-0.44; I^2 18%).[20,27,29,30]

Figure 2. Forest plots summarizing the results of studies comparing the efficacy of topical treatments to prevent the occurrence of cystoid macular edema within 3 months after uncomplicated cataract surgery in non-diabetic, mixed and diabetic populations



CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; 95% CI: 95% confidence interval

Only one RCT provided a direct comparison between topical NSAIDs and a combination treatment of topical corticosteroids and NSAIDs. Unfortunately, it was not possible to include this comparison in the quantitative analyses, since no patient in either treatment group developed CME.[27] Nevertheless, using the common comparator of topical corticosteroids, it was possible to perform an indirect comparison of topical NSAIDs vs a

Table 1. Randomized controlled trials investigating non-diabetic patients

Study	Definition CME	Treatment group
Dieleman *et al*. 2011[46]	CME on OCT (any increase in CPT > 30% compared with the preoperative baseline value developing within 4 weeks after cataract surgery) in combination with a decrease in CDVA of 2 or more lines on the ETDRS chart	Topical CS
Donnenfeld *et al*. 2006[20]	BCVA worse than 20/30 at the 2-week postoperative visit and CME diagnosed using OCT	Topical CS
Donnenfeld *et al*. 2011[19, a]	*Not given*	Topical CS + topical NSAID
Mathys *et al*. 2010[21,a]	An increase of > 25µm in macular thickness in the central 1 mm area on OCT	Topical CS + topical NSAID
Miyake *et al*. 1999[22]	Diagnosed on FA using the Miyake classification	Topical CS
Miyake *et al*. 2001[24]	Diagnosed on FA using the Miyake classification	Topical CS
Miyanaga *et al*. 2009[27]	Decreased VA and obvious CME by OCT	Topical CS
Moschos *et al*. 2012[28]	*Not given*	Topical CS
Negi *et al*. 2006[45]	Snellen BCVA of 6/9 or less and CME on oral FA	Oral AZ + topical CS + subconjunctival CS
Ticly *et al*. 2014[29]	Diagnosed on FA using the Miyake classification; CME on OCT defined as the presence of well-defined cystic fluid pockets or a CST above 315 µm	Topical CS
Wang *et al*. 2013[43]	Impaired BCVA, macular alterations during fundus examination and CRT of > 250µm on OCT and the presence of intraretinal cystoid space beneath the fovea	Oral CS + topical CS[b]
Yavas *et al*. 2007[30]	Diagnosed on FA as fluorescein leakage into the cystic space	Topical CS

[a] Not included in meta-analysis

[b] Combination of more than one treatment group

	Drug	Treatment group	Drug
	Dexamethasone 0.1% (postop)	Subconjunctival CS	Betamethasone 5,7 mg/ml (during surgery)
	Prednisolone 1% (postop)	Topical CS + topical NSAID[b]	Prednisolone 1% (postop) + ketorolac 0.4% (preop + postop)
	Difluprednate 0.05% (postop) + nepafenac 0.1% or ketorolac 0.4% (preop and postop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + nepafenac 0.1% or ketorolac 0.4% (preop and postop)
	Prednisolone 1% (postop) + nepafenac 0.01% (preop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + nepafenac 0.01% (preop) + nepafenac 0.1% (postop)
	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.1% (preop and postop)
	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.5 % (preop and postop)
	Betamethasone 0.1% and Fluorometholone 0.1% (postop)	1. Topical NSAID 2. Topical CS + topical NSAID	1. Bromfenac 0.1% (postop 2. Betamethasone 0.1% and fluorometholone 0.1% (postop) + bromfenac 0.1% (postop)
	Dexamethasone 0.1% (postop)	Topical CS + topical NSAID	Dexamethasone 0.1% (postop) + diclofenac 0.1% (preop and postop)
	AZ 250 mg (end of surgery) + betamethasone 0.1% (postop) + betamethasone 4 mg (during surgery)	Oral AZ + subconjunctival CS + subtenon CS	AZ 250 mg (end of surgery) + betamethasone 4 mg (during surgery) + triamcinolone acetonide 20 or 30 mg (during surgery)
	Prednisolone 1% (preop and postop)	Topical CS + topical NSAID	Prednisolone 1% (preop and postop) + ketorolac 0.4% (preop and postop)
	Prednisolone 15 mg (postop) + fluorometholone 0.1% or dexamethasone 0.1% (postop)	Oral CS+ topical NSAID[b]	Prednisolone 15 mg (postop) + bromfenac 0.1% (postop)
	Prednisolone 1% (postop)	Topical CS + topical NSAID[b]	Prednisolone 1% (postop) + indomethacin 0.1% (postop or preop and postop)

AZ: acetazolamide; BCVA: best corrected visual acuity; CDVA: corrected distance visual acuity; CME: cystoid macular edema; CPT: center point thickness; CRT: central retinal thickness; CS: corticosteroid; CST: central subfield thickness; FA: fluorescein angiography; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; ETDRS: early treatment diabetic retinopathy study; postop: postoperatively; preop: preoperatively; VA: visual acuity

Table 2. Randomized controlled trials investigating non-diabetic and diabetic patients (a mixed population)

Study	Definition CME	Treatment group
Almeida *et al*. 2008[31, a]	*Not given*	Topical CS
Almeida *et al*. 2012[32]	*Not given*	Topical CS
Cable *et al*. 2012[18, a]	*Not given*	Topical CS + topical NSAID
Cervantes *et al*. 2009[33]	CSME associated with vision loss	Topical CS
Chatziralli *et al*. 2011[42, a]	*Not given*	Oral AZ + topical CS + topical NSAID
Miyake *et al*. 2000[23]	Diagnosed on FA using the Miyake classification	Topical CS
Miyake *et al*. 2007[25]	Diagnosed on FA using the Miyake classification	Topical CS
Miyake *et al*. 2011[26]	Diagnosed on FA using the Miyake classification	Topical CS
Nishino *et al*. 2009[41, a]	FA was performed only when CME was suspected to worsen the VA to less than 0.7	Topical NSAID
Weber *et al*. 2013[34, a]	*Not given*	Topical NSAID
Wittpenn *et al*. 2008[35, a]	Definite CME: presence of cystoid changes associated with substantial (≥ 40 µm) retinal thickening on OCT Probable CME: presence of changes in retinal contour and increased macular thickness relative to preoperative baseline, but without definite cystoid changes	Topical CS + topical NSAID

[a] Not included in meta-analysis

[b] Combination of more treatment groups

	Drug	Treatment group	Drug
	Prednisolone 1% (postop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + ketorolac 0.5% (preop and postop)
	Prednisolone 1% (postop)	Topical CS + topical NSAID[b]	Prednisolone 1% (postop) + nepafenac 0.1% or ketorolac 0.5% (preop and postop)
	Prednisolone 1% (during surgery) and difluprednate (postop) + bromfenac 0.09% (preop and postop)	Topical CS + topical NSAID	Prednisolone 1% (during surgery) and difluprednate (postop) + nepafenac 0.1% (preop and postop)
	Dexamethasone 0.1% (postop)	Topical CS + topical NSAID	Dexamethasone 0.1% (postop) + nepafenac 0.1% (preop and postop)
	Acetazolamide 125 mg (preop) + dexamethasone 0.1% (preop and postop) + ketorolac 0.5% (preop)	Oral AZ + topical CS + topical NSAID	Acetazolamide 125 mg + dexamethasone 0.1% (preop and postop) + ketorolac 0.5% (preop and postop)
	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.1% (preop and postop)
	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.1% (preop and postop)
	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Nepafenac 0.1% (preop and postop)
	Bromfenac (preop and postop)	Topical NSAID + topical CS + subconjunctival CS	Bromfenac (preop and postop) + fluorometholone 0.1% (postop) + dexamethasone 0.5 ml (during surgery)
	Indomethacin 0.1% (preop and postop)	Topical NSAID	Ketorolac 0.5% (preop and postop)
	Prednisolone 1% (postop) + ketorolac 0.4% (preop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + ketorolac 0.4% (preop and postop)

AZ: acetazolamide; CME: cystoid macular edema; CS: corticosteroid; CSME: clinically significant macular edema; FA: fluorescein angiography; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; postop: postoperatively; preop: preoperatively; VA: visual acuity

Table 3. Randomized controlled trials investigating diabetic patients

Study	Definition CME	Treatment group
Ahmadabadi *et al*. 2010[37]	Subjective report of decreased vision by the patient, ophthalmoscopic detection of the presence of ME, and confirmation of the diagnosis by FA and OCT examinations at any postoperative visit	Topical CS
Chae *et al*. 2014[38]	> 60 mm increase in CST relative to the screening CST value, as assessed by spectral domain OCT; diagnosed on FA using the Antcliff classification	Placebo
Endo *et al*. 2010[44]	*Not given*	Topical CS
Fard *et al*. 2011[39]	Increase in CPT on OCT after cataract surgery	Placebo
Kim *et al*. 2008[36]	Postsurgical CME was defined as decreased VA and CME on OCT	Topical CS
Singh *et al*. 2012[47]	≥ 30% increase in CSMT relative to the presurgical baseline measurement	Topical CS
Udaondo *et al*. 2011[40]	ME involving or threatening the center of the macula as defined by the ETDRS	Topical CS

CME: cystoid macular edema; CPT: center point thickness; CS: corticosteroid; CSMT: central subfield macular thickness; CST: central subfield thickness; ETDRS: early treatment diabetic retinopathy study; FA: fluorescein angiography;

combination treatment of topical NSAIDs and corticosteroids. This comparison showed no statistically significant difference in the odds of developing CME after cataract surgery with an OR of 0.54 (95% CI 0.13-2.20).

One study compared the efficacy of postoperative corticosteroid eye drops to subconjunctival corticosteroids at the end of cataract surgery in non-diabetic patients. This study showed no statistically significant difference in the odds of developing CME between both treatment groups (OR 1.18; 95% CI 0.53-2.62).[46]

None of the studies investigated the change in FT or MV after cataract surgery. Eight trials reported the change in CDVA within 3 months postoperatively or both the preoperative and postoperative CDVA. None of the treatment comparisons showed significant differences in CDVA change from baseline. An overview of these meta-analyses can be found in figure 3.

Mixed populations

Four trials reported the incidence of CME after cataract surgery in mixed populations, including both diabetic and non-diabetic subjects. Table 2 provides a complete overview of the included studies. The meta-analysis shown in figure 2 suggests that topical NSAIDs significantly reduce the odds of developing CME after cataract surgery, as compared to

	Drug	Treatment group	Drug
	Betamethasone 0.1% (postop)	Topical CS + intravitreal CS	Betamethasone 0.1% (postop) + triamcinolone acetonide 2 mg (during surgery)
		Intravitreal anti-VEGF	Ranibizumab 0.5 mg (during surgery)
	Betamethasone 0.1% & fluorometholone 0.1% (postop)	Topical NSAID	Bromfenac 0.1% (postop)
		Intravitreal anti-VEGF	Bevacizumab 1.25 mg (during surgery)
	Prednisolone 1% (postop)	Topical CS + subtenon CS	Prednisolone 1% (postop) + triamcinolone acetonide (during surgery)
	Prednisolone 1% (postop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + nepafenac 0.1% (preop and postop)
	Dexamethasone 0.1% (postop)	Topical CS + intravitreal anti-VEGF	Dexamethasone 0.1 % (postop) + ranibizumab 5mg (during surgery)

ME: macular edema; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; postop: postoperatively; preop: preoperatively; VA: visual acuity; VEGF: vascular endothelial growth factor

topical corticosteroids (OR 0.05; 95% CI 0.02-0.11; I^2 0%).[23,25,26] This finding was also confirmed by OCT, showing a significantly smaller increase in FT in the topical NSAID group as compared to topical corticosteroids (mean difference -23.20 µm; 95% CI -42.95 to -3.45 µm).[26] Other trials showed that a combination of topical corticosteroids and NSAIDs significantly reduced the postoperative change in MV, as compared to topical corticosteroids as a single-drug treatment. The mean difference was -0.25 mm^3 (95% CI -0.36 to -0.13 mm^3; I^2 0%).[32,33] There was no statistically significant difference between treatment groups in FT change from baseline (mean difference -6.00 µm; 95% CI -15.17 to 3.17 µm).[33] An indirect comparison between topical NSAIDs and a combination of topical corticosteroids and NSAIDs showed no significant difference in the FT change from baseline, with a mean difference of -17.2 µm (95% CI -38.97 to 4.57 µm).

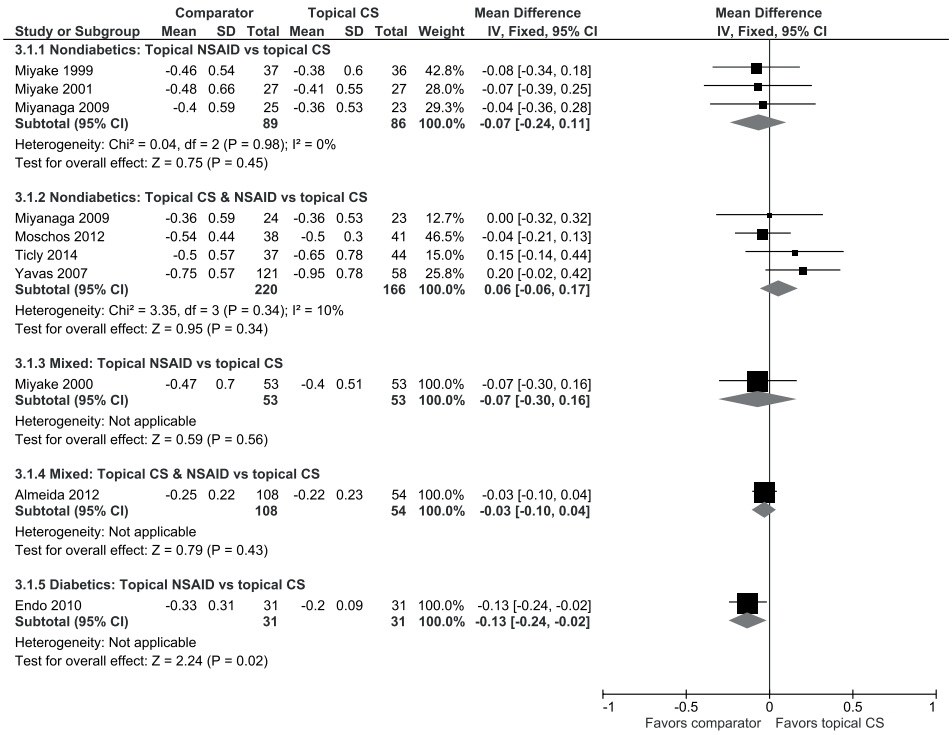
Two trials reported change in CDVA within 3 months postoperatively. None of the comparisons showed significant differences between treatment groups in CDVA change from baseline.

Diabetic patients

Seven trials included diabetic patients with mild to severe NPDR and no diabetic macular edema preoperatively. Five trials reported the incidence of CME after cataract surgery. A complete overview of all articles is presented in table 3. As can be seen in figure 2, a com-

bination of topical corticosteroids and topical NSAIDs reduced the odds of developing CME after cataract surgery as compared to topical corticosteroids as a single-drug treatment (OR 0.17; 95% CI 0.05-0.50).[47] Only one study compared the efficacy of topical NSAIDs vs topical corticosteroids in diabetic patients, but did not report on the incidence of CME. The difference in FT change from baseline between both treatment groups was not statistically significant (mean difference -17.00 µm; 95% CI -36.37 to 2.37 µm). Nevertheless, the study did show a statistically significantly larger improvement in CDVA in the NSAID group as compared to the topical corticosteroid group (mean difference -0.13 logMAR; 95% CI -0.24 to -0.02 logMAR). Preoperative CDVA in the NSAID and corticosteroid group was 0.24 and 0.16 logMAR (20/35 and 20/29 Snellen), respectively, and improved to -0.09 and -0.04 logMAR (20/16 and 20/18 Snellen) at 6 weeks postoperatively.[44]

Figure 3. Forest plots summarizing the results of studies comparing the efficacy of topical treatments on the change in corrected distance visual acuity within 3 months after uncomplicated cataract surgery, as compared to baseline, in non-diabetic, mixed and diabetic populations



CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; 95% CI: 95% confidence interval

While topical treatments have been studied most extensively, several trials investigated the effect of intravitreal treatments on the incidence of CME after cataract surgery in diabetic patients. Two trials showed that intravitreal anti-VEGF injections at the end of cataract surgery did not cause a statistically significant reduction in the odds of developing CME, as compared to placebo (OR 0.68; 95% CI 0.21-2.19) or as an additional treatment to topical corticosteroids (OR 0.13; 95% CI 0.02-1.21).[38,40] One RCT studied the efficacy of intravitreal triamcinolone acetonide in 41 eyes of diabetic patients who also received topical corticosteroids. Four eyes in the control group and no eyes in the triamcinolone group developed CME, but the treatment effect was not statistically significant (OR 0.09; 95% CI 0.00-1.89). CDVA improved from 0.81 and 0.98 logMAR (20/129 and 20/191 Snellen) preoperatively, to 0.13 and 0.09 logMAR (20/27 and 20/25 Snellen) at 3 months postoperatively, in the control group and intravitreal triamcinolone group, respectively. The difference between treatment groups in postoperative CDVA change from baseline (mean difference -0.13 logMAR; 95% CI -0.40 to 0.14) was not statistically significant.[37]

An indirect comparison showed no statistically significant difference in the odds of developing CME after intravitreal corticosteroid vs intravitreal anti-VEGF injections in diabetic patients who also received topical corticosteroids (OR 0.71; 95% CI 0.02-28.76).

Table 4. The efficacy of various treatment strategies to prevent the occurrence of cystoid macular edema after uncomplicated cataract surgery in non-diabetic, diabetic and mixed populations

			Population studied (no. of studies)	**OR (95% CI)**
Topical NSAID	>	Topical CS	Non-diabetics (3)	0.11 (0.03-0.37)
			Mixed population (3)	0.05 (0.02-0.11)
Topical NSAID	≈[a]	Topical CS & topical NSAID	Non-diabetics (n.a.)	0.54 (0.13-2.20)
Topical NSAID & topical CS	>	Topical CS	Non-diabetics (4)	0.21 (0.10-0.44)
			Diabetics (1)	0.17 (0.05-0.50)
Topical CS & intravitreal anti-VEGF	≈	Topical CS	Diabetics (1)	0.13 (0.02-1.21)
Topical CS & intravitreal anti-VEGF	≈[a]	Topical CS & intravitreal CS	Diabetics (n.a.)	0.71 (0.02-28.76)
Topical CS & intravitreal CS	≈	Topical CS	Diabetics (1)	0.09 (0.00-1.89)
Subconjunctival CS	≈	Topical CS	Non-diabetics (1)	1.18 (0.53-2.62)
Subconjunctival CS & subtenon CS & oral AZ	≈	Topical CS & subconjunctival CS & oral AZ	Non-diabetics (1)	0.31 (0.03-3.16)
Topical NSAID & oral CS	≈	Topical CS & oral CS	Non-diabetics (1)	0.06 (0.00-1.10)

[a] Indirect treatment comparison using the Bucher method

AZ: acetazolamide; CME: cystoid macular edema; CS: corticosteroid; n.a.: not applicable; no.: number; NSAID: non-steroidal anti-inflammatory drug, OR: odds ratio; VEGF: vascular endothelial growth factor; 95% CI: 95% confidence interval

Discussion

The current paper compared the efficacy of predefined preventive strategies on the incidence of CME after uncomplicated cataract surgery in non-diabetic, mixed and diabetic populations.

In non-diabetic patients, it was found that topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids. These findings are in line with the results of a recent systematic review by Kessel and associates, reporting a significantly higher prevalence of CME in the corticosteroid group as compared to the NSAID group.[13] The systematic review by Kessel and associates did not investigate the additive effects of combining topical corticosteroids and NSAIDs versus single-drug treatment. The current study demonstrated that a combination of topical NSAIDs and corticosteroids significantly reduced the odds of developing CME as compared to topical corticosteroids, while combination treatment did not show any benefit over topical NSAIDs in an indirect treatment comparison. This suggests that a topical NSAID should always be part of the preventive treatment after cataract surgery in non-diabetic patients. Whether the use of corticosteroid eye drops can be avoided, cannot be concluded from these results. To establish a better evidence-based preventive strategy, the European Society of Cataract and Refractive Surgeons (ESCRS) decided to design a large multicenter study to compare the efficacy of topical NSAIDs, topical corticosteroids and a combination treatment of both drugs to prevent the occurrence of CME after cataract surgery in non-diabetic patients.
Several factors may influence the interpretation of the current study results. Firstly, one should consider the difference in potency of various corticosteroid eye drops. It is known that fluorometholone is a corticosteroid with only low potency, due to a lower penetration of the cornea.[48] Two of three RCTs comparing the efficacy of topical corticosteroids vs topical NSAIDs in the non-diabetic study population used low-potency corticosteroids, which might have caused an overestimation of the efficacy of topical NSAIDs as compared to topical corticosteroids.

The comparison of topical NSAIDs vs combination treatment with topical corticosteroids and NSAIDs was based on an indirect comparison through the common comparator of topical corticosteroids. In the absence of a direct comparison, the Bucher method can be used to compare results of different study populations. However, it should be noted that the Bucher method assumes treatment effects to be constant across different populations.[17] Most trials compared the effect of topical NSAIDs to low-potency corticosteroids, whereas the effect of topical combination treatment was compared to higher-potency corticosteroids. This may have caused an overestimation of the effect of topical NSAIDs as compared to combination treatment with topical corticosteroids and NSAIDs.

A major limitation of this study is the use of various detection methods and definitions to diagnose CME after cataract surgery. Any differences between trials in the efficiency of detecting CME may lead to inaccurate estimates of direct and especially indirect comparisons.[17] Four studies in the non-diabetic population used similar definitions to detect CME on FA.[22,24,29,30] OCT was used in two other studies, but was only performed in patients with a decreased VA.[20,27] As CME often occurs without any visual complaints, the incidence of CME will be higher in studies using FA in all patients. One should note the large differences in the incidence of CME in three studies using FA to detect CME (15.6-19.2%),[22,24,30] as compared to two studies performing an OCT only in patients with decreased VA (1.4-4%).[20,27] The studies using FA in all patients most likely include patients with normal CDVA and may overestimate the incidence of clinically relevant CME, since CME will resolve spontaneously in many cases.[8] Future studies would therefore benefit from standardization of the definition of CME after cataract surgery.[4]

The timing of follow-up visits is a third factor which might influence the interpretation of direct and indirect treatment comparisons. It is known that most cases of CME occur within three months after cataract surgery, with a peak incidence at four to six weeks postoperatively.[3,4] Therefore, the detection rate of CME will be highest in studies with a follow-up of four to six weeks postoperatively. The RCTs investigating the efficacy of topical single-drug treatments scheduled their follow-up visits closer to four to six weeks postoperatively, as compared to studies investigating the effect of combination treatments. Consequently, in an indirect comparison, the effect of combination treatments of topical corticosteroids and NSAIDs might be overestimated when compared to topical NSAIDs.

This study was not designed to investigate the optimal duration of pre- or postoperative topical treatments. Although the anti-inflammatory treatment is usually initiated postoperatively, it is thought that the use of preoperative NSAIDs limits the release of prostaglandins during surgery.[30] Two studies found a significantly lower incidence of CME after cataract surgery in patients starting NSAID treatment one to three days preoperatively as compared to patients treated only postoperatively.[20,30]

In mixed populations, topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids. All studies were performed by the same author and used the Miyake classification to diagnose CME on FA.[23,25,26] As mentioned previously, the definition used to detect CME after cataract surgery may highly influence the reported incidence rates of CME. Therefore, it would be helpful to use an objective outcome measurement (e.g. change in postoperative FT or MV) to compare the efficacy of various treatments. One study showed a significantly smaller increase in FT after cataract surgery and postoperative topical nepafenac as compared to postoperative treatment

with topical fluorometholone.[26] This may suggest that a combination of topical NSAIDs and corticosteroids would also reduce the change in FT after cataract surgery as compared to topical corticosteroid treatment. However, another study could not find a statistically significant difference between eyes treated with a combination of topical nepafenac plus dexamethasone vs dexamethasone eye drops as a single-drug therapy.[33] This deviation may be caused by the use of corticosteroids of various potencies.

The present study also compared the efficacy of various treatments to prevent the occurrence of CME after cataract surgery in diabetic patients. The odds of developing CME were significantly lower after topical combination treatment with an NSAID and corticosteroid, as compared to a single-drug treatment with topical corticosteroids. One multicenter trial treating all patients with prednisolone eye drops for two weeks postoperatively, or longer if considered necessary to treat anterior segment inflammation, provided evidence for this observation.[47] However, an underestimation of the overall incidence of CME in this study may have occurred, as both anterior segment inflammation and CME are a consequence of the underlying inflammatory process after cataract surgery. Although none of the trials studied the efficacy of topical single-drug treatments on the odds of developing CME after cataract surgery, one study did investigate the efficacy of bromfenac vs fluorometholone eye drops in reducing postoperative foveal thickening. This trial reported no significant differences in FT change from baseline between the NSAID and corticosteroid treatment groups. A sub analysis including only patients with NPDR showed a statistically smaller FT change in the bromfenac group at four and six weeks postoperatively.[44] As mentioned previously, fluorometholone can be considered a corticosteroid of only low potency, which might have overestimated the effect of NSAID eye drops in this study.

Whereas different postoperative treatments did not affect CDVA in non-diabetic and mixed populations, diabetic patients showed a statistically significantly larger improvement in CDVA using topical NSAIDs as compared to topical corticosteroids.[44]

Although topical treatments have been studied most extensively, some comparisons could be made regarding the use of intravitreal treatments in diabetic patients. Three studies showed that intravitreal corticosteroid and anti-VEGF treatments might be useful to reduce the odds of developing CME after cataract surgery, but none of the studies was able to show statistically significant results owing to small sample sizes of the included studies. One study showed that a perioperative injection of 0.5 mg ranibizumab prevents the occurrence of CME after cataract surgery at one month postoperatively, but this difference disappeared at three months postoperatively.[38] This may be caused by the limited duration of the treatment effect of intravitreal ranibizumab. An indirect treatment comparison could not find a statistically significant difference in the efficacy of intravitreal

corticosteroid vs intravitreal anti-VEGF injections in diabetic patients who also received a topical corticosteroid. When considering the abovementioned treatment strategies, cataract surgeons are obliged to carefully consider the adverse events reported after intravitreal injections. It should be noted that increased intraocular pressure is reported in 41.2 per 100 patients after intravitreal corticosteroid injection, whereas the incidence is much lower (0.12-0.49 per 100 patients) after intravitreal bevacizumab or ranibizumab injection.[49,50] Other safety concerns with intravitreal injections are mainly associated with the injection procedure. Endophthalmitis, the most dreaded complication after intravitreal injection, was reported in 0.04-0.05 per 100 injections in a recent systematic review summarizing the adverse events after intravitreal anti-VEGF injections reported in 278 articles.[49] Given the paucity of studies on the prevention of CME after cataract surgery in diabetic patients, the ESCRS also decided to set up a European multicenter study investigating the efficacy of intravitreal anti-VEGF and subconjunctival corticosteroid injections to prevent the occurrence of CME after cataract surgery in diabetics.

The purpose of this study was to summarize and integrate the results of previous RCTs on the prevention of CME within three months after uncomplicated phacoemulsification cataract surgery with posterior chamber intraocular lens implantation in non-diabetic and diabetic patients with age-related cataract, without CME preoperatively, and without risk factors for developing CME. Results of this meta-analysis show that topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids in non-diabetic and mixed populations. Furthermore, a combination of topical NSAIDs and corticosteroids significantly reduced the odds of developing CME in non-diabetic and diabetic patients, as compared to topical corticosteroids in a single-drug treatment. Based on an indirect treatment comparison, no difference could be found between topical combination treatment vs topical NSAIDs in non-diabetic patients. None of the included studies was able to show a statistically significant effect of intravitreal corticosteroid or intravitreal anti-VEGF treatments to reduce the odds of developing CME after cataract surgery in diabetic patients.

References

1. Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol. 1953;36(5):599-619.
2. Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. Arch Ophthalmol. 1966;76(5):646-661.
3. Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. Drugs. 2007;67(9):1291-1308.
4. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol. 2012;23(1):26-32.
5. Eriksson U, Alm A, Bjarnhall G, Granstam E, Matsson AW. Macular edema and visual outcome following cataract surgery in patients with diabetic retinopathy and controls. Graefes Arch Clin Exp Ophthalmol. 2011;249(3):349-359.
6. Katsimpris JM, Petropoulos IK, Zoukas G, Patokos T, Brinkmann CK, Theoulakis PE. Central foveal thickness before and after cataract surgery in normal and in diabetic patients without retinopathy. Klin Monbl Augenheilkd. 2012;229(4):331-337.
7. Mentes J, Erakgun T, Afrashi F, Kerci G. Incidence of cystoid macular edema after uncomplicated phacoemulsification. Ophthalmologica. 2003;217(6):408-412.
8. 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(3):397-405.
9. Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg. 2007;33(9):1550-1558.
10. Krepler K, Biowski R, Schrey S, Jandrasits K, Wedrich A. Cataract surgery in patients with diabetic retinopathy: visual outcome, progression of diabetic retinopathy, and incidence of diabetic macular oedema. Graefes Arch Clin Exp Ophthalmol. 2002;240(9):735-738.
11. Dowler JGF, Sehmi KS, Hykin PG, Hamilton AMP. The natural history of macular edema after cataract surgery in diabetes. Ophthalmology. 1999;106(4):663-668.
12. Diabetic Retinopathy Clinical Research Network Authors/Writing C, Baker CW, Almukhtar T, *et al*. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. JAMA Ophthalmol. 2013;131(7):870-879.
13. Kessel L, Tendal B, Jorgensen KJ, *et al*. Post-cataract Prevention of Inflammation and Macular Edema by Steroid and Nonsteroidal Anti-inflammatory Eye Drops: A Systematic Review. Ophthalmology. 2014.
14. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Available at http://handbook.cochrane.org/. Accessed July 9, 2015.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, on behalf of the PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
16. Verhagen AP, de Vet HC, de Bie RA, *et al*. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol.1998;51(12):1235-1241.
17. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol.1997;50(6):683-691.
18. 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(1):997-1004.
19. Donnenfeld ED, Holland EJ, Solomon KD, *et al*. A multicenter randomized controlled fellow eye trial of pulse-dosed difluprednate 0.05% versus prednisolone acetate 1% in cataract surgery. Am J Ophthalmol. 2011;152(4):609-617.
20. Donnenfeld ED, Perry HD, Wittpenn JR, Solomon R, Nattis A, Chou T. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: Pharmacokinetic-response curve. J Cataract Refract Surg. 2006;32(9):1474-1482.
21. Mathys KC, Cohen KL. Impact of nepafenac 0.1% on macular thickness and postoperative visual acuity after cataract surgery in patients at low risk for cystoid macular oedema. Eye (Lond). 2010;24(1):90-96.
22. Miyake K, Ota I, Maekubo K, Ichihashi S, Miyake S. Latanoprost accelerates disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema in early postoperative pseudophakias. Arch Ophthalmol. 1999;117(1):34-40.

23. Miyake K, Masuda K, Shirato S, *et al*. Comparison of diclofenac and fluorometholone in preventing cystoid macular edema after small incision cataract surgery: A multicentered prospective trial. Jpn J Ophthalmol. 2000;44(1):58-67.
24. Miyake K, Ota I, Ibaraki N, *et al*. Enhanced disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema by topical timolol and its preservative in early postoperative pseudophakia. Arch Ophthalmol.2001;119(3):387-394.
25. Miyake K, Nishimura K, Harino S, *et al*. The effect of topical diclofenac on choroidal blood flow in early postoperative pseudophakias with regard to cystoid macular edema formation. Invest Ophthalmol Vis Sci. 2007;48(12):5647-5652.
26. Miyake K, Ota I, Miyake G, Numaga J. Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery. J Cataract Refract Surg. 2011;37(9):1581-1588.
27. Miyanaga M, Miyai T, Nejima R, Maruyama Y, Miyata K, Kato S. Effect of bromfenac ophthalmic solution on ocular inflammation following cataract surgery. Acta Ophthalmol.2009;87(3):300-305.
28. Moschos MM, Chatziralli IP, Pantazis P, Rouvas AA, Sergentanis TN. Is topical diclofenac essential before and after uneventful phacoemulsification cataract surgery? J Ocul Pharmacol Ther.2012;28(4):335-339.29.
29. Ticly FG, Lira RP, Zanetti FR, Machado MC, Rodrigues GB, Arieta CE. Prophylactic use of ketorolac tromethamine in cataract surgery: a randomized trial. J Ocul Pharmacol Ther. 2014;30(6):495-501.
30. Yavas GF, Ozturk F, Kusbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. J Cataract Refract Surg. 2007;33(5):804-807.
31. Almeida DRP, Johnson D, Hollands H, *et al*. Effect of prophylactic nonsteroidal antiinflammatory drugs on cystoid macular edema assessed using optical coherence tomography quantification of total macular volume after cataract surgery. J Cataract Refract Surg. 2008;34(1):64-69.
32. Almeida DRP, Khan Z, Xing L, *et al*. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. J Cataract Refract Surg. 2012;38(9):1537-1543.
33. Cervantes-Coste G, Sanchez-Castro YG, Orozco-Carroll M, Mendoza-Schuster E, Velasco-Barona C. Inhibition of surgically induced miosis and prevention of postoperative macular edema with nepafenac. Clin Ophthalmol.2009;3(1):219-226.
34. Weber M, Kodjikian L, Kruse FE, Zagorski Z, Allaire CM. Efficacy and safety of indomethacin 0.1% eye drops compared with ketorolac 0.5% eye drops in the management of ocular inflammation after cataract surgery. Acta Ophthalmol. 2013;91(1):e15-e21.
35. Wittpenn JR, Silverstein S, Heier J, Kenyon KR, Hunkeler JD, Earl M. A Randomized, Masked Comparison of Topical Ketorolac 0.4% Plus Steroid vs Steroid Alone in Low-Risk Cataract Surgery Patients. Am J Ophthalmol. 2008;146(4):554-560.e551.
36. Kim SY, Yang J, Lee YC, Park YH. Effect of a single intraoperative sub-Tenon injection of triamcinolone acetonide on the progression of diabetic retinopathy and visual outcomes after cataract surgery. J Cataract Refract Surg. 2008;34(5):823-826.
37. Ahmadabadi HF, Mohammadi M, Beheshtnejad H, Mirshahi A. Effect of intravitreal triamcinolone acetonide injection on central macular thickness in diabetic patients having phacoemulsification. J Cataract Refract Surg. 2010;36(6):917-922.
38. Chae JB, Joe SG, Yang SJ, *et al*. Effect of combined cataract surgery and ranibizumab injection in postoperative macular edema in nonproliferative diabetic retinopathy. Retina. 2014 Jan;34(1):149-56..
39. Fard MA, Abyane AY, Malihi M. Prophylactic intravitreal bevacizumab for diabetic macular edema (thickening) after cataract surgery: Prospective randomized study. Eur J Ophthalmol.2011;21(3):276-281.
40. Udaondo P, Garcia-Pous M, Garcia-Delpech S, Salom D, Diaz-Llopis M. Prophylaxis of macular edema with intravitreal ranibizumab in patients with diabetic retinopathy after cataract surgery: a pilot study. J Ophthalmol. 2011;2011:159436.
41. Nishino M, Eguchi H, Iwata A, Shiota H, Tanaka M, Tanaka T. Are topical steroids essential after an uneventful cataract surgery? J Med Invest. 2009;56(1-2):11-15.
42. Chatziralli IP, Papazisis L, Sergentanis TN. Ketorolac plus tobramycin/dexamethasone versus tobramycin/dexamethasone after uneventful phacoemulsification surgery: A randomized controlled trial. Ophthalmologica. 2011;225(2):89-94.
43. Wang QW, Yao K, Xu W, *et al*. Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification. Ophthalmologica. 2013;229(4):187-194.

44. Endo N, Kato S, Haruyama K, Shoji M, Kitano S. Efficacy of bromfenac sodium ophthalmic solution in preventing cystoid macular oedema after cataract surgery in patients with diabetes. Acta Ophthalmol. 2010;88(8):896-900.
45. Negi AK, Browning AC, Vernon SA. Single perioperative triamcinolone injection versus standard postoperative steroid drops after uneventful phacoemulsification surgery. Randomized controlled trial. J Cataract Refract Surg. 2006;32(3):468-474.
46. Dieleman M, Wubbels RJ, Van Kooten-Noordzij M, De Waard PWT. Single perioperative subconjunctival steroid depot versus postoperative steroid eyedrops to prevent intraocular inflammation and macular edema after cataract surgery. J Cataract Refract Surg. 2011;37(9):1589-1597.
47. Singh R, Alpern L, Jaffe GJ, *et al*. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. Clin Ophthalmol.2012;6(1):1259-1269.
48. Awan MA, Agarwal PK, Watson DG, McGhee CN, Dutton GN. Penetration of topical and subconjunctival corticosteroids into human aqueous humour and its therapeutic significance. Br J Ophthalmol. 2009;93(6):708-713.
49. van der Reis MI, La Heij EC, De Jong-Hesse Y, Ringens PJ, Hendrikse F, Schouten JS. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. Retina. 2011;31(8):1449-1469.
50. Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kamppeter BA. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology. 2005;112(4):593-598.

Appendix

Appendix 1. Search strategy used for the MEDLINE database

((((((((((((((“Cataract Extraction”[Mesh]) OR “Lens Implantation, Intraocular”[Mesh]) OR “Phacoemulsification”[Mesh]) OR “Pseudophakia”[Mesh]) OR cataract extract*) OR phakectom*) OR “enzymatic zonulolysis”) OR cataract surger*) OR lens implantation*) OR intraocular lens*) OR phaco*) OR faco*) OR pseudophak*) OR pseudo-phak*) OR pseudofak*) OR pseudo-fak*)

AND

((((((((((((“Edema”[Mesh]) OR “Macular Edema”[Mesh]) OR edema) OR oedema) OR irvine-gass) OR “irvine gass”) OR “cystoid macular dystrophy”) OR thickn*) OR CME) OR CMO) OR PCME) OR PCMO) OR “macular volume”)

AND

((((((((((((((“Randomized Controlled Trial”[Publication Type]) OR “Controlled Clinical Trial”[Publication Type]) OR “Review”[Publication Type]) OR “Review Literature as Topic”[Mesh]) OR “Meta-Analysis”[Publication Type]) OR “Meta-Analysis as Topic”[Mesh]) OR randomized) OR randomised) OR placebo) OR “drug therapy”) OR random*) OR trial) OR groups) OR review) OR rct) OR meta-analysis)

NOT

((animals[mh]) NOT (humans[mh])))

Limits: None

Appendix 2. Characteristics of included studies

Non-diabetic populations

Dieleman *et al*. 2011[46]

Methods		Randomized, open-label study
Participants	n (eyes)	400
Interventions	Topical CS	Dexamethasone 0.1% eye drops 3 times daily for a postoperative period of 4 weeks and a single administration of gentamicin–dexamethasone at the end of surgery.
	Subconjunctival CS	Single subconjunctival injection of betamethasone acetate 5.7 mg/ml at the end of surgery and a single administration of gentamicin–dexamethasone at the end of surgery.
Outcome	Detection method	OCT (time domain)
	Definition	"Clinically significant macular edema was defined as macular edema on OCT (any increase in center point thickness of more than 30% compared with the preoperative baseline value developing within 4 weeks after cataract surgery) in combination with a decrease in corrected distance visual acuity of 2 or more lines on the ETDRS chart."
Follow-up		4 weeks
Conclusion		"A single betamethasone depot at the end of uneventful cataract surgery could be a useful alternative to dexamethasone eye drops 3 times daily for 4 weeks in preventing postoperative intraocular inflammation and macular edema, especially when compliance problems seem to be an issue."
Notes		Not known how many ml of the 5.7 mg/ml betamethasone acetate were used.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"Randomization [...]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Low risk	"5 blocks of 80 sealed envelopes with uniform distribution [...]"
Performance bias (blinding of participants)	High risk	Open-label study
Performance bias (blinding of personnel)	High risk	Open-label study
Detection bias (blinding of outcome assessment)	High risk	Open-label study
Attribution bias (incomplete outcome data)	Unclear risk	"All excluded patients were replaced."

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography; RCT: randomized controlled trial

Donnenfeld *et al*. 2006[20]		
Methods		Double-masked, randomized study
Participants	n (eyes)	100
Interventions	Topical CS	Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.
	Topical CS & NSAID	Ketorolac tromethamine 0.4% 4 times daily for 3 days preoperatively, 3 times every 15 minutes in the hour before surgery and 4 times daily for 3 weeks after the surgery; Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.
	Topical CS & NSAID	Ketorolac tromethamine 0.4% 4 times daily for 1 day preoperatively, every 15 minutes in the hour before surgery and 4 times daily for 3 weeks after the surgery; Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.
	Topical CS & NSAID	Ketorolac tromethamine 0.4% every 15 minutes in the hour before surgery and 4 times daily for 3 weeks after the surgery; Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.
Outcome	Detection method	OCT (type unknown)
	Definition	"All patients with a BCVA worse than 20/30 at the 2-week postoperative visit had OCT at that time, which was evaluated by a masked retinal specialist."
Follow-up		3 months
Conclusion		"The preoperative use of ketorolac tromethamine 0.4% for 3 days followed by 1-day of predosing provided optimum efficacy and superior outcomes relative to 1-hour pretreatment and a placebo."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Bias	**Authors' judgment**	**Support for judgment**
Selection bias (sequence generation)	Low risk	"Group assignment was based on a random-number-generated protocol"
Selection bias (sequence concealment)	Unclear risk	Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Low risk	"Ocular coherence tomography was evaluated by a masked retinal specialist."
Attribution bias (incomplete outcome data)	Unclear risk	No report on drop-out

Quality of RCT (additional items Delphi List)	
Quality measure	**Authors' judgment**
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

BCVA: best corrected visual acuity; CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Donnenfeld *et al*. 2011[19]		
Methods		Multicenter, double-masked, contralateral-eye study
Participants	n (eyes)	126 (of 63 patients)
Interventions	Topical CS & NSAID	Difluprednate 0.05% 7 times preoperatively on the day of surgery, 3 times in surgical recovery and 1 drop every 2 hours for the remainder of day 0. Starting on the day after surgery, 4 times daily for 1 week and twice daily for the subsequent week; Nepafenac 0.1% or ketorolac tromethamine 0.4% beginning 3 days before surgery and continuing for 4 weeks.
	Topical CS & NSAID	Prednisolone 1% 7 times preoperatively on the day of surgery, 3 times in surgical recovery and 1 drop every 2 hours for the remainder of day 0. Starting on the day after surgery, 4 times daily for 1 week and twice daily for the subsequent week; Nepafenac 0.1% or ketorolac tromethamine 0.4% beginning 3 days before surgery and continuing for 4 weeks.
Outcome	Detection method	OCT (time domain or spectral domain) In all cases, each patient had the same OCT used on both eyes.
	Definition	-
Follow-up		30 days
Conclusion		"In this study, difluprednate was shown to provide better results compared with prednisolone acetate in multiple end points after cataract surgery. Difluprednate improved UCVA and BCVA at 1 day after cataract surgery, reduced macular swelling at 2 and 4 weeks after surgery, and reduced endothelial cell loss at 4 weeks after surgery."
Notes		Contralateral eye study. "Patients were assigned randomly to receive either difluprednate or prednisolone for treatment of the first eye; the second eye was assigned the alternative medication."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Bias	**Authors' judgment**	**Support for judgment**
Selection bias (sequence generation)	Low risk	"Allocation of the medication was [...] based on a random number list generated using randomizer.org."
Selection bias (sequence concealment)	Low risk	"Allocation of the medication was concealed from the investigators."
Performance bias (blinding of participants)	Low risk	"Both investigators and patients were masked to the treatment condition."
Performance bias (blinding of personnel)	Unclear risk	Blinding of investigators is reported, but it is not given which investigators (personnel or outcome assessor) were masked.
Detection bias (blinding of outcome assessment)	Unclear risk	Blinding of investigators is reported, but it is not given which investigators (personnel or outcome assessor) were masked.
Attribution bias (incomplete outcome data)	Unclear risk	"Eleven patients (17.5%) were not included for the efficacy end point analysis because of protocol violations" Not specified per treatment group.

Quality of RCT (additional items Delphi List)	
Quality measure	**Authors' judgment**
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

BCVA: best corrected visual acuity; CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial; UCVA: uncorrected visual acuity

Mathys *et al*. 2010[21]

Methods		Non-masked, randomized, parallel-group study
Participants	n (eyes)	84
Interventions	Topical CS & NSAID	Nepafenac 0.01% drops thrice before surgery; Prednisolone acetate 1% four times a day for 1 month.
	Topical CS & NSAID	Nepafenac 0.01% drops thrice before surgery and postoperatively thrice a day for 1 month; Prednisolone acetate 1% four times a day for 1 month.
Outcome	Detection method	OCT (time domain)
	Definition	"Our estimate of a clinically relevant increase in central macular thickness is 25 µm."
Follow-up		8 weeks
Conclusion		"In our study of subjects without known predisposing causes of CME, the increase in postoperative macular thickness was small in both the control and treatment groups. This small increase in macular thickness had no effect on final BCVA in either group."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"using computer-generated random numbers"
Selection bias (sequence concealment)	Unclear risk	"Subjects were randomised according to the even/odd subject identification number, using computer-generated random numbers." Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	High risk	Non-masked
Performance bias (blinding of personnel)	Low risk	"Technicians, who were masked to treatment, measured ETDRS BCVA, and OCT scans were performed."
Detection bias (blinding of outcome assessment)	Low risk	"Experienced ophthalmic photographers, who were masked to treatment, obtained Stratus OCT."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

BCVA: best corrected visual acuity; CME: cystoid macular edema; CS: corticosteroid; ETDRS: early treatment diabetic retinopathy study; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Miyake *et al*. 1999[22]

Methods		Open-label, randomized, controlled study
Participants	n (eyes)	80 Eyes with ocular hypertension, normal-tension glaucoma or primary open-angle glaucoma
Interventions	Topical CS	0.1% fluorometholone acetate was given 4 times daily on the day of surgery and then 3 times a day until the fifth postoperative week.
	Topical NSAID	0.1% diclofenac sodium was given 4 times daily on the day of surgery and then 3 times a day until the fifth postoperative week.
Outcome	Detection method	Fluorescein angiography
	Definition	"I°: Slight fluorescein leakage into the cystic space, but not sufficient enough to enclose the entire fovea centralis. II°: Complete circular accumulation of the fluorescein in the cystic space, but with a diameter of less than 2.0 mm. III°: Circular accumulation of the fluorescein larger than 2.0 mm in diameter."
Follow-up		5 weeks
Conclusion		"Latanoprost therapy enhances disruption of the blood-aqueous barrier and increases the incidence of angiographic cystoid macular edema formation in early postoperative pseudophakias. Because administration of non-steroidal eye drops such as diclofenac seems to prevent the adverse effects of latanoprost therapy [...] we suggest their concurrent application."
Notes		"This study consisted of a randomized double-masked trial for latanoprost and an open-label controlled trial for determining the effects of diclofenac sodium or fluorometholone eye drop use on latanoprost or its placebo." *This review included only eyes receiving a placebo and diclofenac sodium or fluorometholone acetate.*

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"[...] randomly assigned [...]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	High risk	"Because fluorometholone is a milky-white substance, making it difficult to conduct this part of the study as a double-masked trial, we performed it as an open-label study."
Performance bias (blinding of personnel)	High risk	Open-label study
Detection bias (blinding of outcome assessment)	Low risk	"The late phase of fluorescein angiograms was graded [...] in a double-masked manner."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

Miyake *et al*. 2001[24]

Methods		Single-masked, randomized study
Participants	n (eyes)	60
		Eyes with ocular hypertension, normal tension glaucoma or primary open-angle glaucoma
Interventions	Topical CS	0.1% fluorometholone acetate was given 4 times daily on the day of surgery and then 3 times per day for 5 weeks after surgery.
	Topical NSAID	0.5% diclofenac sodium was given 4 times daily on the day of surgery and then 3 times per day for 5 weeks after surgery.
Outcome	Detection method	Fluorescein angiography
	Definition	"I°: Slight fluorescein leakage into the cystic space, but not sufficient enough to enclose the entire fovea centralis. II°: Complete circular accumulation of the fluorescein in the cystic space, but with a diameter of less than 2.0 mm. III°: Circular accumulation of the fluorescein larger than 2.0 mm in diameter."
Follow-up		5 weeks
Conclusion		"Timolol and its preservative, benzalkonium chloride, cause disruption of the blood-aqueous barrier in early postoperative pseudophakia and increase incidence of angiography cystoid macular edema. The concurrent administration of NSAIDs such as diclofenac prevents these adverse effects [...]"
Notes		This study was "a double-masked trial for timolol with preservative, its preservative and non-preserved vehicles and a single-masked trial on the effect of diclofenac sodium and fluorometholone acetate on all three." *This review included only eyes receiving non-preserved vehicles and diclofenac sodium or fluorometholone acetate.*

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"[...] each randomly assigned to [...]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome
Performance bias (blinding of participants)	High risk	"Because fluorometholone is a milky white substance, a double-masked trial was impossible in this part of the study, and we therefore settled on a single-masked trial."
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Low risk	"The late phase of fluorescein angiograms was graded [...] in a double-masked manner."
Attribution bias (incomplete outcome data)	Low risk	"There was no significant difference in the incidence of patients being lost to follow-up or dropped from the study among the 6 groups."

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

Miyanaga *et al*. 2009[27]

Methods		Prospective, randomized study
Participants	n (eyes)	72
Interventions	Topical CS	0.1% betamethasone four times daily for 1 month and then 0.1% fluorometholone four times daily for 1 month.
	Topical NSAID	0.1% bromfenac twice daily until 2 months after surgery.
	Topical CS & NSAID	0.1% betamethasone four times daily for 1 month and then 0.1% fluorometholone four times daily for 1 month; 0.1% bromfenac twice daily until 2 months after surgery.
Outcome	Detection method	OCT (time domain)
	Definition	"Decreased visual acuity and obvious cystoid macular oedema confirmed by optical coherence tomography."
Follow-up		2 months
Conclusion		"There were no significant differences in anti-inflammatory effects among the three treatments. These findings suggest that bromfenac is as effective as betamethasone in minimizing inflammatory reactions after cataract surgery."
Notes		Patients who developed clinically significant macular edema at 1 month after cataract surgery were subsequently withdrawn from the study.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"Patients were randomly allocated to [...]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Moschos *et al*. 2012[28]

Methods		Prospective, randomized study
Participants	n (eyes)	79
Interventions	Topical CS	Chloramphenicol 0.5%/ dexamethasone sodium phosphate 0.1%, 1 drop 4 times a day for 28 days after phacoemulsification.
	Topical CS & NSAID	Chloramphenicol 0.5%/ dexamethasone sodium phosphate 0.1%, 1 drop 4 times a day for 28 days after phacoemulsification; Diclofenac sodium 0.1% 1 drop 3 times a day for 3 days before surgery and 1 drop 3 times a day for 28 days after phacoemulsification.
Outcome	Detection method	OCT (time domain)
	Definition	-
Follow-up		28 days
Conclusion		"The addition of diclofenac did not seem to offer any additional benefit after uneventful phacoemulsification."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	**Authors' judgment**	**Support for judgment**
Selection bias (sequence generation)	Low risk	"Patients were randomized through random number generation [...]"
Selection bias (sequence concealment)	Unclear risk	"Patients were randomized through random number generation [...]" Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality measure	**Authors' judgment**
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Negi *et al*. 2006[45]

Methods		Prospective randomized controlled study
Participants	n (eyes)	54
Interventions	Oral AZ & topical CS & subconjunctival CS	A single dose of 250 mg AZ orally before discharge; Bethamethasone sodium phosphate 0.1%/ neomycin sulfate 0.5% drops 4 times a day for 30 days; 4 mg betamethasone injected subconjunctivally.
	Oral AZ & subconjunctival CS & subtenon CS	A single dose of 250 mg AZ orally before discharge; A single posterior subtenon's injection of 20 or 30 mg triamcinolone; 4 mg betamethasone injected subconjunctivally.
Outcome	Detection method	Oral fluorescein angiography
	Definition	"Angiograms were graded depending on the severity of fluorescein leakage as follows: Grade 1: edema less than perifoveal Grade 2: minimal perifoveal edema Grade 3: moderate perifoveal edema Grade 4: severe perifoveal edema." "Clinical cystoid macular edema was defined as Snellen BCVA of 6/9 or less."
Follow-up		90 days
Conclusion		"A single subtenon's injection of 30 mg triamcinolone seems to be safe and effective as a route of steroid delivery after uneventful phacoemulsification surgery."
Notes		"Initial ethical approval was obtained for the use of 20 mg triamcinolone. However, after the first 10 patients were randomized to the injection group [...] it was decided to modify the protocol. The remaining patients were injected with 30 mg of triamcinolone." "Sub analysis of the injection group, revealed that of the 11 eyes that had angiographic cystoid macular edema at 30 days, 7 were in the group who had received 20 mg of triamcinolone and only 4 of 17 patients (23%) had received the 30 mg dose (p = 0.04)"

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"randomized controlled clinical trial" Insufficient information to permit judgment
Selection bias (sequence concealment)	Low risk	"At the end of the procedure, the operating theater nurse opened the study envelope to ascertain randomization [...]"
Performance bias (blinding of participants)	High risk	No placebo eye drops used in the "injection group".
Performance bias (blinding of personnel)	Low risk	"[...] best corrected visual acuity on the logMAR chart by masked optometrists [...]"
Detection bias (blinding of outcome assessment)	Low risk	"printouts of the angiograms were read by a masked observer [...]"
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

AZ: acetazolamide; BCVA: best corrected visual acuity; CS: corticosteroid; logMAR: logarithm of minimum angle of resolution; RCT: randomized controlled trial

Ticly *et al*. 2014[29]

Methods		Single-center, prospective, double-masked, randomized clinical study
Participants	n (eyes)	91 patients, no. of eyes included in the study was not reported (one eye per patient assumed for this meta-analysis). "Patients with nuclear cataract density of 2 and 3 [...]"
Interventions	Topical CS	Prednisolone acetate 1% 4 times daily for 3 days preoperatively and 5 weeks postoperatively; Dextran/hypromellose (placebo) 4 times daily for 3 days preoperatively and 5 weeks postoperatively.
	Topical CS & NSAID	Prednisolone acetate 1% 4 times daily for 3 days preoperatively and 5 weeks postoperatively; Ketorolac tromethamine 0.4% 4 times daily for 3 days preoperatively and 5 weeks postoperatively.
Outcome	Detection method	OCT (spectral domain) & fluorescein angiography
	Definition	"The primary outcome measured was angiographic cystoid macular edema incidence. We classified cystoid macular edema based on fluorescein angiography using Miyake's classification. Cystoid leakage included petalloid or honeycombed patterns of hyperfluorescence and dye pooling in well-defined foveal or parafoveal spaces." "Cystoid macular edema on OCT was defined as the presence of well-defined cystic fluid pockets [...] or a central subfield thickness above 315 µm."
Follow-up		5 weeks
Conclusion		"There was no difference between ketorolac tromethamine and a placebo with regard to best corrected visual acuity results or prevention of cystoid macular edema after uncomplicated cataract surgery."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"random number table [...]"
Selection bias (sequence concealment)	Low risk	"A pharmacist provided the patient with a small individual envelope, and after viewing the random number, the patient took the respective eye drop bottle."
Performance bias (blinding of participants)	Low risk	"All study participants were blinded to their treatment assignment."
Performance bias (blinding of personnel)	Low risk	"The surgeon and the ophthalmologist who collected the data were not aware of the group assignment of the patients."
Detection bias (blinding of outcome assessment)	Low risk	"The reader of fluorescein angiograms was blinded as to group allocation."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Wang *et al*. 2013[43]

Methods		Prospective, randomized study
Participants	n (eyes)	240
Interventions	Oral CS & topical CS	Oral prednisone tablets 15 mg for 7 days; Ophthalmic fluorometholone 0.1% 3 times a day for 1 month postoperatively.
	Oral CS & topical CS	Oral prednisone tablets 15 mg for 7 days; Ophthalmic dexamethasone 0.1% 3 times a day for 1 month postoperatively.
	Oral CS & topical NSAID	Oral prednisone tablets 15 mg for 7 days; Ophthalmic bromfenac sodium 0.1% twice per day for 1 month postoperatively.
	Oral CS & topical NSAID	Oral prednisone tablets 15 mg for 7 days; Ophthalmic bromfenac sodium 0.1% twice per day for 2 months postoperatively.
Outcome	Detection method	OCT (time domain)
	Definition	"The patients with best-corrected visual acuity impairment and macular alterations were considered possible cystoid macular edema patients and the diagnosis was final confirmed by OCT [...] Cystoid macular edema was defined as central retinal thickness > 250 μm and the presence of intraretinal cystoid space beneath the foveal, with the diagnosis confirmed by the same retinal specialist."
Follow-up		2 months
Conclusion		"Bromfenac sodium was more effective and safer than fluorometholone and dexamethasone as an anti-inflammatory, decreasing macular thickness and preventing cystoid macular edema in age-related cataract patients after cataract surgery."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"Random-numbers table"
Selection bias (sequence concealment)	Unclear risk	"Randomly and prospectively assigned [...] by a random-numbers table." Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	High risk	"The drugs were applied [...] open-labeled."
Performance bias (blinding of personnel)	High risk	"The drugs were applied [...] open-labeled."
Detection bias (blinding of outcome assessment)	High risk	"The drugs were applied [...] open-labeled."
Attribution bias (incomplete outcome data)	Unclear risk	Missing outcome data balanced in numbers across intervention groups. Reasons for drop-out not reported.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Yavas *et al*. 2007[30]

Methods		Prospective, randomized study
Participants	n (eyes)	189 Right eyes of 189 patients
Interventions	Topical CS	1 drop of topical prednisolone acetate 1% 4 times daily for 1 month postoperatively.
	Topical CS & NSAID	1 drop of topical prednisolone acetate 1% 4 times daily for 1 month postoperatively; 1 drop of topical indomethacin 0.1% 4 times daily for 3 days preoperatively and 4 times daily for 1 month postoperatively.
	Topical CS & NSAID	1 drop of topical prednisolone acetate 1% 4 times daily for 1 month postoperatively; 1 drop of topical indomethacin 0.1% 4 times daily for 1 month postoperatively.
Outcome	Detection method	Fluorescein angiography
	Definition	"Slight fluorescein leakage into the cystic space without enclosing the entire central fovea or complete fluorescein accumulation in the cystic space was diagnosed as angiographic cystoid macular edema."
Follow-up		3 months
Conclusion		"Non-steroidal anti-inflammatory drugs decreased the incidence of CME, and their efficacy increased when begun preoperatively."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	**Authors' judgment**	**Support for judgment**
Selection bias (sequence generation)	Unclear risk	"Patients were randomized into 3 groups." Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Low risk	"Fluorescein leakage to diagnose angiographic cystoid macular edema was evaluated by a masked observer."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	**Authors' judgment**
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	No
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CME: cystoid macular edema; CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

Mixed populations

Almeida *et al*. 2008[31]

Methods		Open-label nonmasked randomized study
Participants	n (eyes)	106
Interventions	Topical CS	A 14-day course of prednisolone acetate 1% 4 times a day for 1 week followed by twice a day for 1 week.
	Topical CS & NSAID	A 14-day course of prednisolone acetate 1% 4 times a day for 1 week followed by twice a day for 1 week; 1 drop of ketorolac tromethamine 0.5% (Acular) 4 times a day beginning 2 days before surgery and for 29 days after surgery, for a total of 31 days.
Outcome	Detection method	OCT (time domain)
	Definition	-
Follow-up		1 month
Conclusion		"Used prophylactically after cataract surgery, ketorolac 0.5% was efficacious in decreasing postoperative macular edema."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"Random number assignment"
Selection bias (sequence concealment)	Unclear risk	"Random number assignment" Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	High risk	"Open-label nonmasked study"
Performance bias (blinding of personnel)	High risk	"Open-label nonmasked study"
Detection bias (blinding of outcome assessment)	High risk	"Open-label nonmasked study"
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Almeida *et al*. 2012[32]

Methods		Prospective placebo-controlled parallel-assignment double-masked randomized clinical trial
Participants	n (eyes)	193
Interventions	Topical CS	Prednisolone 1% drops, started on the day of surgery, 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and 1 time a day for 1 week; Placebo eye drops 4 times a day, beginning 1 day before surgery and continued for four weeks.
	Topical CS & NSAID	Prednisolone 1% drops, started on the day of surgery, 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and 1 time a day for 1 week; Nepafenac 0.1% eye drops 4 times a day, beginning 1 day before surgery and continued for four weeks.
	Topical CS & NSAID	Prednisolone 1% drops, started on the day of surgery, 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and 1 time a day for 1 week; Ketorolac 0.5% eye drops 4 times a day, beginning 1 day before surgery and continued for four weeks.
Outcome	Detection method	OCT (time domain)
	Definition	-
Follow-up		1 month
Conclusion		"One month after uneventful phacoemulsification, there was no difference in macular volume between the placebo, ketorolac, and nepafenac. Thus, for patients without risk factors having routine surgery, prophylactic topical NSAIDs are not recommended."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"Patients were randomly assigned to [...]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Low risk	"[...] identical generic drop bottles that were individually made by the hospital investigational pharmacy division."
Performance bias (blinding of participants)	Low risk	"Identical generic drop bottles"
Performance bias (blinding of personnel)	Unclear risk	"Double masked". Unclear whether personnel and/or outcome assessor were blinded.
Detection bias (blinding of outcome assessment)	Unclear risk	"Double masked". Unclear whether personnel and/or outcome assessor were blinded.
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Unclear
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Cable *et al*. 2012[18]		
Methods		Prospective, randomized, investigator-masked, parallel-group, comparative clinical study
Participants	n (eyes)	20
		Patients without preexisting macular or retinal edema or more than two microaneurysms within the fundus
Interventions	Topical CS & NSAID	Prednisolone acetate 1% intraoperatively; Difluprednate once daily for 3 weeks postoperatively; Bromfenac ophthalmic solution 0.09% once daily. Dosing began 3 days before cataract surgery, continuing to day 21 post surgery.
	Topical CS & NSAID	Prednisolone acetate 1% intraoperatively; Difluprednate once daily for 3 weeks postoperatively; Nepafenac ophthalmic suspension 0.1% three times daily. Dosing began 3 days before cataract surgery, continuing to day 21 post surgery.
Outcome	Detection method	OCT (time domain)
	Definition	-
Follow-up		6 weeks
Conclusion		"Both bromfenac and nepafenac resulted in positive clinical outcomes of ETDRS visual acuities. Postoperative measurements of macular volume and retinal thickness of bromfenac subjects showed a trend toward improved vision, less retinal thickening, and more stable macular volumes overall."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Bias	**Authors' judgment**	**Support for judgment**
Selection bias (sequence generation)	Low risk	"[...] according to a computer-generated randomization list [...]"
Selection bias (sequence concealment)	Low risk	"The investigator and technicians recording study data were masked to treatment group assignment for the duration of the trial [...]"
Performance bias (blinding of participants)	Unclear risk	"Subjects were masked to the study drug identity for the entirety of the trial" However, the frequency of administration varied between treatment groups.
Performance bias (blinding of personnel)	Low risk	"All measurements were completed by masked observers."
Detection bias (blinding of outcome assessment)	Low risk	"The investigator and technicians recording study data were masked to treatment group assignment for the duration of the trial [...]"
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)	
Quality measure	**Authors' judgment**
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	Yes

CS: corticosteroid; ETDRS: early treatment diabetic retinopathy study; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Cervantes-Coste *et al*. 2009[33]

Methods		Prospective, randomized, single-masked comparative study
Participants	n (eyes)	60
	Characteristics	Patients without non-controlled diabetes mellitus, based on clinical history and blood glucose level, proliferative diabetic retinopathy, and/or macular edema.
Interventions	Topical CS	Dexamethasone treatment 4 times daily for 10 days after surgery.
	Topical CS & NSAID	Dexamethasone treatment 4 times daily for 10 days after surgery; 1 drop of nepafenac 0.1% 3 times daily 1 day prior to surgery, every 15 minutes 1 hour prior to surgery and 3 times daily for 6 weeks afterward.
Outcome	Detection method	OCT (time domain)
	Definition	"Clinically significant macular edema associated with vision loss."
Follow-up		6 weeks
Conclusion		"Prophylactic use of nepafenac was effective in reducing macular edema after cataract surgery and in maintaining trans-operative mydriasis."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"[…] patients were randomly selected […]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (blinding of personnel)	High risk	"The identity of patients receiving nepafenac was concealed form the surgeon." Other personnel was not masked (single-masked study).
Detection bias (blinding of outcome assessment)	High risk	Other personnel was not masked (single-masked study).
Attribution bias (incomplete outcome data)	Low risk	"All patients completed the follow-up visits over a 6-week period."

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Chatziralli *et al*. 2011[42]

Methods		Randomized study
Participants	n (eyes)	145
Interventions	Oral AZ & topical CS & NSAID	Half a tablet of acetazolamide 250 mg the night prior to surgery and on the morning before surgery; Ketorolac tromethamine 0.5% three times daily, three days before surgery; Dexamethasone 0.1% five times daily, three days before surgery and 1 drop 4 times per day 28 days after surgery.
	Oral AZ & topical CS & NSAID	Half a tablet of acetazolamide 250 mg the night prior to surgery and on the morning before surgery; Ketorolac tromethamine 0.5% three times daily, three days before surgery and 28 days after surgery; Dexamethasone 0.1% five times daily, three days before surgery and 1 drop 4 times per day 28 days after surgery.
Outcome	Detection method	Fundoscopy & Amsler grid test
	Definition	-
Follow-up		42 days
Conclusion		"The addition of ketorolac did not seem to offer any additional benefit in terms of inflammation-related signs. Four weeks appeared as an adequate treatment interval."
Notes		"In case 1 inflammation-related sign (corneal edema, conjunctival hyperemia or Tyndall reaction) was present on day 28, the treatment was continued. Irrespective of continuation, on day 42 all patients underwent fundoscopy and an Amsler grid test, so as to trace any suspicious signs for the development of clinically significant cystoid macular edema."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"The patients were randomized [...]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	Low risk	"The study was masked to the patients [...]"
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	No
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

AZ: acetazolamide; CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

Miyake *et al*. 2000[23]

Methods		Multicentered, prospective open clinical study
Participants	n (eyes)	118
	Characteristics	Eyes without complications from diabetes mellitus
Interventions	Topical CS	0.1% fluorometholone at 3 hours, 2 hours, 1 hour, and 30 minutes prior to surgery, and 3 times a day for 8 consecutive weeks following surgery.
	Topical NSAID	0.1% diclofenac at 3 hours, 2 hours, 1 hour, and 30 minutes prior to surgery, and 3 times a day for 8 consecutive weeks following surgery.
Outcome	Detection method	Fluorescein angiography
	Definition	"I°: minimal fluorescein leakage into the cystic space but not surrounding the entire fovea; II°: fluorescein leakage surrounding nearly the entire fovea but less than 2.0 mm in diameter; III°: fluorescein leakage surrounding the fovea and larger than 2.0 mm in diameter."
Follow-up		8 weeks
Conclusion		"These findings suggest that diclofenac effectively prevents CME following cataract surgery and that CME is closely related to the breakdown of the blood–aqueous barrier."
Notes		"Five to 15 consecutive patients were enrolled at each site [...]"

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	**Authors' judgment**	**Support for judgment**
Selection bias (sequence generation)	Unclear risk	"[...] eyes were assigned to [...]" The authors assumed that the trial was randomized, because baseline factors were equal in both treatment groups in a study population of > 100 subjects. Nevertheless, there was insufficient information to permit judgment about the sequence generation process.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	High risk	"Open trial"
Performance bias (blinding of personnel)	High risk	"Open trial"
Detection bias (blinding of outcome assessment)	Low risk	"CME was evaluated in a double-masked fashion [...]"
Attribution bias (incomplete outcome data)	High risk	Visual acuity was available for approximately half of the study subject.

Quality of RCT (additional items Delphi List)

Quality measure	**Authors' judgment**
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CME: cystoid macular edema; CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

Miyake *et al*. 2007[25]

Methods		Prospective, double-masked, randomized study
Participants	n (eyes)	62
Interventions	Topical CS	Fluorometholone eye drops four times before surgery (3 hours, 2 hours, and 1 hour and 30 minutes) and three times a day for 5 weeks after surgery.
	Topical NSAID	Diclofenac eye drops four times before surgery (3 hours, 2 hours, and 1 hour and 30 minutes) and three times a day for 5 weeks after surgery.
Outcome	Detection method	Fluorescein angiography
	Definition	"1: slight dye accumulation in the cystic space and incompletely surrounding the fovea; 2: dye accumulation surrounding the fovea with a diameter of less than 2 mm; 3: dye accumulation surrounding the fovea with a diameter greater than 2 mm."
Follow-up		5 weeks
Conclusion		"Reduction of choroidal blood flow, disruption of the blood-aqueous barrier, and incidence of cystoid macular edema in early postsurgical pseudophakic eyes were more effectively prevented chronologically in eyes treated with diclofenac than in those treated with fluorometholone."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"Each patient was randomly assigned [...] using the envelope method"
Selection bias (sequence concealment)	Unclear risk	"Each patient was randomly assigned [...] using the envelope method" Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	Unclear risk	"Double masked study [...]" Unknown whether participants were blinded.
Performance bias (blinding of personnel)	Unclear risk	"Double masked study [...]" Unknown whether personnel was blinded.
Detection bias (blinding of outcome assessment)	Low risk	"Cystoid macular edema [...] was analyzed by one of the authors in a masked fashion."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

Miyake *et al*. 2011[26]

Methods		Randomized double-masked single-center clinical study
Participants	n (eyes)	60
	Characteristics	Patients without diabetic retinopathy
Interventions	Topical CS	Fluorometholone 0.1% one drop 3 times a day starting the day before surgery until 5 weeks postoperatively. An additional 1 drop was given on the day of surgery.
	Topical NSAID	Nepafenac 0.1% one drop 3 times a day starting the day before surgery until 5 weeks postoperatively. An additional 1 drop was given on the day of surgery.
Outcome	Detection method	OCT (spectral domain) & fluorescein angiography
	Definition	"I: slight fluorescein leakage into the cystic space, but not enough to enclose the entire fovea centralis. II: there is complete circular accumulation of the fluorescein in the cystic space, but the diameter of the accumulation is smaller than 2.0 mm. III: the fluorescein leakage surrounds the fovea and is larger than 2.0 mm in diameter."
Follow-up		5 weeks
Conclusion		"Nepafenac was more effective than fluorometholone in preventing angiographic cystoid macular edema and blood-aqueous barrier disruption, and results indicate nepafenac leads to more rapid visual recovery."
Notes		No definition of cystoid macular edema on OCT given.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	**Authors' judgment**	**Support for judgment**
Selection bias (sequence generation)	Unclear risk	"Randomized to" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	Low risk	"The 2 drugs had identical outer appearances and could not be differentiated."
Performance bias (blinding of personnel)	Low risk	"Fluorescein angiography was used to confirm the presence of cystoid macular edema [...] in a double masked manner."
Detection bias (blinding of outcome assessment)	Low risk	"[...] physician determined and graded the severity [...] in a double-masked manner."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	**Authors' judgment**
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Nishino *et al*. 2009[41]

Methods		Single-blind, randomized, prospective study
Participants	n (eyes)	28 (of 21 patients)
Interventions	Topical NSAID	Topical bromfenac sodium every 20 minutes 2 hours prior to surgery and from the day after surgery, twice daily.
	Topical CS & NSAID & subconjunctival CS	0.1% topical fluorometholone 4 times daily; Topical bromfenac sodium every 20 minutes 2 hours prior to surgery and from the day after surgery, twice daily; Subconjunctival injection of approximately 0.5 ml phosphoric acid dexamethasone was injected at the end of the surgery.
Outcome	Detection method	Fluorescein angiography
	Definition	"Fluorescein fundus angiography was performed only when cystoid macular edema was suspected to worsen the visual acuity to less than 0.7."
Follow-up		1 month
Conclusion		"Topical steroid medication may not be absolutely essential after uneventful phaco-emulsification/aspiration plus intraocular lens implantation."
Notes		"Cystoid macular edema was not found in any of patients."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"All participants were prospectively evaluated by randomizing into 2 groups." Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (blinding of personnel)	Unclear risk	"Single-blind study". Unknown whether personnel was blinded.
Detection bias (blinding of outcome assessment)	Unclear risk	"Single-blind study". Unknown whether outcome assessor was blinded.
Attribution bias (incomplete outcome data)	Unclear risk	No report on drop-out

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

Weber *et al*. 2013[34]

Methods		Prospective, multicenter, investigator-masked, parallel-group, randomized, active-controlled clinical study
Participants	n (eyes)	123
	Characteristics	Patients without diabetic retinopathy
Interventions	Topical NSAID	Indomethacin 0.1% one drop four times daily for 3 weeks, beginning 24 hours prior to surgery.
	Topical NSAID	Ketorolac 0.5% one drop four times daily for 3 weeks, beginning 24 hours prior to surgery.
Outcome	Detection method	OCT (time domain)
	Definition	-
Follow-up		90 days
Conclusion		"Indomethacin 0.1% was at least as effective as ketorolac 0.5% at day 1 and more effective than ketorolac 0.5% at day 7 in treating ocular inflammation after uncomplicated cataract surgery."
Notes		"Corticosteroids were to be administered at follow-up visits in the following cases: conjunctival hyperemia grade ≥ 3, ciliary flush grade ≥ 3, fibrinoid exudate, hypopyon, retrocorneal precipitates or posterior synechiae in the study eye." *Non-inferiority trial: the trial was designed to investigate the non-inferiority of indomethacin to ketorolac.*

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"treatment was determined by a unique randomization table"
Selection bias (sequence concealment)	Unclear risk	"Allocation of treatment was determined by a unique randomization table [...]" Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	Low risk	"Both drugs were labelled identically to preserve masking [...] with the patients being masked to the treatment name."
Performance bias (blinding of personnel)	Unclear risk	"The study was investigator-masked [...]" Unknown whether personnel were blinded.
Detection bias (blinding of outcome assessment)	Unclear risk	"The study was investigator-masked [...]" Unknown whether the outcome assessor was blinded.
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	Yes

NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Wittpenn *et al*. 2008[35]

Methods		Prospective, randomized, investigator-masked, multicenter study
Participants	n (eyes)	546
	Characteristics	Patients with no ocular manifestations of systemic diseases
Interventions	Topical CS & NSAID	Four doses of ketorolac 0.4% during the one hour prior to surgery; Prednisolone acetate 1% four times daily after surgery until patients exited the study at weeks four to six; Artificial tear solution (placebo).
	Topical CS & NSAID	Ketorolac 0.4% four times daily for three days prior to surgery, four doses every 15 minutes one hour preoperatively and four times daily until they exited the study at weeks four to six; Prednisolone acetate 1% four times daily after surgery until one 5-ml bottle was empty.
Outcome	Detection method	OCT (type unknown)
	Definition	"Definite CME: Presence of cystoid changes associated with substantial (≥ 40 µm) retinal thickening on OCT. Probable CME: Presence of changes in retinal contour and increased macular thickness relative to preoperative baseline, but without definite cystoid changes. Possible CME: Mild to moderate changes in retinal thickness or contour without cystoid changes."
Follow-up		4-6 weeks "Patients were exited from the study when the surgeon felt the patient had achieved best-obtainable visual acuity and no inflammation was present."
Conclusion		"This study suggests that adding perioperative ketorolac to postoperative prednisolone significantly reduces the incidences of CME and macular thickening in cataract surgery patients already at low risk for this condition."
Notes		"Patients could also be exited from the study if, on postoperative day 1, the surgeon felt the amount of inflammation was greater than expected and, in his best clinical judgment, more aggressive anti-inflammatory treatment was indicated."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"[...] using a randomly generated list"
Selection bias (sequence concealment)	Unclear risk	"[...] using a randomly generated list" Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	Low risk	"The labels were covered. Patients would only have been unmasked if they researched the type and shape of the different bottles."
Performance bias (blinding of personnel)	High risk	"The technical staff was unmasked."
Detection bias (blinding of outcome assessment)	Low risk	"OCT–based diagnosis of CME was made by an experienced and masked retina specialist"
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CME: cystoid macular edema; CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Diabetic populations

Ahmadabadi *et al*. 2010[37]

Methods		Prospective randomized controlled study
Participants	n (eyes)	41
	Characteristics	"Patients with type 2 diabetes and moderate non-proliferative diabetic retinopathy"
Interventions	Topical CS	Betamethasone 0.1% eye drops 6 times a day for 1 week. After 1 week, the betamethasone was tapered over 4 weeks.
	Topical CS & intravitreal CS	Betamethasone 0.1% eye drops 6 times a day for 1 week. After 1 week, the betamethasone was tapered over 4 weeks; Injection of 2 mg of triamcinolone acetonide 3.5 mm posterior to the inferotemporal limbus.
Outcome	Detection method	OCT (time domain) & fluorescein angiography
	Definition	"Clinical cystoid macular edema was defined as a subjective report of decreased vision by the patient, ophthalmoscopic detection of the presence of macular edema, and confirmation of the diagnosis by fluorescein angiography and OCT examinations at any postoperative visit."
Follow-up		6 months
Conclusion		"Intravitreal injection of triamcinolone reduced the amount of increase in center point thickness and central 1.0 mm subfield mean thickness after phacoemulsification in eyes of diabetic patients. Although it also reduced the incidence of CME, it had no effect on visual acuity gain."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"Using computer-generated random numbers [...]"
Selection bias (sequence concealment)	Unclear risk	"Using computer-generated random numbers [...]" Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes (partial)
Intention-to-treat analysis included?	No

CME: cystoid macular edema; CS: corticosteroid; OCT: optical coherence tomography; RCT: randomized controlled trial

Chae *et al*. 2014[38]

Methods		Prospective randomized study
Participants	n (eyes)	80
	Characteristics	"Patients with stable diabetic retinopathy without significant macular edema"
Interventions	Placebo	The needle tip was only touched to the conjunctiva surface.
	Intravitreal anti-VEGF	0.05 ml of a solution containing 0.5 mg of ranibizumab was injected intravitreally at the sclera from 3 mm posterior to the limbus
Outcome	Detection method	OCT (spectral domain) & fluorescein angiography
	Definition	"Postoperative diabetic macular edema was defined as a > 60 mm increase in central subfield thickness relative to the screening central subfield thickness value, as assessed by spectral domain OCT." "Using fluorescein angiography, postoperative diabetic macular edema was scored as follows: (method of Antcliff *et al*): Grade 0: no perifoveal hyperfluorescence Grade 1: incomplete perifoveal hyperfluorescence Grade 2: mild 360° hyperfluorescence Grade 3: severe 360° hyperfluorescence with the hyperfluorescent area being ≈ 1 disk diameter."
Follow-up		6 months
Conclusion		"In patients with stable diabetic retinopathy without significant macular edema, intravitreal ranibizumab injection at cataract surgery may prevent the postoperative worsening of macular edema and may improve the final visual outcome without affecting safety."
Notes		The authors do not mention any (standard) anti-inflammatory treatment, used in addition to the intravitreal or sham injection.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"[...] patients were randomly assigned [...] using a table of random numbers."
Selection bias (sequence concealment)	Unclear risk	"[...] patients were randomly assigned [...] using a table of random numbers." Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	Low risk	"In the sham group, the needle tip touched the conjunctiva surface."
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	High risk	The number of drop-outs reported does not match the number of eyes at baseline and endpoint. Percentages, total number of patients and number of patients with cystoid macular edema reported in the article do not match.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

OCT: optical coherence tomography; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Endo *et al*. 2010[44]

Methods		Prospective open-label study
Participants	n (eyes)	75
	Characteristics	Diabetic patients, no severe diabetic retinopathy
Interventions	Topical CS	Betamethasone sodium phosphate four times daily for 1 week followed by fluorometholone 0.1% for steroid withdrawal four times daily for 5 weeks.
	Topical NSAID	Bromfenac eye drops were instilled twice daily until week 6.
Outcome	Detection method	OCT (time domain)
	Definition	-
Follow-up		6 weeks
Conclusion		"Bromfenac suppressed anterior chamber inflammation and increasing retinal thickening after cataract surgery in patients with non-proliferative diabetic retinopathy."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"[...] using the envelope method."
Selection bias (sequence concealment)	Unclear risk	"[...] using the envelope method." Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	High risk	"open-label study"
Performance bias (blinding of personnel)	High risk	"open-label study"
Detection bias (blinding of outcome assessment)	High risk	"open-label study"
Attribution bias (incomplete outcome data)	Unclear risk	Drop-outs not specified per treatment group

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	No (significant higher HbA1c in bromfenac group)
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; HbA1c: hemoglobin A1c; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Fard *et al*. 2011[39]

Methods		Prospective randomized study
Participants	n (eyes)	63
	Characteristics	Patients with preexisting moderate or severe non-proliferative diabetic retinopathy and a preoperative central macular thickness of < 200 µm on OCT
Interventions	Placebo	Standardized procedure of phacoemulsification with intraocular lens implantation alone.
	Intravitreal anti-VEGF	1.25 mg intravitreal bevacizumab at the end of surgery.
Outcome	Detection method	OCT (time domain)
	Definition	"Increase in center point thickness on OCT after cataract surgery."
Follow-up		6 months
Conclusion		"Intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is effective just for the short term and 6-month results are the same as the control group."
Notes		Standardized procedure not described. The authors do not mention any (standard) anti-inflammatory treatment, used in addition to the intravitreal or sham injection.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"Patients were randomized to [...]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this for the primary outcome measurement (OCT). "Progression of diabetic retinopathy was based on assessment in a masked fashion by a retina specialist."
Attribution bias (incomplete outcome data)	High risk	Number of patients lost to follow-up was higher in the control group. No reasons for drop-out were given.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

OCT: optical coherence tomography; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Kim *et al*. 2008[36]

Methods		Prospective randomized controlled study
Participants	n (eyes)	46 (of 23 patients)
	Characteristics	Noninsulin-dependent diabetic patients and mild to moderate non-proliferative diabetic retinopathy or no retinopathy
Interventions	Topical CS	Prednisolone acetate eye drops 1%, 1 drop 4 times daily from the day of surgery until 1 month and 1 drop 2 times daily for the following 2 weeks.
	Topical CS & Subtenon CS	Prednisolone acetate eye drops 1%, 1 drop 4 times daily from the day of surgery until 1 month and 1 drop 2 times daily for the following 2 weeks; Subtenon capsule injection of triamcinolone acetonide at the end of cataract surgery.
Outcome	Detection method	OCT (type unknown) & fluorescein angiography
	Definition	"Postsurgical cystoid macular edema was defined as decreased visual acuity and cystoid macular edema on OCT."
Follow-up		6 months
Conclusion		"A posterior subtenon injection of triamcinolone acetonide lowered the incidence of cystoid macular edema after cataract surgery in diabetic patients, improved visual recovery, and reduced the amount of central macular thickness increase in the short term (≤ 1 month postoperatively). However, triamcinolone acetonide did not affect DR progression over the 6-month follow-up."
Notes		-

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Low risk	"The assignment [...] was made using computer-generated random numbers."
Selection bias (sequence concealment)	Unclear risk	"The assignment [...] was made using computer-generated random numbers" Unknown whether appropriate safeguards were used.
Performance bias (blinding of participants)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	Paired eye comparison

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; DR: diabetic retinopathy; OCT: optical coherence tomography; RCT: randomized controlled trial

Singh *et al*. 2012[47]

Methods		Multicenter, randomized, double-masked, vehicle-controlled study
Participants	n (eyes)	263
	Characteristics	Diabetic (type 1 or type 2) patients with an existing diagnosis of non-proliferative diabetic retinopathy
Interventions	Topical CS	Prednisolone acetate ophthalmic suspension four times daily for 2 weeks postsurgery or longer if considered necessary to treat anterior segment inflammation.
	Topical CS & NSAID	Prednisolone acetate ophthalmic suspension four times daily for 2 weeks postsurgery or longer if considered necessary to treat anterior segment inflammation; Nepafenac ophthalmic suspension 0.1% three times daily on the day prior to cataract surgery, on the day of surgery and for 90 days thereafter.
Outcome	Detection method	OCT (time domain)
	Definition	"Macular edema was defined as ≥ 30% increase in central subfield macular thickness relative to the presurgical baseline measurement."
Follow-up		90 days
Conclusion		"Nepafenac demonstrated statistically significant and clinically relevant advantages compared with vehicle in preventing macular edema and maintaining visual acuity in diabetic patients following cataract surgery. These advantages were seen at multiple time points over the course of the 90-day therapy period."
Notes		Prednisolone eye drops were used longer if considered necessary to treat postoperative inflammation.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"Enrolled patients were randomized to [...]" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	Low risk	"Double masked, vehicle-controlled study"
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Low risk	"Morphological features, including intraretinal cysts, were analyzed by the reading center in a masked fashion."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial

Udaondo *et al*. 2011[40]

Methods		Prospective randomized controlled intervention study
Participants	n (eyes)	54
	Characteristics	"Patients with some degree of diabetic retinopathy without macular involvement"
Interventions	Topical CS	Dexamethasone eye drops four times a day for one month.
	Topical CS & Intravitreal anti-VEGF	Dexamethasone eye drops four times a day for one month; An intravitreal injection of ranibizumab (0.5 ml of solution at 10 mg/ml) at the end of surgery.
Outcome	Detection method	OCT (Spectral domain)
	Definition	"Clinically significant macular edema was defined as macular edema involving or threatening the center of the macula as defined by the ETDRS."
Follow-up		3 months
Conclusion		"The combination of intravitreal ranibizumab and uncomplicated phacoemulsification avoids the macular thickening measured by OCT in mild to moderate diabetic retinopathy patients without previous macular involvement."
Notes		Postoperative central subfield thickness is only reported for eyes that developed central subfield macular thickness.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' judgment	Support for judgment
Selection bias (sequence generation)	Unclear risk	"Randomized study" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of participants)	Unclear risk	The study did not address this outcome.
Performance bias (blinding of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (blinding of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

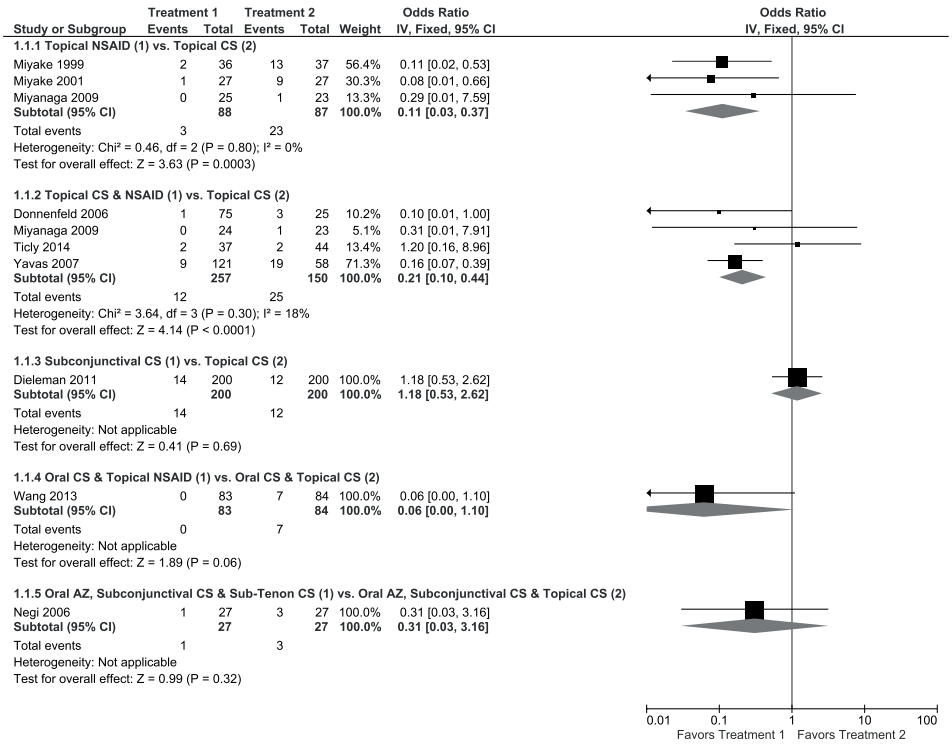
Quality of RCT (additional items Delphi List)

Quality measure	Authors' judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS: corticosteroid; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

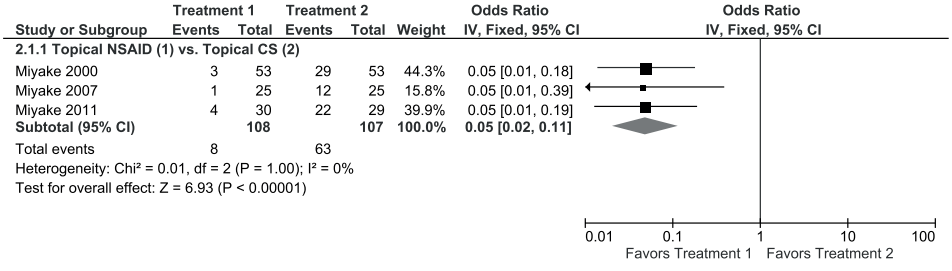
Appendix 3. Additional figures

Figure 1. Odds ratios with 95% confidence intervals for the incidence of cystoid macular edema within 3 months after cataract surgery in non-diabetics



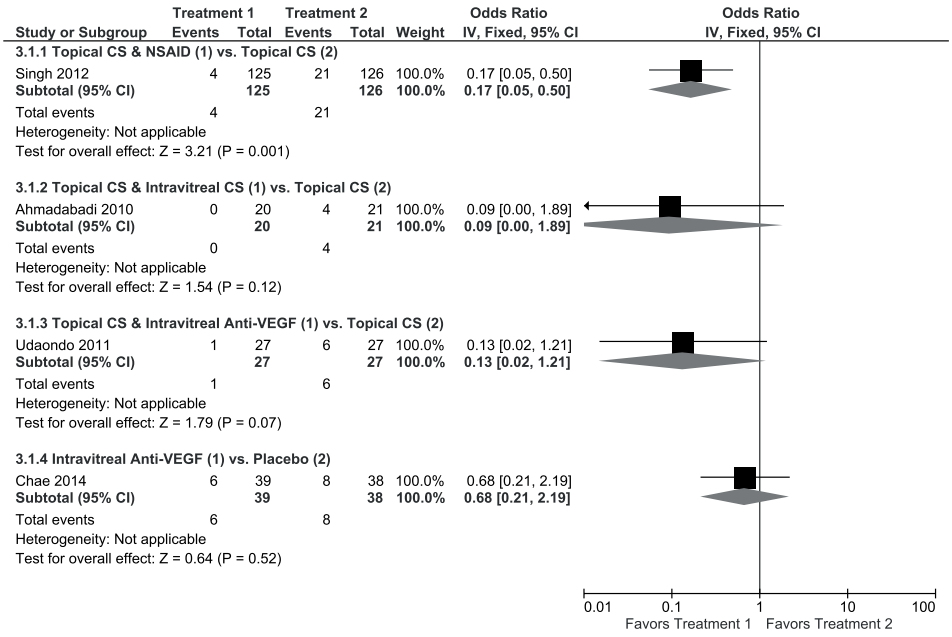
AZ: acetazolamide; CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; 95% CI: 95% confidence interval

Figure 2. Odds ratio with 95% confidence interval for the incidence cystoid macular edema within 3 months after cataract surgery in a mixed population



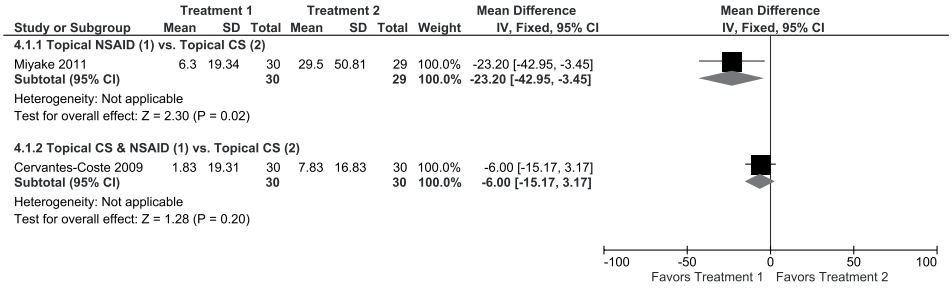
CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; 95% CI: 95% confidence interval

Figure 3. Odds ratios with 95% confidence intervals for the incidence cystoid macular edema within 3 months after cataract surgery in diabetics



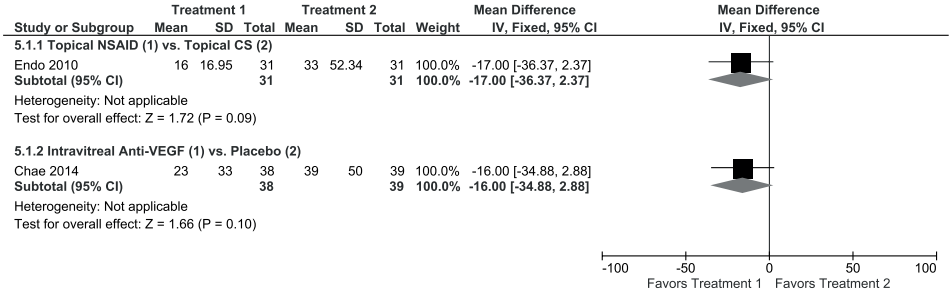
CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; VEGF: vascular endothelial growth factor; 95% CI: 95% confidence interval

Figure 4. Mean differences with 95% confidence intervals for change in central foveal thickness within 3 months after cataract surgery as compared to baseline in a mixed population



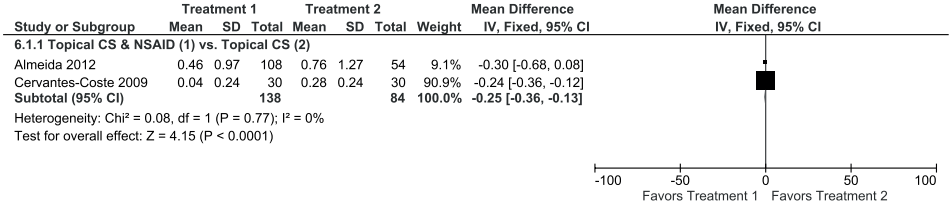
CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; 95% CI: 95% confidence interval

Figure 5. Mean differences with 95% confidence intervals for change in central foveal thickness within 3 months after cataract surgery as compared to baseline in diabetics



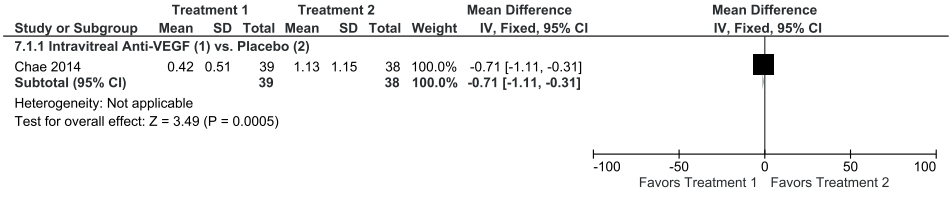
CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; VEGF: vascular endothelial growth factor; 95% CI: 95% confidence interval

Figure 6. Mean difference with 95% confidence interval for change in macular volume within 3 months after cataract surgery as compared to baseline in a mixed population



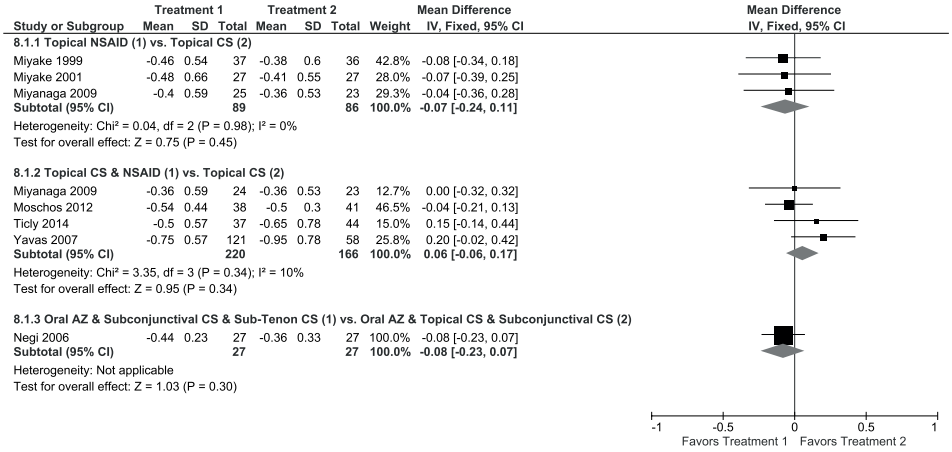
CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; 95% CI: 95% confidence interval

Figure 7. Mean difference with 95% confidence interval for change in macular volume within 3 months after cataract surgery as compared to baseline in diabetics



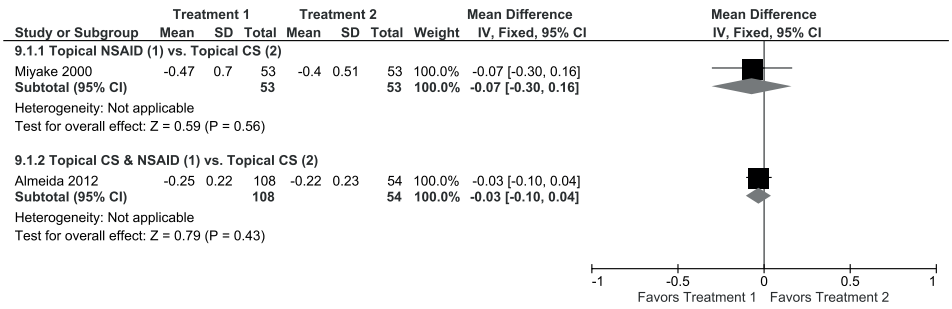
IV: inverse variance; SD: standard deviation; VEGF: vascular endothelial growth factor; 95% CI: 95% confidence interval

Figure 8. Mean differences with 95% confidence intervals for change in corrected distance visual acuity within 3 months after cataract surgery as compared to baseline in non-diabetics



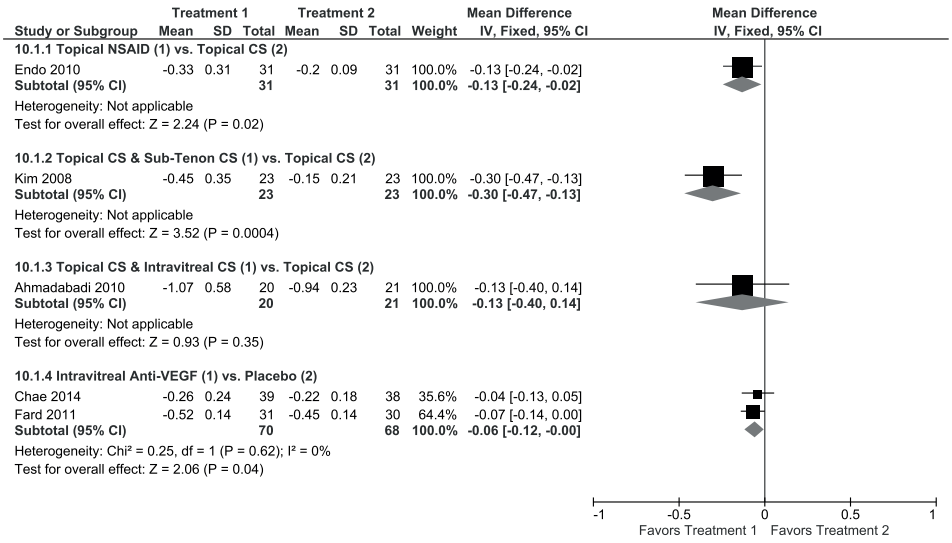
AZ: acetazolamide; CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; 95% CI: 95% confidence interval

Figure 9. Mean differences with 95% confidence intervals for change in corrected distance visual acuity within 3 months after cataract surgery as compared to baseline in a mixed population



CS: corticosteroid; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; 95% CI: 95% confidence interval

Figure 10. Mean differences with 95% confidence intervals for change in corrected distance visual acuity within 3 months after cataract surgery as compared to baseline in diabetics



CS: corticosteroid; df: degrees of freedom; IV: inverse variance; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; VEGF: vascular endothelial growth factor; 95% CI: 95% confidence interval

Figure 11. Risk of bias graph according to the Cochrane Collaboration's tool for assessing risk of bias

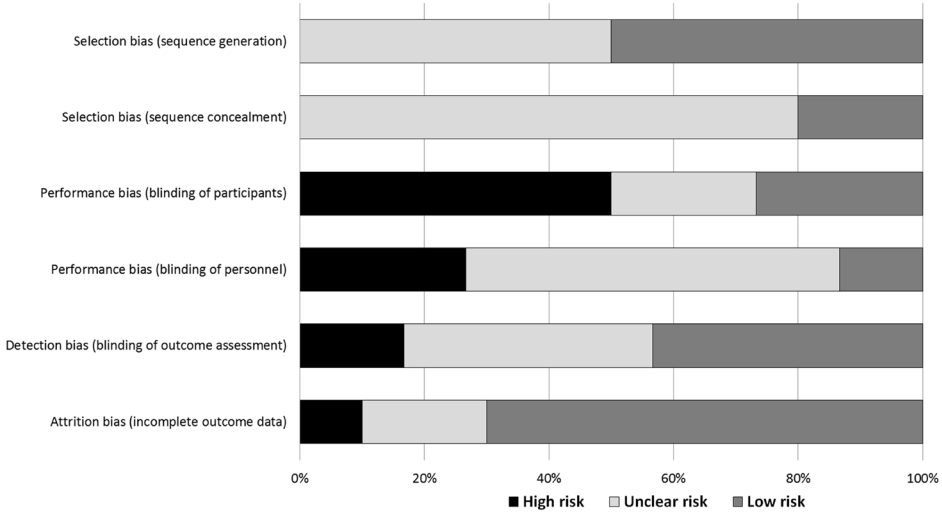
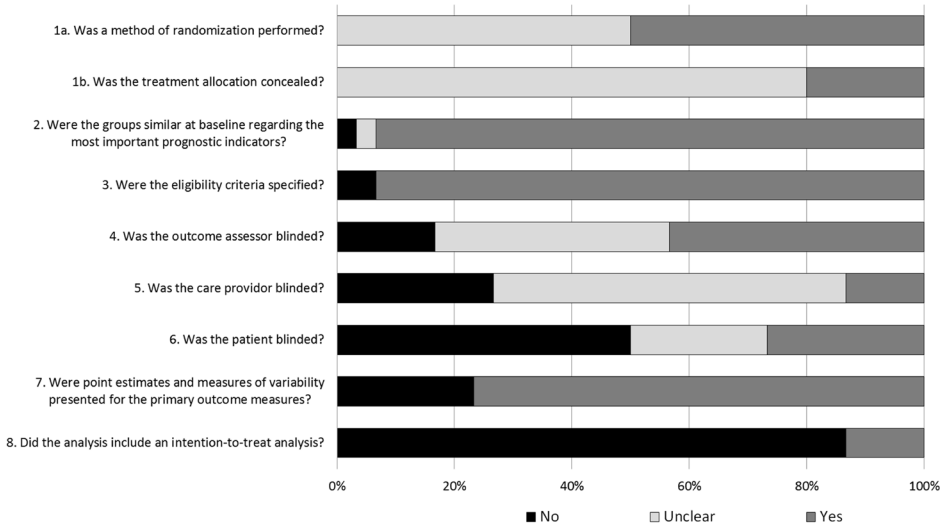


Figure 12. Quality of randomized controlled trials according to the Delphi criteria



Author reply

Author reply to: Prevention of cystoid macular edema after cataract surgery in non-diabetic and diabetic patients: a systematic review and meta-analysis. (Kim SJ, Jampel H. Am J Ophthalmol. 2016 Jan;161:221-2)

Laura H.P. Wielders, Verena A. Lambermont, Jan S.A.G. Schouten, Frank J.H.M. van den Biggelaar, Gill Worthy, Rob W.P. Simons, Bjorn Winkens, Rudy M.M.A. Nuijts
Am J Ophthalmol. 2016 Jan;161:222-3.

We appreciate the interest of drs Stephen Kim and Jampel in our work.[1] The purpose of our systematic review and meta-analysis was to collect and summarize the results of previous randomized controlled trials (RCTs) on the prevention of cystoid macular edema (CME) after cataract surgery. We agree with drs Kim and Jampel that several factors may influence the interpretation of our results. Therefore, we provided a detailed evaluation of the study results in the discussion section, which includes the factors mentioned by drs Kim and Jampel, and discussed below.

We agree with drs Kim and Jampel that visual acuity (VA) is of great clinical importance in the follow-up after cataract surgery. However, many factors may influence postoperative VA. Therefore, we think that VA alone cannot be used as a primary outcome in studies investigating the prevention of CME after cataract surgery. Nevertheless, VA should be incorporated in any definition of clinically significant CME. Unfortunately, we identified numerous definitions in previous studies.

Topical corticosteroids increased the odds of developing CME as compared to non-steroidal anti-inflammatory drugs (NSAIDs) or combination treatment. Previously, Kessel and associates showed that both potent and weaker corticosteroids were less effective than NSAIDs in prevention of CME.[2] Results of ten individual RCTs suggest that topical NSAIDs should be used after cataract surgery in all patients. Whether the use of corticosteroids can be avoided cannot be concluded from our study.

Drs Kim and Jampel refer to a recent study of Tzelikis and associates, who compared topical prednisolone to combination treatment in a mixed population. The authors did not find any differences in mean foveal thickness or VA, which is in line with the results of our meta-analysis.[3] Furthermore, Zaczek and associates recently compared topical combination treatment to topical dexamethasone in non-diabetics and found comparable results.[4] Mechanisms of action of anti-inflammatory treatments are beyond the scope of this review.

Finally, drs Kim and Jampel emphasize the different conclusions reported by the AAO Ophthalmic Technology Assessment Panel.[5] Different conclusion are drawn because both reviews did not include the same original RCTs. The current study provides a complete overview of all relevant RCTs. We performed an extensive literature search, reviewed 161 full-text articles and included 30 individual RCTs. Only 27 full-text articles have been reviewed by the AAO Ophthalmic Technology Assessment Panel, who included 15 trials. Moreover, the panel included many studies investigating the incidence of CME after intracapsular or extracapsular cataract extraction. We decided to exclude these RCTs from our study, since phacoemulsification cataract surgery is the standard of care in most ophthalmic practices.

We excluded one study from our quantitative analysis "because no patient in either treatment group developed CME". This study also did not report mean VA, macular volume or foveal thickness, which is why it could not be included in any meta-analysis.[6]

We agree with drs Kim and Jampel that systematic reviews and meta-analyses cannot fully account for variations between individual studies. Additionally, the quality of included RCTs was moderate to low. We hope that the results of the ESCRS PREvention of Macular EDema after cataract surgery (PREMED) study will provide more evidence-based guidelines.

References

1. Wielders LH, Lambermont VA, Schouten JS, *et al*. Prevention of cystoid macular edema after cataract surgery in nondiabetic and diabetic patients: a systematic review and meta-analysis. Am J Ophthalmol 2015. doi: 10.1016/j.ajo.2015.07.032
2. Kessel L, Tendal B, Jorgensen KJ, *et al*. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. Ophthalmology 2014;121(10):1915-1924.
3. Tzelikis PF, Vieira M, Hida WT, *et al*. Comparison of ketorolac 0.4% and nepafenac 0.1% for the prevention of cystoid macular oedema after phacoemulsification: prospective placebo-controlled randomised study. Br J Ophthalmol 2015;99(5):654-658.
4. Zaczek A, Artzen D, Laurell CG, *et al*. Nepafenac 0.1% plus dexamethasone 0.1% versus dexamethasone alone: effect on macular swelling after cataract surgery. J Cataract Refract Surg 2014;40(9):1498-1505.
5. Kim SJ, Schoenberger SD, Thorne JE, *et al*. Topical Nonsteroidal Anti-inflammatory Drugs and Cataract Surgery: A Report by the American Academy of Ophthalmology. Ophthalmology 2015. doi: 10.1016/j.ophtha.2015.05.014
6. Nishino M, Eguchi H, Iwata A, *et al*. Are topical steroids essential after an uneventful cataract surgery? J Med Invest 2009;56(1-2):11-15.

Chapter 4

European multicenter trial of the prevention of cystoid macular edema after cataract surgery in non-diabetics: ESCRS PREMED study report 1

Laura H.P. Wielders, Jan S.A.G. Schouten, Bjorn Winkens, Frank J.H.M. van den Biggelaar, Claudette A. Veldhuizen, Oliver Findl, Joaquim C.N. Murta, Willem R.O. Goslings, Marie-José Tassignon, Maurits V. Joosse, Ype P. Henry, Alexander H.F. Rulo, José L. Güell, Michael Amon, Thomas Kohnen, Rudy M.M.A. Nuijts, on behalf of the ESCRS PREMED study group

J Cataract Refract Surg. 2018 Apr; 44:429–439

Abstract

Purpose: To compare the efficacy of a topical non-steroidal anti-inflammatory drug, topical corticosteroid, and a combination of both drugs to prevent the occurrence of cystoid macular edema (CME) after cataract surgery in non-diabetic patients.

Setting: Twelve European study centers.

Design: Randomized clinical trial.

Methods: Non-diabetic patients having uneventful cataract surgery were included in this study. Patients were randomized to receive topical bromfenac 0.09% twice daily for two weeks, or dexamethasone 0.1% four times daily with one drop less per day every following week, or a combination of both. The primary outcome was the difference in central subfield mean macular thickness (CSMT) six weeks postoperatively. Secondary outcome measures included corrected distance visual acuity as well as the incidence of CME and clinically significant macular edema (CSME) within six weeks and twelve weeks postoperatively.

Results: This study comprised 914 patients. Six weeks postoperatively, the CSMT was 288.3 µm, 296.0 µm and 284.5 µm in the bromfenac group, dexamethasone group and combination treatment group, respectively (overall $p = 0.006$). The incidence of CSME within twelve weeks postoperatively was 3.6%, 5.1% and 1.5%, respectively (overall $p = 0.043$).

Conclusions: Patients treated with a combination of topical bromfenac 0.09% and dexamethasone 0.1% had a lower risk for developing CSME after cataract surgery than patients treated with a single drug.

Introduction

Worldwide, cataract is the leading cause of preventable and treatable blindness.[1] Cataract surgery can improve visual acuity in many patients with mild to severe visual impairment and is considered one of the most cost-effective of all health care interventions.[2] Even though improvements in modern cataract surgery techniques have significantly decreased the incidence of postoperative complications, cystoid macular edema (CME) remains one of the most important causes of suboptimal visual acuity after otherwise uneventful surgery.[3, 4] CME after cataract surgery, also known as the Irvine-Gass syndrome, was first reported by Irvine in 1953 and discussed by Gass and Norton in 1966.[5, 6] Since then, ophthalmologists have aimed to prevent CME using perioperative topical corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs), albeit current practice varies between organizations and countries.[3, 7] As yet, the optimal approach in routine cataract surgery cases remains debatable because of the high societal costs involved with routine prescription of topical NSAIDs in some countries, such as the United States of America.[8] An Ophthalmic Technology Assessment of the American Academy of Ophthalmology (AAO) does not support the use of topical NSAIDs because of insufficient high-quality evidence with regard to its long-term benefit to prevent vision loss from CME three months or more after cataract surgery.[3] The Cataract Clinical Committee of the American Society of Cataract and Refractive Surgery (ASCRS), on the other hand, recently published a report on topical NSAIDs as an important adjunctive tool for surgeons performing routine and complicated cataract surgery and emphasized the compelling effectiveness of NSAIDs to reduce pain, prevent intraoperative miosis, modulate postoperative inflammation, and reduce the incidence of CME.[7] Two recent systematic reviews of the Cochrane Collaboration and two independent European meta-analyses suggest that topical NSAIDs reduce the risk of developing CME after cataract surgery, although none of them found a clinically relevant effect on mean visual acuity.[9-12]

To further investigate this important clinical question, many ophthalmologists have studied the efficacy of various NSAIDs and corticosteroids to prevent CME after cataract surgery. Most studies compared the efficacy of topical NSAIDs or combination treatment versus corticosteroids alone; however, few studies directly compared the efficacy of combination treatment versus topical NSAIDs.[9] Moreover, the low a priori incidence of CME demands large sample sizes to detect small, yet clinically important, differences.

The PREvention of Macular EDema after cataract surgery (PREMED) study was a randomized controlled clinical multicenter trial designed to directly compare the efficacy of a topical NSAID, a topical corticosteroid, and the combination of both in non-diabetic subjects. The study was funded by the European Society of Cataract and Refractive Surgeons (ESCRS). The aim of the ESCRS PREMED study was to provide evidence-based recommendations that could serve as a basis for clinical guidelines on the prevention of CME after cataract surgery.

Patients and methods

The ESCRS PREMED study was a randomized controlled trial (RCT). The study protocol was approved by the local ethics committees and national authorities of all participating study centers. The study procedures were performed in accordance with the tenets of the Declaration of Helsinki. The study protocol can be found on the U.S. National Institutes of Health Clinical Trial site.[A] A data safety monitoring board (members reported in appendix 1) evaluated the safety of trial participants.

Patient enrolment

Patient recruitment started in Maastricht, the Netherlands, in July 2013. Final inclusion took place at study centers in the Netherlands after a decision was made to stop recruitment on February 8, 2016. The trial included non-diabetic patients 21 years or older who required regular phacoemulsification cataract surgery in at least one eye. Patients were included in one of twelve study centers involved in the ESCRS PREMED study, located in Austria (Hospital of the Brothers of St. John of God and Vienna Institute for Research in Ocular Surgery, Vienna), Belgium (Antwerp University Hospital, Antwerp), Germany (Goethe University Hospital, Frankfurt am Main), Portugal (Centro Hospitalar Universitário Coimbra, Coimbra), Spain (Institute of Ocular Microsurgery, Barcelona) and the Netherlands (VU University Medical Center, Amsterdam; Zuyderland Medical Center, Heerlen; Eye Hospital Zonnestraal, Hilversum; University Eye Clinic Maastricht UMC, Maastricht; Haaglanden Medical Center, The Hague; and Elisabeth-TweeSteden Hospital, Tilburg). All patients signed written informed consent before inclusion.

Only one eye per patient was included in the study, and patients were excluded if they had sustained moderate to severe visual impairment in the other eye according to the definition of the International Statistical Classification of Diseases and Related Health Problems 10th revision.[13] Patients were excluded if they had previous CME, any macular pathology that could influence visual acuity, previous intraocular inflammation or uveitis, retinal vein occlusion, posttraumatic cataract, progressive glaucoma, intraocular pressure (IOP) 25 mmHg or higher, previous steroid-induced IOP elevation, pseudoexfoliation syndrome, or Fuchs endothelial dystrophy in the study eye. Furthermore, patients were excluded if they had intraocular surgery in the study eye. Patients who used topical NSAIDs, corticosteroids, anti-glaucomatous medication or high dosage systemic corticosteroids at the time of screening were excluded, as were patients who received an intravitreal injection with bevacizumab or ranibizumab in the study eye in the previous six weeks, an intravitreal injection with aflibercept in the previous ten weeks, or an intraocular or periocular corticosteroid injection in the previous four months. Finally, patients were excluded if there was a contraindication to the use of any of the investigated drugs.

Surgical technique, patient allocation, and treatment

All patients underwent regular phacoemulsification cataract surgery with intraocular lens (IOL) implantation in the posterior segment and received perioperative and/or postoperative antibiotics according to the standard of care in the participating study center.

Patients were randomly allocated to one of three treatment groups in a 1:1:1 ratio. Stratified block randomization was performed per study center by a local investigator using concealed online software (ALEA version 3.0, FormsVision®, Abcoude, The Netherlands[B]) and a block size of 15 patients. Trial participants were unblinded for the allocated treatment. Patients in the bromfenac group received bromfenac 0.09% eye drops (Yellox) twice daily for two days preoperatively and two weeks postoperatively. Patients in the dexamethasone group received dexamethasone disodium phosphate 0.1% eye drops four times daily for two days preoperatively and one week postoperatively, with one drop less per day every following week. Patients in the combination treatment group received topical bromfenac and dexamethasone in the abovementioned doses. Topical treatments started two days before cataract surgery because previous studies found a lower incidence of CME in patients who started anti-inflammatory treatment preoperatively.[14, 15] No other ocular corticosteroids or NSAIDs were allowed to be used during the course of the study.

Outcome assessments

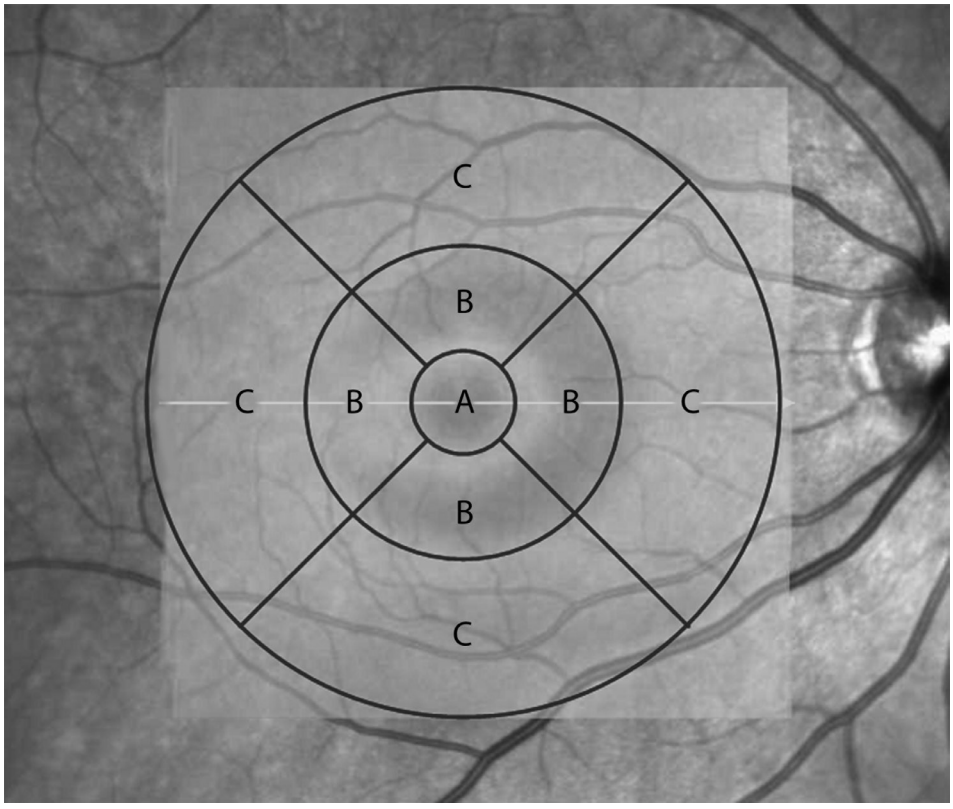
An extensive ophthalmologic examination, including slitlamp evaluation, IOP measurement and fundoscopy of both eyes, was performed at baseline. Cataract was graded according to the Lens Opacities Classification System (LOCS) II and the presence of aqueous cells and flare was graded according to the Standardization of Uveitis Nomenclature (SUN) classification.[16, 17] Subjective refraction and corrected distance visual acuity (CDVA) were measured using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. If patients were unable to read any letter on the ETDRS chart, hand motion or finger counting at a given distance were converted to the logarithm of the minimum angle of resolution (logMAR) equivalent.[18]

A baseline optical coherence tomography (OCT) was performed within three months preoperatively using spectral-domain OCT (SD-OCT) devices (3D OCT, Topcon Corp.; Cirrus HD-OCT, Carl Zeiss Meditec AG; OCT-HS100, Canon Inc.; RTVue-100, Optovue Inc; or Spectralis, Heidelberg Engineering Inc.). Each study center used only one type of SD-OCT device for all preoperative and postoperative measurements. Retinal thickness was measured in accordance with the ETDRS retinal thickness map (figure 1), which includes central subfield mean macular thickness (CSMT) in the central 1.0 mm area, parafoveal thickness in a concentric ring located 1.0-3.0 mm around the fovea, perifoveal thickness in a concentric ring located 3.0-6.0 mm around the fovea, and total macular volume (TMV) in the central 6 mm area.[19] If the preoperative OCT was of insufficient quality (e.g., because of dense

cataract), an alternative baseline measurement was performed at one day postoperatively because previous studies have shown no significant differences between preoperative and one day postoperative retinal thickness measurements.[20]

Postoperative visits were performed six and twelve weeks postoperatively and included a full ophthalmologic examination of the study eye, as reported above. Postoperative CDVA measurements and SD-OCT assessments were performed by a local investigator who was masked for the allocated study treatment.

Figure 1. ETDRS retinal thickness map



A) CSMT in the central 1.0 mm area; B) parafoveal thickness in a concentric ring located 1.0-3.0 mm around the fovea; C) perifoveal thickness in a concentric ring located 3.0-6.0 mm around the fovea. A-C) TMV is calculated for the central 6.0 mm area.
CSMT: central subfield mean macular thickness; ETDRS: early treatment diabetic retinopathy study; TMV: total macular volume

Study outcomes

CME usually occurs within three months postoperatively, with a peak incidence four to six weeks after cataract surgery.[21] Therefore, the primary outcome of this study was the difference in CSMT six weeks postoperatively compared with the baseline value. Secondary outcomes were the difference in CSMT twelve weeks postoperatively, the incidence of CME and clinically significant macular edema (CSME) within six and twelve weeks postoperatively, and CDVA, TMV, parafoveal and perifoveal thickness at six and twelve weeks postoperatively. Furthermore, all adverse events were reported.

CME was defined as an increase in CSMT of 10% or more over baseline, with cystic changes on SD-OCT. Cystoid changes and other retinal pathology were identified by two independent and masked retina specialists of the University Eye Clinic Maastricht UMC+ (appendix 1). CSME was defined as CME with less than 0.2 logMAR CDVA improvement as compared to the preoperative baseline.

Escape treatment

Small studies have shown that a combination of topical corticosteroids and NSAIDs is more effective than single drug treatment in patients with acute CSME after cataract surgery.[22] Patients who developed CSME during the course of this study were therefore treated with bromfenac 0.09% eye drops twice daily and dexamethasone 0.1% eye drops four times daily for four weeks. If CSME resolved within these four weeks, bromfenac was stopped and dexamethasone eye drops were reduced with one drop per day every following week. If CSME persisted after four weeks of topical treatment, patients received one intravitreal injection of 0.05 ml (1.25 mg) bevacizumab. From twelve weeks postoperatively, CSME was treated in accordance with the standard of care at each participating study center. Moreover, a stepwise treatment approach was used if patients developed severe postoperative inflammation, defined as at least 2+ cells according to the SUN classification.

Sample size

The sample size calculation for this study was based on the primary outcome - the difference in CSMT at six weeks postoperatively. Sample size was recalculated, masked for treatment allocation, based on overall nuisance parameters obtained from the first 159 patients included in the study; that is, a standard deviation (SD) of a postoperative CSMT of 42.25 µm and a correlation between the mean preoperative and postoperative CSMT of 0.62. With a total sample size of 741, a mean difference of 10 µm between treatment groups could be detected with 80% power at a Bonferroni-corrected significance level of 0.0167, where forty patients were added to correct for center, center with treatment interactions and other covariates. To compensate for a maximum dropout rate of 20%, the total calculated sample size for this study was 926 patients.

Statistical analysis

No interim analyses were performed during the course of the study. Data were collected in a web-based database (MACRO version 4.4[C]) and were subsequently exported to SPSS Statistics for Windows software (Version 23.0. IBM Corp.) for analysis. Generalized logistic mixed model analyses were performed using the GLMER function within R (Version 3.3.1. The R Foundation for Statistical Computing).[D]

Data were excluded from the final analyses if patients developed a perioperative complication that was expected to increase the risk for developing CME.[4, 23] These included patients with a posterior capsule rupture with or without vitreous loss, zonulolysis, or iris trauma. Other perioperative complications, such as intraoperative floppy iris syndrome without iris trauma, IOL damage, and corneal erosions, were thought not to influence the risk for developing CME. These cases were not excluded from the final analyses.

Categorical data were presented as number of patients (and percentage) and numerical data as means ± SD. Differences between treatment groups in the occurrence of perioperative complications, adverse events, dropout, and reasons for dropout were assessed using chi-square test or Fisher exact test, where appropriate.

Postoperative data analyses were performed with masking for the treatment groups. Because of the Bonferroni adjustment for multiple testing, a p-value less than 0.0167 was considered statistically significant. Linear mixed model analyses using restricted maximum likelihood were used for numerical outcomes that were measured repeatedly, including the primary outcome of the study. Linear mixed models account for the correlation between repeated measurements within a patient and also include data from patients who dropped out of the study. No data were imputed. A likelihood-based approach was used for missing outcome data, including SD-OCT data, for which data were assumed to be missing at random. No missing data were expected for the fixed factors included in the model, such as study center, timing of study visits, and the interaction term treatment group * timing of the study visit. Logistic regression analysis was used to check whether missing outcome data were significantly related to certain patient characteristics. Variables significantly related to missing outcome data were added to the model to ensure missing at random. In addition, baseline patient characteristics that are known to be related to the primary outcome, such as sex, age, and the presence of CME in the fellow eye, were included, while the model without these patient characteristics was used as a sensitivity analysis.[4, 23] A second sensitivity analysis was performed with study center included as a random instead of a fixed factor. A three-way interaction term treatment group * timing of the study visit * study center (plus their two-way interaction terms) was applied to verify whether treatment effect depended significantly on study center. If this three-way

interaction term proved significant, the treatment effect was reported for each center separately. If the three-way interaction term was not significant, it was removed from the model and only the overall treatment effect over all centers was reported.

Generalized logistic mixed model analyses were used for binary outcomes, in which a random intercept on center level was included to account for the nesting of patients within a center. Adaptive Gauss-Hermite approximation (ten quadrate points) was used for estimating the log-likelihood. Odds ratios (ORs) and 95% confidence intervals (CI) were reported for pairwise comparisons.

Because the sample size within a center might be small, the abovementioned analyses were also performed after combining study centers based on location and center type (i.e., academic centers in the Netherlands, non-academic centers in the Netherlands, other West European centers, Central European centers, and South European centers). This was included as a sensitivity analysis.

Finally, per-protocol analyses were performed and compared to the intention-to-treat analyses. Data were excluded from the per-protocol analyses if deviations from the allocated treatment intervention occurred (e.g., patients who received additional NSAID or corticosteroid eye drops).

Results

Population

Figure 2 shows a flow diagram showing the number of patients who were screened, randomized and analyzed in the study. Baseline characteristics of the participants are shown in table 1 and appendix 2.

Twenty-seven patients (3.1%) developed a perioperative complication (appendix 3). There were no significant differences in the number of perioperative complications between treatment groups (p = 0.668). Data of eight patients (0.9%) were not included in the final analyses because the reported perioperative complications have been related to an increased risk for developing CME after cataract surgery.

Table 1. Main baseline characteristics

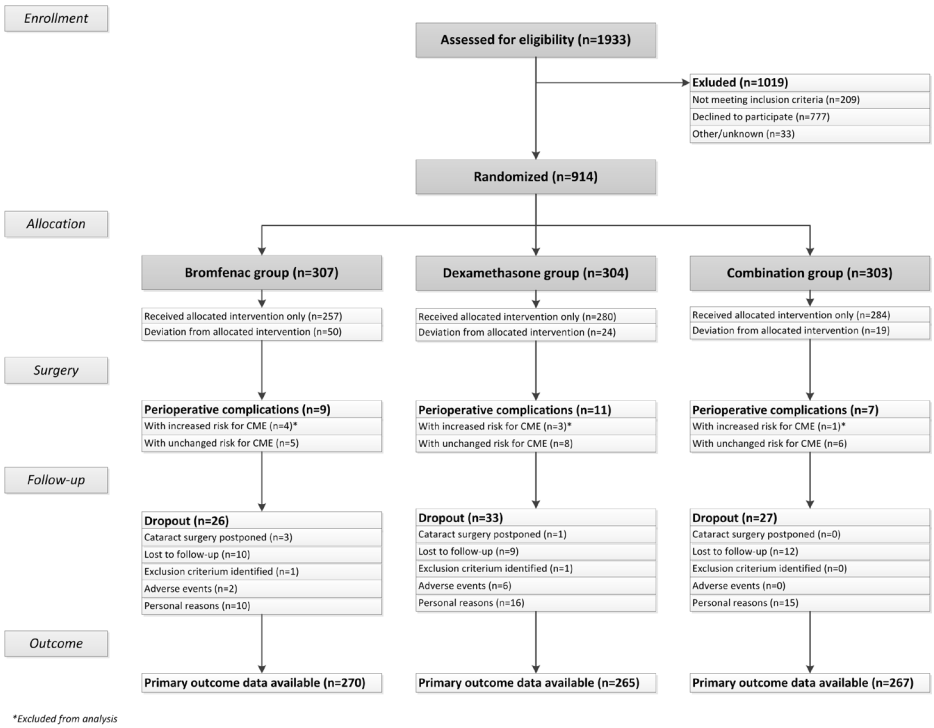
Parameter	Overall (n = 914)	Bromfenac (n = 307)	Dexamethasone (n = 304)	Combination (n = 303)
Mean age (y) ± SD	70.45 ± 8.87	69.70 ± 8.94	71.23 ± 8.73	70.41 ± 8.91
Right eye, n (%)	504/914 (55.1)	182/307 (59.3)	157/304 (51.6)	165/303 (54.5)
Female sex, n (%)	478/914 (52.3)	166/307 (54.1)	163/304 (53.6)	149/303 (49.2)
White race, n (%)	897/914 (98.1)	300/307 (97.7)	301/304 (99.0)	296/303 (97.7)
CME in contralateral eye, n (%)	4/912 (0.4)	0/307 (0.0)	3/302 (1.0)	1/303 (0.3)
Previous anti-VEGF, n (%)	2/909 (0.2)	0/306 (0.0)	1/300 (0.3)	1/303 (0.3)
Type of cataract, n (%)				
Nuclear	777/903 (86.0)	267/304 (87.8)	260/299 (87.0)	250/300 (83.3)
Cortical	610/903 (67.6)	211/304 (69.4)	203/299 (67.9)	196/300 (65.3)
Subcapsular	199/903 (22.0)	72/304 (23.7)	61/299 (20.4)	66/300 (22.0)

CME: cystoid macular edema; VEGF: vascular endothelial growth factor

Although the study included only 914 instead of 926 subjects, the final dropout rate was substantially lower than the accounted for maximum rate of 20%. Of 906 patients suitable for inclusion in the final data analyses, 86 patients (9.5%) (26 in the bromfenac group, 33 in the dexamethasone group, and 27 in the combination treatment group) were dropouts. There were no statistically significant differences between treatment groups in the number of patients who dropped from the study (p = 0.560) or reasons for dropout (p = 0.227). Four patients voluntarily postponed cataract surgery and forty patients withdrew from study participation before the day of cataract surgery. The two patients in the bromfenac group who discontinued participation because of adverse events considered not related to topical NSAID treatment had increased IOP and cerebral metastases of a pre-existing lung carcinoma, respectively. Of the six patients in the dexamethasone group considered dropouts because of adverse events, two patients had red eyes and one developed a cor-

neal erosion. One patient in the dexamethasone group was dropped from the study when CSME was diagnosed; however, primary outcome data were available. One patient in the dexamethasone group discontinued participation after developing lymphatic metastases of a pre-existing rectal carcinoma, and another patient died after developing a cerebrovascular infarction. No patients in the combination treatment group dropped out because of adverse events.

Figure 2. Consort flow diagram showing the number of participants who were screened, randomized and analyzed



Macular thickness and volume

Patients treated with a combination of bromfenac and dexamethasone eye drops had the lowest postoperative macular thickness, after correction for baseline measurements (table 2 and figure 3). At six weeks postoperatively, the mean CSMT was 288.3 µm, 296.0 µm, and 284.5 µm in the bromfenac group, dexamethasone group, and combination treatment group, respectively (overall p = 0.006). After correction for baseline CSMT and other covariables, the mean CSMT was 9.6 µm higher in the dexamethasone group than in the combination treatment group (p = 0.002). It was 6.9 µm higher in the dexamethasone

Table 2. Differences in macular thickness, TMV and CDVA (intention-to-treat analysis)

Parameter	Mean ± SD (no. of patients)		
	Bromfenac	*Dexamethasone*	*Combination*
CSMT (µm)			
Baseline	274.18 ± 25.48 (294)	275.18 ± 27.16 (293)	273.20 ± 24.67 (298)
6 wks	288.28 ± 46.78 (270)	296.04 ± 52.46 (265)	284.51 ± 36.40 (267)
12 wks	283.30 ± 28.03 (264)	283.96 ± 28.64 (263)	283.30 ± 27.38 (262)
Parafoveal thickness (µm)			
Baseline	325.17 ± 19.53 (295)	326.44 ± 20.47 (298)	326.84 ± 21.75 (298)
6 wks	336.50 ± 26.95 (270)	342.40 ± 25.43 (266)	337.54 ± 21.89 (267)
12 wks	334.32 ± 21.60 (265)	336.87 ± 21.10 (263)	336.40 ± 21.33 (263)
Perifoveal thickness (µm)			
Baseline	282.31 ± 16.45 (280)	282.48 ± 17.22 (288)	282.44 ± 18.07 (285)
6 wks	290.79 ± 21.77 (258)	294.85 ± 18.13 (254)	291.19 ± 18.44 (257)
12 wks	288.57 ± 17.48 (256)	291.11 ± 17.73 (254)	291.02 ± 17.19 (255)
TMV (mm^3)			
Baseline	8.29 ± 0.53 (278)	8.29 ± 0.53 (282)	8.28 ± 0.51 (277)
6 wks	8.52 ± 0.70 (256)	8.67 ± 0.58 (249)	8.51 ± 0.61 (256)
12 wks	8.47 ± 0.58 (256)	8.55 ± 0.55 (250)	8.51 ± 0.60 (255)
CDVA (logMAR)			
Baseline	0.29 ± 0.23 (299)	0.29 ± 0.21 (298)	0.29 ± 0.22 (300)
6 wks	0.01 ± 0.12 (276)	0.02 ± 0.14 (274)	0.01 ± 0.12 (274)
12 wks	-0.02 ± 0.10 (270)	-0.01 ± 0.11 (267)	-0.01 ± 0.11 (271)

* Treatment effect after correction for center, sex, age and CME in the fellow eye

‡ Overall effect at that time-point over all three groups

Table 3. Incidence of CME and CSME (intention-to-treat analysis)

Parameter	Incidence rates, n (%)		
	Bromfenac	*Dexamethasone*	*Combination*
CME within 6 wks	11/269 (4.1)	22/270 (8.1)	5/266 (1.9)
CME within 12 wks	11/269 (4.1)	23/270 (8.5)	6/266 (2.3)
CSME within 6 wks	10/274 (3.6)	14/273 (5.1)	2/275 (0.7)
CSME within 12 wks	10/274 (3.6)	14/273 (5.1)	4/275 (1.5)

‡ Overall effect at that time-point over all three groups

CI: confidence interval; CME: cystoid macular edema; CSME: clinically significant macular edema; wks: weeks

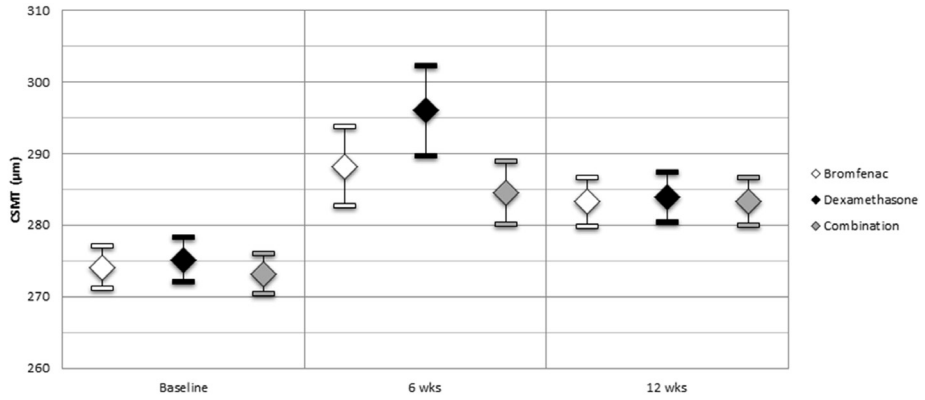
Treatment effect* (95% CI); p-value			
Overall p-value‡	*Dexamethasone vs. bromfenac*	*Bromfenac vs. combination*	*Dexamethasone vs. combination*
0.006	6.91 (0.81, 13.01); 0.026	2.72 (-3.36, 8.80); 0.380	9.63 (3.52, 15.74); 0.002
0.299	1.47 (-0.67, 3.61); 0.178	-1.46 (-3.60, 0.67); 0.178	0.004 (-2.13, 2.14); 0.997
0.002	3.72 (1.08, 6.35); 0.006	0.86 (-1.77, 3.49); 0.520	4.58 (1.94, 7.21); 0.001
0.136	1.80 (-0.02, 3.61); 0.053	-0.52 (-2.34, 1.30); 0.574	1.28 (-0.54, 3.09); 0.167
0.012	2.63 (0.58, 4.67); 0.012	0.15 (-1.89, 2.19); 0.883	2.78 (0.73, 4.82); 0.008
0.008	2.11 (0.69, 3.53); 0.004	-1.78 (-3.19, -0.36); 0.014	0.33 (-1.08, 1.75); 0.645
< 0.001	0.12 (0.07, 0.18); < 0.001	-0.01 (-0.06, 0.05); 0.763	0.12 (0.06, 0.17); < 0.001
0.002	0.07 (0.03, 0.11); 0.001	-0.04 (-0.08, -0.001); 0.045	0.03 (-0.01, 0.07); 0.139
0.327	0.01 (-0.01, 0.03); 0.186	-0.001 (-0.02, 0.02); 0.953	0.01 (-0.01, 0.03); 0.206
0.309	0.01(-0.004; 0.03); 0.128	-0.01 (-0.02, 0.01); 0.546	0.01 (-0.01, 0.03); 0.355

CDVA: corrected distance visual acuity; CI: confidence interval; CME: cystoid macular edema; CSMT: central subfield mean macular thickness; logMAR: logarithm of the minimal angle of resolution; SD: standard deviation; TMV: total macular volume; wks: weeks

Odds ratios (95% CI); p-value			
Overall p-value‡	*Dexamethasone vs. bromfenac*	*Bromfenac vs. combination*	*Dexamethasone vs. combination*
0.002	2.08 (0.99, 4.40); 0.053	2.22 (0.76, 6.50); 0.144	4.65 (1.73, 12.48); 0.002
0.003	2.19 (1.05, 4.60); 0.038	1.85 (0.67, 5.07); 0.234	4.05 (1.62, 10.12); 0.003
0.004	1.43 (0.62, 3.30); 0.398	5.22 (1.13, 24.12); 0.034	7.48 (1.68, 33.36); 0.008
0.043	1.43 (0.62, 3.30); 0.397	2.58 (0.80, 8.36); 0.114	3.70 (1.20, 11.44); 0.023

group than in the bromfenac group, although the difference between the two treatment groups was not statistically significant (p = 0.026). The mean CSMT was 2.7 µm higher in the bromfenac group than in the combination treatment group (p = 0.380). The mean CSMT was comparable in all treatment groups at twelve weeks after cataract surgery (overall p = 0.299).

Figure 3. Observed mean CSMT with 95% confidence intervals



CSMT: central subfield mean macular thickness; wks: weeks

Figure 4 shows the parafoveal thickness, perifoveal thickness, TMV, and CDVA by group over time. Patients treated with topical dexamethasone had a significantly higher parafoveal thickness at six weeks than patients treated with bromfenac (p = 0.006) or with a combination of bromfenac and dexamethasone (p = 0.001). The parafoveal thickness was comparable in the bromfenac group and combination treatment group (p = 0.520). At twelve weeks, the parafoveal thickness was comparable in all treatment groups (overall p = 0.136).

The postoperative perifoveal thickness was also highest in the dexamethasone treatment group. At six weeks, the perifoveal thickness was significantly higher in patients treated with topical dexamethasone than in patients treated with bromfenac or bromfenac and dexamethasone (p = 0.012 and p = 0.008, respectively).

Figure 4. Secondary outcome measures: observed means with 95% confidence intervals.

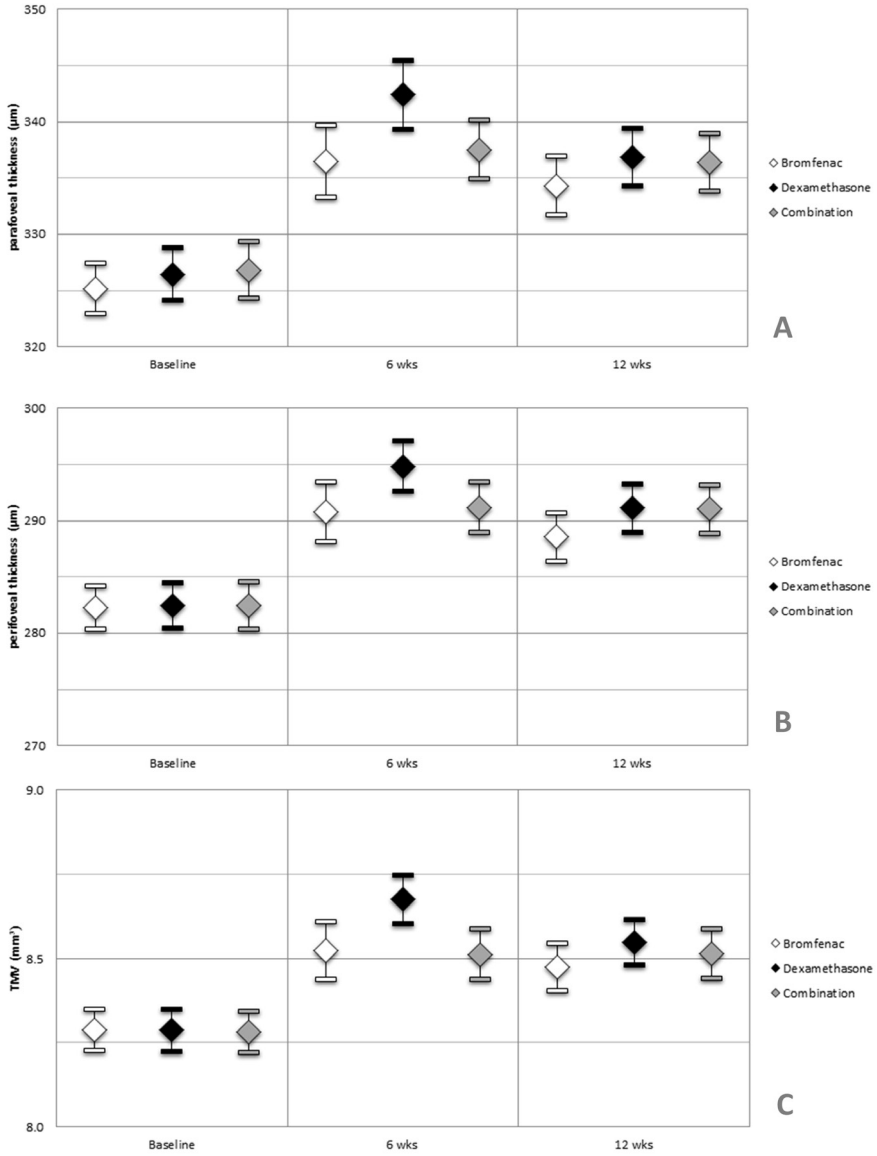
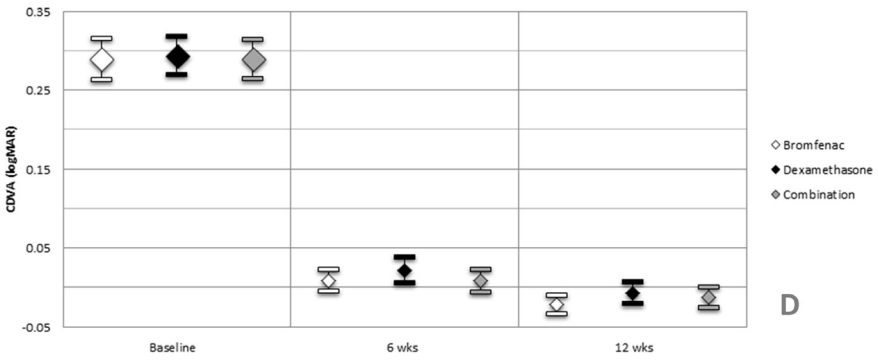


Figure 4. Continued



CDVA: corrected distance visual acuity; logMAR: logarithm of the minimal angle of resolution; TMV: total macular volume; wks: weeks.

There were no significant differences in perifoveal thickness between the bromfenac and combination group (p = 0.883). At twelve weeks, the perifoveal thickness was lowest in the bromfenac treatment group. The mean perifoveal thickness was 2.1 µm higher in dexamethasone group and 1.8 µm higher in the combination treatment group (p = 0.004 and p = 0.014, respectively).

Finally, the mean TMV was significantly higher in the dexamethasone treatment group than in the other treatment groups six weeks postoperatively (p < 0.001). Up to the end of the study, the TMV remained significantly lower in the bromfenac treatment group than in the dexamethasone group (p = 0.001). After Bonferroni correction, there were no statistically significant differences between the bromfenac and combination groups (p = 0.045).

Only overall treatment effects are reported because the effects were not significantly different between study centers for any postoperative outcome. Sensitivity analyses showed similar results with respect to TMV and macular thickness measurements. Per-protocol analyses showed comparable results (appendix 4).

Incidence of cystoid macular edema and clinically significant macular edema

Most cases of CME developed within six weeks postoperatively (table 3). There were clinically important and statistically significant differences in the incidence of CME within six and twelve weeks postoperatively between treatment groups (overall p = 0.002 and p = 0.003, respectively). The odds of developing CME were significantly higher in the dexamethasone treatment group than in the combination group (OR 4.7, 95% CI 1.7-12.5, p = 0.002). The odds were also higher in patients treated with bromfenac eye drops than

in patients in the combination treatment group; however, a pairwise comparison did not reach statistical significance (OR 2.2, 95% CI 0.8-6.5, p = 0.144). A similar pattern was seen twelve weeks postoperatively (table 3).

Although the incidence of CSME remained highest in the dexamethasone treatment group during the course of the study (table 3), the differences were statistically significant at six weeks only (overall p = 0.006 and p = 0.043, within six and twelve weeks respectively).

Sensitivity and per-protocol analyses showed comparable results, and the effects were not significantly different between study centers.

Visual acuity

There were no significant differences in CDVA six and twelve weeks postoperatively between groups (overall p = 0.327 and p = 0.309, respectively) (table 2). Mean final visual acuity was -0.02 logMAR (21/20 Snellen) in the bromfenac treatment group and -0.01 logMAR (20/20 Snellen) in the other treatment groups.

In patients with CSME, the maximum decline in CDVA was up to 0.54 logMAR (20/70 Snellen). The median CDVA decreased to 0.20 logMAR (20/32 Snellen), but improved to 0.07 logMAR (20/26 Snellen) twelve weeks postoperatively.

Adverse events

All adverse events and serious adverse events are shown in appendices 5 and 6. No treatment related serious adverse events were reported during the course of this study. Adverse events occurred in 310 patients. These events were reported in 104 patients (34.3%), 120 patients (39.9%), and 86 patients (28.5%) in the bromfenac group, dexamethasone group and combination treatment group, respectively (overall p = 0.013). Frequently reported adverse events were mild pain or foreign body sensation, dry eyes, tearing and posterior vitreous detachment.

Six weeks postoperatively, the presence of cells on slitlamp examination was reported in 11 of 272 patients (4.0%) in the bromfenac group, 12 of 271 patients (4.4%) in the dexamethasone group, and in 15 of 273 patients (5.5%) in the combination treatment group. Flare was reported in one patient in the combination treatment group. At twelve weeks, anterior chamber cells were reported in 1 of 268 patients (0.4%) in both the bromfenac and combination treatment groups, and in 5 of 264 patients (1.9%) in the dexamethasone group. No patients presented with anterior chamber flare at twelve weeks. No patient had 2+ or more cells according to the SUN classification six or twelve weeks postoperatively.

Mean IOP decreased from 16.1 ± 3.3 mmHg at baseline to 13.4 ± 2.9 mmHg twelve weeks after cataract surgery. There were no statistically significant differences in the mean IOP between treatment groups at six or twelve weeks (overall p = 0.707 and 0.877, respectively). One patient in the bromfenac group developed severely increased IOP and was hospitalized to receive intravenous medication. Four patients in the dexamethasone group and two patients in the combination treatment group received topical treatment to reduce IOP; however, none received a prostaglandin analogue. Two patients in the dexamethasone group and one patient in the combination treatment group received additional oral acetazolamide.

Discussion

Modern phacoemulsification cataract surgery techniques have substantially decreased the incidence of CME after cataract surgery. However, because phacoemulsification is one of the most frequently performed surgical procedures worldwide, even small improvements in perioperative care can be clinically important. Many studies have evaluated the optimum treatment to prevent the CME after cataract surgery; however, most were insufficiently powered to detect small, yet clinically relevant differences between treatment groups. Moreover, most studies did not compare the efficacy of an NSAID only versus combination treatment with a topical corticosteroid. The ESCRS PREMED study included 914 non-diabetic patients and at present is the largest multicenter study directly comparing the efficacy of a topical NSAID, corticosteroid, and combination treatment to prevent CME after cataract surgery.

The overall incidence of CSME in this study was 3.4%, while previous studies have reported a lower incidence of 1.2-2.0% in patients with no risk factors for developing CSME after cataract surgery.[4, 23] However, a fair comparison of incidence rates between studies requires standardization of the applied definitions.[9, 21] The ESCRS PREMED study definition for CME is very sensitive, because of a very low cutoff value with respect to macular thickening; that is, at least a 10% increase in CSMT compared with the preoperative baseline. Moreover, SD-OCT allows detection of very small cystoid changes, and some of them might not be clinically relevant. CSME was defined as the occurrence of CME on OCT and less than 0.2 logMAR improvement in CDVA compared with the preoperative baseline. This definition assumes that modern phacoemulsification cataract surgery leads to at least two lines improvement in CDVA. However, the current study also included patients with a preoperative CDVA of 20/25 Snellen or better who had cataract surgery for decreased quality of vision (e.g. glare or decreased contrast sensitivity) because many national guidelines report that a reduced visual acuity is not the only indication for cataract surgery. Therefore, the PREMED study definition for CSME may have caused a surplus of CME cases to be considered clinically significant.

Previous studies have assed the efficacy of topical anti-inflammatory treatments to prevent vision loss resulting from CME after cataract surgery.[3] The ESCRS PREMED study could not identify a statistically significant difference in the mean postoperative CDVA between treatment groups. Although CDVA decreased to 20/70 Snellen in patients with CSME, those outliers did not cause significant differences with respect to the mean CDVA six and twelve weeks postoperatively. Nevertheless, individual patients will benefit most from optimum prevention of visually significant CME.

The odds ratio of developing CSME within twelve weeks postoperatively was 2.6 in patients treated with topical bromfenac and 3.7 in patients treated with topical dexamethasone compared with the combination treatment group. The incidence of CSME within twelve weeks postoperatively was 3.6%, 5.1% and 1.5% in the bromfenac group, dexamethasone group, and combination treatment group, respectively. Although these differences were not statistically significant after Bonferroni correction ($p = 0.043$), the rates clearly indicate benefit from the use of both bromfenac and dexamethasone eye drops to prevent CSME after uneventful cataract surgery.

Various topical NSAID preparations are available; however, the U.S. Food and Drug Administration (FDA) has not approved any for the prevention of CME after cataract surgery.[3] The European Medicines Agency (EMA) approved nepafenac for prevention of inflammation and macular edema after cataract surgery in diabetic patients, whereas bromfenac is only approved for prevention of postoperative inflammation. Despite this, many ophthalmologists continue to use bromfenac and other topical NSAIDs to prevent CME after cataract surgery because CME is likely a result of an overall postoperative inflammatory response.[3, 21] At the initiation of this European multicenter trial in 2012, the ESCRS PREMED Study Group decided to use bromfenac 0.09% because previous studies indicated better penetration into ocular tissues, extended duration of anti-inflammatory activity and enhanced inhibitory effect on cyclo-oxygenase 2.[7, 24] The results of an indirect network comparison and several small RCTs suggest some differences between NSAID preparations in their efficacy to reduce inflammation after cataract surgery.[25] The quality of evidence, however, is low to moderate, in part because of the small samples in the available studies. Previous studies did not indicate significant differences between various NSAIDs in their efficacy to prevent macular thickening.[25, 26] More recently, reformulated once-daily NSAID preparations have been shown to be effective in preventing inflammation and CME after cataract surgery.[4, 27] Therefore, health care costs and patient comfort could be taken into account when choosing the optimal NSAID to be used as a standard of care in clinical practice.[2, 28]

In the ESCRS PREMED study, the efficacy of bromfenac eye drops was compared with that of dexamethasone 0.1%. Dexamethasone was the corticosteroid of choice because this preparation was used at eight of nine PREMED study centers that included a topical corticosteroid in their standard of care. A previous meta-analysis showed that both potent steroids and weaker steroids are less effective than topical NSAIDs in prevention of CME after cataract surgery.[10]

The primary outcome of the ESCRS PREMED study was the difference in postoperative CSMT. The results suggest that topical bromfenac 0.09% is more effective than topical dexamethasone 0.1% in preventing retinal thickening after cataract surgery. These results

are in line with the conclusions of previous systematic reviews.[9-11] The PREMED study found no statistically significant or clinically relevant differences in the mean macular thickness and TMV six weeks postoperatively between the bromfenac group and combination treatment group. The odds ratio for developing CSME within twelve weeks postoperatively was 2.6 in patients treated with topical bromfenac when compared to patients receiving combination treatment; however, the differences were not statistically significant. In this study, topical bromfenac was used twice daily for two weeks postoperatively, as per the EMA Summary of Product Characteristics 2011.[29] Although the EMA recommends topical bromfenac treatment for two weeks postoperatively, ophthalmologists have studied its use for up to two months after cataract surgery. One small study of 72 patients compared the efficacy of topical bromfenac for two months postoperatively versus combination treatment with a corticosteroid. The study found no significant differences in postoperative inflammatory response and reports no cases of CME in the bromfenac group or the combination treatment group.[30] However, the sample size in this study might have been too small and the study might have had insufficient power to detect clinically relevant differences. Another study reported no added value of using bromfenac eye drops for more than one month postoperatively.[31] Nevertheless, future RCTs are needed to compare the efficacy of topical bromfenac for one month postoperatively versus combination treatment with a corticosteroid to prevent the occurrence of CME and CSME after cataract surgery.

This European RCT has some limitations that are related to its study design and the multinational setting. Firstly, macular thickness and TMV were measured using five different SD-OCT devices. Where some OCT devices measure retinal thickness from the internal limiting membrane to the retinal pigment epithelium (RPE), others use Bruch membrane as the outer retinal boundary. These differences are most relevant in pathologies that affect the RPE-Bruch membrane complex.[32] Because CME is caused by an accumulation of fluid in the inner nuclear and outer plexiform layers of the retina, all OCT devices will detect postoperative changes in macular thickness and TMV. Each study center used only one type of SD-OCT device for all preoperative and postoperative measurements. Furthermore, differences between treatment groups reported in this study were corrected for baseline measurements. Secondly, the current study had a follow-up of three months postoperatively. The currently available literature does not provide clear evidence with regard to the long-term efficacy of topical NSAIDs and/or corticosteroids on CDVA more than three months after regular cataract surgery, although some studies provide long-term results in high-risk patients (e.g. patients with diabetes mellitus or uveitis).[11] The current study has shown benefit to using a combination of topical bromfenac and dexamethasone eye drops up to three months postoperatively. Considering that most cases of CME develop within four to six weeks after cataract surgery, preventive treatments should be optimized in the immediate postoperative period. However, further studies are

needed to determine whether a combination of topical bromfenac and dexamethasone can also prevent the occurrence of CME and CSME after three months postoperatively. Finally, this study was designed to evaluate the optimum preventive strategy for CME in non-diabetic patients with no other risk factors for developing CME. Therefore, the results of this study might not be applicable to patients with diabetes, uveitis, retinal vein occlusion, epiretinal membrane, or other risk factors for developing CME, and in cases of complicated cataract surgery.[4, 23]

Future work will evaluate the cost-effectiveness of topical NSAIDs, corticosteroids and combination treatments after cataract surgery. When choosing the optimum NSAID eye drop for standard care, patient satisfaction, simplicity of drug administration, frequency of drug administration, and ocular comfort should be taken into account. Although the efficacy of various topical NSAIDs seems to be comparable, their cost-effectiveness should be studied in more detail.

In conclusion, the ESCRS PREMED study evaluated the optimum treatment regimen to prevent the occurrence of CME after uncomplicated phacoemulsification cataract surgery in non-diabetic patients with no other risk factors for developing CME. According to the results of this randomized controlled European multicenter trial, the postoperative macular thickness and TMV were lower in patients treated with topical bromfenac 0.09% than in patients treated with topical dexamethasone 0.1%. A combination treatment of dexamethasone and bromfenac eye drops could not further reduce postoperative macular thickness, TMV or CDVA compared with topical bromfenac alone. However, the odds of developing CSME within twelve weeks postoperatively were lowest in the combination treatment group.

References

Peer-reviewed material

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 Global Initiative for the Elimination of Avoidable Blindness: action plan 2006-2011. WHO/PBL/9761 Rev 2. http://www.who.int/blindness/Vision2020_report.pdf, World Health Organization, 2007

3 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

4 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

5 Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol 1953; 36: 599-619

6 Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. Arch Ophthalmol 1966; 76: 646-661

7 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

8 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

9 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

10 Kessel L, Tendal B, Jorgensen KJ, Erngaard D, Flesner P, Andresen JL, Hjortdal J. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. Ophthalmology 2014; 121: 1915-1924

11 Lim BX, Lim CH, Lim DK, Evans JR, Bunce C, Wormald R. Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery. Cochrane Database Syst Rev 2016; 11: CD006683

12 Juthani VV, Clearfield E, Chuck RS. Non-steroidal anti-inflammatory drugs versus corticosteroids for controlling inflammation after uncomplicated cataract surgery. Cochrane Database Syst Rev 2017; 7: CD010516

13 International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). http://www.who.int/classifications/icd/en/, World Health Organization, 2016

14 Donnenfeld ED, Perry HD, Wittpenn JR, Solomon R, Nattis A, Chou T. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: pharmacokinetic-response curve. J Cataract Refract Surg 2006; 32: 1474-1482

15 Yavas GF, Ozturk F, Kusbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. J Cataract Refract Surg 2007; 33: 804-807

16 Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature Working G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005; 140: 509-516

17 Chylack LT, Jr., Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens opacities classification system II (LOCS II). Arch Ophthalmol 1989; 107: 991-997

18 Holladay JT, Prager TC. Mean visual acuity. Am J Ophthalmol 1991; 111: 372-374

19 Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology 1991; 98: 741-756

20 Degenring RF, Vey S, Kamppeter B, Budde WM, Jonas JB, Sauder G. Effect of uncomplicated phacoemulsification on the central retina in diabetic and non-diabetic subjects. Graefes Arch Clin Exp Ophthalmol 2007; 245: 18-23

21 Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol 2012; 23: 26-32

22 Wielders LH, Schouten JS, Aberle MR, Lambermont VA, van den Biggelaar FJ, Winkens B, Simons RW, Nuijts RM. Treatment of cystoid macular edema after cataract surgery. J Cataract Refract Surg 2017; 43: 276-284

23 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
24 Carreno E, Portero A, Galarreta DJ, Herreras JM. Update on twice-daily bromfenac sodium sesquihydrate to treat postoperative ocular inflammation following cataract extraction. Clin Ophthalmol 2012; 6: 637-644
25 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
26 Lee TH, Choi W, Ji YS, Yoon KC. Comparison of ketorolac 0.45% versus diclofenac 0.1% for macular thickness and volume after uncomplicated cataract surgery. Acta Ophthalmol 2016; 94: e177-182
27 Walters TR, Goldberg DF, Peace JH, Gow JA, Bromfenac Ophthalmic Solution 0.07% Once Daily Study G. Bromfenac ophthalmic solution 0.07% dosed once daily for cataract surgery: results of 2 randomized controlled trials. Ophthalmology 2014; 121: 25-33
28 Wilson DJ, Schutte SM, Abel SR. Comparing the Efficacy of Ophthalmic NSAIDs in Common Indications: A Literature Review to Support Cost-effective Prescribing. Ann Pharmacother 2015; 49: 727-734
29 Yellox Summary of product characteristics. European Medicines Agency, 2011
30 Miyanaga M, Miyai T, Nejima R, Maruyama Y, Miyata K, Kato S. Effect of bromfenac ophthalmic solution on ocular inflammation following cataract surgery. Acta Ophthalmol 2009; 87: 300-305
31 Wang QW, Yao K, Xu W, Chen PQ, Shentu XC, Xie X, Weng Y, Zhang L, Jin CF, Wu W, Zhu YN, Yu YH. Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification. Ophthalmologica 2013; 229: 187-194
32 Giani A, Cigada M, Choudhry N, Deiro AP, Oldani M, Pellegrini M, Invernizzi A, Duca P, Miller JW, Staurenghi G. Reproducibility of retinal thickness measurements on normal and pathologic eyes by different optical coherence tomography instruments. Am J Ophthalmol 2010; 150: 815-824

Other cited material

A. U.S. National Institutes of Health Clinical Trials. PRevention of Macular EDema after cataract surgery (PREMED). NCT01774474. Available at: https://clinicaltrials.gov/ct2/show/NCT01774474
B. ALEA, version 3.0, Formsvision BV, Abcoude, The Netherlands. Available at: http://www.aleaclinical.eu/. Accessed February 17, 2018
C. MACRO, Advanced data collection for clinical research. Amsterdam, the Netherlands, Elsevier, 2018. Available at: https://www.elsevier.com/solutions/macro. Accessed February 17, 2018
D. GLMER. The R Foundation for Statistical Computing. Available at: https://www.rdocumentation.org/packages/twidlr/versions/0.0.0.9000/topics/glmer. Accessed February 17, 2018

Appendix

Appendix 1 ESCRS PREMED study group

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Masked retinal specialists
University Eye Clinic Maastricht UMC+, Maastricht: Jan S.A.G. Schouten, Fleur Goezinne

Appendix 2. Additional baseline characteristics

	Overall (n = 914)	Bromfenac (n = 307)	Dexamethasone (n = 304)	Combination (n = 303)
Study center, n (%)				
Center 1	4/914 (0.4)	1/307 (0.3)	2/304 (0.7)	1/303 (0.3)
Center 2	77/914 (8.4)	25/307 (8.1)	26/304 (8.6)	26/303 (8.6)
Center 3	47/914 (5.1)	17/307 (5.5)	15/304 (4.9)	15/303 (5.0)
Center 4	3/914 (0.3)	1/307 (0.3)	1/304 (0.3)	1/303 (0.3)
Center 5	60/914 (6.6)	20/307 (6.5)	20/304 (6.6)	20/303 (6.6)
Center 6	10/914 (1.1)	4/307 (1.3)	3/304 (1.0)	3/303 (1.0)
Center 7	25/914 (2.7)	9/307 (2.9)	7/304 (2.3)	9/303 (3.0)
Center 8	155/914 (17.0)	51/307 (16.6)	52/304 (17.1)	52/303 (17.2)
Center 9	11/914 (1.2)	2/307 (0.7)	5/304 (1.6)	4/303 (1.3)
Center 10	434/914 (47.5)	148/307 (48.2)	142/304 (46.7)	144/303 (47.5)
Center 11	41/914 (4.5)	13/307 (4.2)	15/304 (4.9)	13/303 (4.3)
Center 12	47/914 (5.1)	16/307 (5.2)	16/304 (5.3)	15/303 (5.0)
Patient history				
Cerebrovascular accident, n (%)	61/914 (6.7)	15/307 (4.9)	28/304 (9.2)	18/303 (5.9)
Myocardial infarction, n (%)	55/914 (6.0)	22/307 (7.2)	16/304 (5.3)	17/303 (5.6)
Thromboembolic event, n (%)	18/914 (2.0)	4/307 (1.3)	8/304 (2.6)	6/303 (2.0)
Hypertension, n (%)	432/912 (47.4)	146/307 (47.6)	150/302 (49.7)	136/303 (44.9)
Smoking, n (%)	114/912 (12.5)	47/307 (15.3)	32/302 (10.6)	35/303 (11.6)
Hypercholesterolemia, n (%)	303/912 (33.2)	96/307 (31.3)	108/302 (35.8)	99/303 (32.7)
Type of cataract (LOCS II classification)				
Nuclear, n (%)	777/903 (86.0)	267/304 (87.8)	260/299 (87.0)	250/300 (83.3)
N1	226/738 (30.6)	77/253 (30.4)	78/247 (31.6)	71/238 (29.8)
N2	425/738 (57.6)	151/253 (59.7)	138/247 (55.9)	136/238 (57.1)
N3	87/738 (11.8)	25/253 (9.9)	31/247 (12.6)	31/238 (13.0)
Cortical, n (%)	610/903 (67.6)	211/304 (69.4)	203/299 (67.9)	196/300 (65.3)
C1	228/593 (38.4)	85/207 (41.1)	75/197 (38.1)	68/189 (36.0)
C2	278/593 (46.9)	102/207 (49.3)	90/197 (45.7)	86/189 (45.5)
C3	73/593 (12.3)	16/207 (7.7)	28/197 (14.2)	29/189 (15.3)
C4	14/593 (2.4)	4/207 (1.9)	4/197 (2.0)	6/189 (3.2)
Subcapsular, n (%)	199/903 (22.0)	72/304 (23.7)	61/299 (20.4)	66/300 (22.0)
P1	96/192 (50.0)	27/69 (39.1)	33/60 (55.0)	36/63 (57.1)
P2	56/192 (29.2)	24/69 (34.8)	17/60 (28.3)	15/63 (23.8)
P3	36/192 (18.8)	17/69 (24.6)	7/60 (11.7)	12/63 (19.0)
Anterior subcapsular	4/192 (2.1)	1/69 (1.4)	3/60 (5.0)	0/63 (0.0)
Polar, n (%)	2/903 (0.2)	0/304 (0.0)	1/299 (0.3)	1/300 (0.3)
Mature, n (%)	2/903 (0.2)	2/304 (0.7)	0/299 (0.0)	0/300 (0.0)

LOCS: lens opacities classification system

Appendix 3. Overview of perioperative complications

Event	Overall (n = 874*)	Bromfenac (n = 292)	Dexamethasone (n = 295)	Combination (n = 287)
Perioperative events associated with an increased risk of developing CME, n				
Iris trauma	1	0	1	0
Posterior capsular rupture	4	2‡	1**	1
Zonulolysis	2	1	1	0
IOL exchange	1	1	0	0
Perioperative events associated with no increased risk of developing CME, n				
Capsulorhexis tear	4	2	1**	1
Corneal abrasion	1	0	1	0
Damage to Descemet's membrane	2	0	1	1
Increased IOP	1	0	1	0
IOL damage	2	2	0	0
IOL decentration	1	1	0	0
Narrow pupil without iris trauma	1	0	1	0
IFIS without iris trauma	6	0	3	3
Large subtenon wound required sutures	2	0	1	1

* Forty patients were drop-out before surgery

** One patient developed two complications: a capsulorhexis tear and posterior capsular rupture

‡ Posterior capsular rupture with vitreous loss in one patient

CME: cystoid macular edema; IFIS: intraoperative floppy iris syndrome; IOL: intraocular lens; IOP: intraocular pressure

Appendix 4. Per protocol analyses

Table 1. Differences in macular thickness, TMV and CDVA (per protocol analysis)

Parameter	Mean ± SD (no. of patients)		
	Bromfenac	*Dexamethasone*	*Combination*
CSMT (µm)			
Baseline	273.60 ± 25.85 (248)	275.26 ± 27.14 (269)	273.83 ± 24.58 (280)
6 wks	287.57 ± 48.33 (229)	295.23 ± 52.05 (247)	284.36 ± 35.47 (253)
12 wks	282.52 ± 28.82 (228)	283.42 ± 28.71 (244)	283.54 ± 27.59 (247)
Parafoveal thickness (µm)			
Baseline	324.38 ± 19.43 (249)	326.45 ± 20.69 (274)	327.28 ± 21.79 (280)
6 wks	335.24 ± 27.80 (229)	342.15 ± 25.70 (248)	337.69 ± 21.82 (253)
12 wks	333.03 ± 21.77 (228)	336.71 ± 21.42 (244)	336.49 ± 21.47 (248)
Perifoveal thickness (µm)			
Baseline	281.61 ± 16.29 (238)	282.47 ± 17.67 (265)	282.66 ± 18.09 (267)
6 wks	289.69 ± 22.24 (221)	294.62 ± 18.60 (237)	291.27 ± 18.40 (243)
12 wks	287.30 ± 17.34 (222)	290.92 ± 18.26 (236)	291.16 ± 17.10 (240)
TMV (mm^3)			
Baseline	8.27 ± 0.53 (236)	8.29 ± 0.55 (259)	8.29 ± 0.51 (259)
6 wks	8.50 ± 0.72 (219)	8.67 ± 0.59 (232)	8.52 ± 0.62 (242)
12 wks	8.44 ± 0.59 (222)	8.54 ± 0.57 (232)	8.52 ± 0.60 (240)
CDVA (logMAR)			
Baseline	0.29 ± 0.23 (251)	0.29 ± 0.20 (274)	0.29 ± 0.21 (281)
6 wks	0.01 ± 0.12 (235)	0.02 ± 0.14 (254)	0.01 ± 0.12 (259)
12 wks	-0.02 ± 0.10 (233)	-0.01 ± 0.11 (248)	-0.01 ± 0.11 (256)

CDVA: corrected distance visual acuity; CI: confidence interval; CME: cystoid macular edema; CSMT: central subfield mean macular thickness; logMAR: logarithm of the minimal angle of resolution; SD: standard deviation; TMV: total macular volume; wks: weeks

Table 2. Incidence of CME and CSME (per protocol analysis)

Parameter	Incidence rates, n (%)		
	Bromfenac	*Dexamethasone*	*Combination*
CME within 6 wks	8/288 (3.5)	19/252 (7.5)	3/252 (1.2)
CME within 12 wks	8/288 (3.5)	20/252 (7.9)	4/252 (1.6)
CSME within 6 wks	8/233 (3.4)	11/253 (4.3)	2/260 (0.8)
CSME within 12 wks	8/233 (3.4)	11/253 (4.3)	3/260 (1.2)

[‡] Overall effect at that time-point over all three groups

	Treatment effect* (95% CI); p-value		
Overall p-value‡	*Dexamethasone vs. bromfenac*	*Bromfenac vs. combination*	*Dexamethasone vs. combination*
0.009	6.05 (-0.45, 12.55); 0.068	3.71 (-2.74, 10.16); 0.259	9.76 (3.47, 16.06); 0.002
0.437	1.42 (-0.88, 3.72); 0.226	-1.17 (-3.45, 1.11); 0.314	0.25 (-1.98, 2.48); 0.826
0.003	3.67 (0.80, 6.53); 0.012	1.01 (-1.84, 3.86); 0.488	4.68 (1.90, 7.45); 0.001
0.071	2.22 (0.26, 4.18); 0.026	-0.67 (-2.62, 1.28); 0.502	1.55 (-0.35, 3.45); 0.109
0.016	2.64 (0.41, 4.87); 0.021	0.26 (-1.95, 2.48); 0.816	2.90 (0.74, 5.06); 0.009
0.004	2.45 (0.92, 3.98); 0.002	-2.04 (-3.56, -0.52); 0.009	0.41 (-1.08, 1.89); 0.589
< 0.001	0.12 (0.06, 0.18); < 0.001	-0.01 (-0.07, 0.05); 0.825	0.11 (0.05, 0.17); < 0.001
0.003	0.07 (0.03, 0.11); 0.001	-0.04 (-0.08, 0.002); 0.064	0.03 (-0.01, 0.07); 0.107
0.302	0.02 (-0.01, 0.04); 0.171	-0.001 (-0.02, 0.02); 0.916	0.01 (-0.01, 0.04); 0.193
0.435	0.01(-0.01; 0.03); 0.212	-0.004 (-0.02, 0.01); 0.704	0.01 (-0.01, 0.03); 0.369

***** Treatment effect after correction for center, gender, age and CME in the fellow eye

‡ Overall effect at that time-point over all three groups

	Odds ratios (95% CI); p-value		
Overall p-value‡	*Dexamethasone vs. bromfenac*	*Bromfenac vs. combination*	*Dexamethasone vs. combination*
0.001	2.24 (0.96, 5.23); 0.062	3.02 (0.79, 11.52); 0.106	6.77 (1.98, 23.17); 0.002
0.002	2.37 (1.02, 5.49); 0.044	2.25 (0.67, 7.59); 0.189	5.34 (1.80, 15.87); 0.003
0.192	1.30 (0.51, 3.32); 0.579	4.61 (0.97, 21.99); 0.055	6.00 (1.31, 27.99); 0.021
0.061	1.31 (0.51, 3.33); 0.575	3.06 (0.80, 11.71); 0.103	3.99 (1.10, 14.54); 0.036

CI: confidence interval; CME: cystoid macular edema; CSME: clinically significant macular edema; wks: weeks

Appendix 5. Overview of adverse events

Event	Overall* (n = 906)	Bromfenac (n = 303)	Dexamethasone (n = 301)	Combination (n = 302)
Ocular adverse events, n				
Allergic reaction	5	4	1	0
Aniseikonia	1	1	0	0
Blepharitis or Meibomian gland dysfunction	18	7	8	3
Conjunctivitis	2	1	1	0
Corneal edema	5	2	2	1
Corneal erosion	8	2	1	5
Diplopia	6	2	4	0
Dry eyes	27	7	9	11
Foreign body sensation, mild pain or burning sensation	84	31	25	28
Glare or halos	3	1	1	1
Increased intraocular pressure**	7	0	4	3‡
Intraocular lens decentration	2	0	2	0
Macular hole	1	0	0	1
Map dot fingerprint dystrophy	1	0	1	0
Negative dysphotopsia	8	1	5	2
Ocular migraine	1	0	1	0
Optic neuropathy	1	0	1	0
Photophobia	4	1	1	2
Posterior capsular opacification	6	3	1	2
Pruritus	9	6	1	2
Ptosis	1	1	0	0
Pupillary block	1	0	1	0
Posterior vitreous detachment	20	10	7	3
Redness	18	7	6	5
Unstable or reduced visual acuity	12	5	3	4
Refractive surprise	1	0	1	0
Retinal defect	2	1	1	0
Retinal pigment epithelial detachment	1	0	0	1
Subconjunctival hemorrhage	2	0	1	1
Tearing	34	11	18	5
Trichiasis	1	0	0	1
Uveitis	7	4	1	2
Verrucous skin lesion	1	1	0	0
Wound leak	1	1	0	0
Systemic adverse events, n				
Altered sensation	1	0	1	0
Angina pectoris	2	1	1	0
Ankle distorsion	1	0	0	1
Basal cell carcinoma	1	0	1	0
Bleeding	1	0	1	0
Bursitis	1	0	1	0
Cardiac arrhythmias	5	1	3	1
Deep venous thrombosis	1	0	1	0
Diabetes mellitus (new diagnosis)	1	0	1	0
Electrolyte disorders	1	1	0	0

Appendix 5. Continued

Event	Overall* (n = 906)	Bromfenac (n = 303)	Dexamethasone (n = 301)	Combination (n = 302)
Systemic adverse events, n				
Epigastric hernia	1	0	1	0
Fracture	2	0	2	0
Headache	9	1	3	5
Head trauma	1	0	1	0
Hypertension	1	0	0	1
Infection	2	0	1	1
Inguinal hernia	1	1	0	0
Joint dislocation	1	0	0	1
Nausea	1	1	0	0
Pain	1	0	0	1
Pertussis	1	0	0	1
Polymyalgia rheumatica	1	0	0	1
Urticaria or allergy	4	2	1	1

‡ Eight patients who develop a perioperative complication excluded

* 54 patients developed two or more adverse events during the course of the study

**One patient developed an increased intraocular pressure in the contralateral eye.

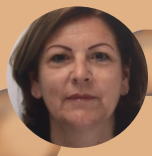
Appendix 6. Overview of serious adverse events

Event	Overall* (n = 906)	Bromfenac (n = 303)	Dexamethasone (n = 301)	Combination (n = 302)
Ocular serious adverse events, n				
Increased intraocular pressure	1	1	0	0
Retinal detachment	2	2*	0	0
Systemic serious adverse events, n				
Cerebral infarction	1	0	1	0
Epileptic seizure	2	0	1	1
Exacerbation inflammatory bowel disease	1	0	0	1
Fracture	3	3	0	0
Infection	2	2	0	0
Malignancy	4	2	2	0
Myocardial infarction	1	0	0	1
Pain after gastroscopy	1	0	1	0

A serious adverse event was defined as an adverse experience that occurred during the study and resulted in death; was life threatening (at the time of the event); required hospitalization or prolongation of existing inpatients' hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; or was an important medical event which may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

‡ Eight patients who develop a perioperative complication excluded

* 1 patient developed a bilateral retinal detachment during the course of the study



Chapter 5

A randomized controlled European multicenter trial on the prevention of cystoid macular edema after cataract surgery in diabetics: ESCRS PREMED study report 2

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Abstract

Purpose: Diabetes mellitus is a major risk factor for developing cystoid macular edema (CME) after cataract surgery. The PREvention of Macular EDema after cataract surgery (PREMED) study compares the efficacy of perioperative treatment strategies, in addition to topical bromfenac 0.09% and dexamethasone 0.1%, to reduce the risk of developing CME after uncomplicated cataract surgery in diabetic patients.

Setting: Twelve European study centers.

Design: A randomized controlled clinical trial, using a 2 x 2 factorial design.

Methods: Diabetic patients undergoing phacoemulsification cataract surgery were randomly allocated to receive no additional treatment, a subconjunctival injection with 40 mg triamcinolone acetonide (TA), an intravitreal injection with 1.25 mg bevacizumab, or a combination of both. Main outcomes were the difference in central subfield mean macular thickness (CSMT), corrected distance visual acuity, and the incidence of CME and clinically significant macular edema (CSME) within six and twelve weeks postoperatively.

Results: A total of 213 patients were included in the study. At six and twelve weeks postoperatively, CSMT was 12.3 µm and 9.7 µm lower in patients who received subconjunctival TA, as compared to patients who did not ($p = 0.007$ and $p = 0.014$, respectively). No patient who received subconjunctival TA developed CME. Intravitreal bevacizumab had no significant effect on macular thickness.

Conclusions: Diabetic patients who received a subconjunctival injection with TA at the end of cataract surgery had a lower macular thickness and macular volume at six and twelve weeks postoperatively, as compared to patients who did not. Intravitreal bevacizumab had no significant effect.

Introduction

Worldwide, an increasing number of people are affected by diabetes mellitus (DM), and many also develop cataract at an early age. Previous studies have indicated a three- to fourfold increase in the prevalence of cataract under the age of 65 in patients with DM, as compared to non-diabetics.[1] Diabetic patients undergoing cataract surgery have an increased risk of developing cystoid macular edema (CME) postoperatively, especially if they are also diagnosed with diabetic retinopathy (DR).[2]

CME after cataract surgery results from a postoperative inflammatory response. An increased vascular permeability causes fluid accumulation in the inner nuclear and outer plexiform layers of the retina, causing CME to develop.[3] Previous research has demonstrated a correlation between the risk of developing CME after cataract surgery and aqueous levels of various inflammatory mediators, such as interleukins and vascular endothelial growth factor (VEGF).[4]

Topical anti-inflammatory treatment with a corticosteroid and a non-steroidal anti-inflammatory drug (NSAID) has been recommended for diabetic patients undergoing cataract surgery.[5] But in spite of such preventive measures, the higher incidence of postoperative CME remains. The present study investigated the use of additional perioperative treatment strategies to further reduce the risk of developing CME in diabetics. This report focuses on the efficacy of a single subconjunctival injection with triamcinolone acetonide (TA) and/or a single intravitreal injection with bevacizumab at the end of cataract surgery, in addition to corticosteroid and NSAID eye drops, in reducing the risk of developing CME after cataract surgery.

Materials and methods

The PREvention of Macular EDema after cataract surgery (PREMED) study is a randomized controlled clinical trial (RCT), funded by the European Society of Cataract and Refractive Surgeons (ESCRS). The study protocol can be found at https://clinicaltrials.gov (identifier: NCT01774474) and was approved by all national authorities and local ethics committees. All study procedures were performed in accordance with the principles of the Declaration of Helsinki. A data safety monitoring board (members shown in appendix 1) evaluated the safety of trial participants.

Patient enrolment

This randomized controlled European multicenter trial included diabetic patients aged 21 years or older who required phacoemulsification cataract surgery. Patients were selected between July 2013 and June 2016 and signed written informed consent before inclusion in the study. Patients were recruited in one of twelve study centers, located in Austria (Hospital of the Brothers of St. John of God, Vienna; Vienna Institute for Research in Ocular Surgery, Vienna), Belgium (Antwerp University Hospital, Antwerp), Germany (Goethe University Hospital, Frankfurt am Main), Hungary (Semmelweis University, Budapest), Portugal (Centro Hospitalar Universitário Coimbra, Coimbra) and The Netherlands (VU University Medical Center, Amsterdam; Zuyderland Medical Center, Heerlen; Eye Hospital Zonnestraal, Hilversum; University Eye Clinic Maastricht UMC+, Maastricht; Haaglanden Medical Center, The Hague; Elisabeth-TweeSteden Hospital, Tilburg).

Only one eye per patient was included in the study and patients were excluded if they were considered functional monoculus as a result of moderate to severe visual impairment in the contralateral eye, as per the definition of the international statistical classification of diseases and related health problems 10th revision (ICD-10).[6] Patients were excluded if they had an increased risk of developing CME in the study eye because of previous intraocular surgery, intraocular inflammation or uveitis, retinal vein occlusion or macular pathology that may influence visual function, other than diabetic macular edema (DME).[2] Moreover, patients who presented with severe preoperative DME (macular thickness ≥ 450 µm) or severe non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR) or vitreous hemorrhage requiring panretinal photocoagulation (PRP) or vitrectomy, were not considered for participation in the study. Patients who used topical NSAIDs, topical corticosteroids or high dosage of systemic corticosteroids at baseline were excluded, as were patients who received an intravitreal injection with bevacizumab or ranibizumab in the study eye in the previous six weeks, an intravitreal injection with aflibercept in the previous ten weeks, or an intra- or periocular corticosteroid injection in the previous four months. Patients with pseudoexfoliation syndrome, Fuchs' endothelial

dystrophy or posttraumatic cataract in the study eye were also excluded. Finally, patients were excluded in case of contraindications for any of the investigated drugs, notably patients with glaucoma, intraocular pressure (IOP) ≥ 25 mmHg, previous steroid induced IOP elevation, systemic bleeding in the previous three months, major systemic surgery in the previous three months or a recent or recurrent cerebrovascular accident (CVA), myocardial infarction or thromboembolic event.

Study treatment

All patients underwent phacoemulsification cataract surgery with implantation of an intraocular lens (IOL) in the posterior segment and received peri- and/or postoperative antibiotics according to the standard of care in the participating study center. All patients received bromfenac 0.09% eye drops (Yellox, Bausch + Lomb®, Montpellier Cedex, France) twice daily for two days preoperatively and two weeks postoperatively, in combination with dexamethasone disodium phosphate 0.1% eye drops four times daily for two days preoperatively and one week postoperatively, and then one drop less per day every following week. No other ocular corticosteroids or NSAIDs were allowed to be used during the course of the study.

Moreover, patients were randomly allocated to one of four treatment groups in a 1:1:1:1 ratio. Stratified block randomization was performed per study center by a local investigator, with a block size of eight patients, using concealed online software (ALEA version 3.0, FormsVision®, Abcoude, The Netherlands). A factorial design was used, as shown in table 1. Patients in the TA group received a subconjunctival injection with 40 mg (1 ml) preservative-free triamcinolone acetonide (TA) at the end of cataract surgery. Patients in the bevacizumab group received an intravitreal injection with 1.25 mg (0.05 ml) bevacizumab (Avastin, Genentech Inc.®, San Francisco, California). Patients in the combination treatment group received a subconjunctival injection with 40 mg TA and an intravitreal injection with 1.25 mg bevacizumab at the end of surgery. Patients in the control group received no additional treatment. Patients were not informed about the randomized study treatment until twelve weeks postoperatively. No sham injections were used. All patients were informed about possible off-label use of the study treatments and gave informed consent.

Table 1. Randomized treatment

		Subconjunctival 40 mg TA	
		No	Yes
Intravitreal 1.25 mg Bevacizumab	No	Control group	TA group
	Yes	Bevacizumab group	Combination group

TA: triamcinolone acetonide

Outcome assessments

An extensive ophthalmological examination of both eyes was performed at baseline. Subjective refraction and corrected distance visual acuity (CDVA) were measured using early treatment diabetic retinopathy study (ETDRS) charts.[7] If patients were unable to read any letter on the ETDRS charts, hand motion or finger counting at a given distance were converted to the logarithm of the minimum angle of resolution (logMAR) equivalent.[8] Ophthalmic examination included slit lamp examination, to grade cataract in accordance with the lens opacities classification system (LOCS) II, and to detect the presence of aqueous cells and flare according to the standardization of uveitis nomenclature (SUN) classification.[9, 10] Intraocular pressure was measured using Goldman applanation tonometry. A fundoscopic examination was performed to evaluate any retinal pathology. DR was graded according to the preferred practice patterns® of the American Academy of Ophthalmology.[11] Recent glycated hemoglobin levels (HbA1c) were recorded whenever available.

Within four weeks preoperatively, a baseline optical coherence tomography (OCT) was performed, using only spectral domain OCT devices (3D OCT, Topcon Corp.; Cirrus HD-OCT, Carl Zeiss Meditec AG; OCT-HS100, Canon Inc.; RTVue-100, Optovue Inc; or Spectralis, Heidelberg Engineering Inc.). Each study center used only one type of OCT device for all pre- and postoperative measurements. If the preoperative OCT scan was of insufficient quality, e.g. due to dense cataract, an alternative baseline measurement was performed at one day postoperatively.[12] Macular thickness was reported according to the ETDRS retinal thickness map, as shown in figure 1.[13] Central subfield macular thickness (CSMT) corresponds to the mean macular thickness in the central 1 mm area. Mean parafoveal and perifoveal thickness were measured in a concentric ring located 1-3 mm and 3-6 mm around the fovea, respectively. Total macular volume (TMV) was measured in the central 6 mm area.

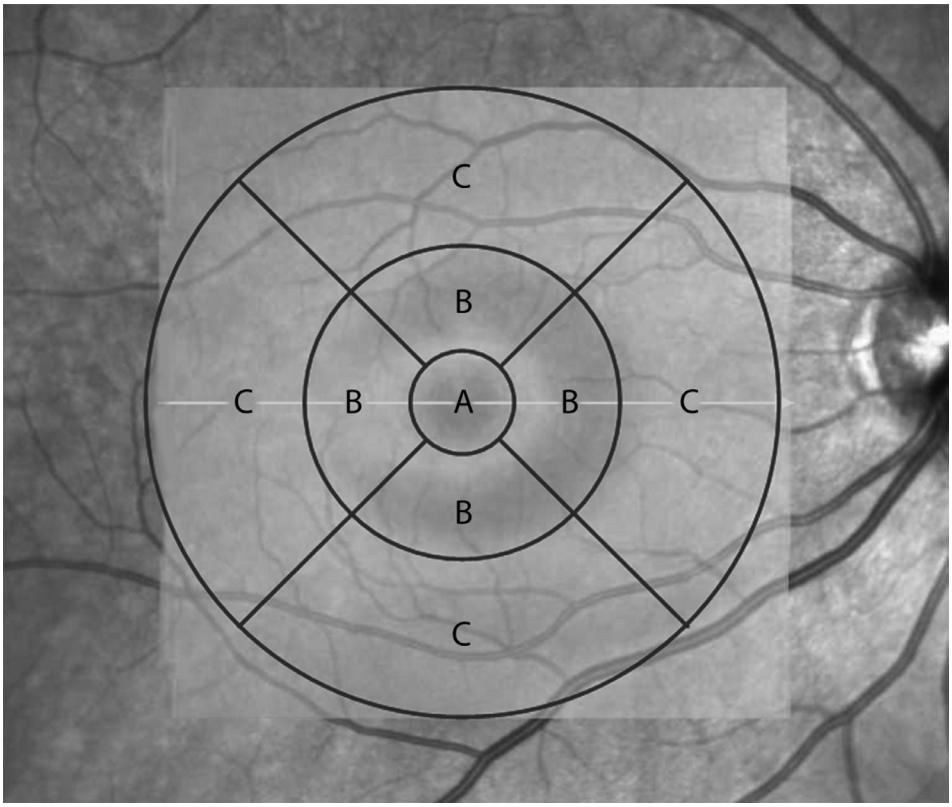
Postoperative visits were performed at six and twelve weeks postoperatively and included a full ophthalmologic examination of the study eye, as described above. A local investigator who was masked for the allocated study treatment performed postoperative CDVA and OCT measurements.

Study outcomes

The primary outcome of the ESCRS PREMED study was the difference between treatment groups with respect to CSMT at six weeks postoperatively, with correction for baseline measurements. Secondary outcomes were the difference in CSMT at twelve weeks postoperatively, and para- and perifoveal thickness, TMV and CDVA at six and twelve weeks postoperatively. IOP was measured at each study visit and all adverse events were reported.

Two independent and masked retina specialists of the University Eye Clinic Maastricht UMC+, assessed the OCT scans in order to identify subfoveal cysts and other retinal pathology. The incidence of CME within six and twelve weeks postoperatively was evaluated. CME was defined as an increase in CSMT of ≥ 10% as compared to baseline with the presence of cysts near the fovea on OCT. The retina specialists did not classify CME into various subgroups, such as pseudophakic cystoid macular edema (PCME) or DME. Clinically significant cystoid macular edema (CSME) was defined as an increase in CSMT of ≥ 10%, with the presence of cysts near the fovea, and less than 0.2 logMAR CDVA improvement as compared to the preoperative baseline.

Figure 1. ETDRS retinal thickness map



A) CSMT in the central 1.0 mm area; B) parafoveal thickness in a concentric ring located 1.0-3.0 mm around the fovea; C) perifoveal thickness in a concentric ring located 3.0-6.0 mm around the fovea. A-C) TMV is calculated for the central 6.0 mm area.
CSMT: central subfield mean macular thickness; ETDRS: early treatment diabetic retinopathy study; TMV: total macular volume

Escape treatment

In case of CSME, patients were treated with an intravitreal injection with 1.25 mg (0.05 ml) bevacizumab, as reported by the Pan-American COllaborative REtina Study group (PACORES).[14, 15] If CSME persisted after four weeks, a second intravitreal injection was given. From twelve weeks postoperatively, CSME was treated in accordance with the standard of care in each participating study center.

Patients who developed severe postoperative inflammation, defined as at least 2+ cells according to the SUN classification, received topical bromfenac 0.09% twice daily and dexamethasone 0.1% four times daily for four weeks. If severe inflammation persisted after four weeks, ophthalmologists were allowed to start other anti-inflammatory eye drops.

Sample size

The sample size calculation for this study was based on the primary outcome, i.e. the difference in CSMT at six weeks postoperatively. A standard deviation (SD) of postoperative CSMT of 50 µm and a correlation between pre- and postoperative CSMT of 0.5 were assumed, based on the results of previous studies.[16, 17] With a total sample size of 209 patients, a mean difference of 25 µm between treatment groups could be detected with 80% power at a Bonferroni-corrected significance level of 0.025, where fifty patients were added to correct for center, center with treatment interactions and other covariates, and a maximum dropout rate of 20% was accounted for.

Statistical analysis

Data were collected in a qualified web-based database (MACRO version 4.4, Elsevier), and were subsequently exported to IBM SPSS Statistics for Windows (Version 23.0, IBM Corp.). No interim analyses were performed during the course of the study. Postoperative data analyses were performed with masking for treatment groups.

Data were excluded from final analyses if patients developed a perioperative complication that was expected to increase the risk of developing CME, e.g. iris trauma or posterior capsular rupture with or without vitreous loss.[18]

Categorical data were presented as numbers (%), and numerical data by means (SD). Linear mixed model analyses using restricted maximum likelihood were used for numerical outcomes that were measured repeatedly, including the primary outcome of the study. Linear mixed models account for the correlation between repeated measurements within a patient and also include data from patients who dropped out of the study. No data were imputed. A likelihood-based approach was used for missing outcome data, including OCT

data, where data were assumed to be missing at random. No missing data were expected for the fixed factors in the model, such as study center and timing of study visits. Logistic regression analysis was used to check whether missing outcome data were significantly related to certain patient characteristics. Variables significantly related to missing outcome data were added to the model to ensure missing at random. Additionally, baseline characteristics that are associated with an increased risk for developing CME were included in the model, i.e. age, gender, type of DM, type of anti-diabetic medication, DR grade, previous PRP and the presence of CME in the fellow eye.[2, 18, 19] The model without these patient characteristics was used as a sensitivity analysis.

Three-way interaction terms treatment group * timing of the study visit * study center (plus their two-way interaction terms) were applied for both treatment arms to verify whether treatment effect depended significantly on study center. If at least one of these three-way interaction terms proved significant, the treatment effect will be reported for each center separately. If the three-way interaction terms were not significant, they were removed from the model and only the overall treatment effect across centers will be reported. If the treatment interaction between TA and bevacizumab proved significant, the effect of one treatment will be reported for different levels of the other. If the interaction between TA and bevacizumab was not significant, the effects of both treatments will be reported separately.

Because the sample size within a study center might be small, the abovementioned analyses were also performed after combining centers based on location and center type, i.e. academic centers in The Netherlands, non-academic centers in The Netherlands, and other European centers. This analysis was included as a sensitivity analysis. An additional sensitivity analysis was performed with study center included as a random instead of a fixed factor.

Finally, per-protocol analyses were performed and compared to the intention-to-treat analyses. Data were excluded from the per-protocol analyses if deviations from the allocated treatment intervention occurred, e.g. patients who received additional NSAID or corticosteroid eye drops during the course of the study.

Since the expected numbers of patients with CME or CSME are small, Fisher's exact tests were used for these binary outcomes. Differences between treatment groups in the occurrence of perioperative complications, adverse events, dropout and reasons for dropout were assessed using chi-square test or Fisher's exact test, where appropriate.

Results

A total of 213 patients were selected for inclusion in the ESCRS PREMED study, as can be seen from figure 2. Baseline characteristics are shown in table 2. The majority of patients were diagnosed with DM type 2 and most of them had no signs of DR. Seven patients had cystic changes on OCT. Sixty patients were randomized to the control group, 51 patients received a subconjunctival injection with 40 mg TA, 50 patients received an intravitreal injection with 1.25 mg bevacizumab, and 52 patients were randomized to the combination treatment group.

Data of seven patients were excluded from the final data-analyses, because perioperative complications were thought to increase the risk of developing CME after cataract surgery. This includes patients who developed a posterior capsular rupture, zonulolysis, anterior chamber bleeding and two patients with incomplete cortex removal. All perioperative complications are listed in appendix 2.

Of the 206 patients suitable for inclusion in the final data analyses, 31 patients (15.0%) did not complete the study follow-up. Ten patients in the control group, twelve patients in the TA group, seven patients in the bevacizumab group and two patients in the combination treatment group were dropouts. As can be seen from figure 2, most patients voluntarily discontinued participation because of personal reasons. One patient in the control group passed away after developing hepatic metastases associated with a pre-existing thyroid carcinoma. One patient in the TA group discontinued participation after developing a CVA.

Macular thickness and volume

The main outcome parameters of this study are given in tables 3 and 4, and figures 3 and 4. After correction for baseline OCT data and other covariables, there was a significant effect of subconjunctival TA on postoperative macular thickness and volume (see table 5). At six and twelve weeks postoperatively, CSMT was on average 12.3 µm and 9.7 µm lower in patients treated with a subconjunctival injection with 40 mg TA, as compared to patients who were not ($p = 0.007$ and $p = 0.014$, respectively). Postoperative para- and perifoveal thicknesses were also lower in patients who received a subconjunctival injection with TA, as compared to patients in other treatment groups. At six and twelve weeks postoperatively, mean TMV was 0.2 mm^3 lower in patients who received a subconjunctival injection with 40 mg TA ($p < 0.001$).

Figure 2. Consort flow diagram showing the number of participants who were screened, randomized and analyzed

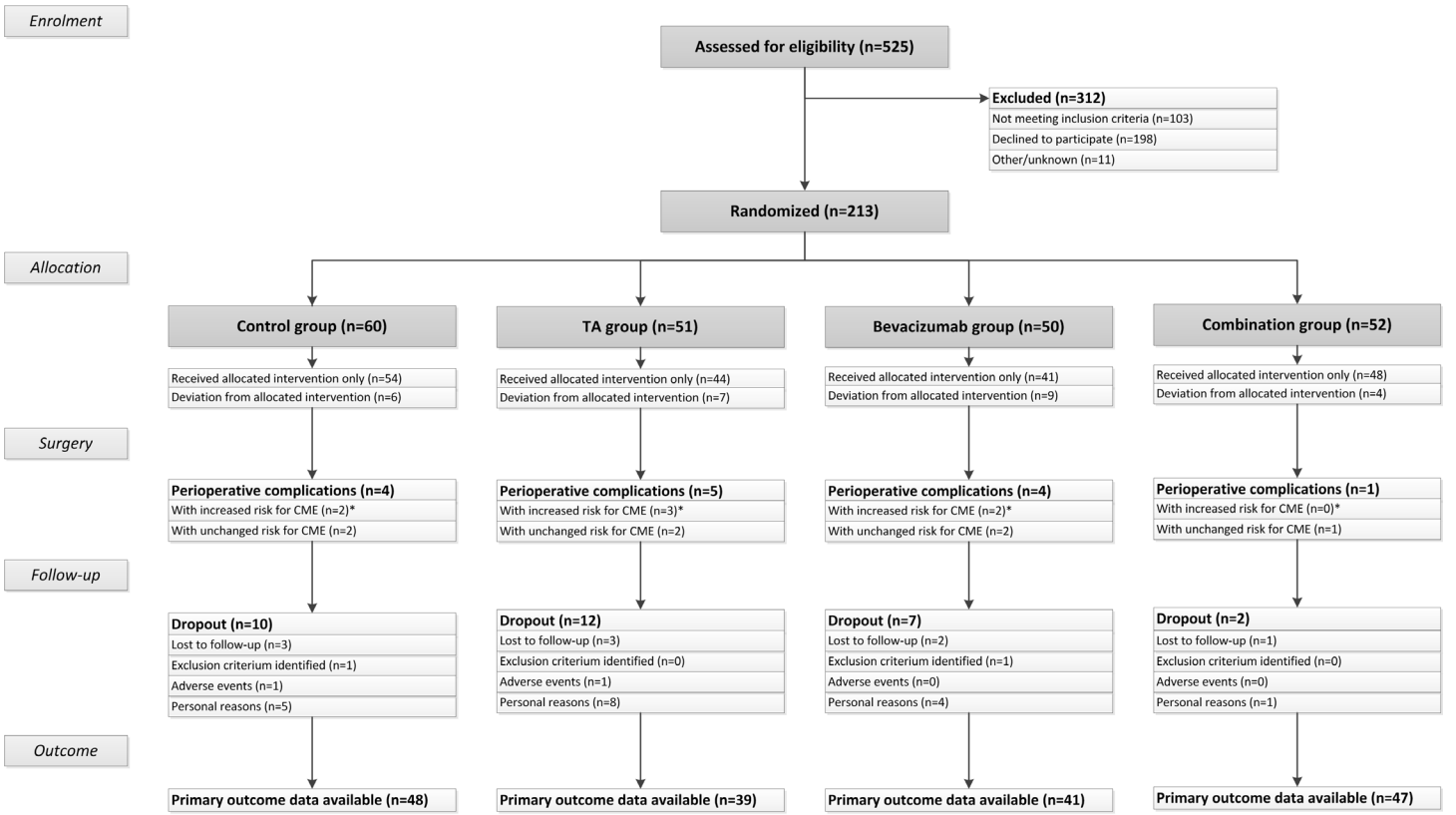


Table 2. Baseline characteristics

	Overall (n = 213)	Control (n = 60)	TA (n = 51)	Bevacizumab (n = 50)	Combination (n = 52)
General Patient Characteristics					
Mean age (y) ± SD	71.23 ± 8.01	71.67 ± 9.36	70.65 ± 7.56	71.90 ± 7.64	70.67 ± 7.22
Right eye, n (%)	121/213 (56.8)	35/60 (58.3)	33/51 (64.7)	25/50 (50.0)	28/52 (53.8)
Female sex, n (%)	97/213 (45.5)	28/60 (46.7)	27/51 (52.9)	22/50 (44.0)	20/52 (38.5)
Caucasian, n (%)	203/213 (95.3)	59/60 (98.3)	49/51 (96.1)	46/50 (92.0)	49/52 (94.2)
Study center, n (%)					
Center 1	1/213 (0.5)	0/60 (0.0)	0/51 (0.0)	0/50 (0.0)	1/52 (1.9)
Center 2	1/213 (0.5)	1/60 (1.7)	0/51 (0.0)	0/50 (0.0)	0/52 (0.0)
Center 3	9/213 (4.2)	3/60 (5.0)	3/51 (5.9)	1/50 (2.0)	2/52 (3.8)
Center 4	9/213 (4.2)	3/60 (5.0)	1/51 (2.0)	3/50 (6.0)	2/52 (3.8)
Center 5	4/213 (1.9)	2/60 (3.3)	0/51 (0.0)	1/50 (2.0)	1/52 (1.9)
Center 6	13/213 (6.1)	4/60 (6.7)	3/51 (5.9)	3/50 (6.0)	3/52 (5.8)
Center 7	7/213 (3.3)	2/60 (3.3)	2/51 (3.9)	1/50 (2.0)	2/52 (3.)
Center 8	40/213 (18.8)	10/60 (16.7)	11/51 (21.6)	10/50 (20.0)	9/52 (17.3)
Center 9	3/213 (1.4)	0/60 (0.0)	0/51 (0.0)	1/50 (2.0)	2/52 (3.8)
Center 10	108/213 (50.7)	29/60 (48.3)	27/51 (52.9)	26/50 (52.0)	26/52 (50.0)
Center 11	8/213 (3.8)	3/60 (5.0)	1/51 (2.0)	2/50 (4.0)	2/52 (3.8)
Center 12	10/213 (4.7)	3/60 (5.0)	3/51 (5.9)	2/50 (4.0)	2/52 (3.8)
DM Characteristics					
Type 2 diabetes, n (%)	204/212 (96.2)	54/60 (90.0)	48/50 (96.0)	50/50 (100.0)	52/52 (100.0)
Mean DM duration (y) ± SD	11.91 ± 9.27	13.79 ± 11.6	10.83 ± 9.06	10.71 ± 7.40	12.00 ± 7.99
Mean HbA1c (mmol/mol) ± SD	55.97 ± 14.32	55.33 ± 12.93	59.02 ± 17.61	56.11 ± 15.06	53.48 ± 11.11
CME in the contralateral eye, n (%)	7/212 (3.3)	0/60 (0.0)	3/50 (6.0)	2/50 (4.0)	2/52 (3.8)
DR grade in the study eye, n (%)					
No DR	177/208 (85.1)	47/58 (81.0)	40/50 (80.0)	43/48 (89.6)	47/52 (90.4)
Mild NPDR	21/208 (10.1)	8/58 (13.8)	8/50 (16.0)	1/48 (2.1)	4/52 (7.7)
Moderate NPDR	10/208 (4.8)	3/58 (5.2)	2/50 (4.0)	4/48 (8.3)	1/52 (1.9)
Severe NPDR or PDR	0/208 (0.0)	0/58 (0.0)	0/50 (0.0)	0/48 (0.0)	0/52 (0.0)
Anti-diabetic medication, n (%)					
Strict diet only, no medication	10/213 (4.7)	2/60 (3.3)	3/51 (5.9)	3/50 (6.0)	2/52 (3.8)
OAD	127/213 (59.6)	27/60 (45.0)	33/51 (64.7)	33/50 (66.0)	34/52 (65.4)
Insulin only	32/213 (15.0)	16/60 (26.7)	6/51 (11.8)	5/50 (10.0)	5/52 (9.6)
OAD and insulin	44/213 (20.7)	15/60 (25.0)	9/51 (17.6)	9/50 (18.0)	11/52 (21.2)
Previous treatments, n (%)					
Previous anti-VEGF	6/210 (2.9)	2/60 (3.3)	3/49 (6.1)	1/49 (2.0)	0/52 (0.0)
Previous intra- or periocular CS	1/210 (0.5)	0/60 (0.0)	1/49 (2.0)	0/49 (0.0)	0/52 (0.0)
Previous PRP	20/210 (9.5)	9/60 (15.0)	5/49 (10.2)	5/49 (10.2)	1/52 (1.9)

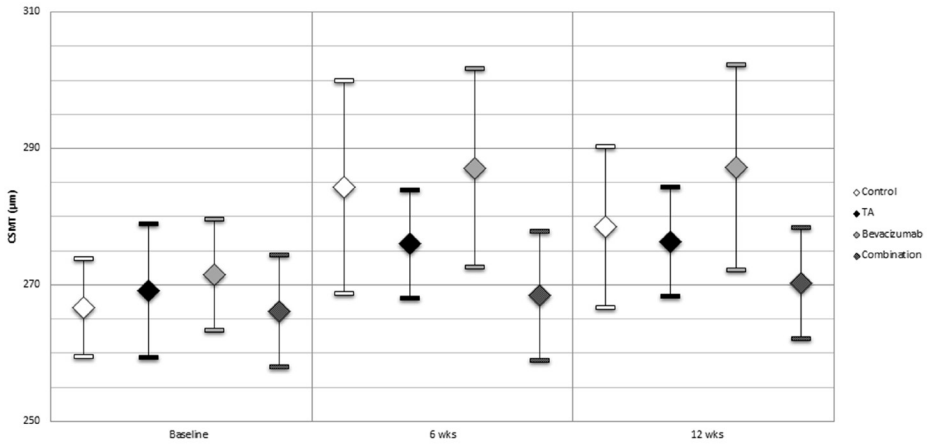
CME: cystoid macular edema; CS: corticosteroid; DM: diabetes mellitus; DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; OAD: oral anti-diabetic drugs; PDR: proliferative diabetic retinopathy; PRP: panretinal photocoagulation; SD: standard deviation; TA: triamcinolone acetonide; VEGF: vascular endothelial growth factor

Table 3. Mean macular thickness, TMV, CDVA and IOP (intention to treat analysis)

Parameter	Mean ± SD (no. of patients)			
	Control	*TA*	*Bevacizumab*	*Combination*
CSMT (µm)				
Baseline	266.65 ± 26.33 (54)	269.20 ± 32.92 (46)	271.55 ± 27.78 (47)	266.18 ± 29.28 (51)
6 wks	284.29 ± 53.75 (48)	276.00 ± 24.61 (39)	287.15 ± 46.17 (41)	268.43 ± 32.16 (47)
12 wks	278.48 ± 39.79 (46)	276.31 ± 23.71 (36)	287.23 ± 46.48 (39)	270.26 ± 27.69 (47)
Parafoveal thickness (µm)				
Baseline	317.69 ± 28.13 (54)	323.09 ± 33.79 (47)	327.47 ± 20.49 (47)	319.51 ± 22.97 (51)
6 wks	331.58 ± 26.88 (48)	329.83 ± 23.16 (40)	339.29 ± 32.71 (41)	319.45 ± 29.02 (47)
12 wks	330.07 ± 23.90 (46)	330.83 ± 22.54 (35)	337.15 ± 35.38 (39)	321.53 ± 16.53 (47)
Perifoveal thickness (µm)				
Baseline	278.29 ± 21.08 (51)	286.02 ± 24.19 (43)	282.96 ± 16.46 (46)	279.78 ± 14.85 (50)
6 wks	287.89 ± 21.16 (46)	295.03 ± 26.17 (37)	292.00 ± 24.40 (40)	281.63 ± 19.05 (46)
12 wks	286.29 ± 20.38 (45)	289.26 ± 20.37 (35)	291.76 ± 24.64 (38)	282.15 ± 13.86 (46)
TMV (mm^3)				
Baseline	8.12 ± 0.63 (50)	8.29 ± 0.55 (43)	8.22 ± 0.56 (46)	8.19 ± 0.50 (50)
6 wks	8.41 ± 0.63 (46)	8.50 ± 0.57 (36)	8.51 ± 0.80 (40)	8.24 ± 0.66 (45)
12 wks	8.35 ± 0.60 (45)	8.43 ± 0.58 (34)	8.51 ± 0.80 (38)	8.27 ± 0.48 (45)
CDVA (logMAR)				
Baseline	0.31 ± 0.21 (57)	0.36 ± 0.31 (47)	0.43 ± 0.30 (48)	0.30 ± 0.21 (52)
6 wks	0.04 ± 0.10 (48)	0.05 ± 0.13 (40)	0.03 ± 0.12 (41)	0.07 ± 0.14 (50)
12 wks	0.02 ± 0.11 (48)	0.03 ± 0.21 (37)	0.03 ± 0.10 (41)	0.02 ± 0.11 (49)
IOP (mmHg)				
Baseline	16.52 ± 3.19 (56)	16.07 ± 3.56 (46)	16.19 ± 3.29 (48)	15.96 ± 3.33 (51)
6 wks	14.90 ± 2.71 (48)	15.95 ± 3.73 (39)	14.30 ± 3.28 (40)	16.78 ± 5.79 (49)
12 wks	14.21 ± 2.57 (47)	16.31 ± 5.38 (36)	13.88 ± 3.33 (41)	16.44 ± 6.18 (48)

CDVA: corrected distance visual acuity; CSMT: central subfield macular thickness; IOP: intraocular pressure; logMAR: logarithm of the minimal angle of resolution; SD: standard deviation; TA: triamcinolone acetonide; TMV: total macular volume; wks: weeks

Figure 3. Observed mean CSMT with 95% confidence intervals



CSMT: central subfield mean macular thickness; TA: triamcinolone acetonide; wks: weeks

In contrast, this study could not identify a significant effect of intravitreal 1.25 mg bevacizumab on postoperative macular thickness. After Bonferroni correction (significance level $\alpha = 0.025$), there were no statistically significant differences with respect to CSMT, parafoveal and perifoveal thickness at six and twelve weeks postoperatively in patients who received an intravitreal injection with bevacizumab, versus patients who did not. At six weeks postoperatively, TMV was 0.1 mm^3 lower in patients who received an intravitreal injection with bevacizumab ($p = 0.023$), but the difference was not significant at twelve weeks postoperatively.

As can be seen from table 5, this study could not identify a significant interaction between subconjunctival TA and intravitreal bevacizumab.
All sensitivity analyses and per protocol analyses showed similar results.

Incidence of CME and CSME

Cysts were detected near the fovea in 15 patients within twelve weeks postoperatively. The incidence of CME and CSME is reported in detail in table 6. As described previously, CME was defined as an increase in CSMT of ≥ 10% as compared to baseline with the presence of cysts near the fovea on OCT. None of the patients who received a subconjunctival injection with TA at the end of cataract surgery developed CME as defined in this study, including two patients with cystic changes on baseline OCT. In contrast, CME developed within twelve weeks postoperatively in eight patients (8.7%) who did not receive TA. CSME was defined as CME with less than 0.2 logMAR CDVA improvement as compared to the

preoperative baseline. Based on this definition, CME was considered clinically significant in four patients (4.3%) who were not treated with TA.

The incidence of CME was comparable in patients who received an intravitreal injection with bevacizumab, and patients who did not. Four patients in each group developed CME (incidence 4.7% and 4.3%, respectively). Three patients with cystoid changes on baseline OCT received intravitreal bevacizumab at the end of cataract surgery. Of these three patients, CME persisted in one and resolved in another. One of these patients dropped out from the study.

Figure 4. Secondary outcome measures, observed means with 95% confidence intervals

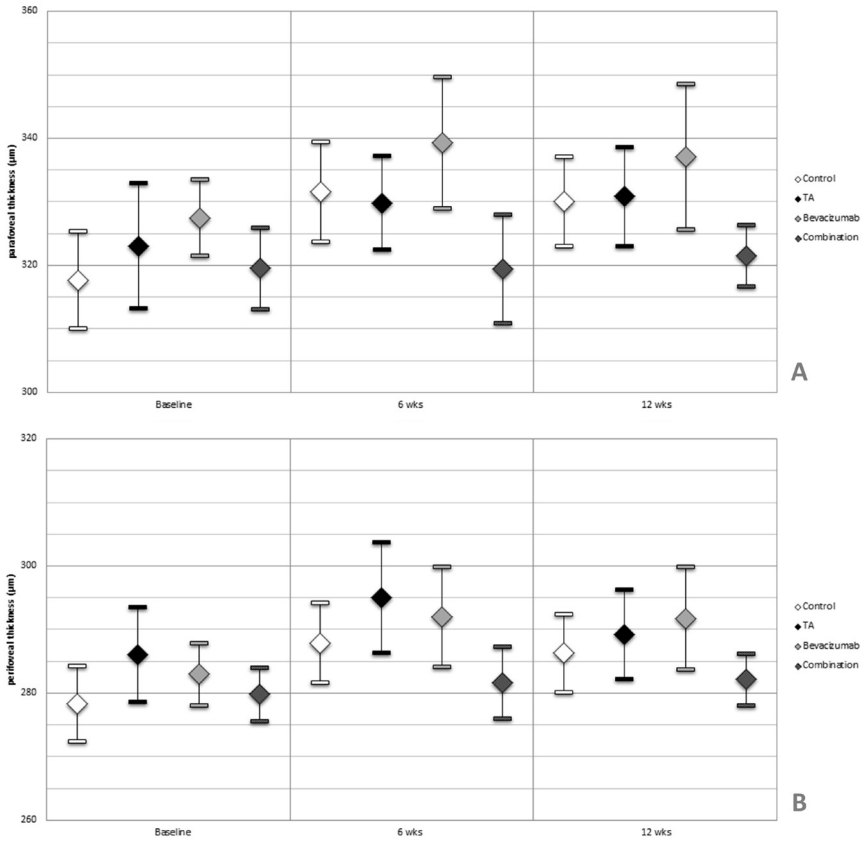
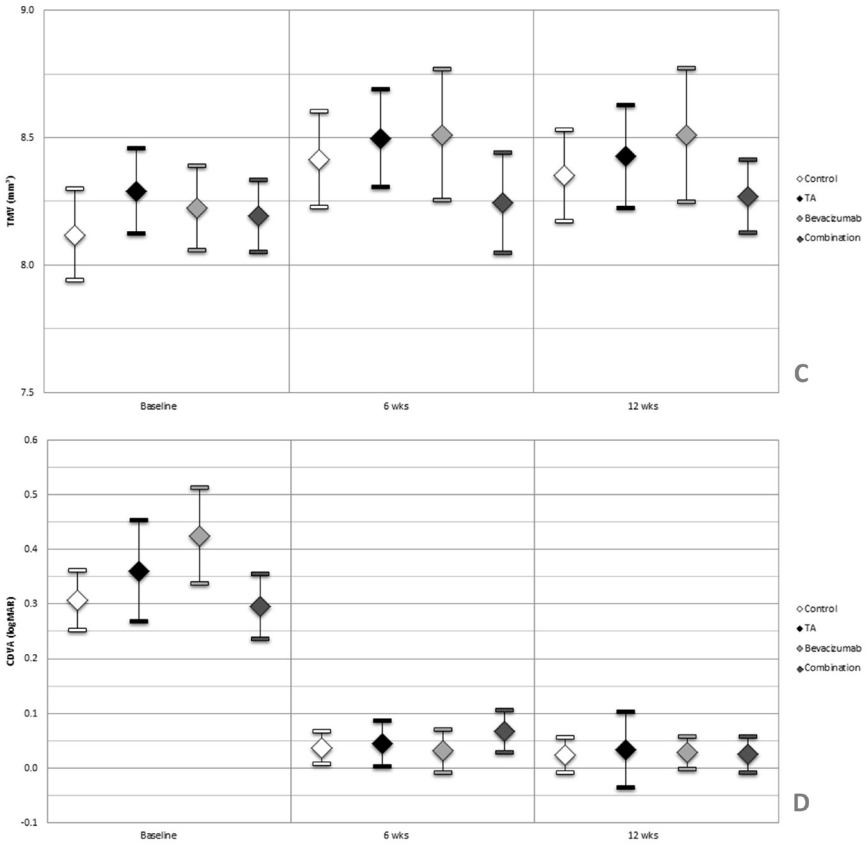


Figure 4. Continued



CDVA: corrected distance visual acuity; logMAR: logarithm of the minimal angle of resolution; TA: triamcinolone acetonide; TMV: total macular volume; wks: weeks

Table 4. Mean difference from baseline for macular thickness, TMV, CDVA and IOP (intention to treat analysis)

Parameter	Mean ± SD (no. of patients)			
	Control	*TA*	*Bevacizumab*	*Combination*
CSMT (µm)				
6 wks	+20.09 ± 42.10 (44)	+3.41 ± 28.48 (39)	+13.48 ± 31.94 (40)	-1.80 ± 19.25 (46)
12 wks	+12.19 ± 27.64 (42)	+5.14 ± 33.72 (36)	+14.11 ± 30.12 (38)	-0.07 ± 13.31 (46)
Parafoveal thickness (µm)				
6 wks	+14.18 ± 22.12 (44)	+5.70 ± 23.13 (40)	+10.68 ± 16.21 (40)	-1.98 ± 33.33 (46)
12 wks	+13.81 ± 20.71 (42)	+4.54 ± 25.45 (35)	+8.00 ± 23.96 (38)	+0.33 ± 17.09 (46)
Perifoveal thickness (µm)				
6 wks	+11.64 ± 15.43 (42)	+7.81 ± 21.99 (36)	+8.28 ± 10.36 (39)	-0.27 ± 18.71 (45)
12 wks	+10.40 ± 14.91 (40)	+2.00 ± 9.15 (34)	+7.81 ± 11.21 (37)	+1.02 ± 9.61 (45)
TMV (mm^3)				
6 wks	+0.30 ± 0.27 (39)	+0.18 ± 0.29 (34)	+0.27 ± 0.26 (36)	+0.06 ± 0.12 (43)
12 wks	+0.24 ± 0.21 (39)	+0.11 ± 0.13 (31)	+0.27 ± 0.23 (34)	+0.06 ± 0.11 (43)
CDVA (logMAR)				
6 wks	-0.26 ± 0.23 (47)	-0.34 ± 0.34 (40)	-0.38 ± 0.35 (41)	-0.23 ± 0.23 (50)
12 wks	-0.27 ± 0.21 (47)	-0.36 ± 0.34 (37)	-0.40 ± 0.30 (41)	-0.28 ± 0.24 (49)
IOP (mmHg)				
6 wks	-1.76 ± 2.63 (46)	-0.08 ± 3.20 (39)	-1.73 ± 2.78 (40)	+0.92 ± 5.53 (48)
12 wks	-2.17 ± 2.81 (46)	+0.08 ± 4.90 (36)	-2.32 ± 2.94 (41)	+0.53 ± 5.75 (47)

CDVA: corrected distance visual acuity; CSMT: central subfield macular thickness; IOP: intraocular pressure; logMAR: logarithm of the minimal angle of resolution; SD: standard deviation; TA: triamcinolone acetonide; TMV: total macular volume; wks: weeks

Table 5. Differences between treatment groups in macular thickness, TMV, CDVA and IOP (intention to treat analysis)

Parameter	Subconjunctival TA		Intravitreal Bevacizumab		Interaction‡
	Treatment effect (95% CI)*	*p-value*	*Treatment effect* (95% CI)*	*p-value*	*p-value*
CSMT (µm)					
6 wks	-12.3 (-21.1, -3.5)	0.007	-7.8 (-16.6, 1.0)	0.083	0.344
12 wks	-9.7 (-17.4, -2.0)	0.014	-2.3 (-9.9, 5.4)	0.563	
Parafoveal thickness (µm)					
6 wks	-10.0 (-15.0, -5.0)	< 0.001	-4.5 (-9.5, 0.4)	0.074	0.357
12 wks	-7.0 (-12.0, -2.0)	0.006	-3.9 (-8.9, 1.1)	0.124	
Perifoveal thickness (µm)					
6 wks	-4.8 (-9.1, -0.5)	0.030	-4.8 (-9.1, -0.5)	0.031	0.294
12 wks	-5.8 (-8.7, -3.0)	< 0.001	-1.1 (-4.0, 1.7)	0.440	
TMV (mm^3)					
6 wks	-0.21 (-0.31, -0.10)	< 0.001	-0.12 (-0.23, -0.02)	0.023	0.587
12 wks	-0.18 (-0.27, -0.10)	< 0.001	-0.04 (-0.12, 0.05)	0.384	
CDVA (logMAR)					
6 wks	0.04 (-0.0002, 0.07)	0.052	0.01 (-0.02, 0.05)	0.437	0.281
12 wks	0.02 (-0.01, 0.06)	0.217	0.01 (-0.03, 0.05)	0.702	
IOP (mmHg)					
6 wks	1.65 (0.58, 2.72)	0.003	0.61 (-0.46, 1.68)	0.260	0.272
12 wks	2.48 (1.20, 3.76)	< 0.001	-0.46 (-1.73, 0.81)	0.475	

* Difference between treatment groups with correction for baseline values, gender, age, CME in the fellow eye, type of DM, type of anti-diabetic drugs, stage of DR, previous PRP

‡ Interaction between subconjunctival TA and intravitreal bevacizumab

CDVA: corrected distance visual acuity; CI: confidence interval; CME: cystoid macular edema; CSMT: central subfield macular thickness; DM: diabetes mellitus; DR: diabetic retinopathy; IOP: intraocular pressure; logMAR: logarithm of the minimal angle of resolution; PRP: panretinal photocoagulation; TA: triamcinolone acetonide; TMV: total macular volume; wks: weeks

Per protocol analyses, as shown in appendix 3, showed comparable results. It should be noted that the abovementioned analyses could not be corrected for study center and other baseline characteristics, due to the small number of patients who developed CME or CSME.

Visual acuity

Mean final CDVA was 0.02 logMAR in the control and combination treatment groups and 0.03 logMAR in the TA and bevacizumab groups (equals 20/21 Snellen in all groups). There were no statistically significant differences between treatment groups with respect to postoperative CDVA at six and twelve weeks postoperatively.

Table 6. Incidence of CME (intention to treat analysis)

Parameter	Incidence rates, no. of patients (%)*					
	TA			*Bevacizumab*		
	No	*Yes*	*p-value‡*	*No*	*Yes*	*p-value‡*
Cysts at baseline	5/95 (5.3)	2/95 (2.1)	0.444	4/98 (4.1)	3/92 (3.3)	> 0.999
Cysts within 6 wks	9/89 (10.1)	2/84 (2.4)	0.058	7/91 (7.7)	4/82 (4.9)	0.542
Cysts within 12 wks	13/85 (15.3)	2/78 (2.6)	0.006	9/85 (10.6)	6/78 (7.7)	0.595
CME within 6 wks	7/92 (7.6)	0/87 (0.0)	0.014	4/93 (4.3)	3/86 (3.5)	> 0.999
CME within 12 wks	8/92 (8.7)	0/87 (0.0)	0.007	4/93 (4.3)	4/86 (4.7)	> 0.999
CSME within 6 wks	3/92 (3.3)	0/89 (0.0)	0.246	3/93 (3.2)	0/88 (0.0)	0.246
CSME within 12 wks	4/92 (4.3)	0/89 (0.0)	0.121	3/93 (3.2)	1/88 (1.1)	0.621

* Missing values for cysts: 16 patients at baseline (7.8%); 33 patients at 6 wks (16.0%), and 43 patients at 12 wks (20.9%). Missing values for CME: 27 patients (13.1%), and CSME: 25 patients (12.1%). No data were imputed
‡ Difference between treatment groups was *not* corrected for baseline variables and study center, due to the low number of patients with CME and CSME
CME: cystoid macular edema; CSME: clinically significant macular edema; wks: weeks

Maximal decline in CDVA in patients with CSME was up to 0.52 logMAR (20/71 Snellen). Median CDVA decreased to 0.24 logMAR (20/30 Snellen) in patients with CSME, and improved to 0.11 logMAR (20/24 Snellen) in those patients at twelve weeks postoperatively.

Intraocular pressure

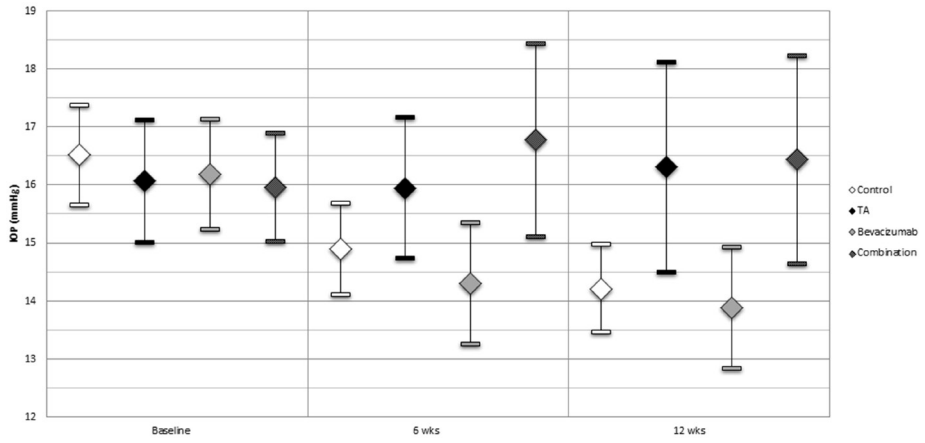
As evident from figure 5 and tables 3-5, postoperative IOP was significantly higher in patients who received a subconjunctival injection with 40 mg TA, as compared to patients who did not. Average IOP was 1.7 mmHg higher at six weeks ($p = 0.003$) and 2.5 mmHg higher at twelve weeks postoperatively ($p < 0.001$).

Six patients who received a subconjunctival injection with 40 mg TA developed an IOP of ≥ 25 mmHg at twelve weeks postoperatively. No patients in the other treatment groups presented with an IOP ≥ 25 mmHg at six or twelve weeks postoperatively. Ten and 15 patients who received subconjunctival TA developed an IOP increase of ≥ 5 mmHg at six and/or twelve weeks after injection, respectively. Only one patient who did not receive TA, presented with an IOP increase of ≥ 5 mmHg during the course of the study. Seven patients who developed an IOP increase were treated with topical IOP lowering drugs. Five patients received a fixed combination of timolol and dorzolamide; one patient received a fixed combination of timolol and brimonidine; and one patient was treated with topical timolol, dorzolamide and tafluprost.

Resection of the TA depot was performed at twelve weeks postoperatively in one patient who developed an IOP of 42 mmHg, uncontrollable with topical brimodine, dorzolamide and timolol. Within two days after resection of the TA depot, the IOP decreased to 24 mmHg. All topical medications could be stopped in the following month, and the IOP normalized to 16 mmHg.

All other patients required no treatment during the course of the study. No patient received oral or intravenous medication, glaucoma surgery or laser treatment.

Figure 5. IOP, observed means with 95% confidence intervals



IOP: intraocular pressure; TA: triamcinolone acetonide; wks: weeks

Anterior chamber inflammation

Although the ESCRS PREMED study was not designed to compare the efficacy of various treatments on anterior chamber inflammation, the observation of cells and flare was standardized using the SUN classification. Thirteen patients presented with anterior chamber cells at six weeks postoperatively. Most patients presented with grade 0.5+ to 1+ cells. One patient in the combination treatment group presented with 2+ cells and one patient in the control group presented with 3+ cells at six weeks postoperatively. No patient presented with anterior chamber cells at twelve weeks postoperatively. Flare was reported in only one patient in the combination treatment group at twelve weeks postoperatively.

Other adverse events

A total of 56 patients developed one adverse event, while thirteen patients experienced two or more adverse events during the course of the study. As reported in appendix 4, burning sensation was the most frequently reported adverse event. Seven patients developed a serious adverse event (see appendix 5). One patient in the TA group, one patient in the bevacizumab group and one patient in the combination treatment group developed a CVA.

Discussion

The ESCRS PREMED study aims to identify the optimal treatment strategy to prevent CME after uncomplicated phacoemulsification cataract surgery. Prevention of CME in patients with DM has attracted special interest, given the higher incidence of cataract and the increased risk of developing CME after cataract surgery in these patients.[1, 2] Previous RCTs have shown that a combination treatment with a topical NSAID and a corticosteroid can effectively reduce the risk of developing CME after uncomplicated cataract surgery in diabetics, as compared to single drug prophylaxis.[5] The ESCRS PREMED study is currently the largest multicenter study to investigate the additional benefit of a subconjunctival injection with TA and/or an intravitreal injection with bevacizumab in prevention of CME after cataract surgery in diabetics.

The rationale for investigating the efficacy of intravitreal anti-VEGF was based on the observation that higher aqueous humor levels of VEGF are correlated with higher post-operative macular thickness values.[4] Nevertheless, previous studies found variable results with respect to the efficacy of intravitreal anti-VEGF injections in preventing CME after cataract surgery.[20, 21] The ESCRS PREMED study could not identify a significant effect of an intravitreal injection with 1.25 mg bevacizumab, in addition to topical combination treatment, in preventing macular thickening after cataract surgery. Moreover, there was no significant interaction of intravitreal bevacizumab with subconjunctival TA.

Previous studies have reported no significant differences in visual acuity outcomes between intravitreal aflibercept, ranibizumab or bevacizumab in patients with mild visual impairment due to diabetic macular edema. Aflibercept and ranibizumab did not prove cost-effective when compared to bevacizumab, which is of special interest in preventative treatment strategies.[22]

The ESCRS PREMED study also investigated the efficacy of a single subconjunctival injection of 40 mg TA. Damage to retinal vasculature, leading to impaired blood-retinal barrier (BRB) function, is a central problem in the diabetic patient. The inflammatory response following cataract surgery causes further breakdown of the already compromised BRB, resulting in an accumulation of fluid in the inner nuclear and outer plexiform layers of the retina.[3] TA and other corticosteroids are powerful anti-inflammatory agents and have been used in ophthalmology for years. A subconjunctival corticosteroid injection has been used as an alternative to corticosteroid eye drops, when compliance problems seem to be an issue.[23] This RCT, however, is the first to identify an additional effect of subconjunctival corticosteroids, in patients who also use a topical corticosteroid and NSAID. The ESCRS PREMED study demonstrates a significantly lower macular thickness and TMV at six and

twelve weeks postoperatively, in patients who received a subconjunctival injection with TA, as compared to patients who did not. In this study population, a subconjunctival TA injection effectively prevented the occurrence of CME in all patients. Additional research is needed to investigate whether the use of topical corticosteroids can be avoided in these high-risk patients, after receiving a subconjunctival TA injection.

Previous studies with a smaller sample size have also shown that an intravitreal injection with TA can reduce postoperative CSMT and prevent the occurrence of CME after cataract surgery.[24] However, the use of intravitreal injections is more invasive and has some disadvantages over subconjunctival injections. In contrast to intravitreal corticosteroid administration, subconjunctival TA depots can be removed surgically in case of a steroid response, in order to rapidly normalize the IOP.[25, 26] The efficacy and risks of other routes of administration remain to be investigated. Promising results have been reported for high frequency topical corticosteroid administration and intravitreal corticosteroid implants in treatment of CME after cataract surgery.[27]

Increased IOP is a well-known complication after local corticosteroid administration. It has been reported in 12.5-50% of patients after intravitreal TA injections, whereas incidence rates up to 20% have been reported after subconjunctival TA injections.[3, 24, 28, 29] The ESCRS PREMED study identified an IOP ≥ 25 mmHg in six patients (7.1%) within twelve weeks after a subconjunctival injection with 40 mg TA. Nevertheless, patients should be monitored for at least one year postoperatively, because IOP may rise later. Active TA depots have been identified at three to thirteen months after a single subconjunctival injection.[25]

The reported incidence of CME after cataract surgery in diabetic patients is 4-7% and increases with the severity of DR.[2, 30, 31] Contradicting statements have been reported on the incidence of postoperative CME in diabetic patients without DR.[2, 31, 32] At baseline, 85% of diabetic PREMED study patients had no signs of DR, which may explain the low overall incidence of CME after cataract surgery in the current study. Moreover, it should be noted that the results of this study may not be valid for extrapolation to patients with DR. The low baseline incidence of DR and low incidence of postoperative CME made this RCT unsuitable for subgroup analyses. Future RCTs should explore the efficacy of subconjunctival corticosteroid injections to prevent CME after cataract surgery in patients with preoperative DR or DME.

Another important topic for future studies is to determine the long-term efficacy of the investigated treatments, as the risk of developing CME may peak after twelve weeks postoperatively in patients with diabetes. While most cases of CME develop within four to six

weeks after cataract surgery, recent work shows that the incidence of CME peaks at three to six months postoperatively in diabetics.[31]

Based on the results of the ESCRS PREMED study, it is not recommended to administer subconjunctival TA in all diabetic patients undergoing cataract surgery, given the low overall incidence of postoperative CME (4.5%), and considering the higher incidence of increased IOP after subconjunctival TA injection (7.1%). For now, a personalized risk assessment should be made for each individual patient, carefully weighing the risk of developing visual impairment due to CME, against the risk of developing an increased IOP and the probability of developing subsequent glaucomatous visual field loss.

Future work should investigate the cost-effectiveness of preventative treatment strategies and their long-term benefit on retinal morphology, CDVA, contrast sensitivity, and quality of life.

In conclusion, the results of the ESCRS PREMED study provide compelling evidence that a single subconjunctival injection with 40 mg TA effectively prevents the development of CME within twelve weeks after cataract surgery in diabetic patients. However, the risk of developing CME after cataract surgery should be carefully weighed against the risk of developing treatment-related complications, such as an increased IOP. The results of this study are promising, but further research should explore the optimal route and dosage of corticosteroid delivery and its long-term benefit. Intravitreal bevacizumab had no significant effect on postoperative CDVA or macular thickness in the investigated diabetic population. The efficacy of both treatments should be further investigated in patients with preoperative DR or DME.

References

1 Pollreisz A, Schmidt-Erfurth U. Diabetic cataract-pathogenesis, epidemiology and treatment. J Ophthalmol 2010; 2010: 608751

2 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

3 Lim LL, Morrison JL, Constantinou M, Rogers S, Sandhu SS, Wickremasinghe SS, Kawasaki R, Al-Qureshi S. Diabetic Macular Edema at the time of Cataract Surgery trial: a prospective, randomized clinical trial of intravitreous bevacizumab versus triamcinolone in patients with diabetic macular oedema at the time of cataract surgery - preliminary 6 month results. Clin Exp Ophthalmol 2016; 44: 233-242

4 Dong N, Xu B, Wang B, Chu L, Tang X. Aqueous cytokines as predictors of macular edema in patients with diabetes following uncomplicated phacoemulsification cataract surgery. Biomed Res Int 2015; 2015: 126984

5 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

6 International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). http://www.who.int/classifications/icd/en/, World Health Organization, 2016

7 Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology 1991; 98: 741-756

8 Holladay JT, Prager TC. Mean visual acuity. Am J Ophthalmol 1991; 111: 372-374

9 Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature Working G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005; 140: 509-516

10 Chylack LT, Jr., Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens opacities classification system II (LOCS II). Arch Ophthalmol 1989; 107: 991-997

11 American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern®Guidelines. Diabetic Retinopathy. San Francisco, CA, American Academy of Ophthalmology, 2016, Available at: www.aao.org/ppp

12 Degenring RF, Vey S, Kamppeter B, Budde WM, Jonas JB, Sauder G. Effect of uncomplicated phacoemulsification on the central retina in diabetic and non-diabetic subjects. Graefes Arch Clin Exp Ophthalmol 2007; 245: 18-23

13 Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991; 98: 807-822

14 Arevalo JF, Maia M, Garcia-Amaris RA, Roca JA, Sanchez JG, Berrocal MH, Wu L, Pan-American Collaborative Retina Study G. Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. Ophthalmology 2009; 116: 1481-1487, 1487 e1481

15 Arevalo JF, Garcia-Amaris RA, Roca JA, Sanchez JG, Wu L, Berrocal MH, Maia M, Pan-American Collaborative Retina Study G. Primary intravitreal bevacizumab for the management of pseudophakic cystoid macular edema: pilot study of the Pan-American Collaborative Retina Study Group. J Cataract Refract Surg 2007; 33: 2098-2105

16 Georgopoulos GT, Papaconstantinou D, Niskopoulou M, Moschos M, Georgalas I, Koutsandrea C. Foveal thickness after phacoemulsification as measured by optical coherence tomography. Clin Ophthalmol 2008; 2: 817-820

17 Akinci A, Batman C, Ozkilic E, Altinsoy A. Phacoemulsification with intravitreal bevacizumab injection in diabetic patients with macular edema and cataract. Retina 2009; 29: 1432-1435

18 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

19 Zhang J, Ma J, Zhou N, Zhang B, An J. Insulin use and risk of diabetic macular edema in diabetes mellitus: a systemic review and meta-analysis of observational studies. Med Sci Monit 2015; 21: 929-936

20 Chae JB, Joe SG, Yang SJ, Lee JY, Sung KR, Kim JY, Kim JG, Yoon YH. Effect of combined cataract surgery and ranibizumab injection in postoperative macular edema in nonproliferative diabetic retinopathy. Retina 2014; 34: 149-156

21 Udaondo P, Garcia-Pous M, Garcia-Delpech S, Salom D, Diaz-Llopis M. Prophylaxis of macular edema with intravitreal ranibizumab in patients with diabetic retinopathy after cataract surgery: a pilot study. J Ophthalmol

2011; 2011: 159436
22 Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T. Curr Opin Ophthalmol 2017
23 Dieleman M, Wubbels RJ, van Kooten-Noordzij M, de Waard PW. Single perioperative subconjunctival steroid depot versus postoperative steroid eyedrops to prevent intraocular inflammation and macular edema after cataract surgery. J Cataract Refract Surg 2011; 37: 1589-1597
24 Ahmadabadi HF, Mohammadi M, Beheshtnejad H, Mirshahi A. Effect of intravitreal triamcinolone acetonide injection on central macular thickness in diabetic patients having phacoemulsification. J Cataract Refr Surg 2010; 36: 917-922
25 Kalina PH, Erie JC, Rosenbaum L. Biochemical quantification of triamcinolone in subconjunctival depots. Arch Ophthalmol 1995; 113: 867-869
26 Athanasiadis Y, Nithyanandrajah GA, Kumar B, Sharma A. Reversal of steroid induced raised intraocular pressure following removal of subconjunctival triamcinolone for cataract surgery. Cont Lens Anterior Eye 2009; 32: 143-144
27 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
28 Diabetic Retinopathy Clinical Research N, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, Ferris FL, 3rd, Friedman SM, Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010; 117: 1064-1077 e1035
29 Sohn EH, Wang R, Read R, Roufas A, Teo L, Moorthy R, Albini T, Vasconcelos-Santos DV, Dustin LD, Zamir E, Chee SP, McCluskey P, Smith R, Rao N. Long-Term, Multicenter Evaluation of Subconjunctival Injection of Triamcinolone for Non-Necrotizing, Noninfectious Anterior Scleritis. Ophthalmology 2011; 118: 1932-1937
30 Diabetic Retinopathy Clinical Research Network Authors/Writing C, Baker CW, Almukhtar T, Bressler NM, Glassman AR, Grover S, Kim SJ, Murtha TJ, Rauser ME, Stockdale C. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. JAMA Ophthalmol 2013; 131: 870-879
31 Denniston AK, Chakravarthy U, Zhu H, Lee AY, Crabb DP, Tufail A, Bailey C, Akerele T, Al-Husainy S, Brand C, Downey L, Fitt A, Khan R, Kumar V, Lobo A, Mahmood S, Mandal K, McKibbin M, Menon G, Natha S, Ong JM, Tsaloumas MD, Varma A, Wilkinson E, Johnston RL, Egan CA, Group UDEU. The UK Diabetic Retinopathy Electronic Medical Record (UK DR EMR) Users Group, Report 2: real-world data for the impact of cataract surgery on diabetic macular oedema. Br J Ophthalmol 2017
32 Liu J, Jones RE, Zhao J, Zhang J, Zhang F. Influence of uncomplicated phacoemulsification on central macular thickness in diabetic patients: a meta-analysis. PLoS One 2015; 10: e0126343

Appendix

Appendix 1 ESCRS PREMED study group

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Appendix 2. Overview of perioperative complications

Event	Total (n = 196*)	Control (n = 56)	TA (n = 43)	Bevacizumab (n = 45)	Combination (n = 52)
Perioperative events associated with an increased risk of developing CME, n					
Anterior chamber bleeding	1	0	0	1	0
Incomplete cortex removal	2	1	0	1	0
Posterior capsule rupture	2	0	2	0	0
Zonulolysis	2	1	1	0	0
Perioperative events associated with no increased risk of developing CME, n					
Capsulorhexis tear	1	1	0	0	0
IFIS without iris trauma	6	1	2	2	1

* 17 patients were drop-out before cataract surgery

CME: cystoid macular edema; IFIS: intraoperative floppy iris syndrome; TA: triamcinolone acetonide

Appendix 3. Per protocol analyses

Table 1. Differences in macular thickness, TMV, CDVA and IOP (per protocol analysis)

Parameter	Subconjunctival TA		Intravitreal Bevacizumab		Interaction‡
	Treatment effect (95% CI)*	*p-value*	*Treatment effect* (95% CI)*	*p-value*	*p-value*
CSMT (µm)					
6 wks	-13.4 (-23.2, -3.6)	0.008	-6.9 (-16.6, 2.8)	0.164	0.437
12 wks	-11.5 (-19.9, -3.1)	0.007	-0.9 (-9.2, 7.5)	0.840	
Parafoveal thickness (µm)					
6 wks	-10.2 (-15.7, -4.7)	< 0.001	-3.8 (-9.3, 1.7)	0.174	0.357
12 wks	-7.1 (-12.5, -1.6)	0.012	-3.1 (-8.5, 2.4)	0.268	
Perifoveal thickness (µm)					
6 wks	-4.3 (-9.0, 0.4)	0.075	-4.3 (-9.0, 0.4)	0.071	0.294
12 wks	-5.5 (-8.6, -2.4)	0.001	-1.0 (-4.1, 2.1)	0.526	
TMV (mm^3)					
6 wks	-0.20 (-0.32, -0.09)	0.001	-0.11 (-0.22, 0.007)	0.065	0.667
12 wks	-0.17 (-0.26, -0.08)	< 0.001	-0.04 (-0.13, 0.06)	0.442	
CDVA (logMAR)					
6 wks	0.03 (-0.01, 0.06)	0.159	0.02 (-0.02, 0.05)	0.332	0.101
12 wks	0.02 (-0.03, 0.06)	0.458	0.01 (-0.03, 0.05)	0.647	
IOP (mmHg)					
6 wks	1.65 (0.49, 2.79)	0.005	0.57 (-0.57, 1.72)	0.326	0.458
12 wks	2.33 (0.92, 3.74)	0.001	-0.53 (-1.93, 0.86)	0.450	

* Difference between treatment groups with correction for baseline values, gender, age, CME in the fellow eye, type of DM, type of anti-diabetic drugs, stage of DR, previous PRP

‡ Interaction between subconjunctival TA and intravitreal bevacizumab

CDVA: corrected distance visual acuity; CI: confidence interval; CME: cystoid macular edema; CSMT: central subfield macular thickness; DM: diabetes mellitus; DR: diabetic retinopathy; IOP: intraocular pressure; logMAR: logarithm of the minimal angle of resolution; PRP: panretinal photocoagulation; TA: triamcinolone acetonide; TMV: total macular volume; wks: weeks

Table 2. Incidence of CME (per protocol analysis)

Parameter	**Incidence rates, no. of patients (%)***					
	TA			***Bevacizumab***		
	No	*Yes*	*p-value*[‡]	*No*	*Yes*	*p-value*[‡]
Cysts at baseline	4/83 (4.8)	2/87 (2.3)	0.435	4/88 (4.5)	2/82 (2.4)	0.683
Cysts within 6 wks	9/79 (11.4)	2/77 (2.6)	0.056	7/81 (8.6)	4/75 (5.3)	0.537
Cysts within 12 wks	13/75 (17.3)	2/71 (2.8)	0.005	9/75 (12.0)	6/71 (8.5)	0.589
CME within 6 wks	7/82 (8.5)	0/78 (0.0)	0.014	4/82 (4.9)	3/78 (3.8)	> 0.999
CME within 12 wks	8/82 (9.8)	0/78 (0.0)	0.007	4/82 (4.9)	4/78 (5.1)	> 0.999
CSME within 6 wks	3/82 (3.7)	0/80 (0.0)	0.245	3/82 (3.7)	0/80 (0.0)	0.245
CSME within 12 wks	4/82 (4.9)	0/80 (0.0)	0.120	3/82 (3.7)	1/80 (1.3)	0.620

* Missing values for cysts: 14 patients at baseline (7.6%); 28 patients at 6 wks (15.2%), and 38 patients at 12 wks (20.7%). Missing values for CME: 24 patients (13.0%), and CSME: 22 patients (12.0%). No data were imputed
‡ Difference between treatment groups was *not* corrected for baseline variables and study center, due to the low number of patients with CME and CSME
CME: cystoid macular edema; CSME: clinically significant macular edema; wks: weeks

Appendix 4. Overview of adverse events

Event	Total (n = 206‡)	Control (n = 58)	TA (n = 48)	Bevacizumab (n = 48)	Combination (n = 52)
Ocular adverse events, n					
Blepharitis or MGD	1	0	1	0	0
Conjunctivitis	1	0	0	1	0
Corneal edema	1	1	0	0	0
Corneal erosion	2	1	0	1	0
Corneal epitheliopathy	1	1	0	0	0
Dry eyes	3	2	1	0	0
Fat prolapse	1	0	1	0	0
Foreign body or burning sensation	14	4	0	4	6
Increased IOP	11	2	3	0	6
Iris prolapse	1	0	0	0	1
Macular hole	1	0	0	1	0
Negative dysphotopsia	1	0	0	1	0
Ocular migraine	1	0	1	0	0
PCO	1	0	1	0	0
Progression of DR	1	1	0	0	0
Pruritus	4	0	0	2	2
PVD	6	4	0	2	0
Redness	3	1	0	0	2
Subconjunctival hemorrhage	2	1	0	0	1
TASS	3	2	0	1	0
Tearing	5	0	3	2	0
Uveitis	1	1	0	0	0
VMT	2	0	0	2	0
Systemic adverse events, n					
Ankle edema	1	0	1	0	0
BCC	1	1	0	0	0
Bleeding	1	0	0	1	0
Cardiac arrhythmias	1	0	1	0	0
Dizziness	1	0	0	1	0
Electrolyte disorders	2	1	0	0	1
Headache	2	1	1	0	0
Muscle cramps	1	0	0	0	1
Neurogenic claudication	1	1	0	0	0
Red cheeks	1	0	1	0	0
Paradontitis	1	0	0	1	0
Thrombocytopenia	1	0	0	0	1
Vitamin deficiency	1	1	0	0	0

‡ Seven patients who developed a perioperative complication excluded

* Thirteen patients developed two or more adverse events during the course of the study

BCC: basal cell carcinoma; DR: diabetic retinopathy; MGD: meibomian gland dysfunction; IOP: intraocular pressure; PCO: posterior capsular opacification; PVD: posterior vitreous detachment; TA: triamcinolone acetonide; TASS: toxic anterior segment syndrome; VMT: vitreomacular traction

Appendix 5. Overview of serious adverse events

Event	Total (n = 206[‡])	Control (n = 58)	TA (n = 48)	Bevacizumab (n = 48)	Combination (n = 52)
Arteriovenous shunt surgery	1	1	0	0	0
Cerebrovascular infarction	3	0	1	1	1
Dizziness	1	0	0	1	0
Infection	1	1	0	0	0
Malignancy	1	1	0	0	0

A serious adverse event was defined as an adverse experience that occurs during the study and results in death; is life threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; or is an important medical event which may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

[‡] Seven patients who developed a perioperative complication excluded

Chapter 6

Treatment of cystoid macular edema after cataract surgery: a systematic review

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Abstract

The purpose of this study was to determine the optimum pharmacologic treatment for cystoid macular edema (CME) after cataract surgery in non-diabetic and diabetic patients. The Cochrane Library, Medline and Embase databases were searched, and all randomized controlled trials (RCTs) that compared at least two pharmacologic strategies for CME after cataract surgery were included. Studies were excluded if preoperative CME or other risk factors for developing CME postoperatively were present. Ten RCTs were included in the systematic review. Five trials included at least 30 subjects. Three RCTs showed a greater visual acuity improvement in patients treated with topical non-steroidal anti-inflammatory drugs (NSAIDs) than with a placebo. Other studies comparing the efficacy of topical NSAIDs, topical corticosteroids, subtenon corticosteroids, oral NSAIDs and oral acetazolamide, did not report significant differences between treatment groups. Therefore, large RCTs are needed to provide evidence-based recommendations for the optimum treatment of CME after cataract surgery.

Introduction

In recent years, the incidence of complications after cataract surgery has significantly decreased because of advanced surgical techniques. Nevertheless, postoperative cystoid macular edema (CME), also known as the Irvine-Gass syndrome, remains an important cause of suboptimal visual acuity after cataract surgery.[1,2] Although acute CME resolves spontaneously in approximately 80% of cases, chronic CME may produce anatomic alterations and sustained visual impairment.[3,4] Despite its low incidence, chronic CME affects many people throughout the world because cataract surgery is among the most frequently performed surgical procedures.[5]

Although modern cataract surgery can be considered a minimally invasive procedure, manipulation during surgery induces a postoperative inflammatory response. During the procedure, inflammatory mediators are released from lens epithelial cells and uveal tissue in the anterior segment. If mediators diffuse to the vitreous and retina, the inflammatory response will cause local vasodilatation and disruption of the blood-retinal barrier. Increased vascular permeability may lead to fluid accumulation in the inner nuclear and outer plexiform layers of the retina, and CME will develop.[6-8] Most research on the pathogenesis of CME after cataract surgery has focused on the role of prostaglandins. Recent studies, however, have shown the importance of other inflammatory mediators such as vascular endothelial growth factor (VEGF) and various cytokines.[7-10] Therefore, various anti-inflammatory drugs have been suggested for the treatment of CME after cataract surgery.

In 2012, a systematic review by the Cochrane Collaboration investigated the efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of CME after cataract surgery.[5] In the same year, Falavarjani *et al*. looked at the use of intravitreal anti-VEGF injections.[11] According to the authors, the available evidence was insufficient to clearly inform practice.

Recently, many studies evaluated CME after cataract surgery.[12,13] The aim of this systematic review was to update and combine previous reviews and to determine the optimum pharmacologic treatment for CME after cataract surgery in non-diabetic and diabetic patients with no other risk factors for developing CME. The review compared the efficacy of various treatment strategies on corrected distance visual acuity (CDVA) and retinal morphology.

Literature search

This systematic review followed the guidelines of the Cochrane Handbook.[A] Results were described according to the principles of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[14] Although the study protocol was designed in advance, it was not registered in an online database. According to Dutch guidelines, no institutional review board approval was required for this study.

Sources and search methods

The research question was designed using the PICOS (Patient, Intervention, Comparison, Outcome, Study design) strategy.[14] The Cochrane Library (1992 to present), Medline (OVID, 1946 to present) and Embase (1947 to present) databases were searched in July 2015, and a search update was performed in May 2016. The search strategy for the Medline database is given in Appendix 1. A similar strategy was used for the other databases. All search strategies included search terms for cataract surgery (cataract extraction, cataract surger*, phaco*), macular edema (Irvine Gass, edema, oedema) and study design (randomized controlled trial, RCT). There were no restrictions on language, publication status, or date. All records were managed using Endnote X7.

All titles and abstracts were screened by two review authors independently. Full articles were obtained for potentially relevant studies and were assessed for eligibility by two authors (L.W. and M.A.) independently. Disagreements were resolved by discussion. The review authors were unmasked for article authors, journal, institution and trial results during the assessment.

The review authors included all randomized controlled trials (RCTs) investigating the optimum pharmacologic treatment for CME after cataract surgery in non-diabetic or diabetic patients. The RCTs that compared at least two pharmacologic strategies of any type, dosage or form were included; those that used other treatments, such as vitrectomy or laser treatment, were excluded. Studies were also excluded if CME was present before cataract surgery, if patients underwent combined surgery such as combined cataract surgery and vitrectomy, or if patients were known to have other risk factors for developing CME, such as retinal vein occlusion or uveitis.[15] To provide a complete overview of the current literature, there were no other restrictions on the population, type of cataract surgery, diagnosis, or duration of CME. Reference lists of all included trials and previously published reviews were searched for additional RCTs by two review authors (L.W. and M.A.) independently.

Data collection and risk of bias assessment

Data were extracted in duplicate by two review authors (L.W. and M.A.) independently. A standardized data extraction form included the following items: study size, study design, definition of CME, inclusion and exclusion criteria, type of interventions, follow-up period, study outcomes and funding sources.

Risk of selection bias, performance bias, detection bias and attrition bias were assessed on the study level, using the Cochrane Collaboration's tool for assessing risk of bias. The Delphi criteria were used to evaluate the quality of the included RCTs based on the method of treatment allocation, blinding of outcome assessors, care providers and patients, evaluation of baseline prognostic factors and eligibility criteria, inclusion of an intention-to-treat analysis, and presentation of point estimates and measures of variability.

Outcome measures

Acute CME was defined as CME with a duration of fewer than four months, while chronic CME had a duration of at least four months.[5] The primary outcome was the percentage of eyes with a CDVA improvement of at least two lines, as reported by the original RCTs. Secondary outcome measures were persistence of the achieved CDVA after cessation of treatment and percentage of eyes with CME improvement according to the definition of the included trials.

Literature analysis

The literature search retrieved 3403 titles and abstracts. Full copies were obtained for 44 potentially relevant titles, and 10 RCTs were suitable for inclusion in the systematic review.[16-25] Figure 1 lists the reasons for exclusion at each stage of the article selection process.

Characteristics of included studies

Characteristics of the included studies are shown in detail in Appendix 2. All but two studies had a small sample size of fewer than 40 subjects. Variations between individual studies precluded a meta-analysis. As seen in table 1, the definition of CME after cataract surgery varied between studies. Generally, patients were included in the study if they had reduced visual acuity with evidence of CME on fluorescein angiography (FA) and/or fundoscopy. One RCT investigated the treatment of acute CME with a duration of 21-81 days,[19] three RCTs included only eyes with chronic CME of at least six months,[17,18,22] two RCTs included eyes with both acute and chronic CME;[16,23] and four studies did not report a minimum or maximum duration of the CME.[20,21,24,25]

Three studies included only non-diabetic patients.[21,22,25] All other studies reported inclusion of both diabetic and non-diabetic patients or did not specify whether diabetic patients were included in the study.[16-20,23,24] In three studies, all patients had phacoemulsification cataract surgery,[19,21,23] and in two other studies, patients had intracapsular or extracapsular cataract surgery.[24,25] The type of surgery was unknown in five studies.[16-18,20,22]

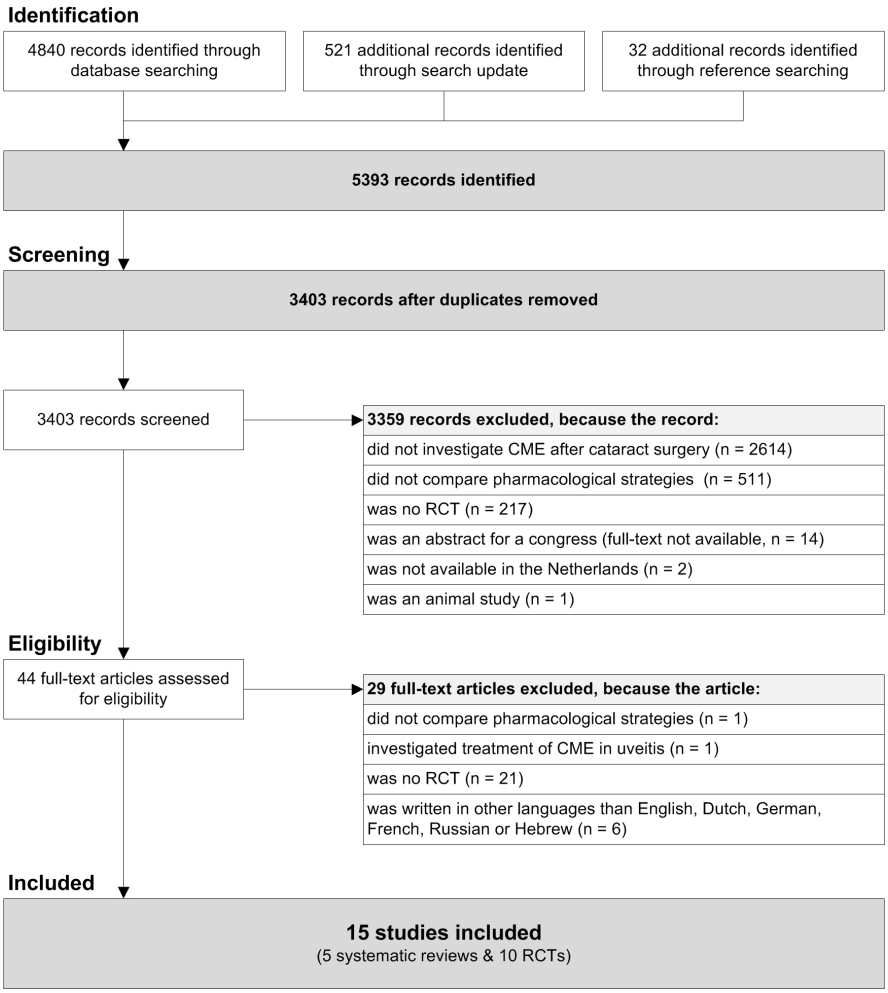
Most of the included studies examined the efficacy of topical corticosteroids and/or NSAIDs in the treatment of CME after cataract surgery.[16-21] One recent study compared the efficacy of subtenon triamcinolone acetonide (TA) versus topical NSAIDs.[23] One study investigated a combination of topical NSAIDs, intravitreal TA and intravitreal anti-VEGF injections.[22] Two studies investigated the use of oral medications.[24,25] Patients were followed up for 8-26 weeks after start of treatment. Outcome definitions of the individual RCTs are shown in Appendix 2.

Quality of evidence

A description of the risk for bias within studies and the quality of the included RCTs is shown in Appendix 2. Despite several measures taken to reduce publication bias, previous studies have shown that approximately 50% of all clinical studies remain unpublished, making non-publication of research an important limitation for systematic reviews and meta-analyses.[26] The current systematic review identified ten studies with a low to moderate quality of evidence. As evident in table 2, the baseline characteristics were similar among treatment groups in six of the ten studies.[17,18,20-23] Most studies applied appropriate

methods to reduce the risk for performance bias. Six studies stated that the participants were masked for their treatment allocation;[17-20,22,24] personnel was masked in six studies.[16-20,23] Methods to reduce the risk for detection bias were described in only two studies in which fluorescein angiograms were read by masked retina specialists.[17,19] Only two studies described the method of randomization, using a computer-generated predetermined randomization schedule.[17,18] The sequence generation was concealed from the investigators in two other studies in which the pharmacy performed the randomization and provided the relabeled eye drop bottles.[19,20] No study performed separate per-protocol and intention-to-treat analyses.

Figure 1. PRISMA flowchart for identification and selection of RCTs



CME: cystoid macular edema; RCT: randomized controlled trial

Table 1. Characteristics of included studies

Study	Population
Topical NSAID vs. placebo	
Burnett *et al*. 1983[16]	Aphakic for ≥ 4 mos; BCVA 20/400-20/50; CME documented by fundus contact lens examination and FA; increased vascular permeability on iris angiography
Flach *et al*. 1987[17]	VA ≤ 20/40 for ≥ 6 mos; clinical and FA evidence of aphakic or pseudophakic CME
Flach *et al*. 1991[18]	Aphakic and pseudophakic patients; VA ≤ 20/40 for ≥ 6 mos; clinical and FA evidence of CME
Topical NSAID vs. topical CS	
Heier *et al*. 2000[19]	FA evidence of CME; VA ≤ 20/40; 21-90 days postoperatively
Singal *et al*. 2004[20]	VA ≤ 20/40; cysts detected with macular contact lens; ≥ 6 wks postoperatively
Topical NSAID vs. topical NSAID	
Rho *et al*. 2003[21]	Non-diabetic patients; BCVA ≤ 20/40; petaloid perifoveal macular edema assessed by contact lens biomicroscopy
Warren *et al*. 2010[22]	Non-diabetic patients; CRT > 250 µm; cysts on biomicroscopy; VA ≤ 20/32 for at least 6 mos
Topical NSAID vs. subtenon CS	
Yüksel *et al*. 2016[23]	CRT > 250 µm; presence of cysts on fundus biomicroscopy; logMAR BCVA ≥ 0.4
Oral NSAID vs. placebo	
Yannuzzi *et al*. 1977[24]	Reduced vision; clinical and FA evidence of CME, ≥ 4 mos postoperatively
Oral AZ vs. placebo	
Curkovic *et al*. 2005[25]	Non-diabetic patients; CME detected with FA; VA < 0.5 Snellen

AZ: acetazolamide; BCVA: best corrected visual acuity; b.i.d.: two times daily; CME: cystoid macular edema; CS: corticosteroid; CRT: central retinal thickness; FA: fluorescein angiography; KCl: potassium chloride; mos: months; NSAID: non-steroidal anti-inflammatory drug; q.i.d.: four times daily; TA: triamcinolone acetonide; t.i.d.: three times daily; VA: visual acuity; wks: weeks; y: years

Duration CME	Treatment group 1	Treatment group 2
Mean: 17 mos	Placebo	Topical fenoprofen q.i.d. for 8 wks
≥ 6 mos	Placebo	Topical ketorolac q.i.d. for 60 days
≥ 6 mos	Placebo	Topical ketorolac q.i.d. for 90 days
Unknown	*1:* Topical prednisolone q.i.d. *2:* Topical ketorolac q.i.d.	*3*: Topical prednisolone + ketorolac q.i.d.
Mean: 17.3/ 7.6 mos	Topical ketorolac q.i.d. for 90 days	Topical prednisolone + ketorolac q.i.d for 90 days
Mean: 4.0/ 4.2 wks	Topical diclofenac q.i.d.	Topical ketorolac q.i.d.
Mean: 9.4 mos	*1*[a]*:* Placebo	*2-4*[a]*:* Topical diclofenac, ketorolac or nepafenac t.i.d. for 16 wks *5*[a]*:* Topical bromfenac b.i.d. for 16 wks
Mean: 4.5/4.8 wks	Topical nepafenac t.i.d. for 12 wks	Posterior subtenon injection of 40 mg TA
Unknown	Placebo	Oral 25 mg indomethacin t.i.d. for 6 wks
Unknown	Topical dexamethasone + flurbiprofen t.i.d. for 8 wks	Topical dexamethasone + flurbiprofen t.i.d. for 8 wks Oral 250 mg AZ + 500 mg KCl t.i.d. for 2 wks; 250 mg AZ daily for 2 wks; 125 mg AZ daily for 4 wks

[a] All patients received intravitreal 4 mg TA + 1.25 mg bevacizumab at study entry & intravitreal bevacizumab at 4 wks

Table 2. Risk of bias (Cochrane Collaboration's tool) and quality of the included RCTs (Delphi list)

	Selection bias (sequence generation)	Selection bias (sequence concealment)	Performance bias (blinding participants)	Performance bias (blinding personnel)	Detection bias (blinding outcome assessment)	Attrition bias (incomplete outcome data)	Prognostic indicators similar at baseline?	Eligibility criteria specified?	Point estimates and measures of variability given?	ITT analysis included?
Burnett *et al*. 1983[16]	?	?	?	-	?	-	?	yes	no	no
Flach *et al*. 1987[17]	-	?	-	-	-	+	yes	yes	yes	no
Flach *et al*. 1991[18]	-	?	-	-	?	-	yes	yes	no	no
Heier *et al*. 2000[19]	?	-	-	-	-	+	?	yes	yes	no
Singal *et al*. 2004[20]	?	-	-	-	?	-	yes	yes	no	no
Rho *et al*. 2003[21]	?	?	?	?	?	?	yes	yes	yes	no
Warren *et al*. 2010[22]	?	?	-	?	?	-	yes	yes	no	no
Yüksel *et al*. 2016[23]	+	?	+	-	?	?	yes	yes	yes	no
Yannuzzi *et al*. 1977[24]	?	?	-	?	?	-	?	yes	no	no
Curkovic *et al*. 2005[25]	?	?	+	?	?	?	?	yes	yes	no

+: high risk of bias; ?: unclear risk of bias; -: low risk of bias; ITT: intention to treat

Topical NSAIDs vs. placebo

Three studies compared the efficacy of topical NSAIDs and of a placebo in the treatment of CME after cataract surgery. The largest multicenter study compared the efficacy of a 90-day treatment with topical ketorolac and with a placebo in 120 aphakic and pseudophakic patients with a diagnosis of chronic CME.[18] The authors reported statistically significantly greater CDVA improvement ($p < 0.05$) in the ketorolac 0.5% group than in the placebo group at 30, 60 and 90 days of treatment. Nine patients in the ketorolac group and two patients in the placebo group experienced a deterioration in CDVA after cessation of treatment, but CDVA recovered in most patients after retreatment with ketorolac eye drops. FA was performed at baseline and 90 days after initiation of treatment and showed a reduction of the CME in 35% and 18% of patients treated with topical ketorolac and with a placebo, respectively.

Two smaller studies confirmed these results, but did not find a statistically significant difference. As seen in table 3, one study compared the efficacy of a 60-day treatment with topical ketorolac 0.5% and with a placebo in 30 eyes of 30 patients with chronic CME.[17] After two months of treatment, 62% of the ketorolac-treated eyes and 8% of the placebo-treated eyes showed an improvement in CDVA. Three of eight eyes showed a decrease in CDVA one month after cessation of the ketorolac eye drops. The CDVA improved after

reinstitution of treatment. Fluorescein angiographic findings improved in two eyes in the ketorolac group and no eyes in the placebo group.

The smallest study compared the efficacy of fenoprofen 1.0% eye drops with that of a placebo.[16] Patients were aphakic for at least four months and had a diagnosis of CME after cataract surgery for two months to three years. At the end of the study, 50% of patients treated with topical fenoprofen and 38% of those treated with a placebo experienced at least a 2-line improvement in Snellen visual acuity with decreased vascular leakage on FA. The CME completely resolved in one patient in each group. Two of three patients who experienced an improvement after fenoprofen treatment redeveloped CME after cessation of treatment.

Topical NSAIDs vs. topical corticosteroids

Many studies have investigated the efficacy of topical NSAIDs versus topical corticosteroids in preventing the occurrence of CME after cataract surgery.[12,13] Unfortunately, only two small studies compared topical NSAIDs and topical corticosteroids in the treatment of CME. Heier *et al*. compared the efficacy of prednisolone 1.0% versus ketorolac 0.5% versus a combination treatment in 28 patients who developed acute CME after uncomplicated cataract surgery.[19] The percentage of patients with at least a 2-line improvement in visual acuity was highest in the group treated with both ketorolac and prednisolone eye drops. One patient in the ketorolac group and one patient in the combination group had a deterioration in CDVA after cessation of treatment, but both patients showed partial or complete recovery after retreatment. Reduction of CME on FA was reported in 78% of patients in the topical combination treatment group and in 50% and 56% of patients in the prednisolone and ketorolac group, respectively.

A small study by Singal *et al*. included eleven patients with both acute and chronic CME.[20] The authors could not find any statistically significant differences in final visual acuity or CME grading between patients treated with ketorolac 0.5% and patients treated with ketorolac 0.5% and prednisolone1%.

Comparison of various topical NSAIDs

Nowadays, several topical NSAID preparations are available, and some investigators have tried to determine the optimum NSAID to treat CME after cataract surgery. Rho *et al*. compared ketorolac 0.5% versus diclofenac 0.1% in 34 eyes of 34 non-diabetic patients with CME after uneventful phacoemulsification cataract surgery with posterior chamber intraocular lens implantation.[21] No significant differences in the mean final visual acuity were found between the study groups. At 26 weeks, the CME had decreased in 89% of the diclofenac-treated eyes and 88% and ketorolac-treated eyes. There was no significant difference in time to the initial CME decrease between the groups.

Table 3. Results of included studies

Study	Treatment (n)	CME elimination, n (%)
Topical NSAID vs. placebo		
Burnett *et al*. 1983[16]	Placebo (8)	1/8 (13)
	Topical fenoprofen (6)	1/6 (17)
Flach *et al*. 1987[17]	Placebo (15)	-
	Topical ketorolac (15)	-
Flach *et al*. 1991[18]	Placebo (59)	-
	Topical ketorolac (61)	-
Topical NSAID vs. topical CS		
Heier *et al*. 2000[19]	Topical prednisolone (8)	-
	Topical ketorolac (10)	-
	Topical prednisolone + ketorolac (10)	-
Singal *et al*. 2004[20,b]	Topical ketorolac (4)	- (50)
	Topical prednisolone + ketorolac (6)	- (50)
Topical NSAID vs. topical NSAID		
Rho *et al*. 2003[21]	Topical diclofenac (18)	14/18 (78)
	Topical ketorolac (16)	12/16 (75)
Oral NSAID vs. placebo		
Yannuzzi *et al*. 1977[24]	Placebo (13)	0/13 (0)
	Oral indomethacin (10)	0/10 (0)
Oral AZ vs. placebo		
Curkovic *et al*. 2005[25]	Topical dexamethasone + flurbiprofen (7)	2/7 (29)
	Topical dexamethasone + flurbiprofen + oral AZ/KCl (7)	6/7 (86)

[a] Statistically significant difference
[b] Eleven patients included; one patient dropped from the study. The randomized treatment of this patient is not reported

A more recent study by Warren *et al*. compared the use of bromfenac 0.09%, nepafenac 0.1%, diclofenac 0.1% and ketorolac 0.4% eye drops in addition to intravitreal injection of 4.0 mg TA and 1.25 mg bevacizumab in the treatment of chronic CME after cataract surgery in non-diabetic patients.[22] Twelve and sixteen weeks after the start of treatment, the nepafenac and bromfenac groups showed a statistically significant reduction in retinal thickness as compared to the control group ($p = 0.0026$ and $p = 0.0046$ at twelve weeks and sixteen weeks, respectively). At 16 weeks, the mean visual acuity improved statistically significantly in nepafenac-treated eyes, compared with placebo-treated eyes ($p = 0.0233$). The authors did not report significant differences between the NSAID treatment groups. The study did not investigate the percentage of eyes with a CDVA improvement of at least two lines or the percentage of eyes with a significant reduction in retinal thickness.

CME reduction, n (%)	≥ 2 lines CDVA improvement, n (%)	CME reduction with ≥ 2 lines CDVA improvement, n (%)
4/8 (50)	3/8 (38)	3/8 (38)
3/6 (50)	3/6 (50)	3/6 (50)
0/13 (0)	1/13 (8)	-
2/13 (15)	8/13 (62)	-
9/49 (18)	10/49 (20)[a]	2/49 (4)[a]
16/46 (35)	22/46 (48)[a]	11/46 (24)[a]
4/8 (50)	4/8 (50)	4/8 (50)
5/9 (56)	6/9 (67)	5/9 (56)
7/9 (78)	8/9 (89)	7/9 (78)
-	-	-
-	-	-
16/18 (89)	-	-
14/16 (88)		-
-	4/13 (31)	-
-	2/10 (20)	-
7/7 (100)	-	-
7/7 (100)	-	-

AZ: acetazolamide; CDVA: corrected distance visual acuity; CME: cystoid macular edema; CS: corticosteroid; KCl: potassium chloride; n: number of eyes at baseline; NSAID: non-steroidal anti-inflammatory drug

Topical NSAIDs vs. subtenon corticosteroids

Although most studies have investigated the efficacy of repeated topical drug administration, once-only treatments are of clinical interest, especially in patients with poor medication adherence. A recent study by Yüksel *et al*. compared the efficacy of a single subtenon injection with 40 mg TA and twice daily administration of nepafenac eye drops.[23] Both treatment groups experienced significant improvement in CDVA and a decrease in central macular thickness from baseline within one month after start of treatment. According to the authors, vision improved after CME resolution if the inner segment/outer segment (IS/OS) layer of the retina was intact and if there were septas between cystic spaces. There were no significant differences in mean CDVA or mean central macular thickness between treatment groups at any time. Longer duration of CME before initiation

of treatment had a negative effect on CDVA in the nepafenac group. This correlation was not found in the TA group. The authors did not report the percentage of eyes with at least a 2-line improvement in CDVA or a decrease in CME. The CME recurred after cessation of treatment in one patient in the nepafenac group, but it resolved after the eye drops were restarted. Four eyes in the TA group received one or two additional subtenon injections because of residual edema or recurrence of CME. No significant increase in intraocular pressure was found in either treatment group.

Oral treatments

Two studies investigated the use of oral treatments for CME after cataract surgery. Neither reported the duration of CME prior to inclusion. Yannuzzi *et al*. studied 23 eyes of 20 patients with CME after conventional intracapsular cataract extraction.[24] Oral treatment with 25 mg indomethacin did not did not improve CDVA or angiographic evidence of CME compared with a placebo.

More recently, Curkovic *et al*. investigated the efficacy of oral acetazolamide and potassium chloride as an additional treatment in patients who also received topical dexamethasone and flurbiprofen.[25] There was no significant difference in the percentage of eyes experiencing a decrease in CME on FA between the groups.

Discussion

Previous studies have indicated the urgent need for high-quality evidence about the optimum pharmacologic treatment for CME after cataract surgery.[5] This review was designed to update previous systematic reviews and to provide a detailed overview of the currently available evidence.

The largest multicenter study in the systematic review investigated the efficacy of topical ketorolac and a placebo in 120 aphakic and pseudophakic patients with chronic CME. Treatment with ketorolac eye drops resulted in a greater improvement in CDVA.[18]

The systematic review identified three RCTs that were not included in previous reviews.[4,5,11] One study investigated the efficacy of 250 mg acetazolamide in addition to topical dexamethasone and flurbiprofen. Using FA, the authors found a complete resolution of CME in 86% of eyes in the acetazolamide group and in 29% in the control group. Unfortunately, this study included only fourteen eyes and was not able to show statistically significant differences.[25] Another study compared the efficacy of a 90-day treatment with ketorolac eye drops and a combination treatment of ketorolac and prednisolone in patients with acute and chronic CME. The study provided data from only ten patients and was not able to show significant differences in CDVA or retinal morphology.[20] A recent study by Yüksel *et al*. investigated the efficacy of a 12-week topical NSAID treatment and of a single subtenon TA injection. The CDVA and retinal morphology improved in both groups, but the authors could not find significant differences between the treatment groups.[23]

The results of the current systematic review indicate a lack of evidence regarding the optimum treatment of CME after cataract surgery. Because of the low incidence of CME and because CME resolves spontaneously in most cases, large multicenter studies with sufficient statistical power are needed to compare the efficacy of various treatment strategies. Although this systematic review suggests there is a benefit from NSAID eye drops, the current literature provides no good-quality evidence regarding other pharmacological treatments. The RCTs comparing topical NSAIDs to other pharmacologic treatments were insufficiently powered to detect small, but clinically relevant, effects. Therefore, future studies are needed to compare the efficacy of NSAID eye drops to other anti-inflammatory treatment regimens.

The first important step towards optimum treatment is to identify the patients who require treatment for CME after cataract surgery. Although previous studies report spontaneous resolution of CME within one year in 80% of cases, one should note that this percentage is cited from a single study that investigated 20 eyes that developed CME after extracapsular

cataract extraction in 1988.[4,27] Since 1988, cataract surgery techniques have become more sophisticated and reduced the seriousness of the postoperative inflammatory response. Given that the incidence of postoperative complications has significantly decreased, there is an urgent need to bring these numbers up to date. Future studies should investigate the natural course of CME after uneventful phacoemulsification cataract surgery to provide evidence-based recommendations of which patients should be treated.

Additional research is needed to investigate the optimum postoperative moment for initiating treatment to prevent the occurrence of permanent retinal damage, while keeping the incidence of treatment-related adverse events to a minimum. Comparison of the efficacy of a stepped-care approach and immediate maximum therapy is of interest. Yüksel *et al*. showed that a long duration of CME had a negative effect on the final CDVA.[23] This correlation might also interfere with the comparison of study results in the current systematic review. Studies investigating the treatment of acute CME will show more beneficial results than those investigating chronic CME because acute CME is more likely to resolve spontaneously.

The results of this systematic review suggest that topical NSAIDs can be used as an effective treatment strategy in patients with CME after cataract surgery. Previous studies did not report any significant differences in efficacy between different NSAID preparations.[21,22] Future studies should therefore compare the efficacy of new treatment modalities and NSAID eye drops, a treatment strategy proven to be effective by Flach *et al*., many years ago.[18] Recent nonrandomized studies have identified various treatment strategies of interest, but further evidence is needed from randomized controlled clinical trials. Corticosteroids are of special interest because their anti-inflammatory properties have been known for many years. Some case reports have shown that a single intravitreal dexamethasone implant can be beneficial in patients with CME after cataract surgery.[28] Intravitreal corticosteroid injections have also shown beneficial results in diabetic patient with macular edema.[29] A recent study of Dang *et al*. compared the efficacy of an intravitreal dexamethasone implant and multiple intravitreal TA injections in 43 diabetic patients who developed CME after uneventful cataract surgery. Over a six-month period, the percentage of patients with at least a 2-line improvement in CDVA was higher in the intravitreal TA group, but the difference was not statistically significant ($p > 0.05$).[30]

Previous studies have found that VEGF plays an important role in the development of CME after cataract surgery.[10,29] Consequently, ophthalmologists have investigated the clinical applicability of intravitreal anti-VEGF injections to prevent and treat refractory CME. Although some retrospective studies report beneficial results in both CDVA and retina

morphology, others could not find significant functional improvement.[31-33] A recent study investigated the use of intravitreal NSAIDs in the treatment of CME after cataract surgery.[34]

Future studies should focus on CDVA improvement and retinal morphology using optical coherence tomography. Other outcomes, such as persistence of the achieved visual improvement after cessation of therapy and effect on contrast sensitivity and on vision-related quality of life, may be of additional interest to determine the optimum strategy.

In conclusion, the results of this systematic review suggest that topical NSAIDs are beneficial in treating chronic CME after cataract surgery, although CME may recur after cessation of treatment. It remains unclear which pharmacologic treatment is most effective in improving CDVA and retinal morphology. Evidence regarding the optimum treatment is of moderate to low quality, which prevents evidence-based recommendations. Large well-designed multicenter studies are needed to investigate the optimum pharmacologic treatment of acute and chronic CME after cataract surgery.

References

Peer-reviewed material

1. Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. Arch Ophthalmol. 1966;76(5):646-661.
2. Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol. 1953;36(5):599-619.
3. Hunter AA, Modjtahedi SP, Long K, Zawadzki R, Chin EK, Caspar JJ, Morse LS, Telander DG. Improving visual outcomes by preserving outer retina morphology in eyes with resolved pseudophakic cystoid macular edema. J Cataract Refract Surg. 2014;40(4):626-631.
4. Shelsta HN, Jampol LM. PHarmacologic therapy of pseudophakic cystoid macular edema: 2010 update. Retina. 2011;31(1):4-12.
5. Sivaprasad S, Bunce C, Crosby-Nwaobi R. Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. The Cochrane database of systematic reviews. 2012;2:CD004239.
6. Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. Drugs. 2007;67(9):1291-1308.
7. Scholl S, Kirchhof J, Augustin AJ. Pathophysiology of macular edema. Ophthalmologica. 2010;224(SUPPL. 1):8-15.
8. Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. Survey of Ophthalmology. 2002;47(4 SUPPL. 1):S203-S218.
9. Roh MI, Kim HS, Song JH, Lim JB, Kwon OW. Effect of Intravitreal Bevacizumab Injection on Aqueous Humor Cytokine Levels in Clinically Significant Macular Edema. Ophthalmology. 2009;116(1):80-86.
10. Funatsu H, Yamashita H, Noma H, Shimizu E, Mimura T, Hori S. Prediction of macular edema exacerbation after phacoemulsification in patients with nonproliferative diabetic retinopathy. J Cataract Refract Surg. 2002;28(8):1355.
11. Ghasemi Falavarjani K, Parvaresh MM, Modarres M, Hashemi M, Samiy N. Intravitreal bevacizumab for pseudophakic cystoid macular edema; a systematic review. Journal of ophthalmic & vision research. 2012;7(3):235-239.
12. 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.
13. Kessel L, Tendal B, Jorgensen KJ, Erngaard D, Flesner P, Andresen JL, Hjortdal J. Post-cataract Prevention of Inflammation and Macular Edema by Steroid and Nonsteroidal Anti-inflammatory Eye Drops: A Systematic Review. Ophthalmology. 2014.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
15. Chu CJ, Johnston RL, Buscombe C, Sallam AB, Mohamed Q, Yang YC. United Kingdom Pseudophakic Macular Edema Study Group. Risk Factors and Incidence of Macular Edema after Cataract Surgery: A Database Study of 81984 Eyes. Ophthalmology. 2015, doi: 10.1016/j.ophtha.2015.10.001.
16. Burnett J, Tessler H, Isenberg S, Tso MO. Double-masked trial of fenoprofen sodium: treatment of chronic aphakic cystoid macular edema. Ophthalmic Surg. 1983;14(2):150-152.
17. Flach AJ, Dolan BJ, Irvine AR. Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. American Journal of Ophthalmology. 1987;103(4):479-486.
18. Flach AJ, Jampol LM, Weinberg D, Kraff MC, Yannuzzi LA, Campo RV, Neumann AC, Cupples HP, Lefler WH, Pulido JS, Lavelle C. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. American Journal of Ophthalmology. 1991;112(5):514-519.
19. Heier JS, Topping TM, Baumann W, Dirks MS, Chern S. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. Ophthalmology. 2000;107(11):2034-2039.
20. Singal N, Hopkins J. Pseudophakic cystoid macular edema: Ketorolac alone vs. ketorolac plus prednisolone. Canadian Journal of Ophthalmology. 2004;39(3):245-250.
21. Rho DS. Treatment of acute pseudophakic cystoid macular edema: Diclofenac versus ketorolac. Journal of Cataract and Refractive Surgery. 2003;29(12):2378-2384.

22. Warren KA, Bahrani H, Fox JE. NSAIDs in combination therapy for the treatment of chronic pseudophakic cystoid macular edema. Retina. 2010;30(2):260-266.
23. Yuksel B, Uzunel UD, Kerci SG, Sagban L, Kusbeci T, Orsel T. Comparison of Subtenon Triamcinolone Acetonide Injection with Topical Nepafenac for the Treatment of Pseudophakic Cystoid Macular Edema. Ocul Immunol Inflamm. 2016:1-7.
24. Yannuzzi LA, Klein RM, Wallyn RH. Ineffectiveness of indomethacin in the treatment of chronic cystoid macular edema. American Journal of Ophthalmology. 1977;84(4):517-519.
25. Curkovic T, Vukojevic N, Bucan K. Treatment of pseudophakic cystoid macular oedema. Collegium antropologicum. 2005;29 Suppl 1(SUPPL. 1):103-105.
26. Thaler K, Kien C, Nussbaumer B, Van Noord MG, Griebler U, Klerings I, Gartlehner G. Uncover Project Consortium. Inadequate use and regulation of interventions against publication bias decreases their effectiveness: a systematic review. J Clin Epidemiol. 2015;68(7):792-802.
27. Bradford JD, Wilkinson CP, Bradford RH, Jr. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. Retina. 1988;8(3):161-164.
28. Sacchi M, Villani E, Gilardoni F, Nucci P. Efficacy of intravitreal dexamethasone implant for prostaglandin-induced refractory pseudophakic cystoid macular edema: case report and review of the literature. Clinical ophthalmology (Auckland, N.Z.). 2014;8:1253-1257.
29. Zhang Y, Ma J, Meng N, Li H, Qu Y. Comparison of intravitreal triamcinolone acetonide with intravitreal bevacizumab for treatment of diabetic macular edema: a meta-analysis. Curr Eye Res. 2013;38(5):578-587.
30. Dang Y, Mu Y, Li L, Mu Y, Liu S, Zhang C, Zhu Y, Xu Y. Comparison of dexamethasone intravitreal implant and intravitreal triamcinolone acetonide for the treatment of pseudophakic cystoid macular edema in diabetic patients. Drug Des Devel Ther. 2014;8:1441-1449.
31. Spitzer MS, Ziemssen F, Yoeruek E, Petermeier K, Aisenbrey S, Szurman P. Efficacy of intravitreal bevacizumab in treating postoperative pseudophakic cystoid macular edema. J Cataract Refract Surg. 2008;34(1):70-75.
32. Arevalo JF, Maia M, Garcia-Amaris RA, Roca JA, Sanchez JG, Berrocal MH, Wu L. Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. Ophthalmology. 2009;116(8):1481-1487, 1487 e1481.
33. Barone A, Russo V, Prascina F, Delle Noci N. Short-term safety and efficacy of intravitreal bevacizumab for pseudophakic cystoid macular edema. Retina. 2009;29(1):33-37.
34. Margalit E, Boysen JL, Zastrocky JP, Katz A. Use of intraocular ketorolac tromethamine for the treatment of chronic cystoid macular edema. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie. 2010;45(4):409-410.

Other cited material

A Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2011: www.cochrane-handbook.org.

Appendix

Appendix 1. Search strategy for MEDLINE database

((((((((((((((("Cataract Extraction"[Mesh]) OR "Lens Implantation, Intraocular"[Mesh]) OR "Phacoemulsification"[Mesh]) OR "Pseudophakia"[Mesh]) OR cataract extract*) OR phakectom*) OR "enzymatic zonulolysis") OR cataract surger*) OR lens implantation*) OR intraocular lens*) OR phaco*) OR faco*) OR pseudophak*) OR pseudo-phak*) OR pseudofak*) OR pseudo-fak*)
AND
((((((((((("Edema"[Mesh]) OR "Macular Edema"[Mesh]) OR edema) OR oedema) OR irvine-gass) OR "irvine gass") OR "cystoid macular dystrophy") OR thickn*) OR CME) OR CMO) OR PCME) OR PCMO) OR "macular volume")
AND
((((((((((((((("Randomized Controlled Trial"[Publication Type]) OR "Controlled Clinical Trial"[-Publication Type]) OR "Review"[Publication Type]) OR "Review Literature as Topic"[Mesh]) OR "Meta-Analysis"[Publication Type]) OR "Meta-Analysis as Topic"[Mesh]) OR randomized) OR randomised) OR placebo) OR "drug therapy") OR random*) OR trial) OR groups) OR review) OR rct) OR meta-analysis)
NOT
((animals[mh]) NOT (humans[mh])))

Limits: none

Appendix 2. Characteristics of included studies

Table 1. Burnett *et al*. 1983[16]

Methods	Randomized, double-masked study
Participants	
n (eyes)	14 (14 patients, one eye per patient assumed)
Country	United States of America
Population	*Chronic aphakic CME:* Aphakic for at least 4 months, with BCVA equal to or better than 20/400 but not better than 20/50; a petaloid appearance of CME as documented by slit-lamp fundus contact lens examination and fundus FA; and an increased vascular permeability evidenced by diffuse leakage of iris vessels on iris FA *Exclusion:* Fundus picture complicated with lipid exudates, microaneurysms, hemorrhage, or signs suggestive of a specific vascular retinopathy in either eye
Type of surgery	Unknown
Duration CME	Mean duration was 17 months (range: 2 months-3 years)
Interventions	
Placebo	Topically applied placebo, methylcellulose, 1 drop 4 times daily for 8 weeks
Topical NSAID	Topically applied 1% fenoprofen 1 drop 4 times daily for 8 weeks
Main outcomes	Increased VA of at least 2 lines by the Snellen chart, along with lessened vascular leakage, as shown by iris and fundus FA. The iris and fundus FA were graded in two parameters: the area of fluorescein diffusion, and the intensity of leaked fluorescein
Follow-up	2 week intervals for at least 8 weeks
Conclusion	"Fenoprofen sodium was found to have no effect on the course of chronic aphakic CME. We believed that the lack of effect may have been due to the duration of edema at the time of treatment or to the small sample size. Larger studies in the immediate postoperative period are suggested."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Unclear risk	Patients were randomly assigned to treatment. Insufficient information to permit judgment
Sequence concealment	Unclear risk	Study does not address this outcome
Blinding participants	Unclear risk	Double-masked study. Insufficient information to permit judgment
Blinding personnel	Low risk	The examiner was masked as to whether the patient received fenoprofen or placebo
Blinding outcome assessment	Unclear risk	Double-masked study. Insufficient information to permit judgment
Incomplete outcome data	Low risk	No patients dropped out from the study

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Unclear
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

BCVA: best corrected visual acuity; CME: cystoid macular edema; FA: fluorescein angiography; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; VA: visual acuity

Table 2. Flach *et al*. 1987[17]

Methods	Double-masked, randomized, placebo-controlled clinical study
Participants	
n (eyes)	30 (of 30 patients)[a]
Country	United States of America
Population	*Chronic CME:* Reduced VA (≤ 20/40) for 6 months or more associated with clinical and FA evidence of aphakic or pseudophakic CME. *Exclusion:* CS or NSAID use within the previous 6 weeks; ocular disease preventing adequate examination; poorly controlled DM or hypertension; preexisting macular disease preventing adequate retinal evaluation; history of more than one ocular operation
Type of surgery	Unknown
Duration CME	≥ 6 months
Interventions	
Placebo	60-day treatment with a vehicle 4 times daily. If distance VA decreased by 2 or more lines at day 90, as compared to day 60, therapy was reinstituted
Topical NSAID	60-day treatment with ketorolac ophthalmic solution 0,5% 4 times daily. If distance VA decreased by 2 or more lines at day 90, as compared to day 60, therapy was reinstituted
Main outcomes	
Outcome 1	≥ 2 lines improvement in Snellen VA
Outcome 2	One-grade improvement or detoriation in FA results. Grade 0) No fluorescein leak in macular area; 1) Semicircle of fluorescein leak in macular area; 2) Full circle leak less than or equal to the optic disk diameter in macular area; 3) Full circle leak greater than optic disk diameter in macular area
Follow-up	30, 60 and 90 days and, depending on their response to cessation of topical treatment, 120 days
Conclusion	"The results of this double-masked, placebo-controlled, randomized study indicate that ketorolac tromethamine 0.5% ophthalmic solution may be of benefit in the treatment of chronic aphakic and pseudophakic macular edema. The improved distance VA observed in the group of patients treated with ketorolac is statistically different from the improved VA in the group of patient treated with placebo."
Notes	FA was not performed at the end of follow-up (90 days).

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Low risk	A computer-generated pre-determined randomization schedule
Sequence concealment	Unclear risk	A pre-determined randomization schedule. Unknown whether this schedule was kept with appropriate safeguards
Blinding participants	Low risk	Packaged in an identical container
Blinding personnel	Low risk	The investigator was unaware of which treatment patients received
Blinding outcome assessment	Low risk	FA were read by one of us who was unaware of changes in VA or results of ocular examinations and was masked to the treatment regimen
Incomplete outcome data	High risk	We anticipated and accepted less than complete FA data as part of this study

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes (partially)
Intention-to-treat analysis included?	No

[a] 26 patients completed the study

CME: cystoid macular edema; CS: corticosteroid; DM: diabetes mellitus; FA: fluorescein angiography; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; VA: visual acuity

Table 3. Flach *et al*. 1991[18]

Methods	Double-masked, randomized, placebo-controlled study
Participants	
n (eyes)	120 (120 patients, one eye per patient assumed)[a]
Country	United States of America
Population	*Chronic CME:* Aphakic and pseudophakic patients with reduced VA (distance VA of 20/40 or less) for 6 months or more associated with clinical and FA evidence of CME *Exclusion:* Use of local or systemic anti-inflammatory drugs (CS, NSAIDs, or more than two 325 mg tablets of aspirin daily) within the preceding 6 weeks; ocular disease preventing adequate examination; unstable DM or systemic hypertension; preexisting macular disease preventing adequate retinal examination
Type of surgery	Unknown
Duration CME	≥ 6 months
Interventions	
Placebo	90-day treatment regimen (1 drop, 4 times daily) with placebo solution. If distance VA had decreased by 2 or more lines at day 120, as compared to day 90, therapy was reinstituted
Topical NSAID	90-day treatment regimen (1 drop, 4 times daily) with ketorolac tromethamine 0.5% ophthalmic solution. If distance VA had decreased by 2 or more lines at day 120, as compared to day 90, therapy was reinstituted
Main outcomes	
Outcome 1	≥ 2 lines improvement in Snellen VA
Outcome 2	FA
Follow-up	30, 60, 90 and 120 days and depending on their response to cessation of treatment 150 days
Conclusion	"The results of our double-masked, placebo-controlled, randomized, multicenter study confirmed the results of a smaller study that reported that treatment with ketorolac tromethamine 0.5% ophthalmic solution for 60 days may provide an improvement in VA in patients with chronic aphakic and pseudophakic CME."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Low risk	A computer-generated pre-determined randomization schedule
Sequence concealment	Unclear risk	A pre-determined randomization schedule. Unknown whether this schedule was kept with appropriate safeguards
Blinding participants	Low risk	Packaged in identical containers
Blinding personnel	Low risk	VA determination was the primary task of one person. This person was unaware of treatments, FA, and details of the clinical examination
Blinding outcome assessment	Unclear risk	Study does not address this outcome
Incomplete outcome data	Low risk	Treatment groups were not statistically different in terms of these missing examinations

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

[a] 95 patients were examined at 90 days of treatment, and 87 were examined at 120 days

CME: cystoid macular edema; CS: corticosteroid; DM: diabetes mellitus; FA: fluorescein angiography; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; VA: visual acuity

Table 4. Heier *et al*. 2000[19]

Methods	Randomized, double-masked, prospective study
Participants	
n (eyes)	28 (28 patients, one eye per patient assumed)[a]
Country	United States of America
Population	*Acute clinical CME:* Angiographic evidence of CME with VA of 20/40 or worse 21-90 days after uncomplicated cataract extraction. *Exclusion:* Use of ophthalmic NSAID or anti-inflammatory agent (other than topical prednisolone), more than 325 mg/day aspirin or systemic CS within 7 days preceding the study; ocular disease preventing adequate examination of the fundus or preventing a clear FA; ocular disease that could be responsible for the decreased VA; DR; unstable systemic disease; previous eye disease resulting in macular edema (other than pseudophakic CME in the fellow eye); ocular surgery other than cataract extraction and IOL implantation
Type of surgery	Uncomplicated phacoemulsification cataract surgery and posterior chamber IOL implantation
Duration CME	Unknown. Inclusion 21-81 days postoperatively
Interventions	
Topical CS	Prednisolone acetate 1.0% and artificial tears 1 drop 4 times daily. If CME was resolved, the medications were tapered at the rate of 1 drop per week. If CME was still present, then medications were continued. If treatment was continued for 3 months, then medications were tapered as above
Topical NSAID	Ketorolac tromethamine 0.5% and artificial tears 1 drop 4 times daily. If CME was resolved, the medications were tapered at the rate of 1 drop per week. If CME was still present, then medications were continued. If treatment was continued for 3 months, then medications were tapered as above
Topical CS & NSAID	Prednisolone acetate 1.0% and ketorolac tromethamine 0,5% 1 drop 4 times daily. If CME was resolved, the medications were tapered at the rate of 1 drop per week. If CME was still present, then medications were continued. If treatment was continued for 3 months, then medications were tapered as above
Main outcomes	
Outcome 1	Final Snellen VA
Outcome 2	≥ 2 lines improvement in Snellen VA
Outcome 3	Average time to VA improvement
Outcome 4	Number of patients with improvement in FA
Follow-up	Monthly intervals. Final examination 1 month after discontinuation of medications (max. 4 months)
Conclusion	"Treatment of acute, visually significant pseudophakic CME with ketorolac and prednisolone combination therapy appears to offer benefits over monotherapy with either agent alone. Patients were more likely to experience recovery of two lines or more of VA. Patients treated with a combination therapy or ketorolac monotherapy responded more quickly than did patients treated with prednisolone alone."

Table 4. Heier *et al*. 2000[19] (Continued)

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Unclear risk	Randomization was performed. Insufficient information to permit judgment.
Sequence concealment	Low risk	Randomization was performed by the pharmacy that supplied the premasked medications
Blinding of participants	Low risk	Study medications were masked to both patients and examiners. Groups 'prednisolone' and 'ketorolac' also received a second medication consisting of artificial tears
Blinding of personnel	Low risk	Study medications were masked to both patients and examiners
Blinding of outcome assessment	Low risk	Two retinal specialists read all FA in a masked fashion
Incomplete outcome data	High risk	Two patients were disqualified after choroidal neovascular membrane and branch retinal vein occlusion

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Unclear
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

[a] 26 patients completed the study

CME: cystoid macular edema; CS: corticosteroid; DR: diabetic retinopathy; FA: fluorescein angiogram; IOL: intraocular lens; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; VA: visual acuity

Table 5. Singal *et al*. 2004[20]

Methods	Prospective, double-masked randomized controlled trial
Participants	
n (eyes)	11 (11 patients, one eye per patient assumed)[a]
Country	Canada
Population	*Clinical pseudophakic CME*: an ETDRS VA of 20/40 Snellen equivalent or worse, together with the clinical presence of cysts detected with macular contact lens, occurring at least 6 weeks after cataract extraction. *Exclusion:* Recent (within the previous 4 weeks) use of CS; preexisting macular disease or diabetic maculopathy detected on FA
Type of surgery	Unknown
Duration CME	*Ketorolac group (mean (± SD))*: 17.3 (±20.9) months *Ketorolac & prednisolone group (mean (± SD))*: 7.6 (±8.4) months
Interventions	
Topical NSAID	0.5% ketorolac tromethamine plus placebo 4 times a day for the duration of the study (90 days).
Topical NSAID & CS	0.5% ketorolac tromethamine plus 1% prednisolone acetate 4 times a day for the duration of the study (90 days)
Main outcomes	
Outcome 1	Mean ETDRS Snellen equivalent VA
Outcome 2	Percent of patients with cysts on retinal examination, using a macular contact lens
Outcome 3	CME grade on FA Grade 0) No leakage; 1) Slight patchy perifoveal leakage; 2) Perifoveal leakage for 360°; 3) Severe leakage
Follow-up	30, 60 and 90 days
Conclusion	"We found no statistically significant difference in outcome between patients who received ketorolac and those who received ketorolac plus prednisolone for acute or chronic CME. The value of topical steroid therapy for chronic CME remains unproven."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Unclear risk	Randomization and coding was performed. Insufficient information to permit judgment
Sequence concealment	Low risk	Randomization and coding was performed by the hospital pharmacy
Blinding participants	Low risk	Both the patient and the examiner were masked as to the identity of the medication
Blinding personnel	Low risk	Both the patient and the examiner were masked as to the identity of the medication
Blinding outcome assessment	Unclear risk	Unknown whether outcome assessors were blinded
Incomplete outcome data	Low risk	Reasons for missing outcome data unlikely to be related to true outcome

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No (measures of variability only for ketorolac group)
Intention-to-treat analysis included?	No

[a] 10 patients completed the study

CME: cystoid macular edema; CS: corticosteroid; ETDRS: early treatment diabetic retinopathy study; FA: fluorescein angiography; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; SD: standard deviation; VA: visual acuity

Table 6. Rho *et al*. 2003[21]

Methods	Randomized prospective study
Participants	
n (eyes)	34 (of 34 patients)
Country	United States of America
Population	*Clinical CME*: Best corrected Snellen VA of 20/40 or worse, with characteristic clinically evident petaloid perifoveal macular edema as assessed by Goldmann contact lens biomicroscopy. *Exclusion:* A history of intraocular surgery, vitreous loss during cataract surgery, CME, uveitis, or vitreoretinal pathology. No patient had a known history of DM or preexisting macular condition
Type of surgery	Uneventful phacoemulsification cataract surgery with posterior chamber IOL implantation
Duration CME	*Diclofenac group (mean (±SD))*: 4.0 (±1.4) weeks *Ketorolac group (mean (±SD))*: 4.2 (±1.4) weeks
Interventions	
Topical NSAID	1 drop 4 times a day of diclofenac sodium 0.1% solution
Topical NSAID	1 drop 4 times a day of ketorolac tromethamine 0.5% solution
Main outcomes	
Outcome 1	Percentage of patients with CME reduction/elimination. The severity of CME was assessed by Goldmann contact lens biomicroscopy. FA was repeated if clinical CME persisted
Outcome 2	Mean time to CME reduction/elimination
Outcome 3	Final Snellen VA
Follow-up	Every 2-4 weeks for 26 weeks
Conclusion	"Diclofenac sodium 0.1% solution and ketorolac tromethamine 0.5% topical ophthalmic solution eye drops were equally effective in reducing the severity and duration of CME after uneventful phacoemulsification with posterior chamber IOL implantation. Either solution may be considered for CME after cataract surgery, especially in patients who may not tolerate corticosteroid treatment."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Unclear risk	Patients were randomized. Insufficient information to permit judgment
Sequence concealment	Unclear risk	Study does not address this outcome
Blinding participants	Unclear risk	Study does not address this outcome
Blinding personnel	Unclear risk	Study does not address this outcome
Blinding outcome assessment	Unclear risk	Study does not address this outcome
Incomplete outcome data	Unclear risk	Study does not address this outcome

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CME: cystoid macular edema; DM: diabetes mellitus; FA: fluorescein angiography; IOL: intraocular lens; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; SD: standard deviation; VA: visual acuity

Table 7. Warren *et al*. 2010[22]

Methods	Randomized, investigator-masked clinical trial
Participants	
n (eyes)	39 (of 39 patients)
Country	United States of America
Population	*Chronic pseudophakic CME*: CRT > 250 µm, presence of cysts on biomicroscopy, and VA ≤ 20/32. FA was used to exclude patients with CME caused by conditions other than Irvine–Gass syndrome. *Exclusion:* DM, uveitis, or any other nonpseudophakic condition that has an associated risk of CME
Type of surgery	Unknown
Duration CME	≥ 6 months. Mean duration was 9.4 months
Interventions	
Placebo	Lubricant eye drops (placebo) twice daily for 16 weeks
Topical NSAID	0.1% of diclofenac 3 times daily for 16 weeks
Topical NSAID	0.4% of ketorolac 3 times daily for 16 weeks
Topical NSAID	0.1% of nepafenac 3 times daily for 16 weeks
Topical NSAID	0.09% of bromfenac twice daily for 16 weeks
All patients were treated with intravitreal triamcinolone (4 mg) & intravitreal bevacizumab (1.25 mg) at study entry; the bevacizumab injection (1.25 mg) was repeated at the week 4 visit.	
Main outcomes	
Outcome 1	Mean reduction in retinal thickness from baseline, using OCT
Outcome 2	ETDRS VA
Follow-up	Weeks 4, 8, 12, 16
Conclusion	"Although NSAID therapy seems to potentiate the improvements produced by corticosteroids and anti-VEGF therapy for chronic pseudophakic CME, only nepafenac- and bromfenac-treated eyes showed reduced retinal thickness at 12 weeks and 16 weeks. Furthermore, nepafenac produced a sustained improvement in VA."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Unclear risk	Patients were randomly assigned… Insufficient information to permit judgment
Sequence concealment	Unclear risk	Study does not address this outcome
Blinding participants	Low risk	Although patients were not masked, this was unlikely to bias the results, because all measurements were objective
Blinding personnel	Unclear risk	Investigator-masked. Insufficient information to permit judgment.
Blinding outcome assessment	Unclear risk	Investigator-masked. Insufficient information to permit judgment
Incomplete outcome data	Low risk	Reasons for missing outcome data unlikely to be related to true outcome

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CME: cystoid macular edema; CRT: central retinal thickness; CS: corticosteroid; DM: diabetes mellitus; ETDRS: early treatment diabetic retinopathy study; FA: fluorescein angiography; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; VA: visual acuity; VEGF: vascular endothelial growth factor

Table 8. Yüksel *et al*. 2016[23]

Methods	Prospective, randomized, interventional clinical trial	
Participants		
n (eyes)	48	
Country	Turkey	
Population	Clinically significant pseudophakic CME: CRT > 250µm, presence of cysts on fundus biomicroscopy, and logMAR BCVA ≥ 0.4 *Exclusion:* vitreomacular traction or epiretinal membrane	
Type of surgery	Unknown	
Duration CME	*Nepafenac group (mean (±SD))*: 4.5 (±3.1) weeks, range 1-12 weeks *TA group (mean (±SD))*: 4.8 (±5.0) weeks, range 1-24 weeks	
Interventions		
Topical NSAID	Topical nepafenac 0.1% three times daily for 12 weeks	
Subtenon CS	A posterior subtenon injection of TA 40 mg, 1,0ml. TA injection was repeated within 2-3 months, if the patient response was inadequate or if there was recurrence evidenced by a decrease in VA or macular thickening on OCT	
Main outcomes		
Outcome 1	Reduction in CRT	
Outcome 2	Improvement in logMAR BCVA	
Follow-up	1, 2, 3 and 6 months	
Conclusion	"Our visual and OCT results suggest that both treatment modalities are effective, with few side-effects. However, nepafenac is more efficacious than subtenon TA in terms of visual gain and its correlation with the reduction in CRT"	
Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	High risk	Randomized clinical trial. However, the authors report that consecutive cases were alternately selected for one of two treatments
Sequence concealment	Unclear risk	Study does not address this outcome
Blinding participants	High risk	One study group received eye drops; the other group received a subtenon injection. The study did not use placebo eye drops or sham injections
Blinding personnel	Low risk	BCVA was measured by a masked resident
Blinding outcome assessment	Unclear risk	Study does not address this outcome
Incomplete outcome data	Unclear risk	Drop-outs from follow-up were excluded
Quality of RCT (additional items Delphi List)		
Prognostic indicators similar at baseline?		Yes
Eligibility criteria specified?		Yes
Point estimates and measures of variability given?		Yes
Intention-to-treat analysis included?		No

BCVA: best corrected visual acuity; CME: cystoid macular edema; CRT: central retinal thickness; CS: corticosteroid; logMAR: logarithm of the minimum angle of resolution; NSAID: non-steroidal anti-inflammatory drug; OCT: optical coherence tomography; RCT: randomized controlled trial; SD: standard deviation; TA: triamcinolone acetonide; VA: visual acuity

Table 9. Yannuzzi *et al*. 1977[24]

Methods	Prospective, controlled, double-masked study
Participants	
n (eyes)	23 (of 20 patients)
Country	United States of America
Population	Reduced vision and clinical and FA evidence of CME 4 months or more after cataract surgery. *Exclusion:* Preexisting macular disease; other ocular conditions associated with CME; more than 75 years of age
Type of surgery	Uncomplicated conventional ICCE
Duration CME	Unknown. Inclusion ≥ 4 months postoperatively
Interventions	
Placebo	Placebo 3 times a day. Six weeks after entering the study, medication was discontinued
Oral NSAID	25 mg of orally administered indomethacin 3 times a day. Six weeks after entering the study, medication was discontinued
Main outcomes	
Outcome 1	Evidence of CME on FA
Outcome 2	At least 2 lines improvement or decrease in VA
Follow-up	3, 6, 10 weeks
Conclusion	"A controlled, double-masked study in which patients with CME of more than 4 months' duration were treated with indomethacin failed to demonstrate a significant visual improvement when compared to patients who were treated with placebo."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Unclear risk	Patients were randomly assigned to... Insufficient information to permit judgment
Sequence concealment	Unclear risk	Study does not address this outcome
Blinding participants	Low risk	Placebo-controlled study. It is unlikely that the blinding has been broken
Blinding personnel	Unclear risk	Study does not address this outcome
Blinding outcome assessment	Unclear risk	Study does not address this outcome
Incomplete outcome data	Low risk	No patients dropped from the study

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Unclear
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CME: cystoid macular edema; FA: fluorescein angiography; ICCE: intracapsular cataract extraction; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; VA: visual acuity

Table 10. Curkovic *et al*. 2005[25]

Methods	Prospective randomized study
Participants	
n (eyes)	14 (of 14 patients)
Country	Croatia
Population	CME detected with FA and VA less than 0.5 according to Snellen optotype *Exclusion:* other eye diseases, which would jeopardize visual function and DM
Type of surgery	Non-complicated extracapsular or phaco cataract surgery
Duration CME	Unknown
Interventions	
Topical CS & NSAID	Topical 0.1% dexamethasone solution 3x and flurbiprofen liquifilm 3 times a day. 8 weeks of therapy
Topical CS & NSAID, oral AZ & KCl	Topical 0.1% dexamethasone solution 3x and flurbiprofen liquifilm 3 times a day. 8 weeks of therapy. Acetazolamide 250 mg 3 times a day along with 500 mg KCl. Acetazolamide for 2 weeks in the full dosage and for another 2 weeks with 250 mg daily and by the follow-up examination 125 mg a day
Main outcomes	
Outcome 1	Number of eyes with evident CME reduction on FA
Outcome 2	Best corrected Snellen VA
Follow-up	8 weeks
Conclusion	"The most favorable option for the CME treatment following up non-complicated cataract surgery is a combination of corticosteroids therapy with NSAID topically along with orally applied acetazolamide due to intensifying and speeding up the resorption of oedema."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)		
Sequence generation	Unclear risk	Randomized study. Insufficient information to permit judgment
Sequence concealment	Unclear risk	Study does not address this outcome
Blinding participants	High risk	One study group received oral medication, whereas the other did not. The study did not use a placebo
Blinding personnel	Unclear risk	Study does not address this outcome
Blinding outcome assessment	Unclear risk	Study does not address this outcome
Incomplete outcome data	Unclear risk	Study does not address this outcome

Quality of RCT (additional items Delphi List)	
Prognostic indicators similar at baseline?	Unclear
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	*No*

AZ: acetazolamide; CME: cystoid macular edema; CS: corticosteroid; DM: diabetes mellitus; FA: fluorescein angiography; KCl: potassium chloride; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; VA: visual acuity

Chapter 7

General discussion

General discussion

Cataract surgery is one of the most commonly performed surgical procedures in the world.[1, 2] Although modern phacoemulsification techniques have significantly decreased the incidence of postoperative complications, cystoid macular edema (CME) remains a major problem, causing delayed visual rehabilitation in 1-2% of patients. Reported incidence rates increase to 4-9% in patients with diabetes mellitus (DM) or other risk factors for developing CME after cataract surgery.[3, 4] For many years, anti-inflammatory drugs have been used to prevent the occurrence of CME, but the absence of solid evidence-based recommendations created remarkable differences between clinical guidelines of leading authorities.[5, 6] This thesis aimed to identify the optimal strategy to prevent and treat CME after cataract surgery.

The clinical significance of cystoid macular edema

CME may develop after cataract surgery as a part of an excessive postoperative inflammatory response, causing a disruption of the blood-retinal barrier.[7] A minority of patients develop CME after cataract surgery and most cases may not be clinically relevant. CME was identified in 5.0% of non-diabetic patients participating in the ESCRS PREvention of Macular EDema after cataract surgery (PREMED) study, whereas only 3.4% of patients developed clinically significant cystoid macular edema (CSME). This difference was also seen in diabetic patients. CME was identified in 4.5% of patients, while only 2.2% went on to develop CSME within twelve weeks postoperatively.

Reported incidence rates differ between studies, depending on the diagnostic methods and definitions used. Optical coherence tomography (OCT) is considered to be the most sensitive method to detect CME, while previous studies have also used fluorescein angiography (FA) or fundoscopy to identify patients with CME after cataract surgery.[8, 9] In OCT-based studies, diverse operational definitions are applied, such as a central macular thickness of more than 250-320 µm, an increase in central macular thickness of 25-60 µm, an increase of at least 10-30%, or general descriptions such as 'obvious CME on OCT'.[10-17] Moreover, some definitions include a decrease in postoperative visual acuity, while others do not include such clinical outcome measures.[11, 12, 18] This diversification with respect to the applied definition of CME, is a central problem in research on pseudophakic cystoid macular edema (PCME), preventing a fair comparison of incidence rates among studies.[19] It is important to settle a uniform definition for PCME, as well as a separate definition for clinically significant PCME.

The ESCRS PREMED study applied a very sensitive OCT-based definition to detect CME. CME was defined as an increase in central subfield macular thickness (CSMT) of at least 10% with cystic changes identified on OCT. CSME was defined as CME with less than 0.2 logMAR improvement in corrected distance visual acuity (CDVA), as compared to the preoperative baseline. The PREMED study definition of CSME assumes that modern phacoemulsification cataract surgery leads to at least two lines CDVA improvement, which might not be the case in patients requiring cataract surgery because of glare or decreased contrast sensitivity.

The optimal definition of PCME remains to be identified. In the first place, this definition should include the presence of cystoid changes in the central 1 mm area of the macula, as defined on OCT.[20] Strict criteria should be included in such a definition to avoid subjective interpretation of OCT images. It is unnecessary to include thickness-based measures, as the presence of cystoid changes will always cause a certain increase in central retinal thickness and/or total macular volume (TMV). By excluding these thickness-based measures, the definition will be applicable to various types of OCT devices, using different built-in software methods to measure retinal thickness and TMV. Secondly, the definition of PCME should include a description of the preoperative condition of the macula, in order to distinguish PCME from other causes of CME.

The optimal definition of clinically significant PCME should also include a certain amount of visual impairment, such as a decrease in CDVA. Generally, PCME does not develop during the immediate postoperative period. Therefore, the definition of clinically significant PCME should include a decrease in CDVA from a one week postoperative baseline value.[19]

Prevention of cystoid macular edema in regular cases

Anti-inflammatory treatments have long been used to prevent the occurrence of CME after cataract surgery, although the optimal anti-inflammatory strategy remained unknown due to a lack of high quality evidence.[21, 22] As a result, standard practice varied between organizations and countries, and remarkable contrasts could be seen between clinical recommendations of leading authorities.[5, 6] We performed a systematic review and meta-analysis to investigate this important clinical question, and found that topical non-steroidal anti-inflammatory drugs (NSAIDs), either in addition to, or instead of, topical corticosteroids can effectively reduce the odds of developing CME after cataract surgery. Our findings are in line with the results of two recent Cochrane reviews.[23, 24] Therefore, we feel that topical NSAIDs should be included in the standard of care after regular cataract surgery.

However, at that point the added value of local corticosteroids remained controversial. Only a few studies directly compared the efficacy of topical NSAIDs versus combination treatment with a topical NSAID and corticosteroid. Based on the results of our meta-analysis, it remained unclear whether the use of corticosteroid eye drops could be avoided. The ESCRS PREMED study is a randomized controlled European multicenter study, directly comparing the efficacy of a topical NSAID versus combination treatment. The study found no statistically significant, nor clinically relevant differences in mean macular thickness or TMV at six weeks postoperatively, between patients treated with a combination of bromfenac 0.09% and dexamethasone 0.1% eye drops, versus patients treated with bromfenac only. Nevertheless, the ESCRS PREMED study group recommends combination treatment with bromfenac and dexamethasone after regular uncomplicated cataract surgery, as the odds of developing CSME are significantly higher in patients treated with topical bromfenac only (odds ratio, OR 2.6), when compared to patients in the combination treatment group.

Which non-steroidal anti-inflammatory drug is best?

The results of ESCRS PREMED study report 1 showed that a combination of NSAID and corticosteroid eye drops effectively reduces the risk of developing CME after cataract surgery. However, there is currently no high-quality evidence to prefer bromfenac 0.09% over other NSAID preparations. Various topical NSAID preparations are available, of which nepafenac and bromfenac are approved by the European Medicine Agency (EMA) for prevention of inflammation and/or CME after cataract surgery.[25, 26] Other NSAIDs are approved to reduce pain associated with corneal refractive surgery, inhibition of intraoperative miosis, and for treatment of seasonal allergic conjunctivitis.[27] The results of previous studies and a recent network analysis could not provide solid evidence to prefer a specific NSAID preparation over others.[28-37]

At this point, the optimal topical NSAID should be chosen based on patient satisfaction, simplicity of drug administration, frequency of drug administration, and ocular comfort. Patient compliance is an important factor which should not be underestimated. Previous studies showed that a higher frequency of eye drop administration correlates with noncompliance in glaucoma patients. The odds of being noncompliant were significantly higher (OR 2.5) if eye drops had to be used more than twice daily, as compared to once-daily administration.[38] However, the results on compliance in glaucoma patients may not be valid for extrapolation to patients undergoing cataract surgery. It should be noted that glaucoma treatment involves life-long administration of eye drops, as compared to two to four weeks treatment in prevention of CME after cataract surgery. Once-daily NSAID preparations have shown to be effective in prevention of CME after cataract surgery.[3, 27, 39] Unfortunately, there are no adherence studies investigating patient compliance with respect to topical anti-inflammatory treatment after cataract surgery.

Finally, costs involved with NSAID treatment vary greatly among various preparations, affecting the cost-effectiveness of this preventative treatment. Once-daily NSAID preparations may be more expensive, but less-frequent dosing improves patient adherence, which may improve the efficacy in preventing CME and inflammation after cataract surgery.[27]

Prevention of cystoid macular edema in diabetics

Diabetic eye disease is becoming an increasing problem, due to an increasing incidence and longer life expectancy of patients with DM.[40] The incidence of DM increases, as a result of changing lifestyles causing reduced physical activity and increased incidence of obesity. The annual increase in the number of patients with DM is estimated at 2.2%. In patients over 60 years old, the incidence of DM will likely double between 2010 and 2030.[41] Patients with DM have an increased risk of developing cataract at an early age.[42] Moreover, DM is a widely accepted and well-known risk factor for developing CME after cataract surgery. Previous studies have shown that a combination of topical corticosteroids and NSAIDs effectively reduces the risk of developing CME after cataract surgery, as compared to single drug treatment, in diabetics with diabetic retinopathy (DR).[37, 40, 43-47]

Additional perioperative interventions may be needed to adequately reduce the odds of developing CME in these high-risk cases. ESCRS PREMED study report 2 has shown that a subconjunctival injection with 40 mg triamcinolone acetonide (TA) can effectively prevent the occurrence of CME in patients with DM. However, it is not recommended to adopt this treatment to all diabetics undergoing cataract surgery. The incidence of an increased intraocular pressure (IOP ≥ 25 mmHg) after a single subconjunctival injection with 40 mg TA was 7.1%, whereas the overall incidence of CME did not exceed above 4.5%. Increased IOP is a common complication of local corticosteroid administration, but prevalence may vary between various routes of administration.[48-51] Other routes of corticosteroid administration may also prevent the occurrence of CME, involving a lower incidence of IOP increase. Previous studies have investigated the use of high frequency prednisolone eye drops, oral prednisolone, intravitreal TA, and subtenon TA.[52-56] The risk-benefit ratio of various dosages and routes of corticosteroid administration should be further explored, considering the efficacy and safety of topical, subconjunctival, subtenon and intravitreal corticosteroid administration.

At this point, a personalized risk assessment should be made for each individual patient, carefully weighing the risk of developing visual impairment due to CME, against the risk of developing an increased IOP and the probability of developing subsequent glaucomatous visual field loss. This personalized risk assessment should also take stock of certain DM characteristics known to increase the risk of developing CME after cataract surgery, such as the duration of DM, insulin dependence, and a history of diabetic macular edema (DME).[4,

[57] Furthermore, it has been shown that the odds of developing CME after cataract surgery correlate with the severity of preoperative DR.[4] Eighty-five percent of patients included in the ESCRS PREMED study had no signs of DR. Consequently, the results of this study may not be valid for extrapolation to patients with mild to severe DR. Future RCTs should explore the efficacy of subconjunctival corticosteroid injections to prevent CME after cataract surgery in patients with preoperative DME or DR.

Prevention of cystoid macular edema in other high-risk patients

Prevention of CME after cataract surgery should ideally begin with a personalized preoperative risk assessment for each individual patient.[58] Previous studies have shown that many patient characteristics may influence the risk of developing CME after cataract surgery. These risk factors include previous development of CME after cataract surgery in the fellow eye, as well as a clinical history of DM, previous retinal vein occlusion (RVO), macular hole, epiretinal membrane (ERM) or uveitis.[3, 4, 59, 60] The optimal strategy before, during and after cataract surgery should be tailored to the needs of the individual patient. Although the ESCRS PREMED study investigated the optimal prevention in patients with and without DM, this study did not investigate patients with other risk factors for developing CME after cataract surgery. The results of the ESCRS PREMED study cannot be extrapolated directly to other high-risk patients, which is why further research is needed. Some research has been done to identify the optimal treatment in patients with ERM or uveitis. Oral prednisolone could not reduce the risk of developing CME after cataract surgery in patients with an ERM.[52] Intravitreal TA prevented the development of CME in 19 eyes of uveitic patients undergoing cataract surgery.[61] One retrospective study reports beneficial results of using intravenous 250-500 mg methylprednisolone during cataract surgery in uveitic patients. Uveitic patients with a history of CME were more likely to develop CME after cataract surgery, although this association was not seen in patients who received intravenous methylprednisolone or oral prednisolone.[62] Given the results of these small studies, there remains a need for RCTs to investigate the optimal prevention of CME in high-risk patients without DM.

Dropless cataract surgery

Eye drops are generally used in ophthalmology because of their presumed ease of administration and low costs.[63] However, previous studies have shown that non-compliance with eye drops is much higher than the average ophthalmologist may suspect. Studies investigating the compliance in glaucoma patients report self-reported non-adherence in 39.2% of patients, as opposed to an ophthalmologist-noticed non-compliance in only 2.1% of patients.[38] Even patients who are reminded about taking their eye drops, often fail to achieve the prescribed eye drop regimen. Suboptimal treatment with anti-inflammatory eye drops is also caused by incorrect instillation, particularly in the elderly cataract

surgery population.[63, 64] Homecare services are frequently involved to correctly instill the prescribed eye drops, which significantly increases the costs of postoperative care. In the subset of patients who adequately instill the prescribed eye drops, less than 3-5% of the instilled drug quantity reaches the aqueous humor.[63, 65] Aqueous drug concentrations vary widely after topical drug administration.[66] A high drug concentration in the tear film is required to achieve adequate intraocular concentrations, which often leads to ocular side effects.[63] These findings are only some of the many reasons why ophthalmologists have investigated the possibility of dropless cataract surgery. Dropless drug administration can be achieved using a variety of application methods, such as subconjunctival, subtenon, intracameral and intravitreous injections. Recently, research has been done on ocular insert devices and drug-delivering intraocular lenses.[67]

Dropless corticosteroid treatment

Periocular corticosteroid injections are frequently used to prevent and treat ocular inflammatory conditions. ESCRS PREMED study report 2 shows that a single subconjunctival injection of 40 mg TA effectively prevents the occurrence of CME after cataract surgery. However, subconjunctival injection of other corticosteroids, such as 5.7 mg/ml betamethasone, are also considered an effective alternative to corticosteroid eye drops.[11] Periocular corticosteroid administration can also be performed through subtenon injection. A subtenon injection of 20-30 mg TA has been used to effectively prevent CME after cataract surgery.[68, 69] Anterior subtenon injections are preferred for prevention and treatment of inflammatory conditions in the anterior segment of the eye, since aqueous TA concentration are significantly higher after anterior subtenon injection, when compared to posterior subtenon TA injection.[56] Although CME after cataract surgery can be classified as a disease of the posterior segment of the eye, the underlying inflammatory response starts in the anterior segment during cataract surgery.[70]

Secondly, corticosteroids can be delivered to the anterior and posterior segment of the eye by intraocular injection. Intracameral injections of an antibiotic drug are frequently used at the end of cataract surgery, but only few studies have investigated the efficacy of intracameral corticosteroids.[71] A recent study reports that an intracameral suspension containing 342-517 µg dexamethasone can effectively reduce inflammation after cataract surgery.[72] An intracameral injection with 1 mg TA has also shown to be an effective alternative to corticosteroid eye drops in reducing inflammation after cataract surgery.[73] However, a minimal dosage of 1.8 mg TA is needed to prevent the occurrence of CME after cataract surgery.[74] Intravitreal corticosteroid injections are frequently used in treatment of retinal diseases, including PCME and DME.[75, 76] A small study showed that an intravitreal injection with 2 mg TA significantly reduces the incidence of CME after cataract surgery in diabetics with DR.[54] Finally, corticosteroids can be delivered to the posterior segment by

transzonular injection.[77] One retrospective study reports visually significant CME in 2% of patients after cataract surgery with a transzonular injection of 3 mg TA.[78]

As reported previously, an increased IOP is the most well-known complication after ophthalmic corticosteroid treatment. The reported incidence varies according to the type of corticosteroid, its dosage and its route of administration.[77] The risk of developing an increased IOP correlates with the aqueous corticosteroid concentration.[56] Unfortunately, previous studies provide inconclusive results regarding the incidence of a corticosteroid-induced increased IOP. Some studies report that low dosage of intracameral TA (1-3 mg) can be used safely without a significant increase in IOP.[73, 74] Similar dosage of intravitreal TA caused an increased IOP in 0.9-62% of patients.[54, 75, 76, 78] The reported incidences after intravitreal TA injection clearly illustrate the inconsistent results of previous studies. Higher dosages of corticosteroids are often used for periocular injection.[69] Whereas an anterior subtenon injection is easier to administrate, an increased IOP is less common after posterior subtenon injection of a corticosteroid.[48, 56] The ESCRS PREMED study reports an IOP of ≥ 25 mmHg in 7.1% of patients within twelve weeks after a single subconjunctival injection of 40 mg TA. Furthermore, 17.9% of patients developed an IOP increase of ≥ 5 mmHg within twelve weeks after subconjunctival TA injection. Whereas the ESCRS PREMED study did not investigate IOP after twelve weeks postoperatively, patients should be followed on a regular basis for approximately one year after a single injection, as subconjunctival TA may remain present until 13 months after injection.[79] Previous case reports show that an increased IOP normalizes within one week after removal of the TA depot.[79, 80]

Dropless non-steroidal anti-inflammatory treatment

NSAID eye drops are generally used in ophthalmology, but less is known about the safety and efficacy of NSAIDs after periocular or intraocular injection. Subconjunctival injection of an NSAID has not been investigated in human eyes, although animal studies report high aqueous and vitreous concentrations after a single anterior subconjunctival injection of 15 mg ketorolac.[81] Instead, recent studies focused on the efficacy of intracameral and intravitreal NSAID treatment.

The EMA recently authorized the use of Omidria, a combination drug containing phenylephrine and ketorolac, to be added to the balanced salt solution as part of the standard irrigation solution during cataract surgery. After dilution of 4 ml Omidria in 500 ml of irrigation solution, the solution contains 0.023 mg/ml ketorolac.[82] Moreover, Omidria can be delivered to the anterior segment of the eye by intracameral injection at the beginning of cataract surgery.[83] Omidria is known to prevent perioperative miosis and to reduce pain after cataract surgery.[67, 82-85] Its efficacy with respect to the prevention of postoperative inflammation and CME remains to be investigated.

An intravitreal injection of ketorolac has been investigated in treatment of CME after cataract surgery, but not for its prevention. Two case reports describe the efficacy of an intravitreal injection of 0.5 mg ketorolac in four patients with chronic CME after cataract surgery. One report showed no improvement in CDVA or central foveal thickness after a single intravitreal injection.[86] A second study reports a decreased macular thickness and improved CDVA after four consecutive intravitreal injection of 0.5 mg ketorolac.[87] Other studies investigated the efficacy of an intravitreal injection with 3-4 mg ketorolac in patients with CME due to diabetes or uveitis. [88, 89]

Small studies have investigated the efficacy of a single intravitreal injection of 0.5 mg diclofenac in patients with CME.[90-94] The first pilot-study investigated the efficacy of intravitreal 0.5 mg diclofenac in ten patients with CME due to various underlying diseases, including one patient with PCME. CDVA improved in 70% of patients at eight weeks after a single intravitreal injection. Macular thickness decreased in 70% of patients, although the CSMT decrease was only minimal in some of them (range 4-96 µm).[91] Others report a decreased CSMT after a single intravitreal injection of 0.5 mg diclofenac patients with uveitic CME.[92] The efficacy of an intravitreal injection of 0.5 mg diclofenac was comparable to an intravitreal injection of 4 mg TA or 1.25 mg bevacizumab in patients with DME.[93, 94] The safety profile of intraocular NSAIDs remains to be investigated. Animal studies report that intravitreal doses up to 3 mg ketorolac or 0.3 mg diclofenac are well tolerated in the retina. The authors suggest that doses as high as 4 mg ketorolac and 0.4 mg diclofenac can be considered nontoxic in adult human eyes.[95] Pilot-studies report no prominent change with respect to electroretinography studies in human eyes within two to three months after intravitreal injection of 0.5 mg diclofenac or 0.5-4 mg ketorolac.[86, 89, 91] However, long term monitoring is needed to detect possible delayed drug toxicity.[95]

It remains debatable whether a single intravitreal NSAID injection is suitable for prevention of postoperative inflammation and CME, considering the half-life of two to three hours after intravitreal injection of diclofenac, flurbiprofen and ketorolac.[96-98] Given the short half-life of intravitreal NSAIDs, authors recommend frequent injections at short intervals (hours-days) to achieve lasting therapeutic levels.[96] The safety of repeated intravitreal NSAID treatment remains to be investigated. Moreover, repeated intravitreal injections increase the risk of endophthalmitis, a dreaded complication that is reported in 4-5 per 10,000 injections.[99] Therefore, some animal research has been done to improve the pharmacokinetics of intravitreal NSAID preparations by using other dosage forms, such as a drug suspension.[97]

Duration of postoperative follow-up

It is essential to monitor cataract surgery patients during the immediate postoperative period, as timely diagnosis and adequate treatment of PCME prevent anatomic alterations and sustained visual impairment.[100] A postoperative follow-up period of six weeks is suggested, given the fact that most cases of PCME develop within four to six weeks postoperatively.[19] This thesis investigated the optimal prevention of CME within three months after uncomplicated cataract surgery. Little research has been done to determine the incidence of PCME developing more than three months postoperatively.[5] Recent studies have indicated that the incidence of CME peaks at three to six months after cataract surgery in diabetics.[101] These findings suggest a longer postoperative follow-up period in patients with an increased risk of developing CME.

Diabetic patients receiving a subconjunctival injection with TA, as reported in ESCRS PREMED study report 2, should be followed for at least one year postoperatively. Whereas the PREMED study reports an increased IOP in 7.1% of patients within twelve weeks postoperatively, IOP may rise at a later stage. Active TA depots, leading to a corticosteroid-induced increased IOP, have been found at three to thirteen months after a single subconjunctival injection.[79]

Differentiation of cystoid macular edema in diabetics

CME is a hallmark of various retinal diseases and may be caused by an inflammatory response, altered vasopermeability, or mechanically by vitreomacular traction.[20] In diabetics, CME after cataract surgery may be caused by a postoperative inflammatory response and/or pre-existing vascular changes. It can be classified as PCME, worsening of DME, or a combination of both.[57] PCME results from a postoperative inflammatory response. Even diabetics without DR have an increased risk of developing PCME, due to an impaired blood-retinal barrier, causing increased leakage of fluid into the retina.[4, 57] By contrast, DME develops from chronic hyperglycemia, causing impaired blood flow, hypoxia, endothelial cell loss and pericyte loss.[17, 20, 37] Exacerbation of DME may be caused by postoperative inflammation after cataract surgery.

ESCRS PREMED study report 2 did not differentiate DME from PCME in patients with diabetes. However, if CME after cataract surgery evolves into chronic CME, it is crucial to define its etiology, as treatment strategies must be adjusted to the pathogenesis of the edema.[37, 57] PCME is best treated with anti-inflammatory agents, such as corticosteroids and NSAIDs, whereas optimal treatment of DME involves intravitreal injections with anti-VEGF or corticosteroids.[57]

Although hard exudates and microaneurysms can be observed in patients with DR, ophthalmologists are unable to differentiate PCME from DME based on the fundoscopic appearance alone, especially in diabetics who recently underwent cataract surgery.[17] Historically, FA was used to differentiate DME from PCME, since PCME is characterized by disc edema on FA. In recent years, OCT has become the preferred method to detect CME and to differentiate PCME from DME. Diffuse retinal thickening, without retinal nerve fiber layer thickening, is typically seen in case of DME. Scattered, well demarcated cystoid changes are confined to the outer nuclear layer, usually occurring, but not limited to the parafoveal and perifoveal regions. A normal foveal depression is preserved in 64% of DME cases. Hard exudates, microaneurysms and microfoci (lipoprotein-rich deposits or lipid-laden macrophages) can be identified in most cases of DME. PCME is characterized by central and symmetric macular edema, typically located in the central 1 mm area of the macula. Central cystoid changes are confined to the inner nuclear layer and subretinal fluid is often seen.[17, 20] Based on these characteristics, retina specialists are able to differentiate DME from PCME and mixed cases in 95% of patients; and comparable results were seen using automated differentiation.[17] Recently, a small retrospective study evaluated the retinal vascular density of patients with PCME using OCT-angiography.[102] However, it remains unclear whether OCT-angiography can improve clinical decision-making in patients with CME after cataract surgery.

Treatment of pseudophakic cystoid macular edema

Although many recent studies have tried to identify the optimal strategy to prevent PCME, there remains a lack of evidence with regard to its treatment. Whereas acute PCME resolves spontaneously in the majority of patients, chronic CME may cause anatomic alterations and sustained visual impairment. Previous research showed that adequate treatment of CME will only lead to visual acuity improvement as long as septas of healthy tissue persist between the cystic spaces and if the photoreceptor inner segment/outer segment (IS/OS) layer remains intact.[103] It is widely accepted that final visual acuity decreases if CME exists for a longer period of time, but it remains unknown what the optimal timing for initiation of treatment is. Although it has been stated that CME resolves spontaneously in 80% of cases, these results are based on only one study investigating the incidence of CME after extracapsular cataract extraction in 1988.[104] Future studies should investigate the optimal timing for treatment initiation, considering the natural course of PCME after modern phacoemulsification cataract surgery.

Due to its low incidence and the fact that CME resolves spontaneously in the majority of cases, large multicenter studies with sufficient statistical power are needed to compare the efficacy of various treatments. Unfortunately, only small studies have addressed this important clinical question. The results of our systematic review showed that topical

NSAIDs, either instead of, or in addition to topical corticosteroids improve CDVA in patients with CME after cataract surgery. Moreover, the time to resolution of CME was shorter in patients treated with a topical corticosteroid and NSAID, as compared to patients treated with a corticosteroid only. Although CME may recur after cessation of treatment, visual acuity recovered in most patients after retreatment with NSAID eye drops. Small studies have shown promising results with respect to intravitreal dexamethasone implants, intravitreal NSAIDs and oral acetazolamide, but further research is needed to confirm the results.[16, 86, 87, 91, 105, 106]

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 Wang W, Yan W, Fotis K, Prasad NM, Lansingh VC, Taylor HR, Finger RP, Facciolo D, He M. Cataract Surgical Rate and Socioeconomics: A Global Study. Invest Ophthalmol Vis Sci 2016; 57: 5872-5881

3 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

4 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

5 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

6 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

7 Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. Drugs 2007; 67: 1291-1308

8 Miyake K, Nishimura K, Harino S, Ota I, Asano S, Kondo N, Miyake S. The effect of topical diclofenac on choroidal blood flow in early postoperative pseudophakias with regard to cystoid macular edema formation. Investigative ophthalmology & visual science 2007; 48: 5647-5652

9 Yavas GF, Ozturk F, Kusbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. J Cataract Refract Surg 2007; 33: 804-807

10 Miyanaga M, Miyai T, Nejima R, Maruyama Y, Miyata K, Kato S. Effect of bromfenac ophthalmic solution on ocular inflammation following cataract surgery. Acta Ophthalmologica 2009; 87: 300-305

11 Dieleman M, Wubbels RJ, Van Kooten-Noordzij M, De Waard PWT. Single perioperative subconjunctival steroid depot versus postoperative steroid eyedrops to prevent intraocular inflammation and macular edema after cataract surgery. Journal of Cataract and Refractive Surgery 2011; 37: 1589-1597

12 Mathys KC, Cohen KL. Impact of nepafenac 0.1% on macular thickness and postoperative visual acuity after cataract surgery in patients at low risk for cystoid macular oedema. Eye 2010; 24: 90-96

13 Wang QW, Yao K, Xu W, Chen PQ, Shentu XC, Xie X, Weng Y, Zhang L, Jin CF, Wu W, Zhu YN, Yu YH. Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification. Ophthalmologica 2013; 229: 187-194

14 Chae JB, Joe SG, Yang SJ, Lee JY, Sung KR, Kim JY, Kim JG, Yoon YH. Effect of combined cataract surgery and ranibizumab injection in postoperative macular edema in nonproliferative diabetic retinopathy. Retina (Philadelphia, Pa) 2013

15 Wittpenn JR, Silverstein S, Heier J, Kenyon KR, Hunkeler JD, Earl M. A Randomized, Masked Comparison of Topical Ketorolac 0.4% Plus Steroid vs Steroid Alone in Low-Risk Cataract Surgery Patients. American Journal of Ophthalmology 2008; 146: 554-560.e551

16 Pepple KL, Nguyen MH, Pakzad-Vaezi K, Williamson K, Odell N, Lee C, Leveque TK, Van Gelder RN. Response of Inflammatory Cystoid Macular Edema to Treatment Using Oral Acetazolamide. Retina (Philadelphia, Pa) 2018

17 Munk MR, Jampol LM, Simader C, Huf W, Mittermuller TJ, Jaffe GJ, Schmidt-Erfurth U. Differentiation of Diabetic Macular Edema From Pseudophakic Cystoid Macular Edema by Spectral-Domain Optical Coherence Tomography. Invest Ophthalmol Vis Sci 2015; 56: 6724-6733

18 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

19 Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Current Opinion in Ophthalmology 2012; 23: 26-32

20 Munk MR, Sacu S, Huf W, Sulzbacher F, Mittermuller TJ, Eibenberger K, Rezar S, Bolz M, Kiss CG, Simader C, Schmidt-Erfurth U. Differential diagnosis of macular edema of different pathophysiologic origins by spectral domain optical coherence tomography. Retina (Philadelphia, Pa) 2014; 34: 2218-2232

21 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
22 Waitzman MB. Topical indomethacin in treatment and prevention of intraocular inflammation--with special reference to lens extraction and cystoid macular edema. Ann Ophthalmol 1979; 11: 489-491
23 Lim BX, Lim CH, Lim DK, Evans JR, Bunce C, Wormald R. Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery. Cochrane Database Syst Rev 2016; 11: CD006683
24 Juthani VV, Clearfield E, Chuck RS. Non-steroidal anti-inflammatory drugs versus corticosteroids for controlling inflammation after uncomplicated cataract surgery. Cochrane Database Syst Rev 2017; 7: CD010516
25 Bromfenac. European public assessment report, summary for the public. European Medicines Agency (EMA), 2017
26 Nepafenac. European public assessment report, summary for the public. European Medicines Agency (EMA), 2016
27 Wilson DJ, Schutte SM, Abel SR. Comparing the Efficacy of Ophthalmic NSAIDs in Common Indications: A Literature Review to Support Cost-effective Prescribing. Ann Pharmacother 2015; 49: 727-734
28 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
29 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
30 Lee TH, Choi W, Ji YS, Yoon KC. Comparison of ketorolac 0.45% versus diclofenac 0.1% for macular thickness and volume after uncomplicated cataract surgery. Acta Ophthalmol 2016; 94: e177-182
31 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
32 Almeida DR, Khan Z, Xing L, Bakar SN, Rahim K, Urton T, El-Defrawy SR. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. J Cataract Refract Surg 2012; 38: 1537-1543
33 Weber M, Kodjikian L, Kruse FE, Zagorski Z, Allaire CM. Efficacy and safety of indomethacin 0.1% eye drops compared with ketorolac 0.5% eye drops in the management of ocular inflammation after cataract surgery. Acta Ophthalmol 2013; 91: e15-21
34 Tzelikis PF, Vieira M, Hida WT, Motta AF, Nakano CT, Nakano EM, Alves MR. Comparison of ketorolac 0.4% and nepafenac 0.1% for the prevention of cystoid macular oedema after phacoemulsification: prospective placebo-controlled randomised study. Br J Ophthalmol 2015; 99: 654-658
35 Jung JW, Chung BH, Kim EK, Seo KY, Kim TI. The Effects of Two Non-Steroidal Anti-Inflammatory Drugs, Bromfenac 0.1% and Ketorolac 0.45%, on Cataract Surgery. Yonsei Med J 2015; 56: 1671-1677
36 Ramakrishnan S, Baskaran P, Talwar B, Venkatesh R. Prospective, Randomized Study Comparing the Effect of 0.1% Nepafenac and 0.4% Ketorolac Tromethamine on Macular Thickness in Cataract Surgery Patients With Low Risk for Cystoid Macular Edema. Asia Pac J Ophthalmol (Phila) 2015; 4: 216-220
37 Yuksel B, Karti O, Kusbeci T. Topical nepafenac for prevention of post-cataract surgery macular edema in diabetic patients: patient selection and perspectives. Clin Ophthalmol 2017; 11: 2183-2190
38 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
39 Walters TR, Goldberg DF, Peace JH, Gow JA, Bromfenac Ophthalmic Solution 0.07% Once Daily Study G. Bromfenac ophthalmic solution 0.07% dosed once daily for cataract surgery: results of 2 randomized controlled trials. Ophthalmology 2014; 121: 25-33
40 Elsawy MF, Badawi N, Khairy HA. Prophylactic postoperative ketorolac improves outcomes in diabetic patients assigned for cataract surgery. Clin Ophthalmol 2013; 7: 1245-1249
41 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87: 4-14
42 Pollreisz A, Schmidt-Erfurth U. Diabetic cataract-pathogenesis, epidemiology and treatment. J Ophthalmol 2010; 2010: 608751
43 Pollack A, Staurenghi G, Sager D, Mukesh B, Reiser H, Singh RP. Prospective randomised clinical trial to evaluate the safety and efficacy of nepafenac 0.1% treatment for the prevention of macular oedema associated with cataract surgery in patients with diabetic retinopathy. Br J Ophthalmol 2017; 101: 423-427

44 Singh RP, Lehmann R, Martel J, Jong K, Pollack A, Tsorbatzoglou A, Staurenghi 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

45 Singh RP, Staurenghi G, Pollack A, Adewale A, Walker TM, Sager D, Lehmann R. Efficacy of nepafenac ophthalmic suspension 0.1% in improving clinical outcomes following cataract surgery in patients with diabetes: an analysis of two randomized studies. Clin Ophthalmol 2017; 11: 1021-1029

46 Sarfraz MH, Haq RI, Mehboob MA. Effect of topical nepafenac in prevention of macular edema after cataract surgery in patients with non-proliferative diabetic retinopathy. Pak J Med Sci 2017; 33: 210-214

47 Entezari M, Ramezani A, Nikkhah H, Yaseri M. The effect of topical sodium diclofenac on macular thickness in diabetic eyes after phacoemulsification: a randomized controlled trial. Int Ophthalmol 2017; 37: 13-18

48 Chew EY, Glassman AR, Beck RW, Bressler NM, Fish GE, Ferris FL, Kinyoun JL, Diabetic Retinopathy Clinical Research N. Ocular side effects associated with peribulbar injections of triamcinolone acetonide for diabetic macular edema. Retina (Philadelphia, Pa) 2011; 31: 284-289

49 Lauer AK, Bressler NM, Edwards AR, Diabetic Retinopathy Clinical Research N. Frequency of intraocular pressure increase within days after intravitreal triamcinolone injections in the diabetic retinopathy clinical research network. Arch Ophthalmol 2011; 129: 1097-1099

50 Lim LL, Morrison JL, Constantinou M, Rogers S, Sandhu SS, Wickremasinghe SS, Kawasaki R, Al-Qureshi S. Diabetic Macular Edema at the time of Cataract Surgery trial: a prospective, randomized clinical trial of intravitreous bevacizumab versus triamcinolone in patients with diabetic macular oedema at the time of cataract surgery - preliminary 6 month results. Clin Exp Ophthalmol 2016; 44: 233-242

51 Sohn EH, Wang R, Read R, Roufas A, Teo L, Moorthy R, Albini T, Vasconcelos-Santos DV, Dustin LD, Zamir E, Chee SP, McCluskey P, Smith R, Rao N. Long-term, multicenter evaluation of subconjunctival injection of triamcinolone for non-necrotizing, noninfectious anterior scleritis. Ophthalmology 2011; 118: 1932-1937

52 Kim S, Kim MK, Wee WR. Additive Effect of Oral Steroid with Topical Nonsteroidal Anti-inflammatory Drug for Preventing Cystoid Macular Edema after Cataract Surgery in Patients with Epiretinal Membrane. Korean J Ophthalmol 2017; 31: 394-401

53 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

54 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

55 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 (Philadelphia, Pa) 2010; 30: 562-569

56 Xu X, Han Y, Kong L, Ding X, Liu F, Cheng L. Clinical implication of triamcinolone in aqueous humor after depository sub-Tenon application. J Cataract Refract Surg 2017; 43: 1383-1390

57 Diabetic Retinopathy Clinical Research Network Authors/Writing C, Baker CW, Almukhtar T, Bressler NM, Glassman AR, Grover S, Kim SJ, Murtha TJ, Rauser ME, Stockdale C. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. JAMA Ophthalmol 2013; 131: 870-879

58 Wielders LHP, Schouten J, Nuijts R. Prevention of macular edema after cataract surgery. Curr Opin Ophthalmol 2018; 29: 48-53

59 Cho HJ, Hwang HJ, Kim HS, Lee DW, Kim CG, Kim BY, Kim JW. Macular Edema after Cataract Surgery in Eyes with Preoperative Retinal Vein Occlusion. Retina (Philadelphia, Pa) 2017

60 Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg 2007; 33: 1550-1558

61 Okhravi N, Morris A, Kok HS, Menezo V, Dowler JG, Hykin PG, Lightman S. Intraoperative use of intravitreal triamcinolone in uveitic eyes having cataract surgery: pilot study. J Cataract Refract Surg 2007; 33: 1278-1283

62 Chiu H, Dang H, Cheung C, Khosla D, Arjmand P, Rabinovitch T, Derzko-Dzulynsky L. Ten-year retrospective review of outcomes following phacoemulsification with intraocular lens implantation in patients with pre-existing uveitis. Can J Ophthalmol 2017; 52: 175-180

63 Bertens CJF, Gijs M, Nuijts R, van den Biggelaar F. Topical drug delivery devices: A review. Exp Eye Res 2018

64 Eaton AM, Gordon GM, Konowal A, Allen A, Allen M, Sgarlata A, Gao G, Wafapoor H, Avery RL. A novel eye drop application monitor to assess patient compliance with a prescribed regimen: a pilot study. Eye (Lond) 2015; 29: 1383-1391

65 Semeraro F, Russo A, Gambicorti E, Duse S, Morescalchi F, Vezzoli S, Costagliola C. Efficacy and vitreous levels of topical NSAIDs. Expert Opin Drug Deliv 2015; 12: 1767-1782
66 Katsev DA, Katsev CC, Pinnow J, Lockhart CM. Intracameral ketorolac concentration at the beginning and end of cataract surgery following preoperative topical ketorolac administration. Clin Ophthalmol 2017; 11: 1897-1901
67 Rhee MK, Mah FS. Cataract Drug Delivery Systems (Dropless vs. Nondropless Cataract Surgery). Int Ophthalmol Clin 2016; 56: 117-136
68 Kim SY, Yang J, Lee YC, Park YH. Effect of a single intraoperative sub-Tenon injection of triamcinolone acetonide on the progression of diabetic retinopathy and visual outcomes after cataract surgery. J Cataract Refract Surg 2008; 34: 823-826
69 Negi AK, Browning AC, Vernon SA. Single perioperative triamcinolone injection versus standard postoperative steroid drops after uneventful phacoemulsification surgery: Randomized controlled trial. J Cataract Refract Surg 2006; 32: 468-474
70 Ersoy L, Caramoy A, Ristau T, Kirchhof B, Fauser S. Aqueous flare is increased in patients with clinically significant cystoid macular oedema after cataract surgery. Br J Ophthalmol 2013; 97: 862-865
71 Endophthalmitis Study Group ESoC, Refractive S. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. J Cataract Refract Surg 2007; 33: 978-988
72 Donnenfeld E, Holland E. Dexamethasone Intracameral Drug-Delivery Suspension for Inflammation Associated with Cataract Surgery: A Randomized, Placebo-Controlled, Phase III Trial. Ophthalmology 2018
73 Karalezli A, Borazan M, Akova YA. Intracameral triamcinolone acetonide to control postoperative inflammation following cataract surgery with phacoemulsification. Acta Ophthalmol 2008; 86: 183-187
74 Gills JP, Gills P. Effect of intracameral triamcinolone to control inflammation following cataract surgery. J Cataract Refract Surg 2005; 31: 1670-1671
75 Conway MD, Canakis C, Livir-Rallatos C, Peyman GA. Intravitreal triamcinolone acetonide for refractory chronic pseudophakic cystoid macular edema. J Cataract Refract Surg 2003; 29: 27-33
76 Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kamppeter BA. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology 2005; 112: 593-598
77 Stringham JD, Flynn HW, Jr., Schimel AM, Banta JT. Dropless Cataract Surgery: What Are the Potential Downsides? Am J Ophthalmol 2016; 164: viii-x
78 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
79 Kalina PH, Erie JC, Rosenbaum L. Biochemical quantification of triamcinolone in subconjunctival depots. Arch Ophthalmol 1995; 113: 867-869
80 Athanasiadis Y, Nithyanandrajah GA, Kumar B, Sharma A. Reversal of steroid induced raised intraocular pressure following removal of subconjunctival triamcinolone for cataract surgery. Cont Lens Anterior Eye 2009; 32: 143-144
81 Rabiah PK, Fiscella RG, Tessler HH. Intraocular penetration of periocular ketorolac and efficacy in experimental uveitis. Invest Ophthalmol Vis Sci 1996; 37: 613-618
82 Omidria. Assessment report. European Medicines Agency (EMA), 2015
83 Bucci FA, Jr., Michalek B, Fluet AT. Comparison of the frequency of use of a pupil expansion device with and without an intracameral phenylephrine and ketorolac injection 1%/0.3% at the time of routine cataract surgery. Clin Ophthalmol 2017; 11: 1039-1043
84 Donnenfeld ED, Whitaker JS, Jackson MA, Wittpenn J. Intracameral ketorolac and phenylephrine effect on intraoperative pupil diameter and postoperative pain in cataract surgery. J Cataract Refract Surg 2017; 43: 597-605
85 Hovanesian JA, Sheppard JD, Trattler WB, Gayton JL, Malhotra RP, Schaaf DT, Ng E, Dunn SH. Intracameral phenylephrine and ketorolac during cataract surgery to maintain intraoperative mydriasis and reduce postoperative ocular pain: Integrated results from 2 pivotal phase 3 studies. J Cataract Refract Surg 2015; 41: 2060-2068
86 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
87 Tsilimbaris MK, Tsika C, Kymionis GD. Intravitreal ketorolac for the treatment of chronic cystoid macular edema after cataract surgery. Ther Clin Risk Manag 2016; 12: 177-182

88 Maldonado RM, Vianna RN, Cardoso GP, de Magalhaes AV, Burnier MN, Jr. Intravitreal injection of commercially available ketorolac tromethamine in eyes with diabetic macular edema refractory to laser photocoagulation. Curr Eye Res 2011; 36: 768-773
89 Kim SJ, Doherty TJ, Cherney EF. Intravitreal ketorolac for chronic uveitis and macular edema: a pilot study. Arch Ophthalmol 2012; 130: 456-460
90 Seth A, Ghosh B, Raina UK, Gupta A, Arora S. Intravitreal Diclofenac in the Treatment of Macular Edema Due to Branch Retinal Vein Occlusion. Ophthalmic Surg Lasers Imaging Retina 2016; 47: 149-155
91 Soheilian M, Karimi S, Ramezani A, Peyman GA. Pilot study of intravitreal injection of diclofenac for treatment of macular edema of various etiologies. Retina (Philadelphia, Pa) 2010; 30: 509-515
92 Ramezani A, Fard Esmaeilpour N, Eskandari A, Rabbanikhah Z, Soheilian R, Soheilian M. Intravitreal diclofenac for refractory uveitic cystoid macular edema. J Ophthalmic Vis Res 2013; 8: 47-52
93 Elbendary AM, Shahin MM. Intravitreal diclofenac versus intravitreal triamcinolone acetonide in the treatment of diabetic macular edema. Retina (Philadelphia, Pa) 2011; 31: 2058-2064
94 Soheilian M, Karimi S, Ramezani A, Montahai T, Yaseri M, Soheilian R, Peyman GA. Intravitreal diclofenac versus intravitreal bevacizumab in naive diabetic macular edema: a randomized double-masked clinical trial. Int Ophthalmol 2015; 35: 421-428
95 Kim SJ, Adams NA, Toma HS, Belair ML, Thorne JE, Green WR, Jabs DA. Safety of intravitreal ketorolac and diclofenac: an electroretinographic and histopathologic study. Retina (Philadelphia, Pa) 2008; 28: 595-605
96 Blazaki S, Tsika C, Tzatzarakis M, Naoumidi E, Tsatsakis A, Tsatsanis C, Tsilimbaris MK. Pharmacokinetics and efficacy of intraocular flurbiprofen. Graefes Arch Clin Exp Ophthalmol 2017; 255: 2375-2380
97 Durairaj C, Kim SJ, Edelhauser HF, Shah JC, Kompella UB. Influence of dosage form on the intravitreal pharmacokinetics of diclofenac. Invest Ophthalmol Vis Sci 2009; 50: 4887-4897
98 Margalit E, Kugler LJ, Brumm MV, Meza JL, Kompella UB, Escobar ER, Christensen GR. The safety of intraocular ketorolac in rabbits. Invest Ophthalmol Vis Sci 2006; 47: 2093-2099
99 van der Reis MI, La Heij EC, De Jong-Hesse Y, Ringens PJ, Hendrikse F, Schouten JS. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. Retina (Philadelphia, Pa) 2011; 31: 1449-1469
100 Shelsta HN, Jampol LM. Pharmacologic therapy of pseudophakic cystoid macular edema: 2010 update. Retina (Philadelphia, Pa) 2011; 31: 4-12
101 Denniston AK, Chakravarthy U, Zhu H, Lee AY, Crabb DP, Tufail A, Bailey C, Akerele T, Al-Husainy S, Brand C, Downey L, Fitt A, Khan R, Kumar V, Lobo A, Mahmood S, Mandal K, McKibbin M, Menon G, Natha S, Ong JM, Tsaloumas MD, Varma A, Wilkinson E, Johnston RL, Egan CA, Group UDEU. The UK Diabetic Retinopathy Electronic Medical Record (UK DR EMR) Users Group, Report 2: real-world data for the impact of cataract surgery on diabetic macular oedema. Br J Ophthalmol 2017; 101: 1673-1678
102 Serra R, Sellam A, Coscas F, Bruyere E, Sieiro A, Coscas GJ, Souied EH. Evaluation of pseudophakic cystoid macular edema using optical coherence tomography angiography. Eur J Ophthalmol 2017: 0
103 Yuksel B, Uzunel UD, Kerci SG, Sagban L, Kusbeci T, Orsel T. Comparison of Subtenon Triamcinolone Acetonide Injection with Topical Nepafenac for the Treatment of Pseudophakic Cystoid Macular Edema. Ocul Immunol Inflamm 2017; 25: 513-519
104 Bradford JD, Wilkinson CP, Bradford RH, Jr. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. Retina 1988; 8: 161-164
105 Curkovic T, Vukojevic N, Bucan K. Treatment of pseudophakic cystoid macular oedema. Collegium Antropologicum 2005; 29: 103-105
106 Sacchi M, Villani E, Gilardoni F, Nucci P. Efficacy of intravitreal dexamethasone implant for prostaglandin-induced refractory pseudophakic cystoid macular edema: case report and review of the literature. Clin Ophthalmol 2014; 8: 1253-1257

Addendum

Summary

Cataract surgery is an effective intervention to restore visual function in many patients with cataract. Recent improvements in cataract surgery techniques have significantly contributed to optimization of postoperative visual rehabilitation. However, pseudophakic cystoid macular edema (PCME) still delays visual recovery in 1-4% of patients after regular uncomplicated surgery. As clarified in **chapter 2**, optimal prevention of PCME starts with a preoperative personalized risk assessment. The risk of developing cystoid macular edema (CME) after cataract surgery is influenced by many patient characteristics, notably diabetes mellitus (DM), which remains the most well-known. Other risk factors include previous retinal vein occlusion, epiretinal membrane, macular hole and uveitis.

Shortly after its first clinical description, ophthalmologists investigated the efficacy of anti-inflammatory agents to prevent the occurrence of PCME. Although topical anti-inflammatory drugs have been used for many years, remarkable differences are seen between clinical guidelines of leading authorities. **Chapter 3** aims to identify the optimal strategy to prevent the occurrence of CME within three months after uncomplicated cataract surgery in patients with and without DM. The results of a structured meta-analysis proved that combination treatment with a topical non-steroidal anti-inflammatory drug (NSAID) and a corticosteroid significantly reduce the odds of developing CME after cataract surgery, as compared to topical corticosteroids alone. Single drug treatment with a NSAID also reduced the odds of developing CME, as compared to single drug treatment with a corticosteroid.

From the results of this systematic review, it remained unclear whether the use of corticosteroid eye drops could be omitted. **Chapter 4** investigates this important clinical question. The PREvention of Macular EDema after cataract surgery (PREMED) study directly compared the efficacy of a topical NSAID, topical corticosteroid and the combination of both in 914 non-diabetic patients. Patients were randomized to receive topical bromfenac 0.09% twice daily for two weeks postoperatively, topical dexamethasone 0.1% four times daily for one week and one drop less per day every following week, or a combination of both. Anti-inflammatory treatment started two days before cataract surgery. The odds of developing clinically significant macular edema (CSME) were higher in patients treated with bromfenac eye drops (odds ratio 2.6) or dexamethasone eye drops (odds ratio 3.7), as compared to patients treated with a combination of both.

DM is a well-known risk factor for developing CME after cataract surgery. **Chapter 5** describes the efficacy of additional perioperative treatments to decrease the incidence of CME in diabetics undergoing regular cataract surgery. A total of 213 diabetic patients

received bromfenac 0.09% and dexamethasone 0.1% eye drops, and were randomly allocated to receive no additional treatment, a single subconjunctival injection with 40 mg triamcinolone acetonide (TA), a single intravitreal injection with 1.25 mg bevacizumab, or a combination of both. Subconjunctival TA prevented the occurrence of CME in all patients, while intravitreal bevacizumab had no significant effect on the incidence of CME or CSME. Nevertheless, the results of this study do not support subconjunctival injection of TA in all diabetic patients undergoing cataract surgery, given the low overall incidence of postoperative CME in this population of diabetics with a low prevalence of diabetic retinopathy, versus the higher incidence of increased intraocular pressure after subconjunctival TA injection.

Although acute PCME resolves spontaneously in the majority of cases, chronic CME may cause anatomic alterations and sustained visual impairment. This is the main reason for immediate attention and appropriate treatment in patients with CME after cataract surgery. Unfortunately, few studies have addressed this important research question. As detailed in **chapter 6**, topical NSAIDs have shown to improve visual acuity in patients with CME after cataract surgery, when compared to placebo. Small studies comparing the efficacy of topical NSAIDs versus topical corticosteroids, oral NSAIDs and oral acetazolamide, could not identify any statistically significant differences between treatment groups. Large randomized controlled trials are needed to provide evidence-based recommendations regarding the optimal treatment for PCME.

Samenvatting

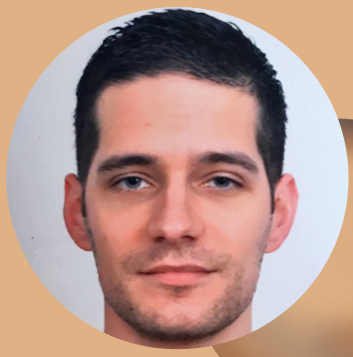
Wereldwijd is cataract is één van de meest voorkomende oorzaken van blindheid en slechtziendheid. Cataractchirurgie is een van de meest uitgevoerde operatieve ingrepen. Moderne chirurgische technieken hebben het aantal complicaties na cataractchirurgie weten terug te dringen en het postoperatieve herstel bespoedigd. Tocht wordt het visuele herstel bij 1-4% van de patiënten vertraagd door het ontstaan van pseudofaak cystoïde maculaoedeem (PCMO). **Hoofdstuk 2** beschrijft de wijze waarop het risico op PCMO kan worden beïnvloed. Patiënten met diabetes mellitus (DM) of status na eerdere retinale veneuze occlusie, een epiretinaal membraan, maculagat of uveitis hebben een verhoogd risico op het ontstaan van cystoïde maculaoedeem (CMO) na cataractchirurgie. Een gepersonaliseerde preoperatieve risicoschatting is daarom van essentieel belang.

Ontstekingsremmende oogdruppels, zoals corticosteroïden en niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's), worden al jaren gebruikt ter preventie van PCMO. Wegens een gebrek aan wetenschappelijke onderbouwing, ontstonden grote verschillen tussen de adviezen en richtlijnen van oogheelkundige instanties. Het systematische review uit **hoofdstuk 3** bundelt de resultaten van eerdere studies. Daaruit wordt geconcludeerd dat een combinatie van NSAID en corticosteroïd oogdruppels de kans op het ontstaan van CMO na cataractchirurgie vermindert, in vergelijking met behandeling met enkel corticosteroïd oogdruppels. Bovendien bleken NSAID's effectiever dan corticosteroïden.

Op basis van eerdere studieresultaten bleef echter onduidelijk of een combinatie van NSAID en corticosteroïd oogdruppels effectiever is dan monotherapie met enkel NSAID oogdruppels. De 'PREvention of cystoid Macular EDema after cataract surgery' (PREMED) studie (**hoofdstuk 4**) vergeleek de effectiviteit van een topicale NSAID, een topicale corticosteroïd en een combinatie van beide. In totaal werden 914 niet-diabeten gerandomiseerd over drie behandelgroepen. Patiënten werden behandeld met bromfenac 0,09% oogdruppels tweemaal daags gedurende twee weken postoperatief, dexamethason 0,1% oogdruppels viermaal daags gedurende één week postoperatief en vervolgens iedere week één druppel per dag minder, of een combinatie van beide druppels. In alle gevallen startte de behandeling twee dagen preoperatief. De resultaten van de PREMED studie toonden aan dat de kans op het ontwikkelen van klinisch significant CMO hoger was bij patiënten die werden behandeld met topicaal bromfenac (odds ratio 2,6) of dexamethason (odds ratio 3,7), ten opzichte van patiënten die werden behandeld met een combinatie van beide.

DM is één van de belangrijkste risicofactoren voor het ontwikkelen van CMO na cataractchirurgie. De PREMED studie onderzocht de effectiviteit van additionele perioperatieve behandelingen, als aanvulling op bromfenac en dexamethason oogdruppels, ter preventie van CMO bij 213 diabeten. Patiënten werden behandeld met een subconjunctivale injectie met 40 mg triamcinolon acetonide (TA), een intravitreale injectie met 1,25 mg bevacizumab, of een combinatie van beide. Daarnaast werd een kwart van de patiënten gerandomiseerd voor de controlegroep. Zoals beschreven in **hoofdstuk 5**, voorkwam een subconjunctivale injectie met TA het ontstaan van CMO bij alle patiënten. Bevacizumab had daarentegen geen effect op de incidentie van CMO na cataractchirurgie. Alhoewel een subconjunctivale injectie met 40 mg TA een effectieve behandeling bleek ter preventie van CMO, wordt deze behandeling niet geadviseerd als standaardmedicatie bij alle diabeten die een cataractoperatie ondergaan. Voor iedere patiënt dienen de voordelen van subconjunctivaal TA te worden afgewogen tegen de nadelen van deze behandeling, met name het risico op een verhoogde oogdruk.

Alhoewel PCMO in de meeste gevallen na enige tijd is geresorbeerd, kan chronisch CMO leiden tot blijvend visusverlies. Daarom dient CMO na cataractchirurgie tijdig opgespoord te worden en verdient het snelle en adequate behandeling. **Hoofdstuk 6** geeft een overzicht van de huidige behandelingsmogelijkheden. NSAID oogdruppels geven een aantoonbare visusverbetering bij patiënten met CMO na cataractchirurgie. Andere studies vergeleken de effectiviteit van NSAID oogdruppels met het effect van corticosteroïd oogdruppels, maar de onderzoeksgroepen waren te klein om significante verschillen tussen de behandelingen aan te tonen. Daarnaast werd het effect van orale NSAID's en oraal acetazolamide onderzocht, maar helaas hadden al deze studies onvoldoende grote onderzoekspopulaties om klinisch relevante effecten op te sporen.



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 oogheelkundig 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, Tsorbatzoglou A, Staurenghi 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 RMMA. 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. Dropless 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 PREMED 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.

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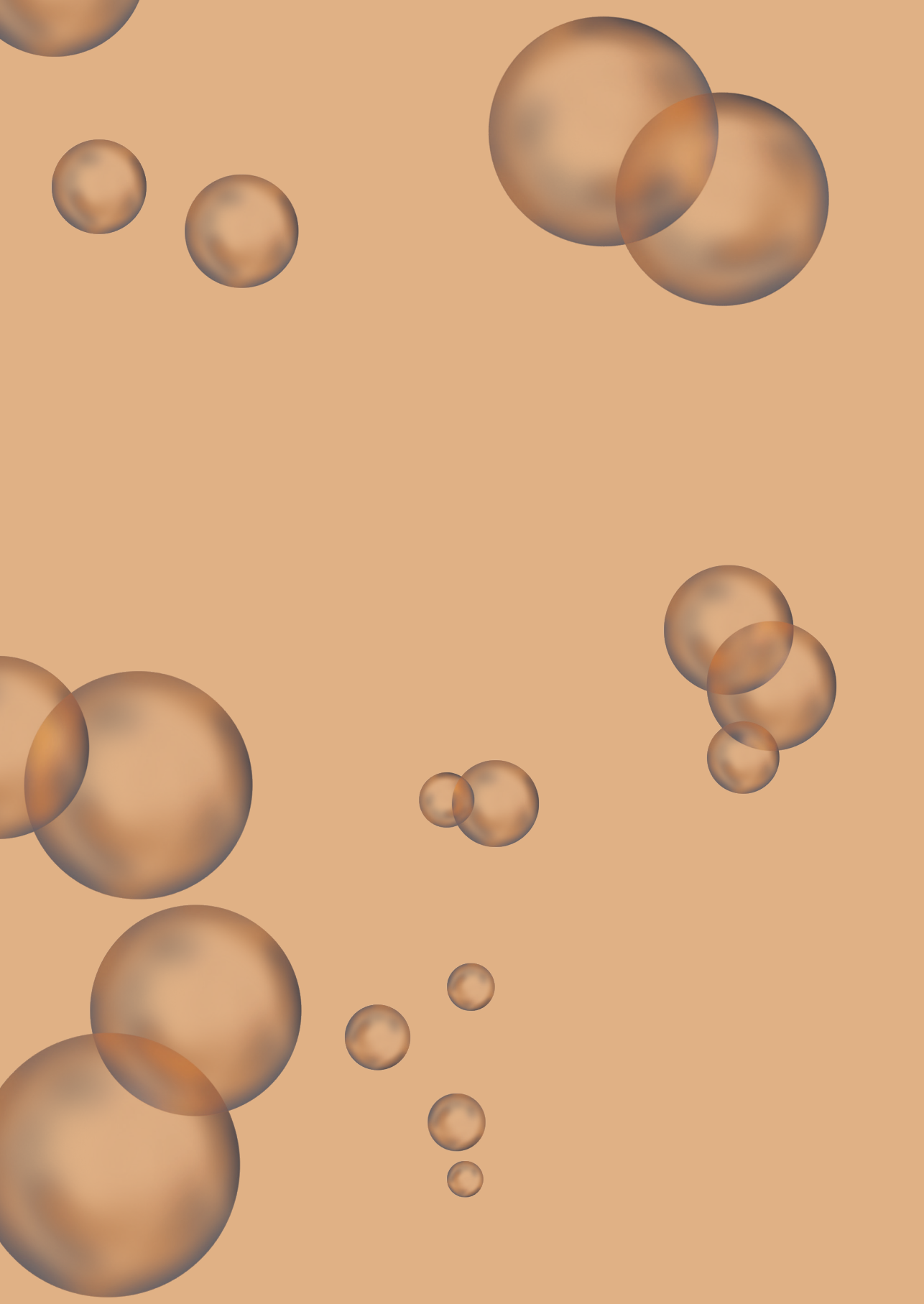

Curriculum vitae

Laura H.P. Wielders was born on December 16th 1986 in Heerlen, the Netherlands. She graduated from secondary school (Trevianum in Sittard) with honors in 2005 and started her medical study at Maastricht University the same year. She was a top 3% student at Maastricht University in 2009 and 2011. During her internships, she participated in a research project at the Academic Center for Epileptology Kempenhaeghe, under supervision of dr. Daniëlle Lambrechts and prof. Marian Majoie. She performed clinical work in the field of neurology for one additional year after graduation from medical study, but her heart was in ophthalmology. In August 2012, she started her PhD project under supervision of prof. Rudy Nuijts, dr. Jan Schouten and dr. Bjorn Winkens at the University Eye Clinic Maastricht UMC+. She coordinated the ESCRS PREvention of Macular EDema after cataract surgery (PREMED) study, and cooperated with thirteen study centers in Austria, Belgium, Germany, Hungary, the Netherlands, Portugal and Spain. She gave more than twenty lectures at various national and international meetings. From January 2016, she is a trainee in ophthalmology at the Maastricht University Medical Center+. Since 2017, she is the secretary of the Dutch national society for trainees in ophthalmology (LVAO).

List of publications

1. Lambrechts DA, **Wielders LHP**, Aldenkamp AP *et al.* The ketogenic diet as a treatment option in adults with chronic refractory epilepsy: efficacy and tolerability in clinical practice. Epilepsy Behav. 2012 Mar;23(3):310-4

2. Aerts AA, Jonker SM, **Wielders LHP** *et al.* Phakic intraocular lens: Two-year results and comparison of endothelial cell loss with iris-fixated intraocular lenses. J Cataract Refract Surg. 2015 Oct;41(10):2258-65.

3. **Wielders LHP**, Lambermont VA, Schouten JSAG *et al.* Prevention of Cystoid Macular Edema After Cataract Surgery in Nondiabetic and Diabetic Patients: A Systematic Review and Meta-analysis. Am J Ophthalmol. 2015 Nov;160(5):968-981

4. **Wielders LHP**, Lambermont VA, Schouten JSAG *et al.* Reply to Kim et al. Am J Ophthalmol. 2016 Jan;161:222-3

5. **Wielders LHP**, Schouten JSAG, Aberle MR *et al.* Treatment of cystoid macular edema after cataract surgery. J Cataract Refract Surg. 2017 Feb;43(2):276-284

6. **Wielders LHP**, Schouten JSAG, Nuijts RMMA. Prevention of macular edema after cataract surgery. Curr Opin Ophthalmol. 2018 Jan;29(1):48-53

7. **Wielders LHP**, Schouten JSAG, Winkens B *et al.* A randomized controlled European multicenter trial on the prevention of cystoid macular edema after cataract surgery in non-diabetics: ESCRS PREMED study report 1. J Cataract Refract Surg. 2018 Apr; 44:429–439

8. **Wielders LHP**, Schouten JSAG, Winkens B *et al.* A randomized controlled European multicenter trial on the prevention of cystoid macular edema after cataract surgery in diabetics: ESCRS PREMED study report 2. Accepted for publication in J Cataract Refract Surg. May 2018