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*Source / Izvornik:* **Medicina Fluminensis, 2019, 55, 142 - 147**

**Journal article, Published version**

**Rad u časopisu, Objavljena verzija rada (izdavačev PDF)**

*Permanent link / Trajna poveznica:* <https://um.nsk.hr/um:nbn:hr:184:522030>

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*Download date / Datum preuzimanja:* **2024-12-25**



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# Nonsteroidal antiinflammatory drugs and treatment of cystoid macular edema

## Nesteroidni protuupalni lijekovi u liječenju cistoidnog makularnog edema

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**Abstract:** Nonsteroidal antiinflammatory drugs (NSAIDs) have become a significant therapeutic adjunctive tool in the routine and complicated intraocular surgery. Topical NSAIDs prevent intraoperative miosis, reduce pain, postoperative inflammation and incidence of cystoid macular edema (CME). Although there is no established protocol for prophylaxis of pseudophakic CME, due to the relationship between proinflammatory prostaglandins and CME, using corticosteroids and NSAIDs could prevent CME. NSAIDs have a synergistic antiinflammatory effect with steroids, but can also be used alone when corticosteroid therapy could be harmful. Prospective clinical trials need to define treatment protocol for topical NSAIDs use, due to their powerful influence to prevent perioperative complications.

**Key words:** cataract; cyclooxygenase inhibitors; macular edema; prostaglandins

**Sažetak:** Nesteroidni protuupalni lijekovi (NSAID, engl. *nonsteroidal antiinflammatory drugs*) postali su značajna dodatna terapija u rutinskim i kompliciranim intraokularnim operacijama. Topički NSAID-i sprječavaju intraoperativnu miozu, smanjuju bol, postoperativnu upalu i učestalost cistoidnog makularnog edema (CME). Iako nema uspostavljenog protokola za profilaksu pseudofakičnog CME-a, zbog veze između proupalnih prostaglandina i CME-a primjena topičkih kortikosteroida i topičkih NSAID-a može spriječiti CME. NSAID-i imaju sinergistički protuupalni učinak sa steroidima, ali se mogu upotrijebiti i sami kada bi kortikosteroidna terapija mogla biti rizična. Zbog njihovog snažnog utjecaja na prevenciju perioperativnih komplikacija potrebna su prospektivna klinička istraživanja za definiranje protokola terapijske primjene topičkih NSAID-a.

**Ključne riječi:** inhibitori ciklooksigenaze; katarakta; makularni edem; prostaglandini

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## INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) have become an significant therapeutic adjunctive tool in routine and complicated intraocular surgery. Topical NSAIDs reduce pain, prevent intraoperative miosis, decrease postoperative inflammation and reduce the incidence of cystoid macular edema (CME)<sup>1</sup>. Although prevention of CME with the use of topical NSAIDs is controversial, their prevalent use following cataract surgery is caused with prophylactic measures to reduce the incidence of pseudophakic CME (PCME) which can cause decreased visual acuity following an uneventful cataract surgery. Topical NSAIDs have a synergistic antiinflammatory effect with steroids, but can also be used alone when corticosteroid therapy could be harmful. Prophylactic use of NSAIDs is cost effective and less harmful compared to burden of developed CME treatment as periocular or intravitreal injections. Prospective clinical trials are needed to define treatment protocol for topical NSAIDs use, due to their powerful influence to prevent perioperative complications. Because of wide disparity of opinion about the most effective antiinflammatory drops for the prevention of CME, it is necessary to select and treat high risk eyes for CME<sup>2</sup>.

According to a survey in 2012 by the American Society of Cataract and Refractive Surgery, 90% of members routinely prescribes a NSAID in addition to, but not as a replacement for a corticosteroid therapy after cataract surgery<sup>3</sup>.

## CYSTOID MACULAR EDEMA (CME)

Cystoid macular edema, also known as Irvine-Gass syndrome, is a complication of cataract surgery with multifactorial pathogenesis that occurs secondary to breakdown of the blood–aqueous and blood–retinal barrier and cystic accumulation of extracellular intraretinal fluid with subsequent decreased and distorted central vision<sup>1,4,5</sup>. During the intraocular surgery, inflammatory mediators diffuse from lens epithelial cells and uveal tissue in the anterior and posterior segment and cause inflammatory response with vasodilatation and fluid accumulation in the inner nuclear and outer plexiform layers of the retina<sup>4,5</sup>. CME usually occurs at approximately 5 (4–12) weeks after

surgery in a healthy population. Macular edema (ME) is often self-limiting with spontaneous resolution within 3–12 months, but a small proportion of people with chronic persistent macular edema and formation of cystic spaces may be difficult to treat.

In patients with diabetes, it is sometimes difficult but crucial to differentiate diabetic macular edema (DME) from postsurgical CME. Munk et al described optical coherence tomography (OCT) criteria to differentiate PCME from DME<sup>5,6</sup>.

Combination of topical nonsteroidal antiinflammatory drugs (NSAIDs) and steroids appears to be effective than either agent alone in the treatment of cystoid macular edema (CME). NSAIDs and steroids have a synergistic effect but topical NSAIDs can be used as individual therapy in high-risk eyes in which steroids can be harmful.

## RISK FACTORS FOR CME

Incidence of visually significant PCME varies from 0,1% to 3,5%<sup>1</sup>. Subclinical pseudophakic CME is detected in almost 30% of patients with fluorescein angiography and 11%–41% with OCT<sup>7</sup>. Clinical CME that persists for more than 6 months is considered chronic, with incidence 9,4%–12,8% of CME cases<sup>8</sup>.

Risk factors increase the incidence of CME: post-surgical CME in the contralateral eye, African-American origin, diabetes mellitus (DM), uveitis, retinal vein occlusion, retinal degeneration, macular degeneration, radiation retinopathy, epiretinal membranes, choroidal tumors, prostaglandin analog use, age<sup>4,5,9</sup>. The incidence may be 20% in surgery complicated with retained lens material, posterior capsule rupture, vitreous loss and vitreomacular traction, excessive intraoperative manipulations, the presence of an anterior chamber intraocular lens<sup>5</sup>.

CME is more common in diabetic patients, especially those with preexisting retinopathies<sup>10</sup>. The rate of development of macular edema in diabetic population (with or without diabetic retinopathy) varies from 31% to 81% after cataract surgery<sup>5</sup>.

Chen et al reported the incidence of ME after cataract surgery as 22,8% in patients with diabetic retinopathy (DR) related to increased level of inflammatory mediators in the vitreous and aqueous humor causing subclinical intraocular inflammation, which may worsen macular edema after cataract surgery<sup>8,9</sup>.

#### NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

The use of NSAIDs to treat CME has a long history back to the 1980s, with reviews of the treatment of aphakic or pseudophakic CME<sup>1</sup>. Nonsteroidal antiinflammatory drugs block the conversion of arachidonic acid by COX-1 (cyclooxygenase-1) and COX-2 (cyclooxygenase-2) enzymes into prostaglandin intermediates<sup>1</sup>. Prostaglandins play a key role in the manifestation of ocular inflammation: contribute to leukocyte migration, cause vasculature dilation and hyperpermeability, increase proteins in the aqueous humor, cause erythema and hyperemia<sup>11</sup>. Prostaglandins also modulate iris smooth-muscle contraction, thus NSAIDs play a role in preventing miosis during surgery<sup>5</sup>.

Nonsteroidal antiinflammatory drugs can be administered systemically, topically or intracamerally. Topically applied NSAIDs are commonly used to manage both anterior and posterior ocular segment inflammation<sup>1,12</sup>. The ocular penetration and efficacy of systemic NSAIDs is questionable compared to topical. Intracameral formulation for cataract surgery to potentially increase mydriasis and reduce pain is available (phenylephrine 1,0% and ketorolac 0,3% injectable solution, Omidria<sup>®</sup>)<sup>1</sup>. This review refers to topical NSAIDs in CME treatment as most common method of application.

Currently available topical ophthalmic NSAIDs are: Bromfenac (Bromday<sup>®</sup> 0,09% Bausch & Lomb; Pro-lensa<sup>®</sup> 0,07% Bausch & Lomb; Xibrom<sup>®</sup> 0,09% ISTA; Yellox<sup>®</sup> 0,9% Croma/Bausch & Lomb); Indomethacin (Indocollyre<sup>®</sup> 0,1% Bausch & Lomb), Diclofenac (Voltaren<sup>®</sup> 0,1% Alcon, Naclof 0,1% Alcon), Flurbiprofen (Ocufer<sup>®</sup> 0,03% Allergan), Ketorolac tromethamine (Ketorolac<sup>®</sup> 0,4%, 0,5% Generic; Acular<sup>®</sup> 0,5% Allergan; Acular<sup>®</sup> LS 0,4% Allergan, Acuvail<sup>®</sup> PF 0,15% Allergan), Nepafenac

(Nevanac<sup>®</sup> 0,1% Alcon/Novartis; Ilevro<sup>®</sup> 0,3% Alcon/Novartis)<sup>1</sup>.

NSAIDs available in Europe are Yellox<sup>®</sup> (bromfenac), Naclof<sup>®</sup> (diclofenac), Indocollyre<sup>®</sup> (indomethacin), Voltaren<sup>®</sup> (diclofenac), Ocufer<sup>®</sup> (flurbiprofen), Ketorolac<sup>®</sup> 0,4%/0,5% (ketorolac tromethamine), Nevanac<sup>®</sup> (nepafenac)<sup>1</sup>. All of mentioned NSAIDs have therapeutic indication for treatment of postoperative inflammation and reduction of pain after cataract surgery, except Ocufer<sup>®</sup> (flurbiprofen) which is used 2 hours before surgery for intraoperative mydriasis<sup>1</sup>. Ketorolac is the only topical NSAID available in a preservative-free formulation (Acuvail<sup>®</sup>, 0,45%)<sup>1</sup>. NSAIDs are used for 4 to 6 weeks postoperatively and treatment can be prolonged for up to 12 weeks in potentially high-risk patients. The newer NSAIDs have been reformulated to increase their potency in less frequent dosing with effect on anterior segment inflammation and postoperative pain<sup>1</sup>.

Nonsteroidal antiinflammatory drugs are not approved by Food and Drug Administration (FDA) for the prevention or treatment of pseudophakic CME and are used off-label. They are also used off-label in treatment of CME caused by other eye pathology: diabetic retinopathy, small CME caused by retinal vein occlusion or uveitis.

#### PROPHYLACTIC USE OF TOPICAL NSAIDS

In this review, current literature available to May 2018 is analyzed to answer is the prophylactic use of topical NSAIDs, either in addition to topical steroids or as individual use, reducing the incidence of macular edema and associated visual function pathology? Is the combination of NSAIDs and corticosteroids more effective than the use of NSAIDs alone?

Several trials about PCME following cataract surgery showed positive effect of NSAIDs on postoperative ME. The topical use of 0,1% diclofenac in patients with DR, 4 times a day for 7 days before cataract surgery and for 30 days, resulted in significantly lower intraocular levels of interleukin-12 (IL-12) and a lower increase in central foveal thickness (CFT) compared to standard postoperative therapy with 0,1% topical dexamethasone 4 times a day for 30 days<sup>9</sup>. In report by

the American Academy of Ophthalmology, NSAID therapy was found effective in reducing PCME and increasing the speed of visual recovery after surgery when compared directly with placebo or topical corticosteroid formulations with limited intraocular penetration. However, efficacy of NSAID use on long-term visual outcomes was unclear<sup>5,13</sup>. Shields et al reported significant reductions in the incidence of clinical PCME with prophylactic use of topical NSAIDs, ketorolac 0,4% or nepafenac 0,1%, adjunctive to topical steroids<sup>14</sup>. McCafferty et al. reported CME incidence 19,5% in eyes with contralateral PCME and 13,1% in DR and found that topical nepafenac 0,3% reduces PCME in patients with preoperative risk factors compared to placebo but shows no benefit in patients without risk factors<sup>4</sup>. Kessel et al. reviewed 6 randomized clinical trials and found that the incidence of postoperative CME was higher at 1 month in the steroid-only patients (25,3%) versus the NSAID-only patients (3,8%)<sup>15</sup>. In study that retrospectively reviewed more than 16 000 phacoemulsification surgeries defined clinical postoperative macular edema as a visual acuity of 20/40 or worse with positive OCT for CME<sup>16</sup>. Compared with eyes that received prophylaxis with topical prednisolone alone, the eyes that were additionally treated with postoperative NSAIDs had a 55% reduction of macular edema<sup>16</sup>.

In their metaanalysis, Wienders et al. suggested that a topical NSAID should always be part of the preventive treatment after surgery in nondiabetic patients, but whether the use of corticosteroid eyedrops can be avoided cannot be concluded from the results<sup>17</sup>.

Bromfenac 0,09%, has good ocular penetration with insignificant systemic reactions following topical administration. Bromfenac has been found to be more potent as a COX-2 inhibitor than diclofenac and ketorolac<sup>7</sup>. Studies have shown that nepafenac may be more potent than ketorolac or diclofenac. Nepafenac seems superior to other NSAIDs in terms of ocular penetration allowing higher and sustained therapeutic levels in retina and choroid<sup>5</sup>.

Rho in his prospective study compared diclofenac 0,1% and ketorolac 0,5% in 34 patients with CME, which developed after uncomplicated cataract surgery. After 3 months, both treatment meth-

ods resulted in a significant reduction in CME and significant improvement in visual acuity<sup>18</sup>.

Studies comparing bromfenac with other NSAIDs observed no significant differences in the CME rates between bromfenac and nepafenac when given alone or in combination with corticosteroid<sup>7,19</sup>.

Warren et al. compared four topical NSAIDs (bromfenac 0,09% 2 times/day, diclofenac 0,1% 3 times/day, ketorolac 0,4% 3 times/day, nepafenac 0,1% 3 times/day) in patients with chronic pseudophakic CME. At 16 weeks, reductions in mean retinal thickness were significantly greater for bromfenac (36%,  $P=0,011$ ) and nepafenac (49%,  $P=0,004$ ), but not for diclofenac and ketorolac compared with placebo (14%). Visual acuity improved significantly only in the nepafenac group<sup>20</sup>.

#### PROPHYLAXIS OF CYSTOID MACULAR EDEMA

The prevention of Irvine–Gass syndrome is challenge because it also affects healthy individuals after uneventful phacoemulsification. Some studies affirm negligible benefit with NSAIDs use after uncomplicated cataract surgery in patients without risk factors, but others support their use as acute CME prophylaxis in uncomplicated cases<sup>5</sup>. In low risk patients, the routine use of preoperative nepafenac was suggested necessary only to achieve a faster visual recovery<sup>5,21</sup>. Prophylactic topical NSAIDs therapy should be considered in high risk patients, like diabetic patients especially those with DR. It seems logical to prevent acute PCME rather than treat it, since treatment of chronic CME usually involves more invasive methods, like intravitreal anti-vascular endothelial growth factor injections, subtenon triamcinolone or intravitreal dexamethasone implant injections. Boscia et al suggested that all diabetic patients undergoing cataract surgery should be treated with topical NSAIDs to prevent acute PCME<sup>22</sup>.

#### UNIVERSAL AND SELECTIVE NSAIDS THERAPY

Combination of topical NSAIDs and steroids appears to be more effective than either agent alone in the treatment of acute CME. NSAIDs and steroids have a synergistic effect on CME prevention but NSAIDs can be used as individual therapy in high-risk eyes in which topical steroids can be

potentially harmful. Monotherapy with NSAIDs may be useful in patients at risk for adverse events from topical steroids: glaucoma steroid responders, diabetics sensitive to systemic absorption, recurrent herpetic keratitis and delayed wound healing cases. Warren et al affirm that effectiveness of topical bromfenac was as effective as the topical steroid (prednisolone acetate) in controlling postoperative inflammation in routine cataract surgery<sup>23</sup>.

There are 2 basic equally valuable approaches to the topical nonsteroidal antiinflammatory drugs (NSAIDs) use in patients undergoing cataract surgery. The universal approach uses topical NSAIDs in combination with topical steroids in all patients. The selective method uses topical NSAIDs for high-risk cases only.

There are 2 basic equally valuable approaches to the topical NSAIDs use in patients undergoing cataract surgery. The universal approach uses topical NSAIDs in combination with topical steroids in all patients. The selective method uses topical NSAIDs for high-risk cases only. The selective cost effective method is designed for low-risk eyes to prevent potential NSAID side effects in eyes<sup>1</sup>.

Kim et al. in their study suggest that there is no greater therapeutic effect of an NSAID on reducing CME if compared with equivalent dosing of a corticosteroid with adequate intraocular penetration<sup>13</sup>. Donnenfeld et al concluded that NSAIDs preoperative use for up to 3 days before cataract surgery accelerate visual recovery in the immediate period after surgery<sup>24</sup>. These results are consistent with other published reports that demonstrate a short-term therapeutic visual function benefit of an NSAID use before surgery, but there is no evidence that this practice affects prevents vision loss from CME at 3 months or more after cataract surgery<sup>13</sup>. Lim et al in their review from 2016 wanted to answer is there evidence for postoperative prophylactic use of topical NSAIDs either in addition to topical steroids or as monotherapy. They identified 34 studies over 5000 people with follow up from 1 to 12 months, with variety of NSAIDs used: ketorolac, diclofenac, nepafenac, indomethacin, bromfenac, flurbiprofen and pranopfen. They con-

cluded that using topical NSAIDs may reduce the risk of developing ME after cataract surgery, but current CME reduction statistics could possibly be 'exaggerated'. Also it is unclear the extent to which NSAID use and reduction in CME incidence has an impact on the visual function and quality of life of patients<sup>25</sup>.

#### SIDE EFFECTS OF NSAID THERAPY

Systemic absorption of most topical NSAIDs is minimal<sup>13</sup>. There are many reports of NSAIDs worsening asthma, but in preexisting asthmatics<sup>1</sup>. Burning, stinging, conjunctival injection, and contact dermatitis are the most commonly reported adverse side effects of NSAIDs<sup>1</sup>. There are reports of superficial punctate keratitis, subepithelial and stromal infiltrates and epithelial defects. Comparative study of over 4500 eyes that received diclofenac, flurbiprofen or ketorolac revealed no corneal melts or other significant corneal events, just 1 case of temporary mild corneal thinning in an eye treated with prednisolone alone in a patient with rheumatoid arthritis<sup>26</sup>. Special care during NSAID therapy and additional monitoring are mandatory in corneal denervation, corneal epithelial defects, rheumatoid arthritis, rosacea, keratitis sicca<sup>1</sup>.

#### DISCUSSION AND CONCLUSION

This controversy in topical NSAID and/or corticosteroid therapy for acute CME led to a first international multicenter randomized controlled clinical study organized by European Society of Cataract & Refractive Surgeons (ESCRS): the PREvention of Macular EDema after cataract surgery (PREMED) study. The PREMED study was designed to answer questions relating prevention of acute CME after cataract surgery in diabetic patients and nondiabetic patients. The patients were randomized to receive topical bromfenac 0,09% twice daily for 2 weeks, dexamethasone 0,1% 4 times daily and then decreasing to 1 drop less per day for the following week, or a combination of both drugs. The patients were then analyzed 6 and 12 weeks postoperatively. The final conclusion was that 'patients treated with a combination of topical bromfenac 0,09% and dexamethasone 0,1% had a lower risk for developing

CME after cataract surgery than patients treated with a single drug<sup>27</sup>.

Prospective studies in this therapeutic area are needed to define optimal protocol for topical NSAID prophylaxis and treatment of acute CME following cataract surgery. Also standardization of acute CME definitions with clinically relevant measures of visual function must be determined.

**Conflicts of interest declaration:** The authors report no conflicts of interest.

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