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The role of perioperative nonsteroidal anti-inflammatory drugs use in cataract surgery

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Abstract
Purpose of review: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used and studied by cataract surgeons for varied benefits in the perioperative period. In this article, we perform a literature review of articles published between 1 January 2016 and 30 June 2018 concerning perioperative NSAID use for patients undergoing cataract surgery.
Recent findings: Literature review revealed five areas of recent study including preoperative NSAID use for iatrogenic inflammation, intraoperative NSAID use for pupillary mydriasis, postoperative NSAID use for prevention of cystoid macular edema (CME), for prevention of pain/inflammation, and for improvement in patient quality of life.
Summary: Recent literature establishes the efficacy of a newly available intracameral phenylephrine–NSAID combination for pupillary mydriasis, postoperative NSAID use for preventing CME in certain high-risk populations, and postoperative NSAIDs for controlling pain and inflammation. However, further high-quality studies are required to determine the long-term effects of perioperative NSAIDs on visual acuity and CME rates.

Keywords: Intraoperative mydriasis, nonsteroidal anti-inflammatory drug, postoperative cystoid macular edema

Introduction
Nonsteroidal anti-inflammatory drugs (NSAIDs), a class of medications that inhibit cyclooxygenase (COX) enzymes from producing pro-inflammatory prostaglandins, have multiple indications in the perioperative period including pain control, reducing inflammation, improving intraocular mydriasis, and preventing postoperative cystoid macular edema (CME). Although the potential benefits of NSAIDs in the perioperative period have been known for years, optimal NSAID medication and dosing regimens have yet to be established. This article reviews the literature concerning perioperative NSAID use between 1 January 2016 and 30 June 2018.

Preoperative Nonsteroidal Anti-inflammatory Drug Use
Many cataract surgeons begin NSAID medications for their patients preoperatively to reduce intraoperative prostaglandin release and blunt postoperative inflammation. In 2017, Katsev *et al*. Obtained serial 100 ml samples of aqueous humor in 12 patients undergoing cataract surgery. Samples were obtained from patients who had received topical ketorolac 3 times over 24h prior to surgery and were collected both after initial paracentesis, and prior to corneal wound hydration. Ketorolac concentrations were significantly reduced at the end of surgery compared with the beginning of surgery with 66.7% of patients having undetectable levels at the end. Although the possible depot effect of preoperative ketorolac dosing in the vitreous cavity remains unclear, the authors noted that ketorolac's short half-life of 2.3h and the removal of free drug by intraoperative irrigation likely renders the postoperative anti-inflammatory effects of preoperative ketorolac minimal. Therefore, they advocated for intraoperative ketorolac use. They also studied interleukin 12 (IL-12) concentration in the aqueous humor of 27 patients with diabetic retinopathy taking diclofenac 0.1% four times daily for 7 days prior to cataract surgery to 30 days following surgery compared with 28 patients who did not receive any perioperative NSAIDs. Samples taken after initial paracentesis found IL-12 concentrations were significantly reduced in the diclofenac group compared with control. Following surgery, patients in the diclofenac group had significantly lower central macular thickness (CMT) measurements by spectral OCT. However, there was no difference in incidence of CME evident on OCT imaging between groups.

Intraoperative Nonsteroidal anti-inflammatory drug use for pupillary Mydriasis

Intraoperative miosis because of prostaglandin release from surgical insult can reduce a surgeon's visualization and lead to intraoperative complications. Omidira, a 1%/0.3% phenylephrine/ketorolac intraoperative injection added to irrigating fluid during cataract surgery was Food and Drug Administration (FDA)-approved in 2014 for prevention of intraoperative miosis and reduction of postoperative pain. demonstrated a significant decline in the use of pupil-expanding Malyugin Rings during uncomplicated phacoemulsification surgery with Omidira compared with balanced salt solution (BSS; 2.95 versus 7.87%; *P*<0.001). Further sub-analysis of patients predisposed to intraocular floppy iris syndrome (IFIS) because of a history of alpha 1 blocker use demonstrated significantly fewer patients required Malyugin Ring use in the Omidria cohort compared with BSS (12.74 versus 24.5%, P¼0.05). Compared Omidria (483 mmol/l phenylephrine and 89 mmol/l ketorolac in 500 ml BSS) to ketorolac (89 mmol/l ketorolac in 500ml BSS), phenylephrine (483 mmol/l phenylephrine in 500ml BSS) and BSS alone on pupil diameter and ocular pain. Intraoperative pupillary mydriasis was significantly larger in the Omidria cohort compared with ketorolac (least mean square difference 0.7þ/ _0.1mm; *P*<0.0001) and BSS (least square mean difference 0.9þ/_0.1mm; *P*<0.0001) whereas intraocular pain was significantly reduced for the Omidria cohort compared with phenylephrine (5.9þ/_2.2; P¼0.009) and BSS (4.6þ/_2.2; P¼0.042) based on the visual analogue scale (VAS). Finally, significantly fewer patients treated with the study drug (6.1%) had an intraoperative pupil diameter smaller than 6.0mm at any point during surgery compared with phenylephrine (22.4%, P¼0.0216), ketorolac (34.6%; P¼0.0004) or BSS (47.2%, *P*<0.0001). The authors conclude Omidria is a well-tolerated and efficacious combination medication that shows superiority to either of its components alone for mydriasis.

Key Points

However, there is conflicting data concerning benefits of NSAID use for patients with baseline diabetic retinopathy. Postoperative NSAIDs may play a role in reducing postoperative Intraoperative irrigation reduces preoperation administered NSAID concentrations to undetectable levels at the conclusion of surgery in a majority of patients. For low-risk patients, postoperative topical NSAIDs do not significantly improve postoperative BCVA, reduce rates of CME, or improve patient-rated quality of vision compared with placebo. NSAIDs significantly reduce incidence of CME, improve BCVA, and reduce CMT thickening in diabetic patients without retinopathy. 1% phenylephrine // 0.3% ketorolac injection added to irrigating solution during cataract surgery significantly reduced the use of iris expansion devices in all patients and patients at high risk of IFIS. The combination of 1% / 0.3% phenylephrine/ketorolac was better at papillary mydriasis than either of its components alone in inflammation. However, data remains inconclusive about the optimal dosing regimen and concurrent use of topical steroids.

Postoperative Nonsteroidal anti-inflammatory drug use for prevention of cystoid macular edema in low-risk patients

Cataract surgeons often use NSAIDs postoperatively to control patient pain, inflammation, and prevent CME, the most prevalent complication affecting postop visual recovery. Large retrospective chart reviews performed in 2016 calculated the incidence of clinical postoperative CME between 1.17 and 2.54% in patients with low risk for CME development. They estimated for patients who develop CME, postoperative costs can nearly double with average ophthalmic charges of $10410 for CME patients compared with $5950 for those without CME. The American Academy of Ophthalmology's preferred Practice Patterns for Adult Cataract Surgery from 2016 states, 'There is evidence that NSAIDs, alone or in combination with topical corticosteroids, decrease the likelihood of postoperative CME.' Although some studies have shown benefit for early visual recovery, none have provided convincing Level I evidence. To date, no high-quality meta-analyses, systemic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias have demonstrated a long-term benefit (i.e. 3 months or longer). A Cochrane review by Lim *et al*. including 34 RCTs published prior to 2016 noted superior BCVA and lower incidence of CME in patients receiving NSAID/steroid combination compared with steroid alone. However, authors deemed this very low certainty evidence as only two cases of CME were reported in the steroid-alone group. Additionally, there were no RCTs published comparing BCVA or CME rates for patients taking NSAIDs alone versus steroids alone at POM 12 visit. In our literature review, no study published between 2016 and 2018 followed low-risk patients beyond 3 months postoperation, and therefore, the long-term benefits of postoperative NSAIDs on visual acuity cannot be commented. On compared central macular thickness (CMT) measurements by Cirrus HD-OCT between 38 patients taking ketorolac 0.45% twice daily and 38 patients taking diclofenac 0.1% four times daily starting 1 day prior to surgery until postoperation week 4 (POW 4). All patients were at low risk for CME development and had uncomplicated cataract surgery with no concurrent use of topical steroid during the study period. CMT measurements of the ketorolac cohort had lower average macular thickness than diclofenac cohort at POM 1 (8.87þ/_9.66 versus 16.36þ/_16.83 mm; P¼0.02) and POM 2 (4.02þ/_10.54 versus 11.92þ/_11.12 mm; *P*<0.01). However, no significant differences in BCVA were noted between treatment groups (POM 1, P¼0.78 and POM 2, P¼0.54). The authors concluded that ketorolac, a COX-1 and COX-2 inhibitor, controlled postoperative inflammation better than diclofenac, a selective COX-2 inhibitor. Additionally, ketorolac's less frequent dosing at twice daily likely improves patient compliance compared with diclofenac's dosing at four times daily. A randomized control trial performed by Stock *et al*. demonstrated no significant differences in Stratus III OCT postoperative CMT values or BCVA at postoperative day (POD) 1, POD 7, and POD 45 when comparing 21 eyes using nepafenac 0.3% daily, 32 eyes using ketorolac 0.5% three times daily, and 24 eyes

using propylene glycol three times daily. Study medications were started 2 days reoperation until POD 45, no concurrent steroids were used in the study period and only low-risk patients were included. The authors concluded that all patients tolerated NSAIDs well in the study period. However, because of small sample sizes, no conclusions could be drawn about which regimen was best for preventing postoperative CME. A meta-analysis published in 2017, corroborated these results finding no significant difference in BCVA at POD 1 [weighted mean difference (WMD) 0.084; P¼0.808], POW 1 (WMD _0.008; P¼0.154) and POM 1 (WMD 0.001; P¼0.179) for 262 patients taking Nepafenac and 274 patients taking ketorolac among five randomized control trials. Similarly, no significant differences were found in CMT at POW 1 (WMD _1.455; P¼0.577) and POM 1 (WMD _2.199; P¼0.771) for 141 patients taking Nepafenac and 145 patients taking Ketorolac in two randomized control trials. Of note, medication strength, dosing regimen, and concurrent use of topical steroids was not standardized among studies. Finally, a randomized control trial performed by Palacio *et al*. compared CMT measurements between 69 patients taking bromfenac 0.09% three times daily and 70 patients taking nepafenac 0.1% three times daily. Study medications were started 5h before surgery and continued until POM 1 visit, with no concurrent topical steroid use and only patients at low risk of CME development were included. Patients in the bromfenac cohort had significantly less CMT thickening.

Postoperative Nonsteroidal Anti-inflammatory Drug Use For The Prevention Of Cystoid Macular Edema In High-Risk Patients

Risk factors for the development of postoperative CME include contralateral CME, posterior capsule rupture, epi-retinal membrane (ERM), macular holes, uveitis, retinal vein occlusion, retinal detachment repairs, and diabetic retinopathy. Incidence of clinical CME following cataract surgery in high-risk patients ranges from 4.2% to 4.5%. According to the Preferred Practice Patterns from the American Academy of Ophthalmology, 'The perioperative prophylactic use of NSAIDs for prevention of CME has been advocated for high-risk eyes based on a number of studies.' However, again there is no level I evidence that visual outcome is improved by the routine use of prophylactic NSAIDs at 3 months or more after cataract surgery in high-risk patients. A retrospective review of 89731 Kaiser Permanente patient charts concluded that the use of topical NSAIDs reduced the incidence of CME compared with those not receiving topical NSAIDs for all patients (1.3 versus 1.7%; $P<0.001$), patients without diabetes (1.1 versus 1.5%; $P<0.001$), and diabetics without retinopathy (0.7 versus 1.1%; P¼0.006). Patients with diabetic retinopathy who used topical NSAIDs, however, did not show a significant reduction in incidence of CME compared with patients with diabetic retinopathy who did not use topical NSAIDs (3.4 versus 3.2%; P¼0.650). The authors concluded that the incidence of CME in the absence of perioperative NSAIDs is nominal for a majority of patients, and therefore, prophylactic NSAIDs have limited utility. In 2018, Alnagdy *et al*. assessed the impact of topical nepafenac 0.1% three times daily, ketorolac tromethamine 0.4% four times daily, and placebo four times daily on patients diagnosed with diabetes without diabetic retinopathy. The study medications were started two days prior to surgery, ended 2 months after surgery and were co-administered with a topical antibiotic-steroid four times daily for 3 weeks. At POM 3 BCVA was significantly better in both NSAID groups compared with placebo (P¼0.04). Furthermore, patients in the NSAID cohort had significantly less CMT thickening by Topcon 3D 1000 OCT measurements at POM 1 (234.5þ/_26.16 versus 255.7þ/_33.2 mm; P¼0.08), POM 2 (235.43þ/_24.21 versus 260.41þ/ _55.8 mm; P¼0.027) and POM 3 (231.7þ/_21.5 versus 267.5 mm; P¼0.004) compared with the placebo cohort. No statistically significant differences in BCVA or CMT were found between nepafenac (0.1%) and ketorolac (0.4%). When evaluating patients with nonproliferative diabetic retinopathy (NPDR) without prior diabetic macular edema (DME), Singh *et al*. demonstrated a significant reduction in incidence of CME for patients taking nepafenac 0.3% daily compared with vehicle (4.1 versus 15.19%; $P<0.001$). Additionally, significantly more patients achieved BCVA gain of greater than 15 letters from preoperative baseline in the nepafenac cohort compared with vehicle (55.4 versus 46.7%, P¼0.003). Although the authors demonstrated a reduction of the incidence of CME with nepafenac use in patients with diabetic retinopathy, the severity of NPDR and response to NSAID therapy was not stratified. A similar study by Sarfraz *et al*. [18] compared nepafenac 0.3% four times daily for 3 months with topical prednisolone 0.1% every 4h for 2 weeks (Allergan) to topical prednisolone alone in patients with NPDR without DME. 3.3% of patients receiving nepafenac developed CME on SD-OCT in the study period compared with 23.3% of patients receiving steroids alone. Similarly, the nepafenac cohort demonstrated significantly less CMT thickening at POM 3 compared with steroid alone (2.33þ/_10.45 versus 12.23þ/ _12.40 mm; P¼0.023). Data was not stratified by diabetic retinopathy severity.

Postoperative Nonsteroidal Anti-inflammatory Drug Use For Prevention Of Pain And Ocular Inflammation

The optimal regimen for preventing postoperative pain and discomfort was widely studied between 2016 and 2018. A Cochrane review involving 48 randomized control trials by Juthani *et al*. attempted to determine whether monotherapy with NSAIDs or corticosteroids is superior for controlling post operation inflammation. Reviewers found moderate certainty evidence that there was no difference in cell grading between treatment groups [mean difference 0.60; 95% confidence interval (CI) _2.19 to 0.99]; however, there was low certainty evidence that NSAIDs alone were superior to corticosteroids alone for controlling flare (mean difference _13.74, 95% CI _21.45 to _6.0). When utilizing corticosteroids in combination with various NSAIDs, a meta-analysis by Zhao *et al*. demonstrated nepafenac significantly reduced postoperative ocular discomfort and hyperemia compared with ketorolac [relative risk (RR)¼0.589, 95% CI 0.436–0.794; P¼0.001 and RR¼0.253, 95% CI 0.115–0.557; P¼0.001 respectively]. No significant differences in anterior chamber inflammation grading were found between medications. Additionally, when comparing bromfenac 0.09% with nepafenac 0.3% no significant differences in the presence of pain, chemosis, photophobia, flare, hyperemia, cellularity or corneal edema were observed at 30 days following cataract surgery.

Postoperative Nonsteroidal Anti-inflammatory Drug Use and Patient Quality Of Life

Although postoperative pain and inflammation can cause significant discomfort for cataract surgery patients, Chatziralli *et al*. analyzed postoperation visual quality of life using VFQ25 questionnaires. No significant differences in the composite scores were found for 70 patients taking Ketorolac 0.5% three times daily compared with 68 patients taking placebo at POD 7, POD 28, and POD 42 (P¼0.833, P¼0.360, and 0.467, respectively). The authors argued that NSAIDs do not improve quality of vision in low-risk patients following cataract surgery.

Conclusion

The best use of perioperative NSAIDs continues to be a source of debate in the ophthalmologic literature. Reviewing articles published between 1 January 2016 and 30 June 2018 revealed new developments at every stage of cataract surgery. Perioperative NSAIDs achieve better intraoperative mydrasis, lower rates of postoperative CME, and improve patient comfort following surgery. Further high-quality studies are needed to establish Level I evidence on the long-term effects of perioperative NSAIDs on visual acuity and CME rates in low-risk and high-risk patients.

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