Current Use of Non-steroidal Anti-inflammatory Drugs in the Treatment of Ocular Inflammation Related to Cataract Surgery

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Abstract

Ocular inflammation and pain are a common consequence of cataract surgery, and if left untreated, may lead to extensive ocular damage, resulting in impaired vision as well as decreased satisfaction with the procedure. Effective management of ophthalmic inflammation after surgery is therefore vital. Topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) have become a mainstay of management of ocular pain and inflammation as a result of their anti-inflammatory activity, analgesic property and established safety record. Numerous studies have demonstrated the efficacy of topical NSAIDs in post-operative prevention of ocular inflammation, inhibition of intra-operative miosis, reduction of pain associated with cataract surgery and pre-operative use to prevent cystoid macular oedema. Studies have also indicated that NSAIDs and steroids act synergistically when administered together, and that a combination of steroid and NSAID therapy is recommended to achieve successful outcomes. With appropriate administration, NSAIDs are safe and effective therapeutic agents, which rarely result in serious local and systemic responses.

Keywords

Cataract surgery, cystoid macula oedema, miosis, non-steroidal anti-inflammatory drugs

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Cataract surgery is an invasive procedure involving an incision and manipulation of ocular tissue, leading to intraocular inflammation. The latter is characterised by redness, swelling, and/or pain. Inflammation arises from the release of prostaglandins (PGs). Activation of phospholipase A_2, following tissue injury during surgery, breaks down cell membrane phospholipids to arachidonic acid. This is then converted to PGs by activation of cyclo-oxygenase (COX) enzymes via the COX-1 and COX-2 pathways. Production of PGs causes local vasodilation and increased vascular permeability resulting in a number of symptoms including hyperaemia, miosis, pain, photophobia and diminished visual acuity secondary to cystoid macular oedema (CMO) – the most common complication of cataract surgery and potentially the most adverse ocular outcome of PG production.[1]

Two agents are primarily employed for the reduction of intraocular inflammation: non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. NSAIDs are potent inhibitors of cyclo-oxygenase enzymes and hence of PG synthesis. Together with corticosteroids, they act on the COX-1 and COX-2 pathways. While corticosteroids inhibit phospholipase A_2, preventing arachidonic acid release from phospholipids, NSAIDs act downstream and more specifically in the cascade by direct inhibition of COX-1 and COX-2 enzymes (see *Figure 1*).[2] Post-operative ocular inflammation is a complex condition owing to the diverse types of tissues that may be affected, including the conjunctiva, retina, sclera, aqueous and vitreous humour, cornea, iris, ciliary body, choroid and retina.[3]

Corticosteroids have a long history of use in the management of ocular inflammation but their efficacy is tempered by serious adverse effects including impairment of wound healing, elevation of intraocular pressure (IOP), progression of cataracts, increased susceptibility to microbial infections owing to a suppressed host immune response, delayed corneal epithelial and stromal wound healing, and safety issues associated with long-term use including glaucoma.[1]

The use of NSAIDs for ocular applications began in the 1970s, when it was found that topical formulations were more effective in intraocular penetration than systemic formulations. Topical NSAIDs have a number of important roles in the treatment of inflammation following ophthalmic cataract surgery. These include prevention of intra-operative miosis during cataract surgery; management of post-operative inflammation; reduction of pain and discomfort following cataract surgery; and prevention and treatment of CMO following cataract surgery.[3] Advantages of NSAIDs over corticosteroids include a reduction in post-operative pain and photophobia, decreased itching in allergic conjunctivitis, decrease in ocular pressure and reduction of intra-operative miosis.[4] However, the development of topical formulations of NSAIDs has been difficult. Most NSAIDs are weakly acidic and ionise at the pH of lachrymal fluid and have limited corneal permeability. Reducing the pH enhances permeability but increases the potential for ocular irritation.[5]

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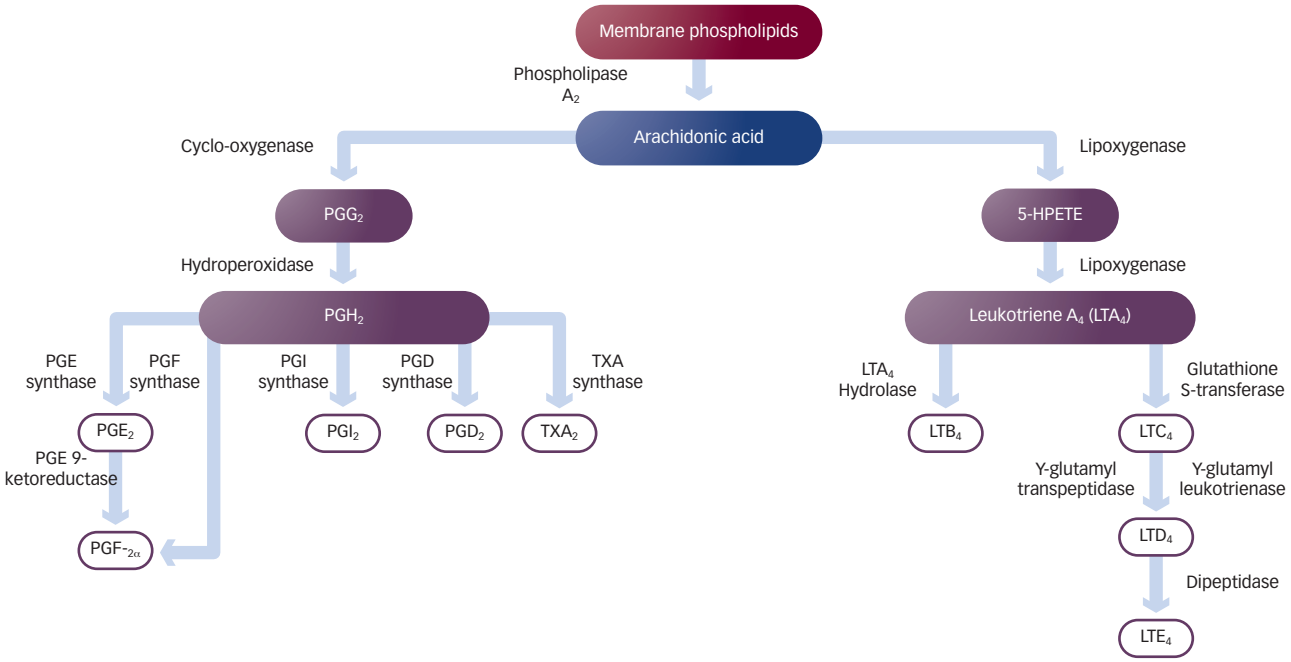
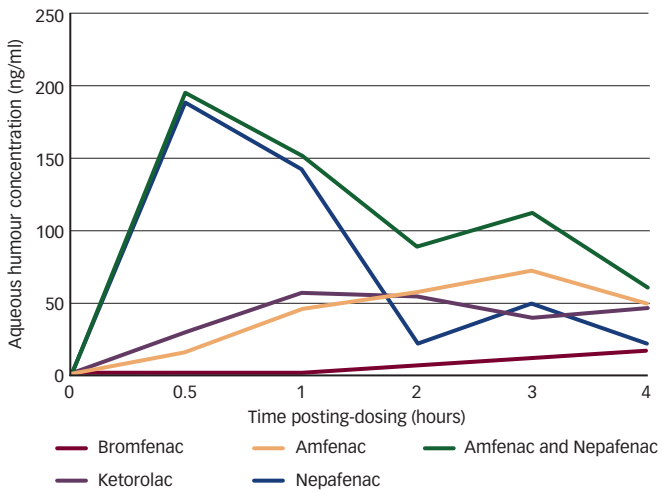
Figure 1: Mechanism of Action of Non-steroidal Anti-inflammatory Drugs



5-HPETE = 5-hydroperoxyeicosatetraenoic acid; LT = leukotriene; PG = prostaglandin; TX = thromboxane. Source: Reddy, Kim, 2011.[2]

NSAIDs with proven efficacy in the treatment and prevention of ocular inflammation include, indomethacin 0.10 % and 1.00 %, flurbiprofen 0.03 %, suprofen 1.00 %, ketorolac tromethamine 0.40 %, 0.45 % and 0.50 %, diclofenac 0.10 % and bromfenac 0.09 %. Among the most recently developed is nepafenac 0.10 %, an amide prodrug that is converted to its active form, amfenac, by intraocular hydrolases.[6] A multicentre double-masked study (n=75) aiming to evaluate the aqueous humour concentrations and COX inhibitory activities of nepafenac, amfenac, ketorolac and bromfenac after topical ocular administration demonstrated that, for example, nepafenac has significantly greater ocular bioavailability than ketorolac tromethamine (see *Figure 2*).[7] Being less polar than other NSAIDs, nepafenac is able to easily penetrate the cornea, enhancing corneal epithelial absorption.[8] As a result, nepafenac is optimally distributed in the cornea, iris, ciliary body and retina/choroid and has longer duration of action at these sites. In terms of safety, the prodrug structure minimises surface accumulation, as it is rapidly distributed through the cornea to the anterior and posterior chambers. As a result, ocular surface complications associated with conventional NSAID therapies may be reduced.[6,8]

Figure 2: Aqueous Humour Drug Concentration Following Dosing with Non-steroidal Anti-inflammatory Drugs



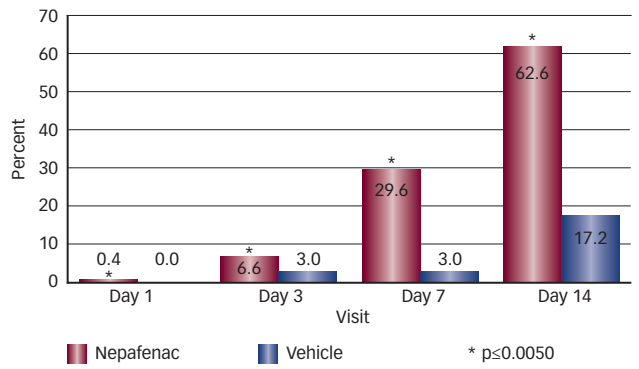
Source: Walters, et al., 2007.[7]

Efficacy Studies Involving Topical Non-steroidal Anti-inflammatory Drugs

Considerable evidence exists to support the use of topical NSAIDs in place of or in addition to topical corticosteroids after cataract surgery, to avoid excessive inflammation and aid in visual recovery. Flurbiprofen 0.03 %, suprofen 1.00 % diclofenac 0.10 %, ketorolac 0.40 %, bromfenac 0.09 % and nepafenac 0.10 % are approved by the US Food and Drug Administration (FDA) and in Europe for topical ocular applications.[3] Diclofenac was approved in the US following a clinical trial in which it was found to have equivalent efficacy to prednisolone in reducing inflammation following cataract surgery.[9]

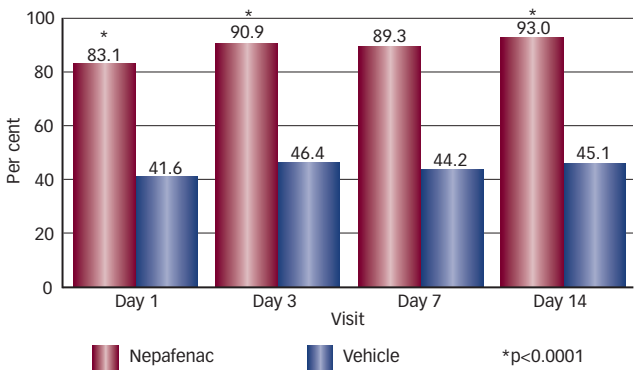
Ketorolac tromethamine has been found to give a comparable reduction to prednisolone acetate in intraocular inflammation and pain following cataract surgery.[10] A comparison of two topical steroids (prednisolone 1.0 % and rimexolone 1.0 %) with ketorolac tromethamine 0.5 % after extracapsular cataract extraction concluded that ketorolac tromethamine controlled intraocular inflammation after cataract extraction without the risk of IOP increase associated with steroid use.[11] A prospective randomised double-masked study to compare the efficacy of ketorolac tromethamine 0.5 % and loteprednol etabonate 0.5 %, reported that ketorolac tromethamine was as effective as loteprednol etabonate in reducing inflammation after routine phacoemulsification and intraocular lens (IOL) implantation.[12] In a randomised, prospective multicentre study, ketorolac tromethamine 0.5 % was found to be as effective as rimexolone 1 % in reducing inflammation after cataract surgery.[13]

Figure 3: Cumulative Percentage Cures (Defined as 0–5 Cells and Absence of Flare) by Visit Using Nepafenac in the Treatment of Ocular Inflammation Following Cataract Surgery



Source: Lane, et al., 2007.[6]

Figure 4: Percentage of Pain-free Patients by Visit Using Nepafenac in the Treatment of Ocular Inflammation Following Cataract Surgery



Source: Lane, et al., 2007.[6]

The most recently developed topical NSAIDs are bromfenac and nepafenac. The efficacy of bromfenac was established in four randomised, double-masked, vehicle or active-controlled, clinical trials.[14] In a randomised double-masked study evaluating the safety and effectiveness of nepafenac in preventing and treating inflammation and pain following cataract surgery, a higher percentage of patients in the nepafenac group were pain-free at all visits (83.1–93.0 %) compared with patients treated with vehicle (41.6–46.4 %) (p<0.0001). Furthermore, the nepafenac-treated group had clinical cure rates (defined as cells plus flare equal to zero) of 62.6 % compared with 17.2 % for vehicle (see *Figures 3* and *4*).[6]

Effect of Non-steroidal Anti-inflammatory Drugs on Intra-operative Miosis

The maintenance of mydriasis is critical during cataract surgery to allow adequate access to the extraction of the crystalline lens and implantation of the IOL without causing trauma to the iris. However, surgically induced miosis is a common complication of cataract surgery as a result of the release of PGs. Miosis may obstruct the surgeon's view during cataract surgery, complicating the procedure and increasing the risk of post-operative inflammation, vitreous loss and capsule rupture.[15,16]

NSAIDs inhibit PG synthesis, subsequently inhibiting intra-operative miosis, as several studies have demonstrated. Topical ketorolac was found to inhibit miosis more effectively than topical diclofenac during extracapsular cataract extraction and intraocular implantation, and gave a more stable mydriatic effect during surgery.[17] NSAIDs also increase the cost-effectiveness of the procedure; the use of ketorolac eliminated the need for the combination of a pre-operative NSAID (flurbiprofen) and post-operative corticosteroid for the prevention of intra-operative miosis and post-operative inflammation in cataract surgery.[18] A study comparing the effects of topical ketorolac 0.5 % with topical 0.03 % flurbiprofen on the inhibition of surgically induced miosis during phacoemulsification cataract surgery concluded that topical ketorolac is an effective inhibitor of miosis during phacoemulsification cataract surgery and confers a stable mydriatic effect throughout surgery.[15] In a prospective, randomised, single-masked comparative study (n=60) of nepafenac, the difference in mean pupil size following phacoemulsification cataract surgery between the control group (6.84±0.93 mm) and the nepafenac group (7.91±0.74 mm) was statistically significant (p<0.001).[16]

Non-steroidal Anti-inflammatory Drugs in the Prevention of Cystoid Macular Oedema

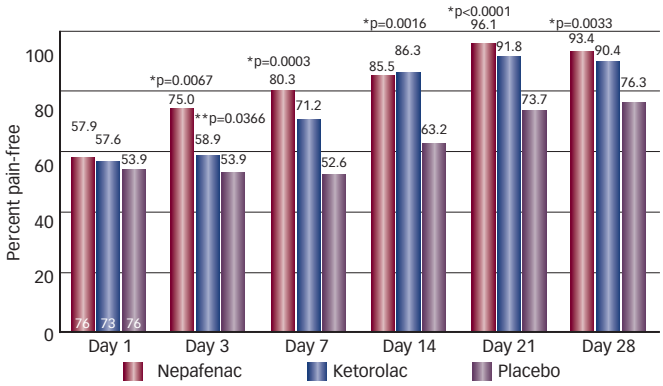
While NSAIDs inhibit the production of PGs, they do not affect PGs that have already been formed. It is important to begin NSAID treatment sufficiently in advance of surgery to inhibit the formation of PGs in response to surgical insult. While post-operative NSAID use is important to control pain and inflammation, pre-operative treatment is essential to improve the results of surgery. However, the pre-operative use of NSAIDs to prevent CMO has been the subject of considerable debate. CMO is caused by inflammation resulting from trauma associated with cataract surgery and is the most common cause of visual decline following uncomplicated cataract surgery.[19] Increased inflammation post-operatively is associated with an increased risk of developing CMO.[20] CMO is defined as angiographic or clinically significant. Angiographic CMO is detected by fluorescein angiogram and it is often not seen on clinical examination of the eye. Clinically significant CMO is observed on biomicroscopic examination and detected on fluorescein angiography. A study found that patients who had angiographic CMO at day 60 were more likely to have had more post-operative inflammation than patients who did not develop CMO.[21]

The exact incidence of overt CMO varies widely but studies suggest that the rate of clinical CMO following modern cataract surgical techniques ranges from 1 to 2 %.[22] The incidence of angiographic CMO may be as high as 19 %.[21] CMO frequently has a late onset, occurring 4–6 weeks post-operatively. CMO is the result of a variety of processes that cause fluid to accumulate in the central retina. The condition is often asymptomatic. Symptoms include blurred or reduced central vision and painless inflammation of the retina. Visual impairment, though usually temporary, can in rare cases lead to permanent loss of vision.[1] Loss of contrast sensitivity is common in patients who have experienced CMO.

Several studies have demonstrated the efficacy of topical NSAIDs in the prevention of CMO. In a multicentre, prospective clinical trial to compare diclofenac and fluorometholone in preventing CMO after small incision cataract surgery, it was found that five weeks after surgery CMO was present in significantly fewer (5.7 %) of the eyes receiving diclofenac than in those receiving fluorometholone (54.7 %) (p<0.001).[23] In a retrospective study, a 2.4 % incidence of CMO was reported with use of prophylactic NSAIDs in 1,659 consecutive

cases of cataract surgery performed by residents over a five-year period. When patients with diabetes were excluded, the rate of CMO was 2.1 %.[24] In a prospective study to compare the efficacy of several prophylactic regimens with ketorolac tromethamine 0.4 %, pre-treatment with NSAID improved visual acuity outcomes significantly in the immediate post-operative period (at one day and two weeks) compared with pre-treatment for one hour or placebo ($p<0.05$ for all).[25] Bromfenac has also been found to have efficacy in preventing CMO after cataract surgery in patients with diabetes.[26] More recently, a randomised study was conducted for comparing nepafenac 0.1 % (approved in the EU for reduction in the risk of post-operative macular oedema associated with cataract surgery in diabetic patients) with fluorometholone 0.1 % in preventing CMO after small-incision cataract extraction with IOL implantation. Five weeks after surgery, the incidence of fluorescein angiographic CMO was significantly lower in the nepafenac group (14.3 %) than in the fluorometholone group (81.5 %) ($P<0.0001$).[27]

Figure 5: Analgesic Effect of Nepafenac



** nepafenac 0.1 % versus placebo, chi-square test. ** nepafenac 0.1 % versus ketorolac 0.5 %, chi–square test. The numbers at the bottom of the day one bar represents the number of evaluable patients in each arm. The number of evaluable patients did not vary across time–points. Source: Nardi, et al., 2007.[29]*

Clinical data show that topical NSAIDs can prevent CMO, but no consensus for their therapeutic usage has been published. It has been recommended that the dosing schedule varies according to risk factors which include pre-existing ocular inflammation, epiretinal or vitreoretinal interface membrane problems, diabetic retinopathy, patients suffering from ocular vascular or cardiovascular disease and patients with history of retinitis pigmentosa.

Non-steroidal Anti-inflammatory Drugs and Pain Relief

NSAIDs provide effective reduction of pain associated with cataract procedures. In a single-centre, double-masked, randomised, placebo-controlled study of 25 patients undergoing cataract surgery, patients reported significantly less ocular pain during the 24 hours following surgery when treated with ketorolac 0.4 % than with placebo ($p=0.02$). Ocular pain was reported for only a single ketorolac 0.4 %-treated eye (4 %) during that period, compared with 39 % of placebo-treated eyes ($p=0.004$).[28] In a larger study (n=100), patients treated with ketorolac tromethamine experienced less intra-operative and post-operative pain compared with a placebo group and did not require additional anaesthesia.[25] In a large trial of bromfenac (n=872), the proportion of patients that were pain-free at one, three and 15 days were significantly higher in the treatment group than in the placebo group.[14] In a multicentre, randomised, placebo- and active-controlled, double-masked clinical trial (n=227), more patients were pain-free at each time-point from day three post-operatively with nepafenac than with placebo, ($p<0.05$) (see *Figure 5*).[29] Pain reduction is an important consideration because patient expectations of outcomes are high in modern cataract surgery and ocular pain or discomfort is a common cause of patient dissatisfaction.

Safety Issues Associated with the Use of Non-steroidal Anti-inflammatory Drugs

Many topical NSAIDs in ophthalmic use can cause a range of adverse events including conjunctival hyperaemia, burning, stinging and corneal anaesthesia.[30,31] A more serious complication is the risk of indolent corneal ulceration and full-thickness corneal melts. Scleral wound melting may arise with any ophthalmic NSAID in patients who have undergone cataract surgery. Moreover, a study found that cases of corneal melt following use of NSAIDs found inconsistent and variable dose/toxicity relationships suggesting that factors other than simple drug toxicity are involved. Corneal melts were found to be more commonly associated with the use of generic NSAIDs.[32] The use of nepafenac in accordance with its approved indications and posology has not been associated with high levels of ocular irritation.[29]

Combined Therapies

While NSAIDs have been shown to reduce inflammation and improve post-operative comfort, they are not successful in all cases. In most of the studies detailed above, patients were not free of inflammation at two weeks. The inflammatory response is complex, involving numerous cells and cytokines, not all of which are inhibited by NSAIDs. Corticosteroids and NSAIDs work at different levels of the arachidonic acid cascade and may provide synergistic effects. The adjunctive use of NSAIDs with steroids optimises surgical outcomes as numerous studies have demonstrated that the combination of an NSAID and steroid is more effective for the treatment of post-operative inflammation,[33] CMO[34] and improving visual acuity than either NSAID or steroid monotherapy. By combining NSAIDs and steroids, the doses of each may be lessened, minimising adverse effects while maintaining efficacy. The concomitant use of topical NSAIDs and corticosteroids should be carefully monitored, particularly among patients at high-risk for corneal injury, such as those with rheumatoid arthritis or fulminate collagen vascular disorders, as such combined therapy has been identified as a risk factor for the development of corneal erosion and possible perforation.[35]

Conclusion

NSAIDs are effective treatment options for a broad range of inflammatory eye disorders, which rarely result in serious local and systemic responses. Furthermore, they are valuable in the treatment of intraocular inflammation, prevention of pain and inhibition of miosis during cataract surgery, and for the prevention of CMO. As our understanding of the pathogenesis of inflammatory eye disorders increases and new, more potent topical formulations of NSAIDs are developed, the clinical indications of NSAIDs are likely to expand. However, given the complexity of the inflammatory response, synergistic effects may be achieved by the concurrent use of NSAIDs and corticosteroids, allowing the dosages of each to be minimised. With appropriate administration, NSAIDs are valuable prophylactic and therapeutic agents in cataract surgery. ■

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