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Topical Nonsteroidal Anti-Inflammatory Therapy in Ophthalmology

Rainer Schalnus

University Eye Hospital, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

Key Words
NSAID · Ocular inflammation · Cystoid macular edema · Cataract surgery · Refractive surgery · Conjunctivitis · Blood-aqueous barrier · Corticosteroid

Abstract
Topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the management and prevention of ocular inflammation and cystoid macular edema related to cataract surgery and the maintenance of mydriasis during cataract surgery. Other common uses are the reduction of discomfort after refractive surgery or in allergic conjunctivitis. NSAIDs primarily act as cyclooxygenase inhibitors and thus reduce the formation of endogenous PGs. Today, several NSAIDs are commercially available: diclofenac, flurbiprofen, indomethacin, ketorolac and suprofen. At present the ophthalmologist has to make a decision between the use of topical corticosteroids, with their potential adverse effects, or of topical NSAIDs, with their possibly increased benefit, unknown effect on ocular pressure, wound healing and corneal tissue, higher costs and limited track record. However, the improvement of surgical techniques might support an increasing use of NSAIDs in the future. Preoperative anti-inflammatory treatment should be considered in eyes at a higher risk of developing severe postoperative inflammatory reactions. This decision has to be made carefully and has to be guided by the clinical circumstances, the spectrum of diagnosis and the individual benefit-risk ratio of each patient.

Introduction

The discovery of the anti-inflammatory effect of cortisone in the middle of the last century had a great impact on modern eye surgery, especially on intraocular lens implantation and the management of ocular inflammation in general [1–5].

It became routine to use topical steroids after cataract surgery. There is controversy as to whether the anti-inflammatory effect compensates for undesired steroid side effects, such as impairment of wound healing. Meanwhile, other risks of topical steroids have become known, such as elevation of intraocular pressure, activation of ocular infection, worsening of viral infection and the development of cataract itself [6–10]. A better understanding of ocular and postsurgical inflammation, especially the breakdown of cell membrane phospholipids and the inhibitory potency of nonsteroidal anti-inflammatory

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Dr. Rainer Schalnus
Haager Weg 8
D–53127 Bonn (Germany)
Tel. +49 228 928 969 0, Fax +49 228 928 969 1, Mobile +49 171 521 9224
E-Mail schalnus@schalnus.com

Table 1. Topical, commercially available NSAIDs for clinical use

Generic name	Brand name	FDA approval
Flurbiprofen 0.03%	Ocufen® Ocuflur®	prophylaxis of surgical miosis
Suprofen 1%	Profenal®	prophylaxis of surgical miosis
Ketorolac 0.5%	Acular®	discomfort due to seasonal allergic conjunctivitis inflammation after cataract surgery discomfort after refractive surgery
Diclofenac 0.1%	Voltaren®	inflammation after cataract surgery pain after refractive surgery
Indomethacin 1%	Indoptol® Chibro-Amuno®	

substances, brought these drugs (NSAIDs) into the field of interest [11–24].

Meanwhile, topically applied NSAIDs are commonly used in the management and prevention of ocular inflammation [14, 25]. NSAIDs primarily act as cyclooxygenase inhibitors and thus reduce the formation of endogenous prostaglandins (PGs) [26]. Endogenous PGs play an important role in the initiation and maintenance of ocular inflammation. Among other effects, endogenous PGs increase the permeability of the blood-ocular barriers, they affect intraocular pressure and produce miosis and conjunctival hyperemia. PGs are mediators within the cellular and humoral inflammation cascade, including allergic reactions and pain response, and are known to have chemokinetic activity. In addition, there is evidence for the potential of NSAIDs to act as a free-radical scavenger; diclofenac was able to reduce formation of leukotrienes in vitro [27].

Although there are only a few FDA-approved indications for commercially available topical NSAIDs, there are many other valid clinical uses for these agents [28]. Today, the potential therapeutic use of NSAIDs in ophthalmic disorders concerns:

- cataract surgery
  - prevention of intraoperative miosis during surgery
  - post- and preoperative anti-inflammatory treatment
  - prevention and treatment of pseudophakic cystoid macular edema (CME)
- relief of symptoms of seasonal allergic conjunctivitis
- reduction of ocular discomfort after refractive surgery
- miscellaneous applications

Commercially Available Preparations of NSAIDs

Today, several topical drugs are commercially available, each primarily a cyclooxygenase inhibitor. For clinical use in ophthalmology, their FDA approvals have been limited solely to specific indications (table 1).

Flurbiprofen, suprofen and ketorolac tromethamine are water-soluble phenylalkonic acids. Flurbiprofen 0.03% (Ocufen, Ocuflur) and suprofen (Profenal) are only approved for the prophylaxis of surgical miosis. Ketorolac 0.5% (Acular) is approved for the treatment of seasonal allergic conjunctivitis and postoperative inflammation after cataract surgery and for the use after refractive surgery.

Diclofenac is a water-soluble phenylacetic acid derivate. Diclofenac 0.1% (Voltaren) has been FDA approved for the management of inflammation following cataract surgery.

In Europe the indole derivate indomethacin, which is not FDA approved, is mainly used to prevent postsurgical inflammation and CME. Indomethacin 1% is commercially available as Indoptol and Chibro-Amuno.

Cataract Surgery

Because of improvements in intraocular lens design and surgical technique, extracapsular cataract extraction with posterior chamber lens implantation has become an extremely safe and successful procedure [3, 29–35]. Nevertheless, during cataract surgery itself or within the postoperative period, specific complications related to PG-induced processes may occur, such as: intraoperative miosis, inflammation, and CME.

At present, topically applied NSAIDs are approved by the FDA for postoperative use only, even though it has become clinical standard to use these drugs both pre- and postoperatively to reduce the inflammatory response of the eye and to prevent undesired miosis during surgery itself [9, 40].

Maintenance of Mydriasis during Cataract Surgery

We know from clinical studies that topical NSAIDs applied preoperatively may prevent excessive miosis during cataract surgery. However, there is considerable variation between the degrees of mydriasis reported by different authors; some investigators were unable to demonstrate any effect at all [15, 36, 37]. It has been suggested that miosis during cataract surgery is partly mediated by PG, although not all studies agree on this [38]. This suggests that mechanisms other than surgical technique or endogenous factors are involved in the pathogenesis of surgical miosis.

Flurbiprofen 0.03% and suprofen 1% were the first NSAIDs approved by the FAD for use as inhibitors of miosis during cataract surgery. This therapeutic effect is shared by all commercially available NSAIDs [9, 39–44].

However, adequate mydriasis is achieved and maintained by good surgical technique, the combination of preoperative parasympatholytic and sympathomimetic eye drops, and a sympathomimetic preparation in the intraocular irrigation solution.

Quantitative Evaluation of the Blood-Aqueous Barrier after Cataract Surgery

To what extent the blood-aqueous barrier (BAB) can be affected by cataract surgery is mainly determined by three factors: (1) the surgical trauma; (2) the material, design and position of the intraocular lens, and (3) the perioperative anti-inflammatory management. The reliability of quantitative evaluation of the BAB in clinical studies is predominantly and strongly related to the observer-independent sensitivity and reproducibility of the detection method used in the study.

Efficacy evaluation of NSAIDs and corticosteroids related to postoperative inflammation can be studied with different techniques: slit lamp bio microscopy, anterior segment fluorophotometry, and laser flare and cell measurement (LFCM) [45]. To meet the current standards of clinical studies, either LFCM or fluorophotometry should be used for a quantitative evaluation of the BAB. Fluorophotometry and LFCM target different degrees and mechanisms of the inflammatory process [46, 47]. Both methods provide quantitative data to assess the permeability of the BAB. The impact of clinical study results on inflammation management to some extent depends on the different methodologies that are used to evaluate intraocular inflammation and/or BAB dysfunction [48–50].

Fluorophotometry determines the so-called fluorescein diffusion coefficient of the BAB [51]. This parameter reflects the BAB permeability towards molecules with the properties of fluorescein. LFCM provides observer-independent detection of the Tyndall phenomenon [52]. According to Rayleigh's law, the aqueous flare intensity allows one to assess the permeability status of the BAB towards proteins. There is evidence that the sensitivity of fluorophotometry seems to be somewhat higher than the sensitivity of laser flare detection in conditions that are supposed to coincide with a mild permeability increase of the BAB [53].

Inflammation after Cataract Surgery

Postoperative Use of NSAIDs

The use of posterior chamber IOLs has reduced the incidence and severity of inflammatory complications. But these complications do occur, especially in eyes with pre-existing anterior segment pathology, in eyes with a damaged BAB due to uveitis, diabetes, glaucoma, preoperated eyes, and in cases with complications at the time of surgery [54–59].

Posterior synechias, pseudophakic cellular precipitates, chronic uveitis, secondary glaucoma, CME and pain are examples of inflammatory complications. The safety and efficacy of modern cataract surgery, with minimal BAB breakdown and low inflammatory response, is primarily due to improvement of surgical techniques like phacoemulsification, capsular fixation of IOL instead of sulcus fixation, small incision surgery or modifications of IOL design and biocompatibility [60–62].

Many well-designed randomized, prospective double-masked clinical studies provide evidence that topical NSAIDs are useful in the prophylaxis and management of postoperative inflammation following cataract surgery [14, 15]. Even with the application of modern surgical technology, there is evidence that treatment with NSAIDs is potentially beneficial [63]. At present diclofenac 0.1%

and ketorolac 0.5% are the only topically applied NSAIDs with FDA approval for the management of inflammation after cataract surgery. However, in Europe many of the commercially available ophthalmic solutions of NSAIDs are used for perioperative anti-inflammatory management. Anti-inflammatory effects from topically applied NSAIDs in eyes undergoing cataract surgery have been demonstrated in many randomized, prospective, double-masked controlled clinical studies. Measurable effects could be shown for diclofenac 0.1%, ketorolac 0.5%, indomethacin 1% and flurbiprofen 0.03% after extra- and intracapsular cataract extraction with and without implantation of an IOL [14, 15, 64–69].

As stated earlier, it is most important to take into account which method is used for the evaluation of BAB permeability when discussing the results of clinical studies related to efficacy and effects of topical anti-inflammatory drugs.

Roberts and Brennan [64] suggested that NSAID treatment appears to be even more effective than topical steroids in re-establishing the BAB, as quantitatively measured with ocular fluorophotometry.

Flach et al. [66] could not find a significant difference between the anti-inflammatory effects of diclofenac 0.1% and ketorolac 0.5% administered after cataract extraction and IOL implantation. In this prospective, randomized, double-masked controlled study, intraocular inflammation was evaluated with slit lamp bio microscopy and LFCM.

In a prospective, randomized, double-masked controlled study Diestelhorst et al. [70] compared the anti-inflammatory efficacy and tolerance of diclofenac sodium 0.1%, flurbiprofen 0.03% and indomethacin 1.0%. Anterior chamber flare intensity following phacoemulsification and posterior chamber IOL implantation indicate that diclofenac is equally effective to indomethacin and more effective than flurbiprofen in reducing inflammation after cataract surgery. Subjective local tolerance of diclofenac was better than the tolerance of flurbiprofen or indomethacin.

Prospective, randomized, double-masked controlled studies provided evidence that ketorolac 0.5% is as effective as the 'new' corticosteroids loteprednol etabonate [71] and rimexolone [72] in reducing inflammation (laser flare intensity) after routine phacoemulsification and IOL implantation.

In their overview, Ohrloff et al. [73] compared 8 studies of similar design, which investigated the efficacy of NSAIDs and corticosteroids after cataract surgery (using the Kowa LCFM), and analyzed the percentage of decrease in anterior chamber flare intensity from day 1 to 4 after surgery. Monotherapy with dexamethasone 0.1% ophthalmic solution revealed the strongest anti-inflammatory potential, followed by prednisolone 1.0%. The inflammatory response was reduced by 48 [74–76] and 34% [77, 78], respectively. Diclofenac 0.1% seems to be the most effective NSAID. The decrease of the inflammatory response was 33% in eyes treated with diclofenac sodium [70, 75, 79] compared to 23% using flurbiprofen 0.03% and 19% after application of indomethacin 1% [77] ophthalmic solutions. The best lowering of inflammatory response was 52%, achieved in eyes treated with a combination of diclofenac 0.1% and dexamethasone 0.1% [75, 76], compared to 42%, using a combination of diclofenac 0.1% and prednisolone 1% [80], and 20% after treatment with indomethacin 1% plus prednisolone 1% [77].

Many studies that analyze NSAID effects on postoperative inflammation include the concurrent administration of corticosteroids. There is good evidence that NSAIDs and corticosteroids have a potential for synergistic activity [81, 82]. This makes it difficult to conclude from these studies whether the detected effects on postoperative inflammation are related to NSAID treatment alone or whether there is a synergistic effect due to the combined pharmacological activities of the NSAID and the topical corticoid. The potential of a concurrent corticosteroid treatment to mask the tendency for a given NSAID to cause ocular irritation should be considered.

Preoperative Use of NSAIDs

The standard procedure is not to use anti-inflammatory medication before cataract surgery. If PG release at the time of surgery is a major factor in the development of postoperative inflammation, pretreatment with an NSAID should be considered. A prospective study gave evidence that this could minimize the amount of inflammatory reaction that occurs initially after cataract surgery [9]. In this study, there was a significant difference in anterior chamber flare intensity 1 day after surgery between the group that had been pre-treated for 3 days before surgery and the control group without NSAID pretreatment. No statistically significant difference was evident between controls and a group that was pretreated only 1 h before surgery. Another randomized, controlled multicenter trial could not reveal a significant difference in inflammatory response between groups treated with ketorolac tromethamine 0.5% 30 min preoperation and 1 day after surgery [83].

The effectiveness of anti-inflammatory corticosteroids is mediated through their broad impact on both the

cyclooxygenase and lipoxygenase pathways by inhibiting phospholipase A2 activity on phospholipids, decreasing the production of arachidonic acid and the release of other proinflammatory substances, like leukotrienes with their chemotaxic properties [12]. Therefore the preoperative use of topical corticosteroids could have a valuable impact on the reduction of the postoperative inflammatory response, especially in patients with diabetes, uveitis or other conditions enhancing the breakdown of the BAB. Rimexolone and loteprednol etabonate, two new corticosteroids, may offer good anti-inflammatory efficacy with greatly reduced risk for elevation of intraocular pressure [84].

Treatment and Prevention of CME after Cataract Surgery

CME is the most frequent cause of visual loss following modern cataract surgery; any method of preventing it or treating it would be of great benefit [85, 86]. The incidence of asymptomatic angiographic CME is much more common than the incidence of symptomatic CME. Presumably angiographic CME is present in about 20% of eyes that underwent phacoemulsification. Chronic visually significant and symptomatic macular edema occurs in 1–2% of all patients who undergo cataract surgery [87].

Up to date there is no FDA-approved therapy for the management or prevention of CME following cataract surgery. On the other hand, there is evidence that the application of topical NSAIDs is potentially beneficial in relation to CME [86, 88].

NSAIDs seem to be effective in the prophylaxis of angiographic CME [88–90]. Miyake et al. [91] found significant better visual acuity in patients treated with indomethacin for 2 months after surgery compared to untreated patients. Subsequent studies of the prophylactic use of topical indomethacin [92], diclofenac [93–95] and ketorolac [96] demonstrated a reduction in angiographic CME, but could not prove a statistically significant and enduring clinical effect of topical NSAIDs on symptomatic CME.

However, in a large randomized, double-masked study, the flurbiprofen-CME study group demonstrated a lower incidence of symptomatic CME compared to controls, tested with contrast sensitivity and Snellen visual acuity measurements after application of indomethacin and flurbiprofen for 6 months after cataract surgery, but the effects were not sustained [97]. As most of the CME treatment studies include the concurrent use of corticosteroids, these studies represent the effects of a combined therapy with synergistic effects of NSAIDs and corticosteroids.

There is evidence that topical ketorolac 0.5% without concurrent corticosteroids may improve visual acuity in chronic symptomatic CME, as has been shown in randomized, double-masked controlled studies [98–100].

Miyake et al. [101] concluded from a randomized, multicenter, prospective clinical trial that the incidence CME might be closely related to the breakdown of the BAB.

Reduction of Discomfort after Refractive Surgery and Corneal Abrasion

After topical diclofenac application, Thomas-Barberan et al. [102] found reduced levels of PG E2 in the aqueous humor of rabbits that had undergone PRK.

Diclofenac 0.1% and ketorolac 0.5% are FDA approved to reduce photophobia and pain after refractive surgery [103–106]. Kaiser et al. [107] compared corneal healing time after contact lens-unrelated traumatic corneal abrasion (less than 10 mm in diameter) in patients with patching and patients who received ketorolac 0.5% without patching. Both groups received topical antibiotics.

Allergic Conjunctivitis

Allergy affects more than 15% of the world population; in westernized industrialized countries the prevalence is probably 30%. Allergy commonly affects various target organs, and the ocular component may be the most common and initially the most prominent disabling feature [108, 109]. Topically applied NSAIDs could provide a safer alternative to corticosteroids for the use of handling discomfort and symptoms of allergic eye disease. Ketorolac 0.5% ophthalmic solution is FDA approved for discomfort due to seasonal allergic conjunctivitis [110–112].

In a randomized, double-masked, multicenter parallel-group study with patients suffering from seasonal allergic conjunctivitis, the efficacy of topical ketorolac 0.5% and levocabastine 0.05% was compared to controls [113]. Ketorolac produced the greatest improvements, however, there was no significant difference to levocabastine.

Some studies could demonstrate positive effects in managing symptoms of acute allergic conjunctivitis with

topical diclofenac sodium 0.1% [114] and treating contact lens-associated giant papillary conjunctivitis or veneral conjunctivitis with suprofen [115, 116].

Other Potential Uses of Topical NSAIDs

Many other indications have been suggested for topical NSAIDs, such as inflamed pterygia and pingueculae, laser trabeculoplasty, glaucoma and strabismus surgery [117–120].

It has been suggested that topical diclofenac sodium has the potential to prevent opacification of the posterior capsule after cataract extraction and posterior chamber lens implantation [121]. A randomized, double-masked, prospective clinical study could prove that this assumption related neither to diclofenac nor to ketorolac [122].

Safety and Toxicity of Topical NSAIDs

Topically applied ophthalmic NSAIDs may lead to local irritation of the eye; absorption through the nasal mucosa results in systemic exposure and holds potential for the occurrence of adverse systemic events or complications [123]. Whether this is of clinical importance is not yet clear.

Local irritant effects of topical ophthalmic NSAIDs include transient burning, stinging, conjunctival hyperemia and corneal anesthesia.

Although corneal complications related to the topical use of NSAID ophthalmic solutions are not very common, corneal infiltrates, epithelial defects or superficial punctuate keratitis have been observed [124–126]. However, corneal cytotoxicity and adverse ocular effects are known complications after the use of many topically applied ophthalmic preservations in general [127–133].

A more serious complication involves recent reports about the association of topical ophthalmic NSAIDs with indolent corneal ulceration and full-thickness corneal melts [134–139]. However, the analysis of NSAID-associated corneal events should implicate the exact diagnosis and reason for treatment, knowledge of concurrent topical and general drug therapy and the diagnosis of any other ocular disease in each case. Dry eyes or the concurrent use of topical corticosteroids or antibiotics might be identified as possible cofactors of other causes that lead to severe corneal damage using topical NSAIDs [140–145]. For this reason NSAIDs should be applied at least under special awareness of such potential cofactors.

Reports supporting theories of potential pharmacodynamic mechanisms leading to corneal damage related to NSAIDs should not alter the advantageous benefit-risk ratio of topical NSAID ophthalmic solutions when employed in a reasonable and appropriate manner, until clinical evidence will change paradigms.

For this reason topical NSAID use must be judiciously indicated and carefully monitored for adverse events, as is good clinical practice with any drug treatment.

New topical NSAID ophthalmic solutions are in the phase of preclinical testing to be evaluated for their efficacy, safety and potential clinical use [146–148].

At present, the ophthalmologist has to decide between the use of topical corticosteroids, with their potential adverse effects on wound healing and intraocular pressure, and topical NSAIDs, with their possibly increased benefit but unknown effects on ocular pressure, wound healing and corneal tissue, higher costs and limited track record.

Valuable and reliable analyses that provide cost-effectiveness data and evidence-based guidelines for anti-inflammatory management in ophthalmology, especially in cataract surgery, will be needed in the future. This would throw light on the question to what extent an intensified perioperative anti-inflammatory therapy – among other factors – could possibly increase the quota of cataract removals (even under exceptional circumstances) that could be done in outpatient settings [149–155].

However, the improvement of surgical techniques might support an increasing use of NSAIDs in the future. Preoperative anti-inflammatory treatment should be considered in eyes at higher risk of developing severe postoperative inflammatory reactions.

This decision has to be made carefully and has to be guided by the clinical circumstances, the spectrum of diagnosis of each individual and the individual benefit-risk ratio of each patient.

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