EJPMR, 2026, 13(11), 251-255 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

PREOPERATIVE TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN THE PREVENTION OF INTRAOPERATIVE FLOPPY IRIS SYNDROME: A REVIEW ARTICLE

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DOI: https://doi.org/10.5281/zenodo.23803579

How to cite this Article: Malak Faraj Abdalla Harahsheh, MD*[1]. (2026). Preoperative Topical Nonsteroidal Anti-Inflammatory Drugs In The Prevention Of Intraoperative Floppy Iris Syndrome: A Review Article. European Journal of Pharmaceuticaland Medical Research, 13(11), 251–255.
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Article Received on 04/10/2026 **Article Revised on 24/10/2026** **Article Published on 01/11/2026**

ABSTRACT

Intraoperative floppy iris syndrome is a form of small pupil in which the iris becomes flaccid and billows with irrigation currents, prolapses toward the incisions, and constricts progressively during cataract surgery. It is most strongly associated with tamsulosin, an alpha-1A adrenoceptor antagonist, and it prolongs surgery and raises the risk of intraoperative complications. Standard dilating drops often fail in affected eyes because the iris dilator muscle is pharmacologically impaired. However, part of the pupil constriction seen during surgery is driven by prostaglandins released in response to surgical trauma. Topical nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase, reduce prostaglandin synthesis, and are used routinely before cataract surgery to maintain mydriasis. This review summarizes the pathophysiology of intraoperative floppy iris syndrome, the pharmacology of the available topical agents (flurbiprofen, ketorolac, diclofenac, bromfenac, and nepafenac), and the clinical evidence for their use. Randomised and comparative studies in cataract surgery show that ketorolac, nepafenac, and bromfenac help to maintain pupil diameter, and head-to-head comparisons favor ketorolac and nepafenac over flurbiprofen. Direct evidence in patients at risk of the syndrome comes mainly from intracameral phenylephrine-ketorolac, which reduced iris prolapse and billowing in men taking tamsulosin. No high-quality trial has tested preoperative topical nonsteroidal anti-inflammatory drugs alone against placebo for preventing the syndrome itself. These drugs are best regarded as a low-risk adjunct within a multimodal strategy that also uses atropine, intracameral epinephrine, viscoelastic agents, and mechanical pupil expansion when needed.

KEYWORDS: Intraoperative floppy iris syndrome; Nonsteroidal anti-inflammatory drugs; Cataract surgery; Tamsulosin; Miosis; Phacoemulsification.

INTRODUCTION

Intraoperative floppy iris syndrome (IFIS) was first described in 2005 by Chang and Campbell in patients taking tamsulosin.[1] It consists of three features: a flaccid iris stroma that undulates and billows with intraocular fluid currents, a tendency of the iris to prolapse toward the phacoemulsification and side-port incisions despite well-constructed wounds, and progressive pupil constriction despite standard preoperative dilation.[1,2] Together these features make surgery harder and increase the rate of complications.[1,3]

The link with systemic alpha-1 adrenoceptor antagonists is strong. Tamsulosin carries the highest risk. In the original series, the syndrome occurred in 63% and 94% of tamsulosin users in the retrospective and prospective groups, respectively.[1] A meta-analysis found a markedly higher risk with tamsulosin than with alfuzosin, and a lower but real risk with other alpha-blockers.[4] Hypertension has also emerged as a risk factor in several series.[4,5] Other drugs have been reported in case-level studies, including finasteride, labetalol, chlorpromazine, and donepezil, although the evidence for these is weak.[5]

In a prospective Indian series of 1003 eyes, IFIS occurred in 68.3% of eyes of tamsulosin users and prolonged operating time (mean 11.68 versus 10.01 minutes).[5] Notably, every patient in that series had already received

a topical nonsteroidal anti-inflammatory drug (flurbiprofen or nepafenac) before surgery, which shows that the syndrome occurs despite routine prophylaxis.[5] Contemporary multicenter data indicate that complication rates can be kept low when surgeons recognize the risk and prepare for it.[6]

The syndrome cannot always be predicted, although poor pharmacological dilation before surgery can help to identify eyes at risk.[7] Because stopping tamsulosin before surgery does not reliably remove the risk, prevention relies on pharmacological and surgical measures.[2] Topical nonsteroidal anti-inflammatory drugs are given before almost every cataract operation, mainly to maintain mydriasis and control inflammation.[8] Their role specifically in IFIS is less well defined. This review therefore examines the rationale, the pharmacology, and the clinical evidence for preoperative topical nonsteroidal anti-inflammatory drugs in the prevention of IFIS, and identifies the gaps that remain.

PATHOPHYSIOLOGY AND RATIONALE FOR NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Mechanism of intraoperative floppy iris syndrome

The iris dilator muscle contracts through alpha-1A adrenoceptors, which predominate in the iris as they do in the prostate.[9,10] Tamsulosin binds these receptors with high affinity and selectivity. In an isolated rabbit tissue model, tamsulosin and alfuzosin differed in their effects on iris dilator contraction, which fits the clinical observation that tamsulosin carries the greater risk.[10] Because the blockade is a pharmacological loss of dilator tone, topical mydriatics cannot fully overcome it, and the effect may persist after the drug is stopped.[2,9] Structural change in the dilator muscle has been proposed as one reason for this persistence.[9]

Surgical miosis and prostaglandins

Even in normal eyes, pupil size tends to fall once the anterior chamber is entered, despite adequate preoperative dilation. Surgical trauma breaks down the blood-aqueous barrier and releases prostaglandins into the aqueous humour, which constrict the iris sphincter.[11] Prostaglandin levels in the aqueous rise after lens extraction, and mechanical stimulation of the iris produces a similar release in experimental models.[12,13] Intraoperative miosis matters clinically. In an older series of 1000 extracapsular cases, a small pupil was associated with more intraoperative complications.[14]

Rationale for nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase and so reduce prostaglandin synthesis. This is the basis for their routine use to prevent surgically induced miosis.[8,15] In eyes at risk of IFIS, two processes probably overlap: loss of dilator tone from alpha-1 blockade, and prostaglandin-mediated constriction triggered by iris contact, billowing, and prolapse during irrigation. Nonsteroidal anti-inflammatory drugs act only on the second process. They cannot restore adrenergic dilator function. This is a mechanistic inference rather than a demonstrated effect, and it explains why these drugs are best expected to limit the progressive miosis component of the syndrome, not to prevent billowing and prolapse on their own.

TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS: PHARMACOLOGY AND AGENTS

Five topical agents are in common use around cataract surgery: flurbiprofen, ketorolac, diclofenac, bromfenac, and nepafenac. All inhibit cyclooxygenase, but they differ in chemical class, potency, and tissue penetration.[8,16] Nepafenac is a prodrug. It crosses the cornea and is converted by intraocular hydrolases into its active metabolite, amfenac, which gives targeted delivery to the inner eye.[17]

Table 1: Topical nonsteroidal anti-inflammatory drugs studied for miosis prevention.

Agent	Concentration in cited studies	Use in the cited studies
Flurbiprofen	0.03%	Long-standing comparator in miosis trials; given about 2 hours before surgery in one Indian series[5]
Ketorolac	0.4%, 0.5%	Four drops at 15-minute intervals from 1 hour before surgery in a randomised trial[18]
Diclofenac	0.1%	Compared with ketorolac 0.5% for inhibition of miosis[19]
Bromfenac	0.1%	Twice daily for 3 days before femtosecond laser cataract surgery[20]
Nepafenac	0.1%	Four drops at 15-minute intervals before surgery in a randomised comparison with flurbiprofen[21]

Regimens therefore vary widely, from a short run of drops in the hour before surgery to scheduled dosing for several days. No single regimen has been established as best for eyes at risk of IFIS. Short preoperative courses are generally well tolerated, but corneal adverse events have been reported with prolonged use, and the ASCRS review discusses these safety points in detail.[8]

CLINICAL EVIDENCE

Evidence from routine cataract surgery

Most trials of topical nonsteroidal anti-inflammatory drugs were done in unselected patients, and their

outcome was pupil diameter during surgery, not the presence of IFIS (Table 2).

Table 2: Selected studies of topical nonsteroidal anti-inflammatory drugs and intraoperative pupil size.

Study	Design	Comparison	Main finding
Solomon et al., 1997[15]	Comparative trial	Ketorolac 0.5% vs flurbiprofen 0.03%	Ketorolac gave a more stable mydriatic effect through surgery
Sanatkar et al., 2016[18]	Randomised, 84 patients	Ketorolac 0.5% vs no ketorolac	End-of-surgery pupil 8.01 ± 0.67 mm vs 7.34 ± 1.0 mm (P = 0.018)
Chen et al., 2017[20]	60 patients, femtosecond laser surgery	Bromfenac 0.1% vs placebo	Smaller change in pupil size and lower aqueous prostaglandin E2 (P < 0.001)
2021 trial[21]	Randomised, 160 patients	Nepafenac 0.1% vs flurbiprofen 0.03%	Less pupil reduction with nepafenac; shorter phacoemulsification time (P = 0.004)
Sarkar et al., 2015[22]	Randomised, small incision surgery	Nepafenac 0.1% vs flurbiprofen 0.03%	Nepafenac more effective at the end of surgery[21]
Atanis et al., 2011[23]	Comparative	Nepafenac 0.1% vs ketorolac 0.5%	Nepafenac more effective inhibitor of miosis[21]
Zanetti et al., 2012[24]	Randomised	Nepafenac 0.1%, ketorolac 0.4%, placebo	Both drugs beat placebo; no difference between them[21]
Cervantes-Coste et al., 2009[25]	60 patients	Nepafenac 0.1% vs placebo	Greater pupil diameter with nepafenac[21]

Together these studies show that preoperative topical nonsteroidal anti-inflammatory drugs help to keep the pupil dilated, and that ketorolac and nepafenac outperformed flurbiprofen in direct comparisons. The comparison between nepafenac and ketorolac is inconsistent across studies.[23,24] The 2021 trial excluded patients taking alpha-1 blockers, which is typical of this literature, so its results cannot be applied directly to eyes at risk of IFIS.[21]

Evidence in eyes at risk of intraoperative floppy iris syndrome

Two sources are directly relevant. The first is the Indian series of 1003 eyes, in which every patient received flurbiprofen or nepafenac about 2 hours before surgery.[5] Even so, 28 of 41 tamsulosin users (68.3%) developed IFIS. Routine topical prophylaxis therefore did not prevent the syndrome in most affected patients. Because the series had no untreated comparison group, it cannot show how much the drops helped.

The second source is a randomised study of 50 eyes of men with a history of tamsulosin use. Both groups received topical tropicamide and phenylephrine before surgery. One group then received phenylephrine 1.0% with ketorolac 0.3% in the irrigating solution, and the other received saline.[26] Iris prolapse occurred in 3 of 25 eyes (12.0%) with phenylephrine-ketorolac and in 14 of 25 eyes (56.0%) with saline (P < 0.001). Miosis and iris billowing were also reduced.[26] This result supports the idea that a ketorolac-containing regimen can improve iris behavior in at-risk eyes. It does not isolate the effect of a topical nonsteroidal drug, because ketorolac was given inside the eye, and because phenylephrine, an alpha-1 agonist, acts directly on the blocked receptor.

Gap in the evidence

In the sources reviewed here, no randomised trial compared preoperative topical nonsteroidal anti-inflammatory drugs alone with placebo for preventing IFIS in patients taking alpha-1 blockers. The existing data show that these drugs maintain pupil size in general, and that a nonsteroidal-containing intracameral regimen helps at-risk eyes. The direct effect of topical pretreatment on billowing, prolapse, and complication rates in IFIS remains unproven.

MULTIMODAL PREVENTION AND PRACTICAL CONSIDERATIONS

No single measure reliably prevents IFIS, so management combines several.[2] Stopping tamsulosin before surgery is not an effective solution.[2] The main options are:

1. **Preoperative atropine.** Topical atropine 1% has been used, in combination with intracameral non-preserved epinephrine, to manage the syndrome.[27]
2. **Intracameral epinephrine.** Non-preserved epinephrine injected into the anterior chamber was proposed for IFIS prophylaxis soon after the syndrome was described.[28]
3. **Intracameral phenylephrine-ketorolac.** This combination reduced iris prolapse in at-risk eyes (see Clinical Evidence).[26]
4. **Viscoelastic agents.** Dense or viscoadaptive viscoelastics help to hold the iris in place, and the Indian series used one in several eyes with IFIS.[2,5]
5. **Mechanical expansion.** Iris hooks and pupil expansion rings are the fallback when drugs fail.[2]
6. **Surgical technique.** Well-constructed incisions and lower fluidic settings reduce iris movement.[2]

Within this framework, topical nonsteroidal anti-inflammatory drugs have a defined but limited role. They are cheap, widely available, and already given before most cataract operations for inflammation and pain.[8] They address the prostaglandin component of miosis, and they carry little added risk when given for a short preoperative course. They should be regarded as one layer of a multimodal plan, not as a substitute for epinephrine, phenylephrine, or mechanical devices in patients taking alpha-1 blockers. A reasonable approach, based on the evidence above and not on a published guideline, is to identify at-risk patients before surgery, give the usual topical nonsteroidal drug as the baseline layer, and have intracameral epinephrine or phenylephrine-ketorolac and a pupil expansion device available.

Limitations of this review

This is a narrative review, not a systematic one, and the search was not exhaustive. The trials of topical nonsteroidal drugs are small, differ in drug, dose, timing, and method of pupil measurement, and usually excluded patients taking alpha-1 blockers. Few studies report IFIS grade, prolapse, or complication rates as outcomes.

CONCLUSION

Preoperative topical nonsteroidal anti-inflammatory drugs are a rational, low-risk part of IFIS prevention because they limit prostaglandin-mediated miosis. Randomised trials in general cataract surgery show that they help to maintain pupil size, and nepafenac and ketorolac performed better than flurbiprofen in head-to-head comparisons. However, these drugs do not correct the alpha-1 blockade that causes the syndrome. In one large prospective series, routine topical prophylaxis did not prevent IFIS in most tamsulosin users, and no randomised trial has tested topical nonsteroidal drugs alone for this purpose. They are best used as the baseline layer of a multimodal plan that includes intracameral epinephrine or phenylephrine-ketorolac, viscoelastic agents, and pupil expansion devices when needed. Future trials in patients taking alpha-1 blockers should compare topical nonsteroidal pretreatment with placebo, and with intracameral regimens, using standardized grading of iris billowing, prolapse, and miosis.

ACKNOWLEDGEMENTS: None.

Funding: None.

Conflict of interest: None.

REFERENCES

1. Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. J Cataract Refract Surg, 2005; 31(4): 664-73.
2. Chang DF, Braga-Mele R, Mamalis N, Masket S, Miller KM, Nichamin LD, et al. ASCRS White Paper: clinical review of intraoperative floppy-iris syndrome. J Cataract Refract Surg, 2008; 34(12): 2153-62.
3. Chang DF, Braga-Mele R, Mamalis N, Masket S, Miller KM, Nichamin LD, et al. Clinical experience with intraoperative floppy-iris syndrome: results of the 2008 ASCRS member survey. J Cataract Refract Surg, 2008; 34(7): 1201-9.
4. Chatziralli IP, Sergentanis TN. Risk factors for intraoperative floppy iris syndrome: a meta-analysis. Ophthalmology, 2011; 118(4): 730-5.
5. Goyal S, Dalela D, Goyal NK, Chawla S, Dhesi R, Kamboj B, et al. Intraoperative floppy iris syndrome in Indian population: a prospective study on incidence, risk factors, and impact on operative performance. Indian J Ophthalmol, 2014; 62(8): 870-5.
6. Chang DF, Osher RH, Wang L, Koch DD. Prospective multicenter evaluation of cataract surgery in patients taking tamsulosin (Flomax). Ophthalmology, 2007; 114(5): 957-64.
7. Casuccio A, Cillino G, Pavone C, Spitale E, Cillino S. Pharmacologic pupil dilation as a predictive test for the risk for intraoperative floppy-iris syndrome. J Cataract Refract Surg, 2011; 37(8): 1447-54.
8. Hoffman RS, Braga-Mele R, Donaldson K, Emerick G, Henderson B, Kahook M, et al. Cataract surgery and nonsteroidal antiinflammatory drugs. J Cataract Refract Surg, 2016; 42(9): 1368-79.
9. Schwinn DA, Afshari NA. Alpha(1)-adrenergic receptor antagonists and the iris: new mechanistic insights into floppy iris syndrome. Surv Ophthalmol, 2006; 51(5): 501-12.
10. Palea S, Chang DF, Rekik M, Regnier A, Lluel P. Comparative effect of alfuzosin and tamsulosin on the contractile response of isolated rabbit prostatic and iris dilator smooth muscles; possible model for intraoperative floppy-iris syndrome. J Cataract Refract Surg, 2008; 34(3): 489-96.
11. Grob SR, Gonzalez-Gonzalez LA, Daly MK. Management of mydriasis and pain in cataract and intraocular lens surgery: review of current medications and future directions. Clin Ophthalmol, 2014; 8: 1281-9.
12. Miyake K, Sugiyama S, Norimatsu I, Ozawa T. Prevention of cystoid macular edema after lens extraction by topical indomethacin (III). Radioimmunoassay measurement of prostaglandins in the aqueous during and after lens extraction procedures. Albrecht Von Graefes Arch Klin Exp Ophthalmol, 1978; 209(2): 83-8.
13. Ambache N, Kavanagh L, Whiting J. Effect of mechanical stimulation on rabbits' eyes: release of active substance in anterior chamber perfusates. J Physiol, 1965; 176(3): 378-408.
14. Guzek JP, Holm M, Cotter JB, Cameron JA, Rademaker WJ, Wissinger DH, et al. Risk factors for intraoperative complications in 1000 extracapsular cataract cases. Ophthalmology, 1987; 94(5): 461-6.
15. Solomon KD, Turkalj JW, Whiteside SB, Stewart JA, Apple DJ. Topical 0.5% ketorolac vs 0.03%

flurbiprofen for inhibition of miosis during cataract surgery. Arch Ophthalmol, 1997; 115(9): 1119-22.
16. Kim SJ, Flach AJ, Jampol LM. Nonsteroidal anti-inflammatory drugs in ophthalmology. Surv Ophthalmol, 2010; 55(2): 108-33.
17. Walters T, Raizman M, Ernest P, Gayton J, Lehmann R. In vivo pharmacokinetics and in vitro pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac. J Cataract Refract Surg, 2007; 33(9): 1539-45.
18. Sanatkar M, Goudarzi M, Ghassemi H, Keyhanian M, Yaghooti AA, Sadrossadat H, et al. The effect of prophylactic administration of ketorolac ophthalmic suspension on prevention of surgically induced miosis in patients undergoing cataract surgery. Arch Anesthesiol Crit Care, 2016; 2(2): 184-8.
19. Srinivasan R, Madhavaranga. Topical ketorolac tromethamine 0.5% versus diclofenac sodium 0.1% to inhibit miosis during cataract surgery. J Cataract Refract Surg, 2002; 28(3): 517-20.
20. Chen H, Lin H, Chen W, Zhang B, Xiang W, Li J, et al. Topical 0.1% bromfenac sodium for intraoperative miosis prevention and prostaglandin E2 inhibition in femtosecond laser-assisted cataract surgery. J Ocul Pharmacol Ther, 2017; 33(3): 193-201.
21. Ankur K. Shrivastava, Swatishree Nayak, Mary Anto. Efficacy of nepafenac versus flurbiprofen in maintaining intraoperative mydriasis during phacoemulsification: a comparative study. Clin Ophthalmol, 2021; 15: 1085-93.
22. Sarkar S, Mondal KK, Roy SS, Gayen S, Ghosh A, De RR. Comparison of preoperative nepafenac (0.1%) and flurbiprofen (0.03%) eye drops in maintaining mydriasis during small incision cataract surgery in patients with senile cataract: a randomized, double-blind study. Indian J Pharmacol, 2015; 47(5): 491-5.
23. Atanis R, Tuano PM, Vicencio J, Martinez JM, Verzosa L. Effect of topical ketorolac tromethamine and topical nepafenac on maintaining pupillary dilation during phacoemulsification. Philipp J Ophthalmol, 2011; 36(1): 23-7.
24. Zanetti FR, Fulco EAM, Chaves FRP, da Costa Pinto AP, Arieta CEL, Lira RPC. Effect of preoperative use of topical prednisolone acetate, ketorolac tromethamine, nepafenac and placebo, on the maintenance of intraoperative mydriasis during cataract surgery: a randomized trial. Indian J Ophthalmol, 2012; 60(4): 277-81.
25. 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: 219-26.
26. Silverstein SM, Rana V, Stephens R, Segars L, Pankratz J, Rana S, et al. Effect of phenylephrine 1.0%-ketorolac 0.3% injection on tamsulosin-associated intraoperative floppy-iris syndrome. J Cataract Refract Surg, 2018; 44.
27. Masket S, Belani S. Combined preoperative topical atropine sulfate 1% and intracameral nonpreserved epinephrine hydrochloride 1:4000 for management of intraoperative floppy-iris syndrome. J Cataract Refract Surg, 2007; 33(4): 580-2.
28. Shugar JK. Use of epinephrine for IFIS prophylaxis. J Cataract Refract Surg, 2006; 32(7): 1074-5.