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REVIEW ARTICLE

The comparative efficacy and safety of topical non-steroidal anti-inflammatory drugs for the treatment of anterior chamber inflammation after cataract surgery: a systematic review and network meta-analysis

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Abstract
Purpose Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of anti-inflammatory drugs that are used in ophthalmologic surgery. These drugs do not have a steroid structure, but can inhibit surgery-induced miosis, anterior chamber inflammation, and cystoid macular edema (CME). However, the application of NSAIDs remains controversial. Therefore, we performed a meta-analysis to assess the efficacy and safety of NSAIDs for the treatment of anterior chamber inflammation after cataract surgery.
Methods Relevant articles were identified from the PubMed, Embase, and Cochrane databases up to October 2016. The therapeutic effect of NSAIDs on anterior chamber inflammation was evaluated. The important outcomes of overall anterior chamber inflammation, freedom from ocular pain, and treatment-related/serious ocular adverse events were analyzed by using a random-effects network meta-analysis. The quality of evidence was assessed via the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach.
Results A total of 19 trials assessing 7,234 patients were included in our meta-analysis. Diclofenac was the most likely to improve anterior chamber inflammation after cataract surgery, followed by nepafenac, ketorolac, bromfenac, and flurbiprofen. Nepafenac was most likely to improve postoperative ocular pain relief, followed by bromfenac and ketorolac. Our analysis of treatment-related/serious ocular adverse events revealed that piroxicam was most likely to have the fewest related adverse events, but the robustness of this finding was low. Diclofenac was another near-ideal drug, followed by nepafenac, bromfenac, and ketorolac.
Conclusions NSAIDs are effective drugs compared to placebos for the relief of anterior chamber inflammation. Furthermore, diclofenac, nepafenac, ketorolac, and bromfenac demonstrated relatively greater significant effects than those of other NSAIDs.

Keywords Non-steroidal anti-inflammatory drugs · Anterior chamber inflammation · Cataract surgery · Meta-analysis

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Introduction

A cataract is the clouding of the lens that may occur because of protein denaturation in the lens [1]. Nearly half of patients with blindness were found to have cataracts (approximately 20 million), and cataracts have also been found to be the leading cause of serious vision loss worldwide [2–4]. Cataract-related reductions in visual acuity cannot be rectified by wearing glasses; thus, cataract surgery is the treatment for cataract patients with advanced disease.

Cataract removal surgery can be performed at any disease stage, and 90% of patients can achieve a corrected vision of 20/40 or better [5, 6]. Phacoemulsification is the most widely used cataract surgery in the developed world and employs ultrasonic energy to emulsify the cataract lens [7]. Varying degrees of inflammation will occur after surgery due to mechanical damage and the reaction of the residual lens epithelium with the foreign intraocular lens [8]. These factors can cause membrane disorders of local ocular cells, the production of active phospholipase A2, and the release of arachidonic

acid. Arachidonic acid may be transformed into prostaglandin (PG) by epoxidase catalysis [9]. The aggregation of PG in the eyes can lead to corestenoma during surgery and the release of inflammatory factors into aqueous fluid.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of anti-inflammatory drugs without a steroid structure that can prevent the transformation of arachidonic acid into PG [10]. During cataract surgery, NSAIDs may inhibit surgery-induced miosis, anterior chamber inflammation, and cystoid macular edema (CME), as well as relieve perioperative ocular itching and pain. NSAIDs were first approved by the FDA to prevent surgically induced miosis [11]. Newer NSAIDs are being investigated for their ability to reduce the incidence of CME after cataract surgery. CME is a major complication after cataract surgery and remains the primary cause of surgical visual disorders. The pathogenesis of CME is unclear; however, most researchers believe that inflammation after cataract surgery is the primary cause of CME [12]. Whether NSAIDs can effectively prevent the development of CME remains controversial. Recent comprehensive analyses investigated the ability of NSAIDs to reduce the incidence of CME after cataract surgery; however, a positive effect was not observed [13–16].

Although ambiguity surrounds NSAIDs regarding CME prevention, NSAIDs play an important role in cataract surgery. In this study, we explored the value of topical NSAID application for inhibiting anterior chamber inflammation. NSAID ophthalmic preparations have very similar anti-inflammatory mechanisms, yet their therapeutic efficacies differ. Therefore, this study attempted to analyze the effects of various NSAIDs using a network meta-analysis.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [17].

Data search strategy and selection criteria

A literature search was independently performed by two investigators using electronic databases, including PubMed, Embase, and the Cochrane Library, to identify articles published prior to October 2016 using the following search keywords: "cataract surgery," "random*," and "topical*." The bibliographies of the obtained publications and the references of the relevant reviews were checked to ensure that no relevant studies were unintentionally omitted. The studies included in this meta-analysis met the following criteria: (1) the study had a blinded, randomized controlled trial (RCT) design, where one group was treated with NSAIDs and another group was treated with a blank, placebo, or alternate NSAID; (2) the study included patients after cataract surgery; (3) the patients received anti-inflammatory treatment after surgery; and (4) one of the following outcomes was included in the study: anterior chamber inflammation, ocular pain relief, or treatment-related/serious ocular adverse events. The exclusion criteria included the following: (1) non-cataract surgery studies; (2) steroid drug-related studies and experimental/control groups combined with steroid drug therapy; (3) anesthesia-related studies; (4) surgical method-related studies; and (5) undesired outcome studies. Reviews, case reports, conference reports, basic research, and editorial comments were also excluded.

Data extraction and quality assessment

Two investigators independently extracted the following information from each eligible study: the name of the first author, publication year, location, sample size, average age (total or experimental group), ratio of males to females, experimental intervention, control intervention, and follow-up time. We assessed the methodological quality of the included trials using the Cochrane Collaboration tool [18]. Studies were graded as having a "low risk," "high risk," or "unclear risk" of bias across the seven specified domains.

We were primarily interested in the treatment effect of NSAIDs on the relief of anterior chamber inflammation after cataract surgery. Therefore, we selected and analyzed three important outcomes for clinical decision making according to GRADE guidelines. Our analysis included overall anterior chamber inflammation, subjects with 0–5 anterior chamber cells and the complete absence of anterior chamber flare, the number of ocular pain-free patients during the early postoperative period following surgery, and the incidence of treatment-related/serious ocular adverse events. We also used the GRADE approach to assess the network meta-analysis quality, with four levels graded from high (best) to very low (worst) [19]. This method considered the quality of direct and indirect evidence, as well as the quality of network evidence according to the inconsistency between direct and indirect evidence and the intransitivity among all related pieces of evidence. We performed "node splitting" to separate the indirect evidence from the direct evidence to inform these evaluations [20].

Statistical analysis

We performed a meta-analysis using a random-effects model. For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the sizes of the effects. We also used a random-effects network meta-analysis for mixed multiple treatment comparisons because this approach fully preserves the within-trial randomized treatment comparisons in each trial [21]. To rank the treatments for each outcome, we used surface under the cumulative ranking (SUCRA) probabilities [22]. Comparison-adjusted funnel

plots were used to determine whether small-study effects were present in our analysis [23].

Results

Literature search

Figure 1 shows the flow of study inclusion in the meta-analysis. We identified 1,127 articles after duplicates were removed. Of these, 1,042 were excluded after the titles and abstracts were screened. The full text of the remaining 85 articles was assessed, and 66 articles were excluded for the following reasons: undesired outcomes (36); experimental/control groups combined with steroid drug therapy studies (18); studies without a blinded design (7); duplicate publications (2); non-cataract surgery studies (2); and letters to the editor (1). Ultimately, 19 trials assessing 7,234 patients were included in our systematic review [24–42] (Fig. 1, Table 1).

The included studies were published between 1987 and 2015. The average subject age ranged from 65 to 75 years, and there were more women than men. All included patients received cataract surgery (phacoemulsification or extracapsular cataract extraction) with posterior chamber intraocular lens implantations, except one early article [42]. Three articles included patients with moderate-to-severe ocular inflammation after cataract surgery [34, 36, 41], which is an indirect degradation factor according to GRADE.

In our study, the researched topical NSAIDs were bromfenac, diclofenac, flurbiprofen, indomethacin, ketorolac, nepafenac, and piroxicam. One article included two RCTs [25], and one article had a three-arm design [39]. Three studies researched comparisons among NSAIDs [37–39], and another study researched comparisons between NSAIDs and placebos. The follow-up duration of the included studies ranged from one day to six weeks. In this meta-analysis, we included RCT studies with a blind design. Most studies were well designed; thus, the overall quality of the included studies was satisfactory (Fig. 2).

A total of 13 studies included findings of anterior chamber inflammation. The included NSAIDs were bromfenac, diclofenac, flurbiprofen, ketorolac, and nepafenac. All included drugs were directly compared with a placebo; there was also a direct comparison between diclofenac and flurbiprofen

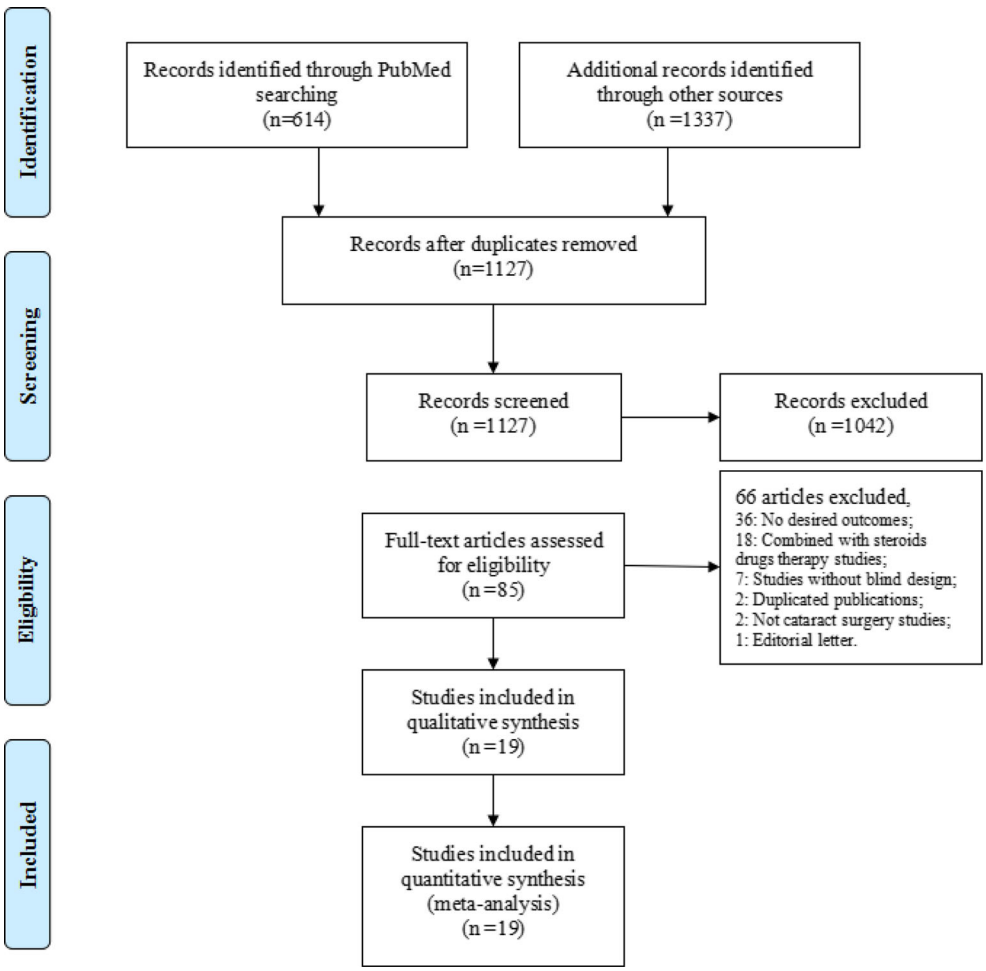

Fig. 1 PRISMA flowchart illustrating the selection of studies included in our analysis

Table 1 Characteristics of the included studies

Author	Year	Location	Sample Size	Age (years)#	Male/ Female	Type of Surgery	Experimental	Control	Follow-up##
John A. Hovanesian [24]	2015	U.S.	808	69 ± 9.4	335/473	Cataract surgery or refractive lens exchange	Ketorolac 0.3%	Placebo	14 D
Satish S. Modi [25]	2014	Europe; U.S.	2022	68.9 ± 9.22	866/1156	Phacoemulsification with posterior chamber IOL implantation	Nepafenac 0.1% Nepafenac 0.3%	Placebo Placebo	6 W
Thomas R. Walters [26]	2014	U.S.	440	68.4 ± 10.7	153/287	Cataract surgery with posterior chamber IOL implantation	Bromfenac 0.07%	Placebo	22 D
Jiro Numaga [27]	2011	Japan	211	NA	98/113	Cataract extraction with IOL implantation	Nepafenac 0.1%	Placebo	14 D
Bonnie A. Henderson [28]	2011	U.S.	872	68.9 ± 10.2	359/513	Cataract surgery with posterior chamber IOL implantation	Bromfenac 0.09%	Placebo	14 D
Eric D. Donnenfeld [29]	2011	U.S.	511	70(28–94)	218/293	Phacoemulsification with posterior chamber IOL implantation	Ketorolac 0.45%	Placebo	14 D
W. Andrew Maxwell [30]	2008	U.S.	212	70.4 ± 10.6	91/121	Phacoemulsification with posterior chamber IOL implantation	Nepafenac 0.1%	Placebo	14 D
Robert H. Stewart [31]	2007	U.S.	527	69.7	246/281	Cataract surgery with posterior chamber IOL implantation	Bromfenac 0.09%	Placebo	14 D
Stephen S. Lane [32]	2007	U.S.	476	70(27–93)	NA	Cataract surgery with posterior chamber IOL implantation	Nepafenac 0.1%	Placebo	14 D
B. Scuderi [33]	2003	Italy	40	75.1 ± 7.12	18/22	Phacoemulsification with posterior chamber IOL implantation	Piroxicam 0.5%	Placebo	1 M
Kerry D. Solomon [34]	2001	U.S.	104	69 ± 12	38/66	Cataract surgery with IOL implantation	Ketorolac 0.5%	Placebo	14 D
Robert Stewart [35]	1999	U.S.	176	72(53–94)	74/102	Cataract extraction with IOL implantation	Ketorolac 0.5%	Placebo	1 D
Jeff Jeoer [36]	1999	U.S.	102	71 ± 8	49/53	Cataract surgery with posterior chamber IOL implantation	Ketorolac 0.5%	Placebo	14 D
Allan J. Flach [37]	1998	U.S.	120	71(47–89)	113/7	Cataract surgery with posterior chamber IOL implantation	Diclofenac 0.1%	Ketorolac 0.5%	30 D
I. Kocak [38]	1998	Turkey	43	65 ± 9	21/22	Cataract extraction with IOL implantation	Diclofenac 0.1%	Flurbiprofen 0.03%	6 W
Michael Diestelhorst [39]	1996	Germany	117	72 ± 1	26/73	Phacoemulsification with posterior chamber IOL implantation	Diclofenac 0.1% Indomethacin 1%	Flurbiprofen 0.03%	14 D
J. Elliott Blaydes [40]	1993	U.S.	233	71.2 ± 1	82/151	Phacoemulsification with posterior chamber IOL implantation	Flurbiprofen 0.03%	Placebo	14 D
Manus C. Kraff [41]	1994	U.S.	148	70.6 ± 9.3	58/90	Phacoemulsification with posterior chamber IOL implantation	Diclofenac 0.1%	Placebo	14 D
David Sabiston [42]	1987	U.S.	72	73.7 ± 11.2	39/33	Cataract extraction surgery	Flurbiprofen 0.03%	Placebo	14 D

Abbreviations: IOL Intraocular lens; NA Not available.

#: Mean ± Standard Deviation; Median(Minimum-Maximum).

##: D day; W week.

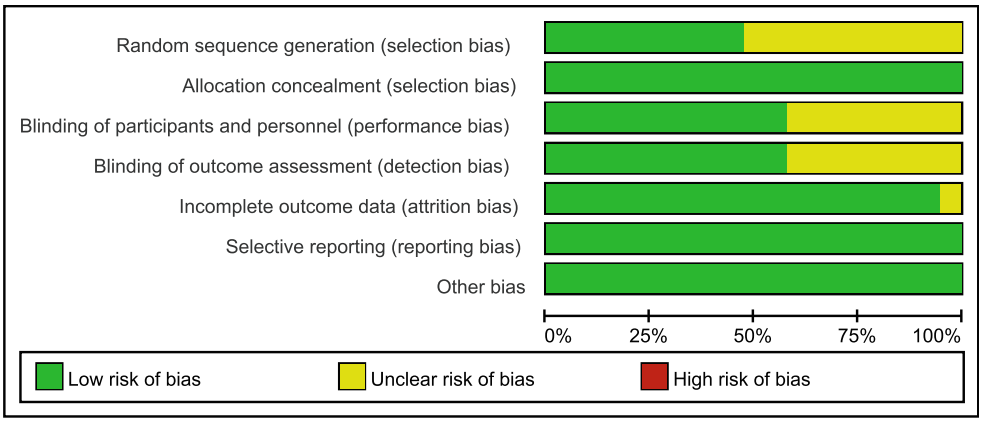

Fig. 2 Risk of bias graph for each included study

(Fig. 3a); in this figure, the nodes are weighted according to the number of studies that evaluated each treatment, and the edges are weighted according to the precision of the direct estimate for each pairwise comparison. In pairwise comparisons, bromfenac was significantly inferior to nepafenac regarding anterior chamber cells and flare reduction in indirect and network comparisons (logOR: −0.58; 95% CI: −1.11 to −0.05). Bromfenac was significantly superior to the placebo in direct and network comparisons (logOR: 1.04; 95% CI: 0.62 to 1.46). Diclofenac was superior to flurbiprofen in indirect (logOR: 1.38; 95% CI: 0.21 to 2.55) and network comparisons (logOR: 0.98; 95% CI: 0.06 to 1.90). Diclofenac was also superior to the placebo in direct (logOR: 2.19; 95% CI: 1.26 to 3.13) and network comparisons (logOR: 1.94; 95% CI: 1.13 to 2.75). Flurbiprofen was significantly better than the placebo for controlling ocular inflammation in all comparisons (network: logOR 0.96; 95% CI: 0.29 to 1.62). Ketorolac showed a significant advantage over the placebo in the network comparison (logOR: 1.31; 95% CI: 0.80 to 1.82), as did nepafenac (logOR: 1.63; 95% CI: 1.30 to 1.95) (Table 2). In terms of SUCRA rank, diclofenac was the most likely to improve anterior chamber

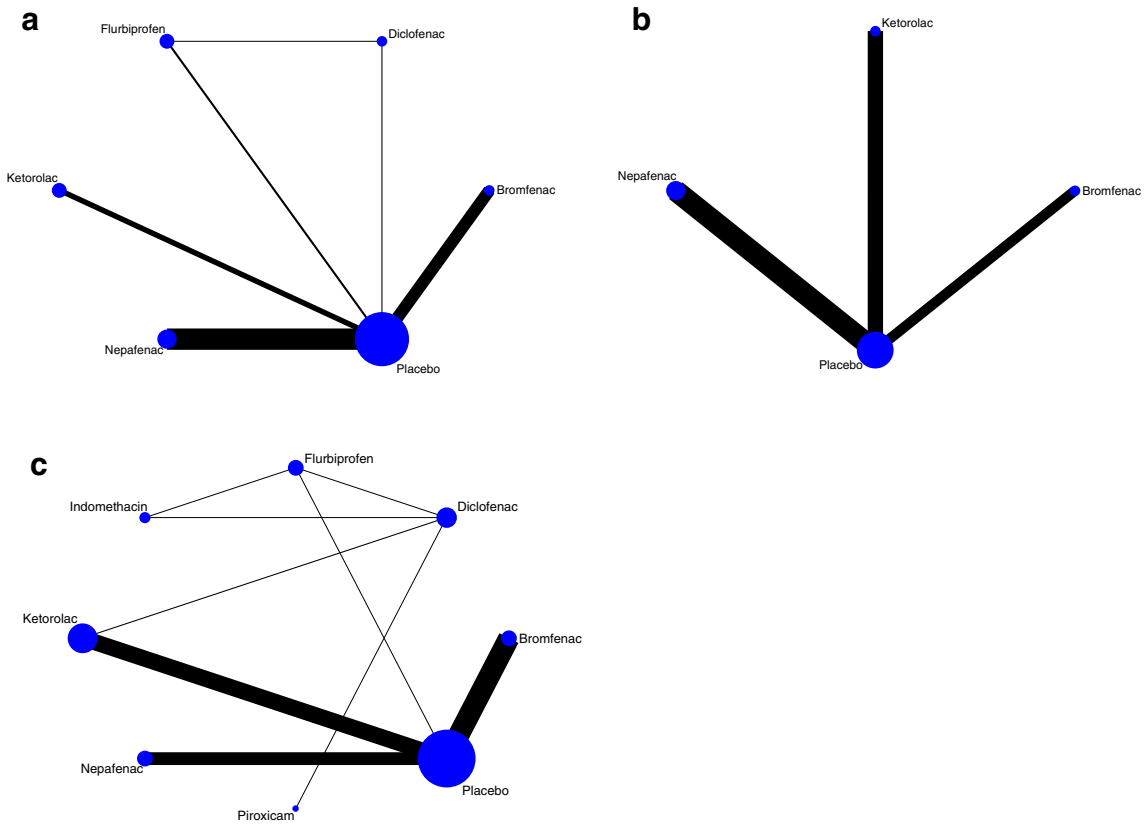

Fig. 3 Network of comparisons for all major outcomes included in the analysis. **a**. Anterior chamber inflammation; **b**. freedom from ocular pain; and **c**. treatment-related/serious ocular adverse events

Table 2 The summary comparisons of effect size and quality of three main outcomes

Outcomes/Interventions	No. of studies	Direct comparisons		Indirect comparisons		Network comparisons	
		logOR (95%CI)	Quality	logOR (95%CI)	Quality	logOR (95%CI)	Quality
Anterior chamber inflammation							
Bromfenac vs.							
Diclofenac				−0.89 (−1.81,0.02)	Moderate*	−0.89 (−1.81,0.02)	Moderate*
Flurbiprofen				0.09 (−0.70,0.87)	Moderate*	0.09 (−0.70,0.87)	Moderate*
Ketorolac				−0.27 (−0.93,0.39)	Low*,†	−0.27 (−0.93,0.39)	Low*,†
Nepafenac				**−0.58 (−1.11,-0.05)**	Low*,†	**−0.58 (−1.11,-0.05)**	Low*,†
Placebo	2	**1.04 (0.62,1.46)**	Moderate*	NA	NA	**1.04 (0.62,1.46)**	Moderate*
Diclofenac vs.							
Flurbiprofen	1	0.40 (−1.02,1.82)	Very low*,†,‡	**1.38 (0.21,2.55)**	Moderate*	**0.98 (0.06,1.90)**	Low*,#
Ketorolac				0.63 (−0.33,1.59)	Low*,†	0.63 (−0.33,1.59)	Low*,†
Nepafenac				0.30 (−0.57,1.18)	Low*,†	0.30 (−0.57,1.18)	Low*,†
Placebo	1	**2.19 (1.26,3.13)**	Moderate*	1.21 (−0.37,2.80)	Very low*,†,‡	**1.94 (1.13,2.75)**	Low*,#
Flurbiprofen vs.							
Ketorolac				−0.35 (−1.18,0.47)	Low*,†	−0.35 (−1.18,0.47)	Low*,†
Nepafenac				−0.67 (−1.41,0.07)	Low*,†	−0.67 (−1.41,0.07)	Low*,†
Placebo	2	**0.81 (0.11,1.52)**	Moderate*	**1.79 (0.09,3.50)**	Very low*,†,‡	**0.96 (0.29,1.62)**	Moderate*
Ketorolac vs.							
Nepafenac				−0.31 (−0.92,0.29)	Low*,†	−0.31 (−0.92,0.29)	Low*,†
Placebo	3	**1.31 (0.80,1.82)**	Low*,†	NA	NA	**1.31 (0.80,1.82)**	Low*,†
Nepafenac vs.							
Placebo	4	**1.63 (1.30,1.95)**	Low*,†	NA	NA	**1.63 (1.30,1.95)**	Low*,†
Ocular pain relief							
Bromfenac vs.							
Ketorolac				0.86 (−0.09,1.81)	Moderate*	0.86 (−0.09,1.81)	Moderate*
Nepafenac				−0.58 (−1.45,0.29)	Low*,†	−0.58 (−1.45,0.29)	Low*,†
Placebo	2	**1.80 (1.12,2.49)**	Moderate*	NA	NA	**1.80 (1.12,2.49)**	Moderate*
Ketorolac vs.							
Nepafenac				**−1.45 (−2.30,-0.59)**	Low*,†	**−1.45 (−2.30,-0.59)**	Low*,†
Placebo	2	**0.94 (0.28,1.60)**	Moderate*	NA	NA	**0.94 (0.28,1.60)**	Moderate*
Nepafenac vs.							
Placebo	4	**2.38 (1.84,2.92)**	Low*,†	NA	NA	**2.38 (1.84,2.92)**	Low*,†
Treatment-related/serious ocular adverse events							
Bromfenac vs.							
Diclofenac				−0.29 (−1.68,1.11)	Low*,†	−0.29 (−1.68,1.11)	Low*,†
Flurbiprofen				0.75 (−0.72,2.21)	Moderate*	0.75 (−0.72,2.21)	Moderate*
Indomethacin				0.49 (−1.55,2.54)	Low*,‡	0.49 (−1.55,2.54)	Low*,‡
Ketorolac				0.16 (−0.61,0.93)	Low*,†	0.16 (−0.61,0.93)	Low*,†
Nepafenac				−0.06 (−0.98,0.85)	Low*,†	−0.06 (−0.98,0.85)	Low*,†
Piroxicam				−2.61 (−5.34,0.11)	Very low*,†,‡	−2.61 (−5.34,0.11)	Very low*,†,‡
Placebo	3	**0.65 (0.14,1.16)**	Moderate*	NA	NA	**0.65 (0.14,1.16)**	Moderate*
Diclofenac vs.							
Flurbiprofen	1	0.43 (−1.57,2.44)	Low*,‡	NA	NA	1.03 (−0.46,2.52)	Low*,‡
Indomethacin	1	0.43 (−1.57,2.44)	Low*,‡	NA	NA	0.78 (−1.06,2.62)	Low*,‡
Ketorolac	1	0.74 (−0.65,2.13)	Very low*,†,‡	−0.61 (−3.27,2.05)	Low*,†	0.45 (−0.78,1.68)	Low*,†
Nepafenac				0.22 (−1.28,1.73)	Low*,†	0.22 (−1.28,1.73)	Low*,†
Piroxicam	1	−2.33 (−4.66,0.01)	Very low*,†,‡	NA	NA	−2.33 (−4.66,0.01)	Very low*,†,‡
Placebo				0.94 (−0.36,2.24)	Moderate*	0.94 (−0.36,2.24)	Moderate*

Table 2 (continued)

Outcomes/Interventions	No. of studies	Direct comparisons		Indirect comparisons		Network comparisons	
		logOR (95%CI)	Quality	logOR (95%CI)	Quality	logOR (95%CI)	Quality
Flurbiprofen vs.							
Indomethacin	1	0 (−1.84,1.84)	Low*,‡	NA	NA	−0.25 (−2.00,1.49)	Low*,‡
Ketorolac				−0.58 (−2.00,0.83)	Low*,†	−0.58 (−2.00,0.83)	Low*,†
Nepafenac				−0.81 (−2.37,0.75)	Low*,†	−0.81 (−2.37,0.75)	Low*,†
Piroxicam				**−3.36 (−6.13,-0.59)**	Very low*,†,‡	**−3.36 (−6.13,-0.59)**	Very low*,†,‡
Placebo	1	−0.50 (−2.15,1.15)	Moderate*	0.85(−1.66,3.36)	Very low*,†,‡	−0.10 (−1.47,1.28)	Moderate*
Indomethacin vs.							
Ketorolac				−0.33 (−2.31,1.65)	Very low*,†,‡	−0.33 (−2.31,1.65)	Very low*,†,‡
Nepafenac				−0.56 (−2.67,1.56)	Low*,†	−0.56 (−2.67,1.56)	Low*,†
Piroxicam				**−3.11 (−6.08,-0.13)**	Very low*,†,‡	**−3.11 (−6.08,-0.13)**	Very low*,†,‡
Placebo				0.16 (−1.82,2.14)	Moderate*	0.16 (−1.82,2.14)	Moderate*
Ketorolac vs.							
Nepafenac				−0.23 (−1.17,0.72)	Low*,†	−0.23 (−1.17,0.72)	Low*,†
Piroxicam				**−2.78 (−5.42,-0.13)**	Very low*,†,‡	**−2.78 (−5.42,-0.13)**	Very low*,†,‡
Placebo	5	0.54 (−0.05,1.14)	Low*,†	−0.81 (−3.75,2.14)	Very low*,†,‡	0.49 (−0.09,1.07)	Low*,†
Nepafenac vs.							
Piroxicam				−2.55 (−5.33,0.23)	Very low*,†,‡	−2.55 (−5.33,0.23)	Very low*,†,‡
Placebo	3	0.71 (−0.03,1.46)	Low*,†	NA	NA	0.71 (−0.03,1.46)	Low*,†
Piroxicam vs.							
Placebo				**3.26 (0.59,5.94)**	Very low*,†,‡	**3.26 (0.59,5.94)**	Very low*,†,‡

Abbreviations: CI confidence interval; logOR logarithm odds ratio; NA not available.

* Study limitation; † Indirectness; ‡ Imprecision; # Incoherence.

inflammation after cataract surgery, followed by nepafenac, ketorolac, bromfenac, and flurbiprofen (Fig. 4a). Although the quality of the network data for diclofenac was low, the results remained robust due to the high quality of the studies overall.

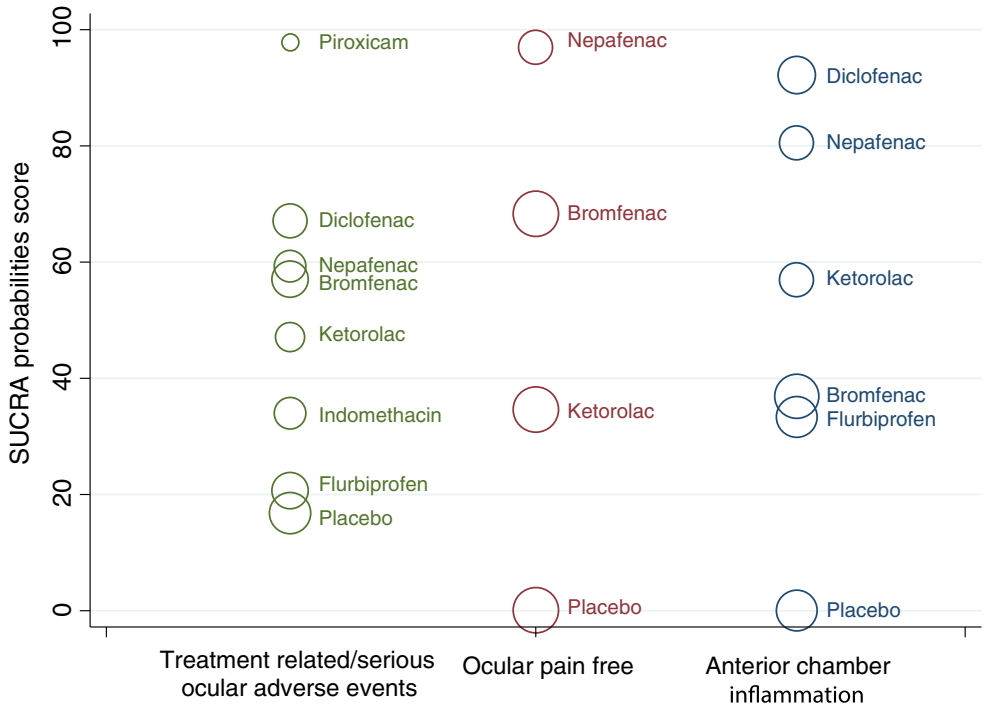

Fig. 4 The SUCRA score of each NSAID in all primary outcomes. The circles are weighted by the average evidence quality

Additionally, the comparison-adjusted funnel plot used to assess publication bias and determine the presence of small-study effects did not indicate a publication bias (Fig. 5a).

Eight articles reported an outcome of ocular pain relief after surgery. Bromfenac, ketorolac, and nepafenac were included, all of which were directly compared to placebos but not to other drugs (Fig. 3b). In indirect and network comparisons, ketorolac was significantly inferior to nepafenac in relieving ocular pain relief after cataract surgery (logOR: −1.45; 95% CI: −2.30 to −0.59). In direct and network comparisons, a higher proportion of patients reported ocular pain relief with the application of an NSAID than the placebo; these NSAIDs included bromfenac (logOR: 1.80; 95% CI: 1.12), ketorolac (logOR: 0.94; 95% CI: 0.28 to 1.60), and nepafenac (logOR: 2.38; 95% CI: 1.84 to 2.92) (Table 2). Nepafenac was most likely to improve postoperative ocular pain relief, followed by bromfenac and ketorolac (Fig. 4b). Notably, only three NSAIDs were included in these comparisons. A global inconsistency was found in our test ($p < 0.001$); thus, further studies are needed to confirm these results. The comparison-adjusted funnel plot revealed no clear publication bias (Fig. 5b).

Fifteen articles examined treatment-related/seriously adverse events. They analyzed seven NSAIDs: bromfenac, diclofenac, flurbiprofen, indomethacin, ketorolac, nepafenac, and piroxicam. The drugs that were directly compared to a placebo included bromfenac, flurbiprofen, ketorolac, and nepafenac. The drugs that were directly compared to diclofenac included flurbiprofen, indomethacin, ketorolac, and piroxicam. There was also a direct comparison between flurbiprofen and indomethacin (Fig. 3c). For pairwise comparisons, there were no significant differences between NSAIDs and placebos regarding related adverse events. In direct and network comparisons, only bromfenac (logOR: 0.65; 95% CI: 0.14 to 1.16) and piroxicam (logOR: 3.26; 95% CI: 0.59 to 5.94) resulted in significantly fewer related adverse events than did the placebos. Additionally, flurbiprofen (logOR: −3.36; 95% CI: −6.13 to −0.59), indomethacin (logOR: −3.11; 95% CI: −6.08 to −0.13) and ketorolac (logOR: −2.78; 95% CI: −5.42 to −0.13) were significantly inferior to piroxicam in both indirect and network comparisons. However, the quality of evidence for these indirect comparisons was very low (Table 2). The SUCRA results showed that although there were fewer differences among the NSAIDs, these drugs were overall slightly better than the placebos regarding related adverse events. This finding indicated that piroxicam is most likely to have the fewest related adverse

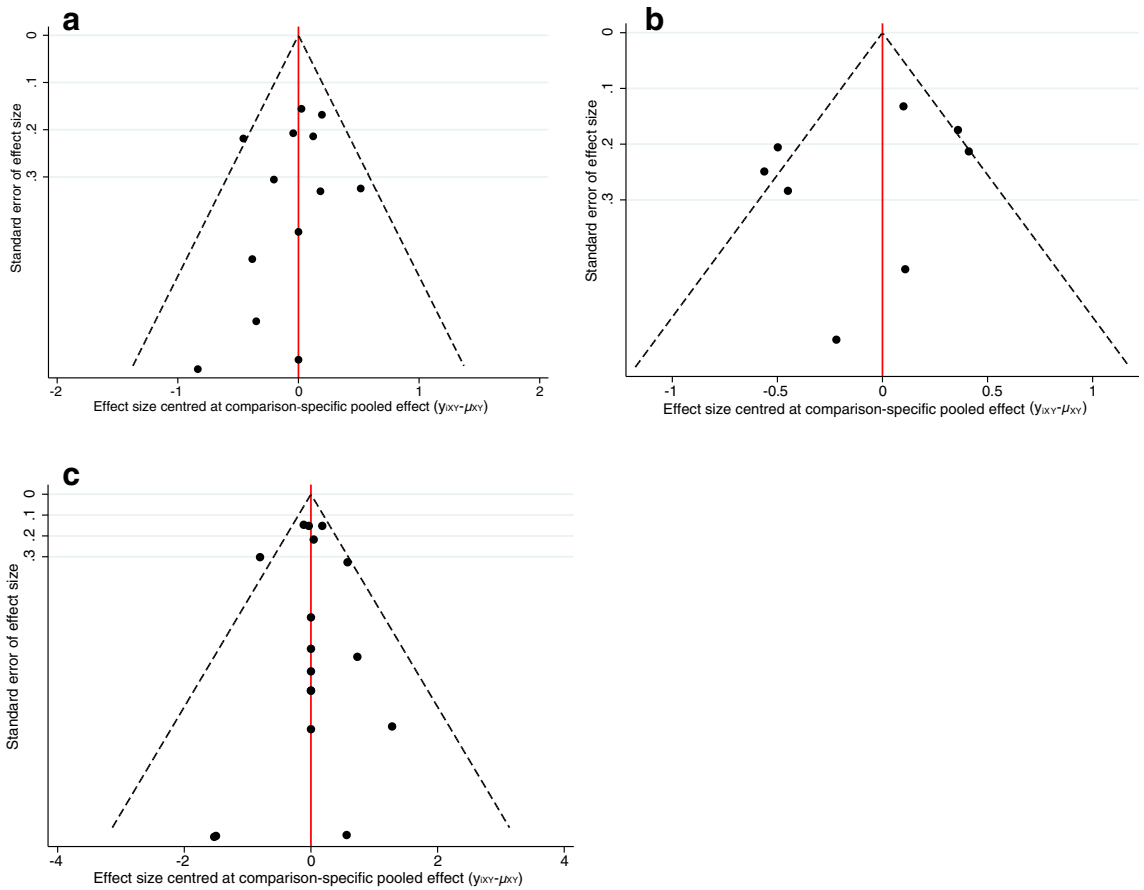

Fig. 5 The comparison-adjusted funnel plot for assessing all primary outcomes. **a**. Anterior chamber inflammation; **b**. freedom from ocular pain; and c. treatment-related/serious ocular adverse events

events. However, due to the very low evidence quality, further studies are needed for robust results. In addition to piroxicam, diclofenac is another nearly ideal drug, followed by nepafenac, bromfenac, and ketorolac (Fig. 4c). The comparison-adjusted funnel plot did not reveal any obvious publication bias (Fig. 5c).

Discussion

In this study, we performed a network meta-analysis to assess the efficacy and safety of NSAIDs for anterior chamber inflammation treatment after cataract surgery. The results included overall anterior chamber inflammation, ocular pain-free events, and treatment-related/serious ocular adverse events. Diclofenac was most likely to improve anterior chamber inflammation after cataract surgery followed by nepafenac, ketorolac, bromfenac, and flurbiprofen. Nepafenac was the most likely to reduce postoperative ocular pain, followed by bromfenac and ketorolac. Finally, piroxicam was the most likely to show the fewest related adverse events, but the evidence exhibited low robustness. Moreover, diclofenac was another nearly ideal drug, followed by nepafenac, bromfenac, and ketorolac. In a comprehensive analysis, compared with placebos, NSAIDs were shown to be effective drugs for reducing anterior chamber inflammation and ocular pain relief; NSAIDs also had fewer treatment-related/serious ocular adverse events. Furthermore, diclofenac, nepafenac, ketorolac, and bromfenac demonstrated relatively greater significant effects.

Anterior chamber cells and the presence of anterior chamber flare were the primary measurements for anterior chamber inflammation reduction; however, the evaluation criteria differed slightly among the included studies. Our analysis used 0–5 anterior chamber cells and the absence of flare as inflammation relief criteria. However, some studies used non-anterior chamber cells and the absence of flare as assessment criteria [25]. We included only three types of NSAIDs in our ocular pain relief analysis, and criteria were based on the subjective judgments of the patients. However, because only well-designed RCTs were included in our analysis, the influence of subjective assessment on the outcome was reduced. Adverse event-related outcomes were somewhat subjective due to varying assessment criteria among the assessors and studies. However, we analyzed only treatment-related or serious adverse events that emerged when these events had a negative impact on the administration of NSAIDs. Additionally, we did not analyze the pupil size results because the degree of miosis is also affected by individual differences, ocular stress reactions, and mydriatic drugs.

This study included the topical NSAIDs most commonly used in ophthalmology. Among them, diclofenac belongs to the phenyl acetic acid category, nepafenac belongs to the phenylacetamide category, and ketoprofen and bromfenac belong to the acetic acid category. Notably, diclofenac has unique characteristics. In addition to its ability to inhibit prostaglandin synthesis by suppressing cyclooxygenase, diclofenac shows bacteriostatic activity by inhibiting bacterial DNA synthesis and the lipoxygenase pathway, as well as reducing the formation of leukotrienes [43, 44]. These reactions may further suppress inflammation after cataract surgery with fewer serious adverse events.

The incidence of CME has been significantly reduced because cataract surgery has become more minimally invasive. Notably, cataract extraction with intraocular lens implantation is more minimally invasive and produces less inflammation than does intracapsular or extracapsular cataract extraction. However, constant technological optimization reducing the need for physical stimulation, ultrasonic influence, intraoperative perfusion fluid, viscoelastic agents, and other adjuvant drugs may also reduce inflammatory reactions after surgery. In aged cataract patients, phacoemulsification provided more advantages in uncorrected visual acuity and surgically induced astigmatism than did manual incision cataract surgery [45]. Theoretically, the perioperative application of NSAIDs may further prevent inflammatory reactions and reduce the incidence of CME. However, current systematic reviews could not make definitive conclusions because of a lack of high-quality evidence [13–16]. One study considered NSAIDs to be effective in chronic CME after cataract surgery [13]; however, another study suggested that while NSAIDs may accelerate visual recovery a few weeks after surgery, the long-term effects remain unclear [16]. NSAIDs were also found to have advantages in the treatment of CME compared to steroidal drugs [46]. Therefore, the effects of NSAID treatment on acute and chronic CME remain controversial.

Although this study excluded all steroid-related and combined treatment studies, corticosteroid drugs combined with antibiotics may reduce ocular bacterial flora and inflammation after cataract surgery [47], and a combination with NSAIDs may reduce the incidences of CME and macular thickening [48]. Treatment with steroid drugs can produce severe adverse reactions, including hypoadrenocorticism, ulcer disease, increases in intraocular pressure, and a high risk of secondary ocular infections. NSAIDs are superior to steroid drugs for inhibiting PG synthesis and reducing the incidence of CME. Moreover, with fewer adverse effects, NSAIDs have been reported to decrease visual acuity and sticky sensations. They also have a low probability of inducing corneal melting and perforation, which require monitoring in clinical applications.

In contrast with other reviews, we analyzed important inflammation-related outcomes according to GRADE recommendations and classified the quality of evidence into four levels using both direct and indirect comparisons. Although this approach required subjective assessments, the transparency of these choices should be enhanced.

There are several limitations to our study. First, our analysis was performed at the study level and not at an individual level. Second, our study included only inflammation-related outcomes; the effects on CME remain controversial. Third, our analysis had unexplained heterogeneity and global inconsistency, which may have resulted from differences in the administered doses, operation processes, concomitant treatments, or follow-up durations.

Conclusion

In conclusion, NSAIDs represent a class of drugs that are more effective for reducing anterior chamber inflammation and relieving ocular pain than placebos. NSAIDs also show fewer treatment-related/serious ocular adverse events. Diclofenac, nepafenac, ketorolac, and bromfenac have relatively greater significant effects than other topical NSAIDs.

Authors' contributions PD conceived of the study; PD and YL searched the literature and collected the data; YL performed the statistical analyses; PD drafted the manuscript; JwL reviewed the manuscript. All authors have read and approved the final paper.

Compliance with ethical standards

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Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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