European Journal of Inflammation

Letter to the editor

European Journal of Inflammation
2015, Vol. 13(2) 130–135

DOI: 10.1177/1721727X15601732
eji.sagepub.com
SAGE

Topical bromfenac for post-cataract extraction: A systematic review and pooled analysis

M-Z Zhai,[1,2*] H-H Wu,[1,3*] J-J Li,[1*] L-P Jiang,[4] Z-S Gao,[5] W Hu,[1] Y Liu[6*] and Y-T Wang[1*]

Abstract

Bromfenac, a promising ophthalmic non-steroidal anti-inflammatory drug, has been used once daily for postoperative ocular inflammation and pain with satisfying efficacy, however, no integrated conclusion on its safety in clinical settings has been drawn. The purpose of this pooled analysis is to investigate the safety and efficacy of once daily bromfenac for ocular inflammation and pain among patients after cataract extraction (CE). MEDLINE, PsycINFO, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to September 2014. Randomized controlled trials (RCTs) that studied topical bromfenac after CE were analyzed. Included studies were systemically reviewed, and effects were summarized using odds ratio (OR) with suitable effect model. Four RCTs involving 2294 participants were included. Topical bromfenac significantly increased the proportion of cleared ocular inflammation (OR, 2.37; 95% confidence interval [CI], 1.83–3.07; P <0.00001), ocular pain free (OR, 5.14; 95% CI, 4.07–6.49; P <0.00001), and decreased risk of overall adverse events (OR, 0.47; 95% CI, 0.38–0.58; P <0.00001). Bromfenac has been shown to be a safe and effective treatment for postoperative pain and inflammation in subjects undergoing CE. This is evidenced by the lower incidence of adverse events and the low scores for ocular pain and inflammation across multiple RCTs. However, demographics, co-morbidities of study participants, and the amount of co-medication were not reported, these possible sources of heterogeneity should be examined in future clinical trials.

Keywords

bromfenac, cataract extraction, meta-analysis

Received 26 May 2015; accepted 27 July 2015

Introduction

The leading cause of blindness all over the world is cataracts[1] and one common solution for cataracts is cataract extraction (CE) which reduces a patient's visual impairment by more than one-third;[2,3] however, the postoperative inflammation and pain is a clinic challenge. Cyclooxygenases (COXs) play important roles in synthesizing prostaglandins that contribute to the onset of postoperative pain and inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COXs so as to inhibit postoperative pain and inflammation. It is becoming prevalent to begin NSAIDs dosing anywhere from 1–2 days before surgery to reduce postoperative inflammation and pain.[4]

[1]Department of Emergency, Xi'jing Hospital, Fourth Military Medical University, Xi'an, PR China
[2]Department of Medical Psychology, Fourth Military Medical University, Xi'an, PR China
[3]Department of Anesthesiology, Fuzhou General Hospital of Nanjing Military Region, Fuzhou, PR China
[4]Department of Ophthalmology, the Second People's Hospital of Rongcheng, Rongcheng, PR China
[5]Department of Ophthalmology, Second People's Hospital of Shanxi Province, Xi'an, PR China
[6]Department of Outpatient, Xi'jing Hospital, Fourth Military Medical University, Xi'an, PR China
*Equal contributors.

Corresponding authors:
Yu-Tong Wang, Department of Emergency, Xi'jing Hospital, Fourth Military Medical University, No. 15 West Changle Road, Xi'an, 710032, PR China.
Email: wangyutong@fmmu.edu.cn

Ya Liu, Outpatient Department, Xi'jing Hospital, Fourth Military Medical University, No. 15 West Changle Road, Xi'an, 710032, PR China.
Email: liuya@fmmu.edu.cn

Bromfenac, a highly potent inhibitor for both COX-1 and 2 isoforms, belongs to the NSAID class but exhibits unique characteristics[5] that enhances lipophilicity and facilitates its moving across the epithelial layers[5] and prolongs the duration of analgesic and anti-inflammatory effect.[6,7] These superior therapeutic benefits of bromfenac have led to its ophthalmic use especially for the pain and inflammation control after CE.[8–10] Once-daily[11] dosing was previously approved in the USA and Japan and limiting the ocular exposure to bromfenac may result in decreased adverse events (AEs), which is important because, historically, ocular NSAID use has resulted in small numbers of corneal erosions or melts.[12–15] However, clinical consensus has not been reached concerning the safety of bromfenac. We thus performed the current systematic review and pooled analysis with the hope of reaching clinical consensus on the local application of bromfenac for CE.

Materials and methods

We performed the current pooled analysis following the QUORUM guidelines (Quality of Reporting of Meta-analyses)[16] and the recommendations of the Cochrane Collaboration.[17]

Data sources and searches

The electronic databases screened were MEDLINE, PsycINFO, Scopus, EMBASE, and The Cochrane Library (issue 9 of 12, September 2014) from 1990 to September 2014 by using the search phrases (bromfenac OR bromfenac ophthalmic solution OR BromDay OR Xibrom OR Yellox OR Prolensa) AND (cataract OR cataract surgery OR cataract extraction OR CE). A hand search in reference sections of included trials, published meta-analyses, and relevant review articles was conducted to identify additional articles.

Study selection

Any study meeting the following criteria was included in the current analysis: (1) Any randomized controlled trial (RCT), controlled clinical trial designed with at least two groups that one control group receiving vehicle-controlled ophthalmic solution, and the other receiving once-daily dosing of any type of topical bromfenac ophthalmic solution; (2) Patients of any age and gender undergoing CE; and (3) Trials reporting at least one outcome mentioned below.

Outcome measurement

Primary efficacy outcomes were the proportion of cleared ocular inflammation as determined by a summed ocular inflammation score (SOIS) of 0 and ocular pain free. Postoperative ocular inflammation was measured by SOIS, and ocular pain was evaluated by the ocular comfort grading assessment (OCGA) reported in the participants' diaries.

Secondary efficacy outcomes were the drug-related reasons for discontinuation, including adverse events, lack of efficacy, and receiving other rescue medication.

Safety outcomes were the common adverse events, including ocular inflammation, ocular pain, foreign body sensation, and systemic adverse events.

Data extraction

Characteristics of patients and trial design were recorded. If the data were unavailable in the article, the corresponding authors were contacted for missing information. If the outcomes in the published studies were presented in graph only, Image J software (Version 2.1.4.7, National Institutes of Health, USA, http://imagej.nih.gov) was used to retrieve the related data.

All data were independently extracted using a standard data collection form by two reviewers, and then entered into Review Manager analysis software (RevMan, Version 5.2.7) using the double-entry system by the other two reviewers. All discrepancies were rechecked and consensus was reached by discussion with a third reviewer. A record of reasons for excluding studies was kept.

Assessment of study quality and risk of bias

A critical quality evaluation of the included studies was performed by two reviewers by using a 5-point Jadad scale.[18] The risk of bias was then further independently evaluated according to the recommendations from the Cochrane collaboration.[17]

Assessment of heterogeneity and publication bias

We pooled all studies reporting the same primary or secondary outcomes together. The study heterogeneity

at overall level was then investigated by using a χ^2 test and calculated I^2.[19] When I^2 was smaller than 50%, a low heterogeneity was rated and the data were pooled with a fixed effect model. When I^2 was over 50%, a significant heterogeneity was rated and the data were pooled with a random effects model.[19] Subgroup analyses were used to identify the significant heterogeneity derived from different time points after CE (1 day, 3 ± 1 days, 8 ± 1 days, and 15 ± 1 days).

We performed the sensitivity analyses and L'Abbe graph to examine the effect of primary outcomes by excluding studies with significant clinical heterogeneity, and investigated the potential publication bias by using graphical (Begg's funnel plot)[20,21] and statistical tests (Egger's test).[21]

Statistical analysis

Binary variables were pooled by using odds ratio (OR) with 95% confidence intervals (CIs). If the 95% CI covered the value of 1, we considered that the difference between bromfenac and placebo group was not statistically significant. For the adverse events with significant difference between bromfenac and placebo group, number needed to treat (NNT) was further calculated. The pooled analyses were performed with RevMan according to Cochrane Handbook for Systematic Reviews of Interventions[19] and Stata 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Search results

The literature search yielded 52 citations. Initially, 21 records were removed because of duplicate publication. On a more detailed review, an additional 13 papers were excluded for the following reasons: pre-clinical experiments, comments, editorial, case reports, and reviews. Fourteen more papers were further excluded because of lacking parallel placebo control. Finally, the remaining four publications,[22–25] reporting data from 10 RCTs, met our selection criteria and were included in the pooled-analysis (Supplementary Figure 1).

Characteristics of the included studies

All 10 included RCTs were designed as prospective, randomized, double-blinded and placebo controlled trials, and their main characteristics were presented in Supplementary Table 1. In total, 1392 patients were randomly assigned to receive topical bromfenac ophthalmic solution, and 902 patients were assigned to placebo groups receiving vehicle-controlled ophthalmic solution.

Methodological quality and risk of bias

The Jadad score of each included study was presented in Supplementary Table 1, and all the quality scores were 5. The bias risk of included studies was presented in Supplementary Table 2.

Pooled analyses of primary efficacy outcomes

Postoperative ocular inflammation: All trials reported the proportion of cleared ocular inflammation as determined by an SOIS score of 0. The pooled analysis revealed that topical bromfenac improved ocular inflammation within 15 postoperative days compared with placebo (Supplementary Figure 2, OR, 2.37; 95% CI, 1.83–3.07; P <0.00001; also see Supplementary Figure 3). The I^2 value of 71% indicated significant heterogeneity.

High heterogeneity revealed by subgroup analysis was rated in postoperative days 3 (I^2 = 85%) and 8 (I^2 = 56%). Since the SOIS score of 0 was defined as a cell count of 0–5 and bromfenac was delivered 12–36 h after CE in the study from Donnenfeld's group,[22] this might have introduced bias to the pooled analysis. Besides, the postoperative day 3 data from the Henderson[24] study might have biased the pooled results (Supplementary Figure 4). Interestingly, when the data on postoperative day 3 from these two studies were excluded, there was no heterogeneity (OR, 1.35; 95% CI, 0.82–2.24; P = 0.24; I^2 = 0%), which was against the pooled one (OR, 3.64; 95% CI, 1.03–12.81; P = 0.04; I^2 = 85%). Other subgroup analyses on the different time points revealed that exclusion of Donnenfeld's study could not alter the pooled effect size and all the analyses were without heterogeneity (Supplementary Table 3).

Postoperative ocular pain: All trials reported that the proportion of ocular pain free was determined by an OCGA pain score of 0. The pooled analysis revealed that topical bromfenac attenuated postoperative ocular pain within 15 days compared with placebo (Supplementary Figure 5, OR, 5.14; 95% CI, 4.07–6.49; P <0.00001; also see Supplementary Figure 3). The I^2 value of 75% indicated significant heterogeneity.

High heterogeneity revealed by subgroup analysis was rated in day 1 (I^2 = 56%) because bromfenac was administered at 12–36 h after the CE in the Donnenfeld study, while at 24 h prior to surgery in other studies. However, the result (OR, 3.16; 95% CI, 2.52–3.96; P <0.00001; I^2 = 25%) was not significantly different from the pooled one (OR, 2.84; 95% CI, 2.11–3.84; P <0.00001; I^2 = 56%) when Donnenfeld[22] was excluded (Supplementary Table 3, Supplementary Figure 4). The subgroup analysis at other time points showed that there was the similar effect size with the pooled one, and all these analyses were without any heterogeneity (Supplementary Table 3).

Pooled analyses of secondary efficacy outcomes

Drug-related reasons for discontinuation: All trials reported the drug-related reasons for discontinuation (Supplementary Figure 6). The pooled analysis revealed that the patients in the topical bromfenac group experienced less discontinuation because of adverse events (OR, 0.28; 95% CI, 0.20–0.38; P <0.00001; I^2 = 0%), lack of efficacy (OR, 0.08; 95% CI, 0.06–0.11; P <0.00001; I^2 = 0%), or receiving other rescue medication (OR, 0.19; 95% CI, 0.14–0.27; P <0.00001; I^2 = 0%).

Pooled analyses of safety outcomes

All studies reported the common adverse events including ocular inflammation, ocular pain, foreign body sensation, and systemic adverse events in a total of 1690 patients (Supplementary Table 4). The pooled analysis revealed that the patients in the topical bromfenac group experienced fewer overall adverse events (OR, 0.47; 95% CI, 0.38–0.58; P <0.00001; I^2 = 46%; NNT = 6). Lower incidence of ocular inflammation (OR, 0.68; 95% CI, 0.50–0.94; P = 0.02; I^2 = 0%; NNT = 33) and ocular pain (OR, 0.47; 95% CI, 0.34–0.65; P <0.00001; I^2 = 0%; NNT = 15) were observed in the topical bromfenac group. No group difference in both foreign body sensation (OR, 0.96; 95% CI, 0.65–1.40; P = 0.82; I^2 = 0%) and systemic adverse events (OR, 1.51; 95% CI, 0.94–2.43; P = 0.09; I^2 = 0%) was observed between topical bromfenac and placebo groups.

Publication bias

Publication bias was found in the proportion of ocular pain free according to both Begg's funnel plot (Supplementary Figure 7) and Egger's test (Supplementary Table 5).

Discussion

The utility of ophthalmic NSAIDs for the control of ocular inflammation, reduction of ocular pain, as well as prevention and treatment of cystoid macular edema (CME) has been well documented in previous studies.[26–28] Bromfenac ophthalmic solution has received FDA approval based upon the clearance of anterior chamber (AC) inflammation after cataract surgery.[6,7] Recently, Wang et al.[29] and Sher et al.[30] reported on the role of bromfenac in managing ocular pain and discomfort following refractive surgery. The clinical benefits of bromfenac have been extensively discussed in several comparative studies including the treatment of external or anterior ocular inflammatory diseases, allergic conjunctivitis, as well as postoperative inflammation. Bromfenac was found to be 3.7, 6.5, and 18 times more potent than diclofenac,[31] amfenac,[32] and ketorolac,[33] respectively in inhibiting COX-2 activity. Since the clinical consensus has not been reached concerning the safety of bromfenac, we performed the current pooled analysis to offer evidence for the safety and efficacy of topical bromfenac in reducing overall ocular pain and inflammation during the whole postoperative period.

A previously published investigation[34] comparing bromfenac and diclofenac revealed that AC cells were significantly lower in the bromfenac group from postoperative day 3 till the end of the follow-up; meanwhile, flare levels were comparable at all time points assessed. Our pooled analysis demonstrated that the number of patients with SOIS of 0 was significantly increased at postoperative day 3. Furthermore, both mean cells and flare grade were markedly decreased after bromfenac administration when SIOS was investigated. Although bromfenac and ketoroloc were both well tolerated by patients undergoing laser in situ keratomileusis (LASIK), Epi-LASIK, and laser-assisted subepithelial keratomileusis (LASEK), bromfenac was superior in controlling postoperative pain.[29] Moreover, efficacy in reducing photophobia and no effect on corneal epithelial healing were also demonstrated.[30] Our analysis also revealed a decreased overall incidence of adverse events. However, headache, a systemic adverse event with obvious increasing incidence, might attract additional attention.[35]

The validity of the RCTs analyzed was limited for the following reasons. First, the different SOIS score criteria and dose strategies were described in Donnenfeld's study. Second, when combined with other pain relief medicine, the influence of co-medication needs to be further discussed. Third, most of the subjects recruited were not accompanied by excluded chronic ocular or systemic pathology for CE. The identification of patient characteristics associated with positive and negative therapeutic ocular outcomes are needed to better identify a clinical "niche" for topical bromfenac administration. Fourth, all four papers included in the analysis are data from the US. This fact causes some bias. Finally, as some data were only given as graphs instead of original data and we failed to contact the authors, image J was utilized to restore the related data. Thus, some small potential sources of heterogeneity could not be examined.

This pooled analysis came to the same conclusion that bromfenac is an effective treatment for postoperative inflammation and pain after CE. However, since the merits of all studied RCTs in the current analysis were weakened by the unreported demographics, co-morbidities of study participants, and the potential bias, higher quality and more strictly controlled clinical trials are required to identify the details of patients' outcome assessments, hospital costs, and length of hospital stay. Since there are currently three ongoing trials without data and one at the recruiting stage, it is important to inform the researchers to pay attention to the above-mentioned issues.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This work is partly supported by the Social Development and Technique Improvement Project of Shaanxi Province: 2008K18-01-62 and 2011K14-07-15, and Intramural Grant of the Xijing Hospital (XJZT14M16).

References

1. Groessl EJ, Liu L, Sklar M et al. (2013) Measuring the impact of cataract surgery on generic and vision-specific quality of life. *Quality of Life Research* 22: 1405–1414.
2. Buch H, Vinding T, La Cour M et al. (2004) Prevalence and causes of visual impairment and blindness among 9980 Scandinavian adults: The Copenhagen City Eye Study. *Ophthalmology* 111: 53–61.
3. Buch H, Vinding T and Nielsen NV (2001) Prevalence and causes of visual impairment according to World Health Organization and United States criteria in an aged, urban Scandinavian population: The Copenhagen City Eye Study. *Ophthalmology* 108: 2347–2357.
4. O'Brien TP (2005) Emerging guidelines for use of NSAID therapy to optimize cataract surgery patient care. *Current Medical Research and Opinion* 21: 1131–1137.
5. Skjodt NM and Davies NM (1999) Clinical pharmacokinetics and pharmacodynamics of bromfenac. *Clinical Pharmacokinetics* 36: 399–408.
6. Miyanaga M, Miyai T, Nejima R et al. (2009) Effect of bromfenac ophthalmic solution on ocular inflammation following cataract surgery. *Acta Ophthalmologica* 87: 300–305.
7. Jones J and Francis P (2009) Ophthalmic utility of topical bromfenac, a twice-daily nonsteroidal anti-inflammatory agent. *Expert Opinion on Pharmacotherapy* 10: 2379–2385.
8. Bucci FA Jr and Waterbury LD (2011) Prostaglandin E2 inhibition of ketorolac 0.45%, bromfenac 0.09%, and nepafenac 0.1% in patients undergoing phacoemulsification. *Advances in Therapy* 28: 1089–1095.
9. Endo N, Kato S, Haruyama K et al. (2010) Efficacy of bromfenac sodium ophthalmic solution in preventing cystoid macular oedema after cataract surgery in patients with diabetes. *Acta Ophthalmologica* 88: 896–900.
10. Si EC, Bowman LM and Hosseini K (2011) Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *Journal of Ocular Pharmacology and Therapeutics* 27: 61–66.
11. Robin AL, Novack GD, Covert DW et al. (2007) Adherence in glaucoma: Objective measurements of once-daily and adjunctive medication use. *American Journal of Ophthalmology* 144: 533–540.
12. Asai T, Nakagami T, Mochizuki M et al. (2006) Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. *Cornea* 25: 224–227.
13. Gaynes BI and Fiscella R (2002) Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: A safety review. *Drug Safety* 25: 233–250.
14. Isawi H and Dhaliwal DK (2007) Corneal melting and perforation in Stevens Johnson syndrome following topical bromfenac use. *Journal of Cataract and Refractive Surgery* 33: 1644–1646.
15. Feiz V, Oberg TJ, Kurz CJ et al. (2009) Nepafenac-associated bilateral corneal melt after photorefractive keratectomy. *Cornea* 28: 948–950.
16. Moher D, Cook DJ, Eastwood S et al. (1999) Improving the quality of reports of meta-analyses

of randomised controlled trials: The QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 354: 1896–1900.
17. Bero L and Rennie D (1995) The Cochrane Collaboration. Preparing, maintaining, and disseminating systematic reviews of the effects of health care. *Journal of the American Medical Association* 274: 1935–1938.
18. Jadad AR, Moore RA, Carroll D et al. (1996) Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials* 17: 1–12.
19. Higgins JPT and Green S (eds) (2009) *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2*. London: Cochrane Collaboration.
20. Begg CB and Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50: 1088–1101.
21. Egger M, Davey Smith G, Schneider M et al. (1997) Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 315: 629–634.
22. Donnenfeld ED, Holland EJ, Stewart RH et al. (2007) Bromfenac ophthalmic solution 0.09% (Xibrom) for postoperative ocular pain and inflammation. *Ophthalmology* 114: 1653–1662.
23. Silverstein SM, Cable MG, Sadri E et al. (2011) Once daily dosing of bromfenac ophthalmic solution 0.09% for postoperative ocular inflammation and pain. *Current Medical Research and Opinion* 27: 1693–1703.
24. Henderson BA, Gayton JL, Chandler SP et al. (2011) Safety and efficacy of bromfenac ophthalmic solution (Bromday) dosed once daily for postoperative ocular inflammation and pain. *Ophthalmology* 118: 2120–2127.
25. Walters TR, Goldberg DF, Peace JH et al. (2014) Bromfenac ophthalmic solution 0.07% dosed once daily for cataract surgery: Results of 2 randomized controlled trials. *Ophthalmology* 121: 25–33.
26. Colin J (2007) The role of NSAIDs in the management of postoperative ophthalmic inflammation. *Drugs* 67: 1291–1308.
27. Romac I, Gabric N, Dekaris I et al. (2011) Resolution of pseudophakic cystoid macular edema with combination therapy of topical corticosteroids and nonsteroidal anti-inflammatory drugs. *Collegium Antropologicum* 35 Suppl 2: 281–284.
28. DeCroos FC and Afshari NA (2008) Perioperative antibiotics and anti-inflammatory agents in cataract surgery. *Current Opinion in Ophthalmology* 19: 22–26.
29. Wang XJ, Wong SH, Givergis R et al. (2011) Evaluation of analgesic efficacy of bromfenac sodium ophthalmic solution 0.09% versus ketorolac tromethamine ophthalmic solution 0.5% following LASEK or Epi-LASIK. *Clinical Ophthalmology* 5: 1451–1457.
30. Sher NA, Golben MR, Bond W et al. (2009) Topical bromfenac 0.09% vs. ketorolac 0.4% for the control of pain, photophobia, and discomfort following PRK. *Journal of Refractive Surgery* 25: 214–220.
31. Speelman L, Akyildiz AC, den Adel B et al. (2011) Initial stress in biomechanical models of atherosclerotic plaques. *Journal of Biomechanics* 44: 2376–2382.
32. Yanni JM, Graff G and Hellberg MR (1995) Topically administrable compositions containing 3-benzoylphenylacetic acid derivatives for treatment of ophthalmic inflammatory disorders. Fort Worth, TX: Alcon Laboratories, Inc., assignee. U.S. Patent 5,475,034.
33. Waterbury LD, Silliman D and Jolas T (2006) Comparison of cyclooxygenase inhibitory activity and ocular anti-inflammatory effects of ketorolac tromethamine and bromfenac sodium. *Current Medical Research and Opinion* 22: 1133–1140.
34. Ohara K OA, Miyamoto T et al (2004) Effect of bromfenac sodium on postoperative inflammation. *Japanese Journal of Cataract and Refractive Surgery* 18: 168–173.
35. Stewart RH, Grillone LR, Shiffman ML et al. (2007) The systemic safety of bromfenac ophthalmic solution 0.09%. *Journal of Ocular Pharmacology and Therapeutics* 23: 601–612.