https://doi.org/10.5114/ko.2019.84564

(03)

Comparison of efficacy and safety of postoperative treatment with loteprednol etabonate and bromfenac after phacoemulsification

Porównanie skuteczności i bezpieczeństwa stosowania etabonianu loteprednolu i bromfenaku po zabiegu fakoemulsyfikacji zaćmy

Magdalena Kucharczyk-Pośpiech[1], Piotr Jurowski[2], Wiktoria Kubisiak[2], Monika Chwiałkowska-Karam[2], Michał Wilczyński[1], Sylwia Konarska[1], Wojciech Omulecki[1]

[1] Department of Ophthalmology, Norbert Barlicki Memorial Teaching Hospital No. 1, Medical University of Lodz, Poland
Head: Professor Wojciech Omulecki MD, PhD
[2] Department of Ophthalmology and Visual Rehabilitation, Central Veterans Hospital, Medical University of Lodz, Poland
Head: Professor Piotr Jurowski MD, PhD

Abstract: Aim: Comparison of efficacy and safety of loteprednol etabonate and bromfenac after phacoemulsification.
Material and Methods: Multicenter prospective case series. Consecutive 58 patients (58 eyes) were randomly assigned to the one of the study groups regarding postoperative treatment. Patients in Group I used 0.09% bromfenac 2 times diurnally for 30 days, and patients in Group II used 0.5% loteprednol etabonate 4 times diurnally for 30 days. The laser flare-cell photometry, slit lamp examination, tonometry and optical coherence tomography of macula were performed preoperatively and postoperatively at 1, 7, 30 and 90 days.
Results: The distance best corrected visual acuity was 0. 93 in group I and 0.91 in w group II. Laser Flare Photometry, central macular thickness and intraocular pressure was not significantly different during the 3 months of treatment between the groups ($p > 0.05$). In both groups, there were no abnormalities in routine slit lamp examination of the anterior and posterior segment.
Conclusions: The results of the study suggest that topical bromfenac and topical loteprednol etabonate had similar effect on laser flare-cell photometry and foveal thickness in the postoperative period after uneventful phacoemulsification.
Key words: loteprednol etabonate, bromfenac, phacoemulsification, cataract, steroids, NSAIDs.
Abstrakt: Cel: porównanie skuteczności i bezpieczeństwa stosownia etabonianu loterprednolu i bromfenaku po zabiegu fakoemulsyfikacji zaćmy.
Materiał i metody: badanie było prospektywne, dwuośrodkowe. 58 pacjentów (58 oczu) zakwalifikowanych do zabiegu usunięcia zaćmy zostało losowo przydzielonych do jednej z dwóch grup różniących się schematami leczenia pooperacyjnego. Pacjenci z grupy I stosowali 0,09% bromfenak 2 razy dziennie przez 30 dni. W grupie II stosowano poopracyjnie 0,5% etabonian loteprednolu 4 razy dziennie przez 30 dni. Przedoperacyjnie oraz w 1., 7., 30. oraz 90. dobie od zabiegu badano najlepszą skorygowaną ostrość wzroku, mierzono ciśnienie wewnątrzgałkowe, wykonywano badanie w lampie szczelinowej, flarymetrię oraz optyczną koherentną tomografię plamki.
Wyniki: po 3 miesiącach od operacji usunięcia zaćmy najlepsza skorygowana ostrość wzroku do dali wynosiła 0,93 w grupie I oraz 0,91 w grupie II. Koncentracja komórek białkowych w komorze przedniej, centralna grubość plamki oraz ciśnienie wewnątrzgałkowe nie różniły się w sposób istotny statystycznie między grupami w 3-miesięcznym okresie obserwacji ($p > 0,05$). Podczas badania w lampie szczelinowej w żadnej z grup nie stwierdzono nieprawidłowości przedniego lub tylnego odcinka oka.
Wnioski: wyniki tej pracy sugerują, że krople oczne z bromfenakiem i etabonianem loteprednolu, zastosowane po niepowikłanym zabiegu usunięcia zaćmy, mają podobny wpływ na koncentrację komórek białkowych w komorze przedniej oraz centralną grubość plamki.
Słowa kluczowe: etabonian loteprednolu, bromfenak, fakoemulsyfikacja, zaćma, steroidy, NLPZ.
The authors declare no conflict of interest/ Autorzy zgłaszają brak konfliktu interesów w związku z publikowaną pracą

Introduction

The management of inflammation is crucial in modern cataract surgery. Various schemes of postoperative anti-inflammatory pharmacological management are advocated.

Excessive postoperative ocular inflammation can lead to many complications, including: anterior and posterior synechiae formation, corneal edema, pseudophakic cystoid macular edema (PCME) and raised intraocular pressure (IOP) (1–4).

ISSN 0023-2157 Index 362646

Currently, two drug groups are used to control ocular inflammation: nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids, administrated either alone or in combination (4, 5). NSAID is established as the most potent agent controlling inflammation and preventing cystoid macular edema (4).

Bromfenac is the most potent of the approved ophthalmic NSAIDs. It is 3.7 times more potent than diclofenac and 18 times more potent than ketorolac in inhibiting the COX-2 enzyme (6).

Loteprednol etabonate (LE) is unique among corticosteroids due to the fact that it is rapidly metabolised, imparting a lower risk of side effects (7).

Efficiency, toxicity and anti-inflammatory activity of bromfenac, applied topically after phacoemulsification, has never been compared to a steroid LE.

The purpose of this randomized, prospective clinical study was to compare the relative effectiveness and safety of bromfenac 0.09% and LE 0.5% in their ability to reduce postoperative inflammation after uneventful cataract surgery.

Material and Methods

This multicenter prospective randomized study included patients with age-related cataract undergoing phacoemulsification with posterior chamber intraocular lens (PC IOL) implantation.

Adequacy of sample size was calculated for an analysis involving the use of continous variables in a paired study design. Based on preliminary data a mean laser flare photometry 6.9 ph/ms values increased about 4.4 ph/ms with standard deviation of 6.7 ph/ms. With these assumptions, the minimum sample size to detect postoperative flare increase in each group required for the study with a power of 90% at a significance level 5% was calculated as $(1.96 + 1.28)^2 \times 6.7^2/4.4^2 = 24$ eyes.

The patients were randomly assigned to one of two groups. In order to randomize patients, we used the RANDBETWEEN function of MS Excel, which generates random numbers, and we assigned consecutive patients to 2 groups according to randomly generated odd or even numbers.

Inclusion criteria were: distance best corrected visual acuity (DBCVA) between 0.1 and 0.5, and cataract nuclear sclerosis grade II and III according to LOCS III scale. Patients having uneventful phacoemulsification with PC IOL implantation were enrolled.

All surgeries were performed between November 2013 and October 2014. The study was approved by the institutional ethics committee, and all patients signed written informed consent to take part in the study. The trial has been published with the reference number: ISRCTN70915202.

Patients with ocular infection, glaucoma, uveitis, diabetes, pseudoexfoliation syndrome, prior ocular trauma or intraocular surgery, corneal diseases, ocular tumors, optic nerve atrophy, autoimmune diseases, endocrine, renal, neurological, psychiatric disorders were excluded from the study. Patients included into the study had not been using any anti-inflammatory medication for 2 weeks prior to cataract surgery and they had no allergy to LE or bromfenac.

To dilate the pupil before surgery 1.0% tropicamide and 2.5% phenylephrine were instilled. Local anesthesia was used with topical 0,5% proparacaine hydrochloride, followed by 2% lidocaine gel.

The surgeries were performed by 3 experienced surgeons (W.O., P.J., M.W.). All patients were operated using the same technique of phacoemulsification (Stop and Chop). First, a self-sealing 2.2 mm wide clear corneal incision was created temporally. Continuous curvilinear capsulorrhexis was done with microforceps under protection of a viscoelstic device (OVD). Two side-ports were created with a 20-gauge MVR blade in the clear cornea, 90 degrees away from the main incision, for bimanual aspiration and irrigation. Phacoemulsification and aspiration were performed and a single-piece hydrophobic acrylic foldable lens (AcrySof® IQ SN60WF, Alcon) was implanted with an injector through the main incision.

All patients used topical ofloxacin 4 times daily for 10 days postoperatively with an addition of the respective topical anti-inflammatory drug. The patients were randomized into 2 groups. Patients in Group I used a non-steroidal anti-inflammatory drug (0.09% bromfenac) 2 times daily for 30 days postoperatively. This group consisted of 34 eyes of 34 patients, including 24 women (70.6%) and 10 men (29.4%) aged between 46 and 88 years old (mean = 67.29, SD = ±10 years). Patients in Group II used steroidal anti-inflammatory drug (0.5% loteprednol etabonate) 4 times daily for 30 days postoperatively. This group consisted of 24 eyes of 24 patients, including 13 women (54.2%) and 11 men (45.8%) aged from 53 to 89 years old (mean = 68.8, SD = ±9.6 years).

The follow-up examinations were performed on the first day and 1, 4, and 12 weeks postoperatively. Laser flare photometry was done using Kowa FM -600 (Kowa Co. Ltd). Measurements were done at the same time of the day on scheduled visits. Seven laser flare photometry measurements with values greater than 0 and which backgrounds differed less than 15% were saved. For all patients the highest and the lowest values of flare were excluded, according to the manufacturer's guidelines. The remaining 5 measurements were averaged. All measurements were taken with undilated pupils. The routine examination at each visit included also the best corrected visual acuity evaluation on the Snellen chart, intraocular pressure, anterior and posterior segment evaluation, measurements of foveal retina thickness using Optical Coherence Tomography (Topcon 3D OCT-1000 Mark II and Zeiss Stratus OCT Version 4.0.5 (0076) and endothelial cell density measured with Tomey EM-3000 and Topcon SP 2000P Confocal Microscope.

Statistical analysis was done using nonparametric tests: Wilcoxon test and Mann-Whitney U test. Calculations were done using Addinsoft XLSTAT 2008 software for the significance level $\alpha = 0.05$.

Results

In both groups the statistically significant improvement in DBCVA was observed on the 1st day after the surgery ($p = 0.0001$) and between the 1st and the 90th day ($p = 0.002$).

There was no significant difference between groups in DBCVA ($p = 0.049$ at 12 weeks) (Tab. I).

In both groups, there were no abnormalities in routine slit lamp examination of the anterior and posterior segment.

The laser flare photometry values increased significantly in both groups on the first postoperative day compared with preoperative baseline values ($P < 0.05$). The LFP values were decreasing in both groups from the 1st till 90th day after cataract

	Preoperative BCVA/ Przedoperacyjna BCVA	Postoperative BCVA/ Pooperacyjna BCVA			
		1st day/ 1. dzień	1st week/ 1. tydzień	1st month/ 1. miesiąc	3rd month/ 3. miesiąc
Group I/ Grupa I	0.39 ± 0.13	0.81 ± 0.24	0.88 ± 0.15	0.89 ± 0.17	0.93 ± 0.12
Group II/ Grupa II	0.32 ± 0.17	0.48 ± 0.27	0.75 ± 0.21	0.81 ± 0.2	0.84 ± 0.16

Tab. I. Best corrected visual acuity.
Tab. I. Najlepsza skorygowana ostrość wzroku.

surgery. There were no statistically significant differences in LFP between preoperative and 90th day after phacoemulsification in both groups ($p > 0.05$) and between the two groups at all time points ($p > 0.05$) (Fig. 1).

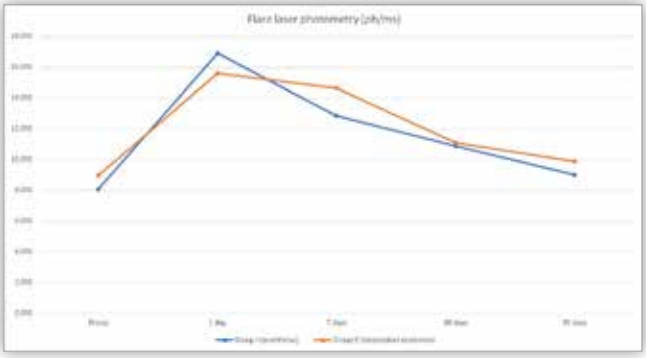

Fig. 1. Flare laser photometry (ph/ms).
Ryc. 1. Flarymeria laserowa (ph/ms).

The central macular thickness was not significantly different after 3 months of treatment in both groups ($p = 0.594$). In one eye of Group I (2.9%) and in one eye of Group II (4.2%) the pseudophakic cystoid macular edema (PCME) occurred, which totally resolved after 3 months. No long-term vision impairment was observed in these patients. There were no statistical significant differences in central macular thickness between the two groups at all time points ($p > 0.05$) (Fig. 2).

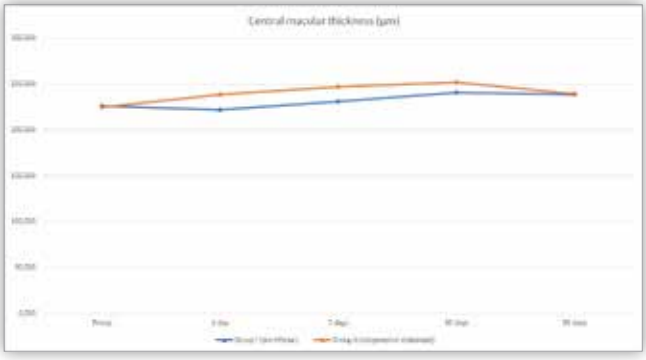

Fig. 2. Central macular thickness (μm).
Ryc. 2. Centralna grubość plamki (μm).

The intraocular pressure (IOP) was not significantly different at any time of follow-up in both groups ($p > 0.05$). Preoperatively mean IOP in bromfenac group was 14.6 mmHg and in LE group it was 14.8 mmHg. After 1 month of treatment IOP was 13.6 in Group I and 15.0 in Group II. None of the patients in our study developed a clinically significant IOP elevation (Tab. II).

Mean corneal endothelial cell density decreased from 2487.4 cell/mm^2 ± 267.4 preoperatively to 2334.5 cell/mm^2 ± 366.678 after 3 months in Group I (9.4%) and from 2293.9 cell/mm^2 ± 287.9 to 2233.4 cell/mm^2 ± 436.7 in Group II (9.7%). After 3 months of the follow-up there was no statistically significant difference in average corneal endothelium cell density loss between the groups ($p > 0.05$).

Discussion

Bromfenac is effective in the anti-inflammatory regimen after cataract surgery, simplifying the post-operative eyedrop scheme, reducing costs and allowing to avoid the side effects of topical steroids. The topical NSAID and topical steroid LE had a similar effect on LFP, foveal thickness, IOP and endothelial cell density. There were no remarkable toxicities associated with the two treatments. In both groups no patients complained about ocular surface disorders. Our study is the first comparison of topical administration bromfenac and LE.

The results of our study concerning clinical effects of bromfenac are consistent with ESCRS PREMED Study where Wielders et al. compared efficacy of a topical bromfenac, topical dexamethasone, and a combination of both after cataract surgery (8). In ESCRS PREMED Study the incidence of CME was 4,1% in bromfenac group while in our research 2,9% 12 weeks postoperatively. Lower incidence of CME in our study can be caused by longer administration of bromfenac – 4 weeks *vs*. 2 weeks in PREMED study.

Some studies report that topically applied NSAIDs are comparable to topically administered corticosteroids in their ability to control post-cataract inflammation (8–10). The study of Jung et al. (11) found that adding NSAIDs (bromfenac 0.1%) to topical steroid reduces intraoperative miosis, postoperative inflammation and macular thickness changes more effectively than postoperative steroid alone (12–13). Moreover, Coassin et al. (14)

	Preoperative IOP/ Przedoperacyjne IOP	Postoperative IOP/ Pooperacyjne IOP			
		1st day/ 1. dzień	1st week/ 1. tydzień	1st month/ 1. miesiąc	3rd month/ 3. miesiąc
Group I/ Grupa I	14.5 ± 2.23	14.99 ± 3.73	14.34 ± 4.02	13.6 ± 2.45	13.49 ± 2.35
Group II/ Grupa II	14.73 ±2.22	14.55 ± 2.74	14.53 ± 2.81	14.85 ± 2.87	14.04 ± 2.45

Tab. II. Intraocular pressure.
Tab. II. Ciśnienie wewnątrzgałkowe.

ISSN 0023-2157 Index 362646

found that addition of bromfenac 0.09% eyedrops to topical dexamethasone causes significant reduction of the postoperative flare in pseudoexfoliation patient.

Furthermore, topically administered NSAIDs may be more effective in stabilizing the blood–aqueous barrier as measured by laser flare photometry of the anterior chamber after uneventful cataract surgery (15). The results of laser flare photometry from 7th day examination are in accordance with the outcome of a systemic review by Kessel et al. (12).

However, an advantage of our study is that our patients did not receive any anti-inflammatory drugs preoperatively. Flach et al. (15) administered flurbiprofen 0.03% ophthalmic solution preoperatively during comparative study of postoperative effects of topically administered ketorolac 0.5% or diclofenac 0.1% which could reinforce early postoperative anti-inflammatory effect of tested drugs.

Additionally, Sahu et al. (1) administered topical NSAIDs 1 day prior to phacoemulsification which is in line with an investigation by Schultz et al. (16) and Chen (13) who proved that NSAID pretreatment led to reduced prostaglandin release after cataract surgery.

Zielińska at al. (17) showed that dicloabak with loteprednol etabonate coused faster decrease tendency of laser flare-cell photometry value comparing to group treated with loteprednol etabonate only.

Wielders et al. (18) in a meta-analysis confirms that topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids, in nondiabetic and mixed populations. In our study, in two patients with pseudophakic macular edema resolved spontaneously, which is in accordance with AAO review that indicate no visual benefit of using NSAIDs than steroid (19).

However, this study has some limitations. Initially the recruited LE taking group included 30 patients, but only 80% of them agreed to participate in this study, resulting in a small sample size.

Study of the effect of NSAIDs on postoperative macular edema would require a larger number of participants. Therefore, the value of our findings is limited, due to a small number of patients. Although all surgeries in our study were performed by 3 surgeons, we are convinced that it did not affected the outcomes of our study since they were using the same technique and equipment for of cataract surgery and they are very experienced.

Lane et al. showed safety of topical using the combination of eyedrops with LE and bromfenac after cataract surgery (20). Nevertheless, we would like to emphasise that our study is unique due to the fact that we were the first who investigated the effects of monotherapy with bromfenac after phacoemulsification.

There is still not enough data to prove that bromfenac and LE are equally effective after phacoemulsification although our study is suggesting this. Thus, further detailed studies, based on a larger population, are needed.

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The paper was originally received 06.02.2019 r. (KO-00198-2019)/
Praca wpłynęła do Redakcji 06.02.2019 r. (KO-00198-2019)
Accepted for publication 02.04.2019/
Zakwalifikowano do druku 02.04.2019 r.

Reprint requests to (Adres do korespondencji):
Magdalena Kucharczyk-Pośpiech, MD
Department of Ophthalmology, Medical University of Lodz
Norbert Barlicki Memorial Teaching Hospital No. 1
ul. Kopcińskiego 22
90-153 Łódź, Poland
e-mail: kucharczykma@gmail.com

ISSN 0023-2157 Index 362646