Anti-Inflammation Efficacy of 0.1% Nepafenac and 0.1% Fluorometholone in Postoperative Uncomplicated Phacoemulsification and Iol Implantation

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Abstract

Purpose:

To compare efficacy of inflammatory control in uncomplicated postoperative phacoemulsification with intraocular lens implantation between 0.1% Nepafenac (Nevanac®, Alcon) and 0.1% Fluorometholone acetate (Flarex®, Alcon)

Study design:

Prospective randomized clinical trial

Method:

Sixty-two eyes from 62 postoperative cataract surgery patients were randomized to either receive 0.1% Nepafenac (Nevanac®, Alcon) or 0.1% Fluorometholone acetate. Age, sex, diagnosis, and initial intraocular pressure (IOP) were recorded pre-operatively. Post-operative prescription 0.5% Moxifloxacin (Vigamox®, Alcon), preservative free tear were prescribed in both groups. Intraocular pressure, anterior chamber cell/flare, patient's discomfort interview were recorded on 1-day, 1-week, 3-week, 6-week and 12-week post-operatively. Statistical compared by Mann-Whitney U test for anterior chamber cells & Patients' comfort and by Independent-Samples T test for Intraocular pressure (IOP).

Results:

There were no significant difference of age, sex, diagnosis and initial IOP between 2 groups (p = 0.33, 0.346, 0.62, 0.879, respectively). Anti-inflammatory efficacy comparing by anterior chamber cells and flare between 2 groups at 1-day, 1-week, 6-week and 12-week post-operatively revealed no significant difference between two groups (p = 0.334, 0.501, 0.192, 0.09). However, in 3-week post-operation Nevanac group showed significant difference in anterior chamber cells less than Fluorometholone group (p = 0.011). There were only three patients who had faint

anterior chamber, 2 patients in Nevanac group and 1 in Fluorometholone group. All three patients' flare disappeared at the next follow up visit. There was no significant difference in postoperative intraocular pressure between Nevanac and Fluorometholone groups at any visits (p = 0.568, 0.854, 0.18, 0.431, and 0.432). Patients' comfort between 2 groups at 3-week report Nevanac group seem to have more patient comfort than Fluorometholone group (p = 0.038).

Conclusions:

0.1% Nepafenac provides good control of intraocular inflammation after phacoemulsification with intraocular lens implantation, comparable with 0.1% Fluorometholone, without many corticosteroids complications. Although there were no statistically significant difference of intraocular pressure between 2 groups for IOP, Nevanac seem to be as comfortable as Fluorometholone, which may provide more benefit than previous ophthalmic NSAIDs.

Introduction

According to advanced technology in phacoemulsification, patients restore their vision with less complication. However, intraocular surgery may stimulate inflammatory cascade which produce many inflammatory mediators such as cyclooxygenase 1 & 2 (COX-1 & COX-2) enzyme, Prostaglandins (PGs), and etc. Topical corticosteroids have been used as a first line medication for postoperative anti-inflammation, which block inflammation at level of phospholipase A2 (as figure 1)[1]. Although topical corticosteroids have high efficacy for control inflammation, on the other hand corticosteroids have many adverse effects such as increase intraocular pressure[2], inhibition of corneal epithelial or stromal healing, and increasing risk of infection (from reducing immune system).

Prescribing topical prednisolone or dexamethasone preparations which have high potency for decrease inflammation also have many adverse effects. Soft steroids have lower anti-inflammatory effect than prednisolone or dexamethasone but also have less adverse effects such as Loteprednol etabonate 0.2% (Alrex, Bausch & Lomb) and 0.5% (Lotemax, Bausch & Lomb) or Fluorometholone acetate. The new ophthalmic topical NSAIDs (effect at level of cyclooxygenase enzyme, as figure 1[1]) were also developed for postoperative inflammation control. Furthermore some studies have found that topical NSAIDs also prolong pupillary dilated time[3] and another benefit of topical NSAIDs was preservation of ocular immune system. Polanski JR, et al. has found that topical NSAIDs can reduce many adverse effects of topical corticosteroids such as corticosteroids induced glaucoma, cataract and potentiating of infection[4]

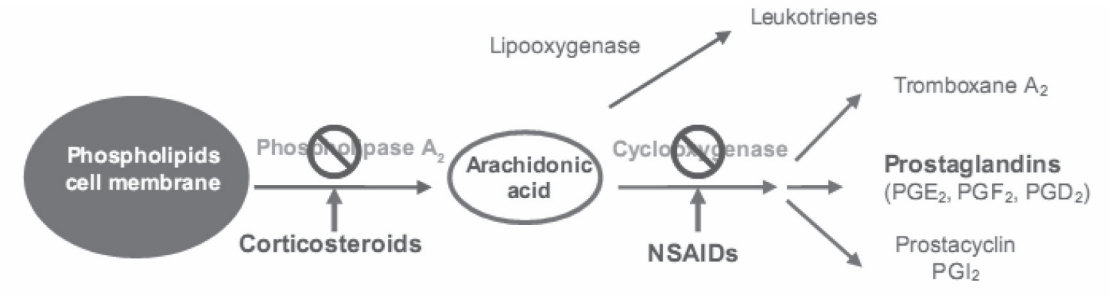


Figure 1 Demonstrate anti-inflammatory pathways of Corticosteroids & NSAIDs[1]

Many topical NSAIDs such as furbiprofen, diclofenac, ketorolac, and bromfenac, are relatively water-soluble phenylalkanoic and phenylacetic acids. Because of their inherent water solubility, phenylalkanoic and phenylacetic acids would be predicted to have limited ability to penetrate corneal epithelium. Nepafenac is an amide prodrug analog of amfenac approved for use in the US for the treatment of post-operative inflammation after cataract surgery. Nepafenac requires hydrolysis to the more active amfenac (figure 2)[5]

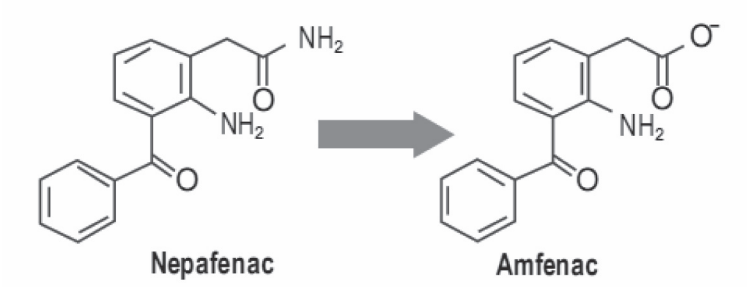


Figure 2 Deamination of Nepafenac to the active compound amfenac[5]

Corneal absorption of a drug depends on its lipid solubility, its polarity, and degree of ionization. Unlike the acidic nature of the other topical NSAIDs, ophthalmic Nepafenac being a base maintained as an ophthalmic solution at pH 7.4 would exist more as a unionized drug and is therefore absorbed readily across the cornea at higher levels of tear pH so allows Nepafenac to rapidly penetrate the cornea. Ke, et al 2000 used rabbit corneal tissue to compare corneal permeability found that Nevanac was 4, 19, and 28 times greater than diclofenac, bromfenac, and ketorolac respectively. Walters, et al 2007 studied in human (in vivo) shown that topical Nepafenac have faster time to C-max and higher aqueous humor concentration than either bromfenac or ketorolac.

Nepafenac is unique, in that its bioconversion to amfenac is targeted to the iris, ciliary body and the retina/choroid, suggesting Nepafenac may have prolonged activity in the vascularized tissues of the eye (Ke, et al 2000). Gamache, et al. 2000 found that Nepafenac have more complete and longer duration of inhibition of iris/ciliary body prostaglandin synthesis than diclofenac. This study aims to compare the efficacy of inflammatory control of 0.1% Nepafenac to topical corticosteroids 0.1% Fluorometholone in uncomplicated post-phacoemulsification with intraocular lens patients. The primary outcome of study was anterior chamber cell in each follow up time at postoperative 1-day, 1-week, 3-week, 6-week and 12-week. Secondary outcome were anterior chamber flare, postoperative intraocular pressure, and patients' comfort.

Materials & methods

This study was prospective, randomized, and double blind clinical trial in single eye center (Thammasat hospital eye center, Thailand). Patients who decided to obtain cataract surgery (phacoemulsification with intraocular lens implantation) and included in the study were advised and signed the informed consent.

Inclusion criteria

Patients obtained uncomplicated phacoemulsification with intraocular lens implantation.

Exclusion criteria

1. Patients who could not visit along study's follow up schedule
2. Patients who could not use postoperative eyedrops along study's guideline
3. Patients who have complicated surgery such as ruptured posterior chamber, vitreous loss
4. Patients who have allergic to any medicine in the study

Every patient was free to discontinue from this study at any time without giving reasons. Every uncomplicated phacoemulsification and intraocular lens implant patients from September 2008 to April 2009 were randomized prescribed either 0.1% Nepafenac (Nevanac, Alcon) or 0.1% Fluorometholone. Both 2 groups were self instilled in the treated eye according to this schedule every 2 hours in first postoperative day then reduced to 4 times per day until follow up times. Medication will be discarded after slit lamp examination showed no cell & flare in anterior chamber but they still have appointment for follow up according to this study's schedule. Both 2 groups obtained 0.5% Moxifloxacin (Vigamox, Alcon) 4 times per day as antibiotic prophylaxis.

In preoperative time, patients' baseline data were recorded such as age, sex, diagnosis, and initial intraocular pressure then patients was examined in postoperative 1-day, 1-week, 3-week, 6-week and 12-week. In every follow up visits patients was examined by same ophthalmologist. Data recorded such as anterior chamber cells & flare, intraocular pressure, and patients' comfort Grading anterior chamber cell were grade 0 for 0 cell/mm^2, grade 1 for 1-5 cell/mm^2, grade 2 for 6-20 cell/mm^2, grade 3 for 21-50 cell/mm^2, and grade 4 for >50 cell/mm^2

Grading anterior chamber flare was graded as the Standardization of Uveitis Nomenclature (SUN). Grade 0 for none, grade 1 for faint flare, grade 2 for moderate flare (iris & lens details clear), grade 3 for marked flare (iris & lens details hazy), grade 4 for intense flare (fibrin or plasmoid aqueous). This parameter was not statistically compared between groups because there were only 3 patients that had anterior chamber flare.

Initial and postoperative intraocular pressure of all patients was measured by Goldmann applanation. Patients' comforts were evaluated by patients: grade 1 for very comfort, grade 2 for mild discomfort, grade 3 for moderate discomfort, grade 4 for very discomfort, and grade 5 for severe discomfort.

Statistics

All data recorded from each patient were statistically compared by using SPSS program (version 13). P-value <0.05 was considered to be clinically significance. Demographic data, age, and initial IOP were compared by independent t-tests. Sex was compared by Fisher's Exact test and for diagnosis were compared by Mann Whitney U test. For postoperative data, anterior chamber cells, patients' comfort were compared by Mann Whitney U test and postoperative IOP were compared by independent t-tests.

Results

62 eyes from 62 participants were enrolled in the study. Sixteen patients excluded because of incomplete data (10 patients) and losses follow up (6 patients). There were 46 eyes from 46 patients in this study (22 eyes in Nevanac group and 24 eyes in Fluorometholone group) and there were no statistically significant difference of baseline data between 2 groups. Demographic data are shown in Table 1.

Table 1 Demographic data of patients in this study

	Nevanac	Fluorometholone	Total number	*p*-value
Number of patients	22	24	46	
Age (years)	69.04 ± 8.82	66.79 ± 6.49	-	0.333
Sex	M 5 F 17	M 9 F 15	14 32	0.346
Diagnosis	SIC 5 ACG 16 OAG 1	SIC 6 ACG 14 OAG 4	11 30 5	0.62
Initial IOP (mmHg)	16.18 ± 4.40	16 ± 3.56		0.879

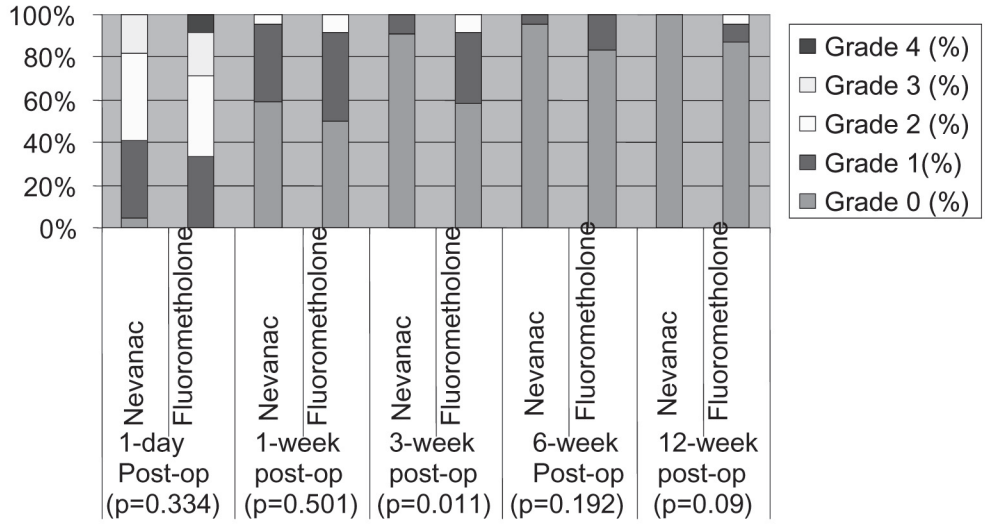
Efficacy of post cataract surgery inflammation control

Anterior chamber cells between 2 groups were compared at each postoperative time showed as Table 2 & Figure 3

Table 2 Compare anterior chamber cells of 2 groups in each follow up time (amount of patients: %)

		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1-day	Nevanac	1 (4.5%)	8 (36.4%)	9 (40.9%)	4 (18.2%)	0
	Fluorometholone	0	8 (33.3%)	9 (37.5%)	5 (20.8%)	2 (8.3%)
1 week	Nevanac	13 (59.1%)	8 (36.4%)	1 (4.5%)	0	0
	Fluorometholone	12 (50.0%)	10 (41.7%)	2 (8.3%)	0	0
3 weeks	Nevanac	20 (90.0%)	2 (9.1%)	0	0	0
	Fluorometholone	14 (58.3%)	8 (33.3%)	2 (8.3%)	0	0
6 weeks	Nevanac	21 (95.5%)	1 (4.6%)	0	0	0
	Fluorometholone	20 (83.3%)	4 (16.7%)	0	0	0
12 weeks	Nevanac	22 (100.0%)	0	0	0	0
	Fluorometholone	21 (87.5%)	2 (8.3%)	1 (4.2%)	0	0

Figure 3 Compare grading of anterior chamber cell between 2 medications in percent of each group



There were no significant differences between anterior chamber cells at postoperative 1-day, 1-week, 6-week, and 12-week (p = 0.334, 0.501, 0.192, 0.09) between 2 groups. However, Nevanac showed significant less anterior chamber cells than Fluorometholone at 3-week postoperative (p = 0.011).

There were only 3 patients who have demonstrated grade 1 anterior chamber flare (2 patients from Nevanac group and 1 patient from Fluorometholone group) and flare disappeared in next follow up visit. This parameter was not statistically compared because of small number of patients.

Effect to postoperative intraocular pressure

There are no significant difference of post-operative IOP between 2 eye drops at all visit times (p = 0.568, 0.854, 0.18, 0.431, and 0.432 for 1-day, 1-week, 3-week, 6-week and 12-week, respectively). Average postoperative IOP showed in Table 3.

Table 3 Compare mean IOP ± SD at each follow up time

Follow up time	Medication	N	Mean IOP (mmHg)	SD	*p* value
1-day IOP	Nevanac	22	20.68	9.23	0.568
	Fluorometholone	24	19.25	7.13	
1-week IOP	Nevanac	22	15.32	4.74	0.854
	Fluorometholone	24	15.08	3.71	
3-week IOP	Nevanac	22	14.68	3.62	0.18
	Fluorometholone	24	16.12	3.55	
6-week IOP	Nevanac	22	14.81	3.63	0.431
	Fluorometholone	24	15.66	3.61	
12-week IOP	Nevanac	22	14.14	3.19	0.432
	Fluorometholone	24	15.04	4.47	

Patients comfort

Due to incomplete postoperative records in some patients so we had small amount of data about patients' comfort to statistically compare (N = 31, 30, 31, 27, and 21 patients at 1-day, 1-week, 3-week, 6-week and 12-week, respectively). Results showed that no difference for patients' comfort between 2 groups at day 11-day, 1-week, 6-week and 12-week but at 3-week Nevanac showed more patients' comfort than Fluorometholone (p = 0.038).

Discussion

There are many previous studies compared the efficacy of topical corticosteroids with topical NSAIDs for inflammatory control in post-cataract surgery such as Christoph Hirneiß, et al[6] reported that efficacy of inflammation control after cataract extraction by assessment of anterior chamber cells by 2 topical corticosteroids (1% prednisolone and 1% rimexolone) and 1 topical NSAIDs (ketorolac, 0.5% tromethamine) did not differ (p = 0.165), while flare in the anterior chamber was lowest (p = 0.008) in the NSAID group. Calvin W., et al[7] compared effect of 0.1% diclofenac eye drops or 1% prednisolone eye drops by assessment of cell and flare by slit-lamp and objectively by measurement with a laser cell and flare meter, which showed no statistically significant difference in postoperative inflammation between two treatment groups. Another study of Sayaka Asano, et al[8] compared 0.1% diclofenac and 0.1% betamethasone in preventing cystoid macular edema (CME) and blood-aqueous barrier (BAB) disruption after small-incision cata-

ract surgery and reported that 5 weeks after surgery, incidence of fluorescein angiographic CME was lower in the diclofenac group (18.8%) than in the betamethasone group (58.0%) (p<.001). At 1 and 2 weeks, the amount of anterior chamber flare was statistically significantly less in the diclofenac group than in the betamethasone group (p<.05). At 8 weeks, intraocular pressure was statistically significantly higher in the betamethasone group (p = .0003).

In this study, 0.1% Nepafenac provided good control of intraocular inflammation after uncomplicated phacoemulsification with intraocular lens implantation comparable with 0.1% Fluorometholone acetate. Using 0.1% Nepafenac post-operatively in some particular patients such as steroids responders or younger age patients may be useful. This study enrolled many glaucoma patients and still showed no significant difference in raising IOP post-operatively, which may be because we compared between 0.1% Nepafenac with soft steroids (0.1% Fluoromet holone acetate). 0.1% Nepafenac seems to be as comfortable as 0.1% Fluorometholone for use in post-phacoemulsification with intraocular lens implantation that may provide benefit more than previous ophthalmic NSAIDs that patients always have pain or stinging when used.

Reference

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การศึกษาเรื่องการเปรียบเทียบประสิทธิภาพในการลดการอักเสบระหว่าง 0.1% NEPAFENAC และ 0.1% FLUOROMETHOLONE ในผู้ป่วยหลังการผ่าตัดต้อกระจกที่ไม่มีภาวะแทรกซ้อน

นายแพทย์ชินสุต อรุณากูร
แพทย์หญิงปิยะดา พูลสวัสดิ์
ผู้ช่วยศาสตราจารย์ แพทย์หญิงมัญชิมา มะกรวัฒนะ
ภาควิชาจักษุวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

บทคัดย่อ

จุดประสงค์ของการศึกษา

เพื่อเปรียบเทียบประสิทธิภาพในการลดการอักเสบในผู้ป่วยหลังการผ่าตัดต้อกระจกที่ไม่มีภาวะแทรกซ้อน ระหว่าง 0.1% Nepafenac (Nevanac®) และ 0.1% Fluorometholone (Flarex®)

รูปแบบของการศึกษา

Prospective randomized clinical trial

วิธีการศึกษา

ติดตามผู้ป่วยหลังการผ่าตัดต้อกระจกที่ไม่มีภาวะแทรกซ้อน 62 ตา จากผู้ป่วย 62 คน โดยทำการเลือกสุ่มโดยให้กลุ่มหนึ่งได้รับ 0.1% Nepafenac (Nevanac®) และอีกกลุ่มหนึ่งได้รับ 0.1% Fluorometholone (Flarex®) ผู้ป่วยทุกรายหลังผ่าตัดจะได้รับ 0.5% Moxifloxacin (Vigamox) ข้อมูลต่างๆ เช่น อายุ, เพศ, การวินิจฉัยของโรค, ความดันตา ก่อนการผ่าตัด และติดตามภาวะการอักเสบ (cell/flare), ความสบายตาหลังการใช้ยา, และความดันลูกตาที่ระยะเวลาหลังผ่าตัดที่ 1 วัน, 1 สัปดาห์, 3 สัปดาห์, 6 สัปดาห์ และ 12 สัปดาห์, ใช้ MannWhitney U test เปรียบเทียบทางสถิติของข้อมูลภาวะการอักเสบ และความสบายตาหลังการใช้ยา จะใช้ และ Independent-Sample T test ในการเปรียบเทียบทางสถิติข้อมูลอื่นๆ

ผลของการศึกษา

ไม่มีความแตกต่างกันทางสถิติของ อายุ, เพศ, การวินิจฉัยของโรค, ความดันตา ระหว่างกลุ่มที่ได้รับการศึกษาทั้งสองกลุ่ม (P = 0.33, 0.346, 0.62, 0.879) ภาวะการอักเสบ (cell/flare) หลังการผ่าตัด

ระหว่างทั้งสองกลุ่มที่ระยะเวลา 1 วัน, 1 สัปดาห์, 6 สัปดาห์ และ 12 สัปดาห์ ไม่มีความแตกต่างกันทางสถิติ (P = 0.334, 0.501, 0.192, 0.09) อย่างไรก็ตามพบว่า ที่ 3 สัปดาห์กลุ่มผู้ป่วยที่ได้รับ Nepafenac มีการอักเสบ (anterior chamber cells) น้อยกว่าในกลุ่มที่ได้รับ Fluorometholone (P = 0.011) ส่วนความดันตาพบว่า ไม่มีความแตกต่างกันทางสถิติของทั้งสองกลุ่มในทุกสัปดาห์ที่ทำการติดตามผล (P = 0.568, 0.854, 0.18, 0.431 และ 0.432 ตามลำดับ) ความสบายตาหลังการใช้ยาพบว่า ที่ 3 สัปดาห์ กลุ่มที่ใช้ Nevanac มีความสบายตามากกว่ากลุ่มที่ใช้ Fluorometholone (p = 0.038)

สรุป

0.1% Nepafenac (Nevanac®) สามารถควบคุมการอักเสบหลังทำการผ่าตัดต้อกระจกที่ไม่มีภาวะแทรกซ้อนได้ใกล้เคียงกับ 0.1% Fluorometholone (Flarex®) ซึ่งอาจเป็นข้อบ่งชี้ในการเลือกใช้ 0.1% Nepafenac (Nevanac) เพื่อหลีกเลี่ยงผลข้างเคียงของสเตียรอยด์ ในผู้ป่วยที่อาจเคยมีประวัติได้รับผลข้างเคียงจากการใช้สเตียรอยด์ เช่น ความดันลูกตาสูงหลังได้รับยา ผู้ป่วยอายุน้อย ผู้ป่วยที่มีความเสี่ยงในการเกิดโรคต้อหินอื่นๆ ในแง่ของความสบายตา 0.1% Nepafenac (Nevanac®) เป็นยาในกลุ่ม NSAIDs ที่ให้ความสบายตาได้ใกล้เคียงกับ 0.1% Fluorometholone (Flarex®) ซึ่งเป็นข้อได้เปรียบกว่ายา NSAIDs ในอดีต