Comparison of Topical Prednisolone Acetate, Ketorolac Tromethamine and Fluorometholone Acetate in Reducing Inflammation after Phacoemulsification

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Abstract

Aims : To compare the efficacy and ocular adverse effects of topical prednisolone acetate, ketorolac tromethamine, and fluorometholone acetate in reducing inflammation after phacoemulsification.

Method : One hundred and twenty eyes were enrolled in a prospective, investigator-masked, randomized controlled trial. Each drug was prescribed 4 times a day for 28 days. The following data were recorded weekly: visual acuity, intraocular pressure, slit lamp biomicroscopy, grading of cells and flare in the anterior chamber, and ocular symptoms.

Results : The number of eyes with a minimal amount of cells in the anterior chamber in the ketorolac group was less than the prednisolone group on day 7 (11:20, $p = 0.008$) and day 14 (23:31, $p = 0.015$), and than fluorometholone group on day 7 (11:21, $p = 0.011$). Intraocular pressure in the prednisolone group was higher than the ketorolac group on day 21 (14.6:12.2 mmHg, $p = 0.016$). One eye in the prednisolone group had intraocular pressure of 32 mmHg. Burning sensation was reported frequently in the ketorolac group.

Conclusion : All 3 drugs were effective in reducing post-operative inflammation. The efficacy of prednisolone acetate and fluorometholone acetate was comparable. Ketorolac tromethamine showed less efficacy than corticosteroids, however, it did not induce ocular hypertension.

Key word : Prednisolone Acetate, Ketorolac Tromethamine, Fluorometholone Acetate, Phacoemulsification

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Topical corticosteroids have been used to control inflammation after cataract surgery. Prednisolone acetate suspension is one of the potent corticosteroids widely prescribed for this purpose. In addition to its effectiveness in reducing inflammation, there are associated ocular adverse effects including increased intraocular pressure, delayed wound healing and increased risk of infection[1].

There have been several studies testing other drugs for their efficacy compared with prednisolone acetate to find equivalent alternatives with fewer complications. Among these drugs are nonsteroidal anti-inflammatory drugs (NSAIDs) and other corticosteroids. NSAIDs have been used to replace corticosteroids in selected conditions. Ketorolac tromethamine, one of the NSAIDs, has been demonstrated to be as effective as prednisolone acetate to reduce post-operative inflammation after cataract surgery[2-4].

Fluorometholone, another corticosteroid, has been shown less likely to increase intraocular pressure than the others[5]. It is classified as a weak anti-inflammatory agent. However, formulation of fluorometholone as an acetate derivative can significantly increase its effectiveness equivalent to prednisolone acetate in animal studies[6].

The purpose of this study was to compare the efficacy and ocular adverse effects of topical prednisolone acetate 1 per cent, ketorolac tromethamine 0.5 per cent, and fluorometholone acetate 0.1 per cent in reducing inflammation after phacoemulsification and intraocular lens implantation.

MATERIAL AND METHOD

This 4-week, prospective, investigator-masked, randomized controlled trial comparing topical prednisolone acetate 1 per cent (Pred Forte®, Allergan, Inc., Irvine, CA), ketorolac tromethamine 0.5 per cent (Acular®, Allergan, Inc.), and fluorometholone acetate 0.1 per cent (Flarex®, Alcon Laboratories, Inc., Fort Worth, TX) was performed at the Department of Ophthalmology, Siriraj Hospital Mahidol University, Thailand. The study protocol was approved by the ethical clearance committee on human rights related to research involving humans, Faculty of Medicine Siriraj Hospital. Informed consent was obtained from all participants.

Consecutive eyes of non-diabetic patients who had undergone phacoemulsification and intraocular lens implantation performed by two surgeons (A.D. and L.A.) without intra-operative complication were enrolled in the study. Exclusion criteria included glaucoma, hypersensitivity to the study drugs, using any corticosteroids or NSAIDs in the recent 3 months, previous intraocular surgery, and accompanying ocular diseases or corneal lesions that interfered with intraocular examination.

One hour pre-operatively, the pupil was dilated with tropicamide 1 per cent and neosynephrine 10 per cent four times every 10 minutes. Flurbiprofen sodium 0.03 per cent was also used four times every 15 minutes to stabilize the pupil during the operation. The surgery was performed under topical anesthesia using tetracaine 0.5 per cent.

The technique of phacoemulsification included the temporal-approached clear corneal incision, anterior capsulorrhexis, phacoemulsification of the lens nucleus, irrigation and aspiration of the lens cortex, anterior and posterior capsule polishing, intraocular lens implantation, and aspiration of the viscoelastic substance. The corneal incision was sutured in case of being extended to accommodate rigid intraocular lens or instability of the anterior chamber. A mixture of tobramycin 0.3 per cent and dexamethasone 0.1 per cent ophthalmic solution (Tobradex®, Alcon Laboratories, Inc., Fort Worth, TX) was applied immediately after the surgery.

Patients were randomized to receive as their post-operative medication either prednisolone acetate, ketorolac tromethamine, or fluorometholone acetate. Each drug was prescribed 4 times a day starting after baseline examination on the next morning after surgery. Patients were instructed to continue their medication for 4 weeks.

Baseline and four successive weekly ocular examinations were performed by a single ophthalmologist (T.S.) who was masked to allocation. At each visit, best-corrected visual acuity was measured using the Snellen chart. Intraocular pressure was measured using the Goldmann applanation tonometer. Conjunctival injection was evaluated and graded 0 (no injection), 1 (faint red), 2 (visible red) and 3 (purple red). The cornea was examined using slit lamp biomicroscopy to look for edema and superficial punctate keratitis. Corneal edema was graded 0 (no edema), 1 (visible Descemet's fold), 2 (microcystic epithelial edema or increasing corneal thickness not over 25%), and 3 (increasing corneal thickness over 25%). Superficial punctate keratitis was graded 0 (no appearance), 1 (appearing less than 50% of the corneal surface), 2 (appearing more than 50% of the corneal surface), and 3 (confluent epithelial plaque). Cells and flare in the anterior chamber were graded under x 20 mag-

nifying slit lamp biomicroscopy with high-intensity slit beam of 1 x 3 mm observing at the central part of the anterior chamber. The number of cells in the anterior chamber was graded 0 (no cell detectable), trace (1-5 cells), 1+ (6-15 cells), 2+ (16-25 cells), 3+ (26-50 cells), and 4+ (more than 50 cells). Anterior chamber flare was graded 0 (no flare), 1+ (just detectable), 2+ (visible flare with clear iris details), 3+ (hazy iris details), and 4+ (fibrin appearing in anterior chamber). All patients were interviewed for ocular symptoms of irritation, pain, tearing, burning sensation, photophobia, and discomfort. The severity of each symptom was graded 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

The study would be terminated if ocular examination showed post-operative endophthalmitis or increasing intraocular pressure of more than 30 mmHg and the patients would be treated accordingly.

For statistical analysis, chi-square was used to compare data of nominal scale, such as sex and eye laterality. Intraocular pressure was compared among groups by ANOVA test. Other data including age, best-corrected visual acuity, and ocular signs and symptoms were tested by Kruskal-Wallis and Mann-Whitney tests. Results were considered significant when the p-value was less than 0.05.

RESULTS

One hundred and twenty eyes of 102 patients undergoing cataract surgery were enrolled in the study. Thirty-nine eyes were allocated to receive prednisolone acetate 1 per cent, 40 eyes to ketolorac tromethamine 0.5 per cent, and 41 eyes to fluorometholone acetate 0.1 per cent. Two eyes in the prednisolone group and 2 eyes in the fluorometholone group were lost to follow-up and were excluded from the study.

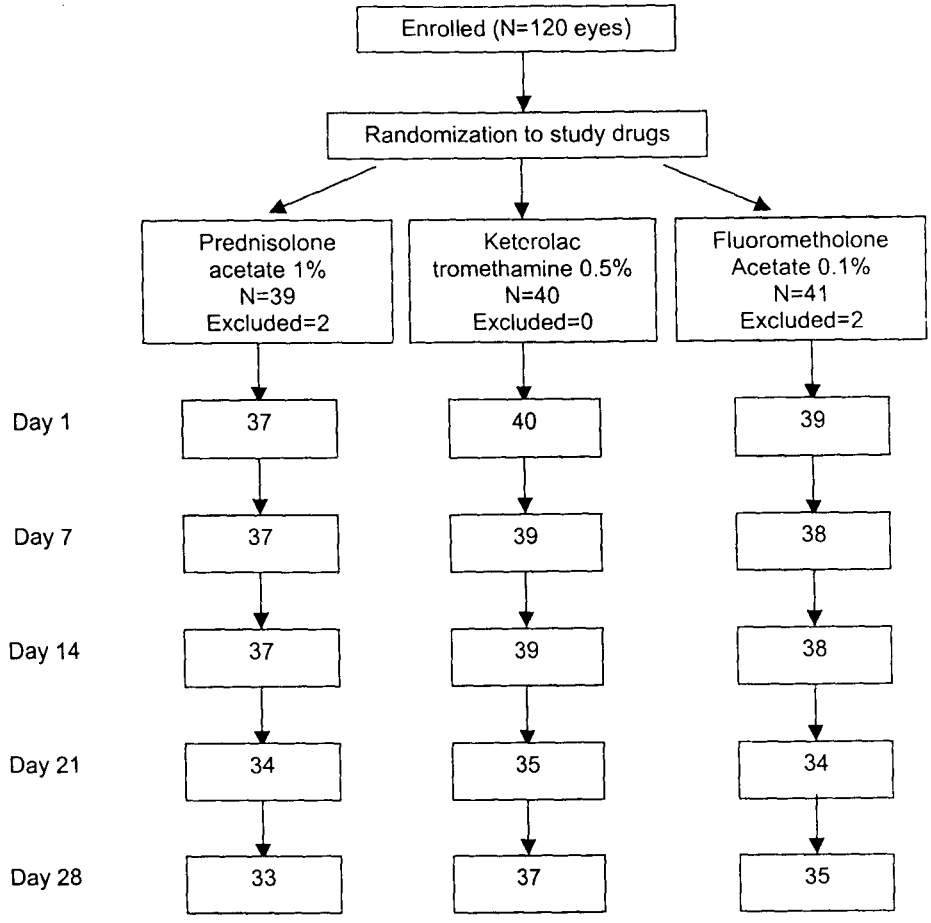

Fig. 1. Number of eyes in each group at various time points of data collection.

Therefore, the authors analyzed data of 37 eyes in the prednisolone group, 40 eyes in the ketorolac group, and 39 eyes in the fluorometholone group. Fig. 1 shows the number of eyes in each group followed-up on day 1, 7, 14, 21 and 28. There was no significant difference in demographic data among the 3 groups as shown in Table 1.

From baseline data collected on post-operative day 1 prior to the application of the drugs, there was no significant difference among groups in visual acuity, intraocular pressure, inflammation of conjunctiva and cornea, and number of cells and flare in the anterior chamber (Table 2). Eye irritation occurred less frequently in the fluorometholone group compared to the ketorolac group ($p = 0.015$). Other symptoms including pain, tearing, burning sensation, photophobia, and ocular discomfort were similar.

After medication was started, best-corrected visual acuity at each visit was comparable among the groups. One patient in the prednisolone group revealed an intraocular pressure of 32 mmHg on day 21 and was terminated from the study. Mean intraocular pressure on day 21 of the prednisolone group and ketorolac group was 14.67 ± 3.88 and 12.28 ± 2.81 mmHg respectively ($p = 0.016$). The authors also compared the change of the intraocular pressure from pre-operative level among the three groups at each visit. There was a rise of post-operative intraocular pressure in the prednisolone group with statistically significant difference from the ketorolac group on day 14 ($p = 0.022$), day 21 ($p = 0.014$), and day 28 ($p = 0.013$) (Table 2).

Degrees of conjunctival injection, corneal edema, superficial punctate keratopathy and grading of aqueous flare were shown to be equal among the groups. The authors found a significantly fewer number of eyes in the ketorolac group having a minimal amount of aqueous cells (5 cells or less) compared to the prednisolone group on day 7 ($p = 0.008$) and day 14 ($p = 0.015$), and to the fluorometholone group on day 7 ($p = 0.011$).

Ocular symptoms including eye irritation, tearing, photophobia and pain were comparable among the groups. Burning sensation was reported more frequently in the ketorolac group. However, the median of severity grading was mild. It showed significant difference compared to the prednisolone group on day 14 ($p = 0.004$) and day 28 ($p = 0.007$), and to the fluorometholone group on day 14 ($p = 0.010$). Nevertheless, no patient was withdrawn from the study because of this symptom.

Besides the intraocular pressure elevation, another post-operative complication was found. One patient in the fluorometholone group developed endophthalmitis on day 11. He was successfully treated with a single injection of intravitreal amikacin and vancomycin. The culture from the vitreous specimen was negative. Best-corrected visual acuity at 4 months after treatment was 6/6.

DISCUSSION

The authors studied the efficacy of 3 drugs in reducing inflammation after phacoemulsification and intraocular lens implantation. Prednisolone and fluorometholone are corticosteroids, while ketorolac is a non-steroidal anti-inflammatory drug. The current study has shown competency of all three drugs in reducing post-operative inflammation. However, ketorolac has been demonstrated to have a slower anti-inflammatory effect compared to corticosteroids. The number of eyes with a minimal amount of anterior chamber cells in the ketorolac group was found to be fewer than the other groups on day 7 and day 14 post-operatively.

Ketorolac has been demonstrated to have equivalent efficacy to prednisolone acetate in reduc-

Table 1. Demographic features and pre-operative data.

	Prednisolone	Ketorolac	Fluorometholone	P-value
Male : Female	14 : 23	14 : 26	15 : 20	0.427*
Mean age ± SD (yr)	63.3 ± 12.2	61.8 ± 12.8	63.2 ± 11.4	0.731†
Right eye : Left eye	19 : 18	19 : 21	20 : 19	0.927*
% of eyes with BCVA < 6/12	70.3	77.5	69.6	0.684†
Mean IOP ± SD (mmHg)	13.84 ± 3.05	14.37 ± 2.38	14.29 ± 3.03	0.679‡

Note : BCVA = best-corrected visual acuity
* Chi-square test, † Kruskal Wallis test, ‡ ANOVA test

Table 2. Summary of the outcome measures at each visit.

Parameter	Group	Day 1	%	Day 7	%	Day 14	%	Day 21	%	Day 28	%	P-value*
Number of eyes with BCVA ≥ 6/12	P	31	83	32	86	31	83	28	82	30	90	
	K	30	75	35	89	33	84	29	82	33	89	
	F	36	94	36	94	38	100	33	97	34	97	
Mean IOP ± SD (mmHg)	P	13.8 ± 4.6		13.7 ± 3.3		14.2 ± 3.5		14.6 ± 3.8(1)		14.2 ± 3.0		0.016†(1)
	K	14.7 ± 3.8		12.8 ± 3.6		12.6 ± 2.5		12.2 ± 2.8(1)		12.5 ± 2.9		
	F	14.5 ± 4.3		12.8 ± 2.9		13.4 ± 3.7		13.8 ± 3.6		14.0 ± 4.2		
Mean change of IOP from pre-operative level ± SD (mmHg)	P	-0.05 ± 4.4		-0.05 ± 3.3		0.37 ± 3.6(2)		0.53 ± 4.3(3)		0.39 ± 2.9(4)		0.022†(2)
	K	0.39 ± 4.1		-1.6 ± 3.9		-1.5 ± 2.3(2)		-2.1 ± 2.9(3)		-1.8 ± 3.3(4)		0.014†(3)
	F	0.24 ± 4.2		-1.3 ± 2.7		-.86 ± 3.9		-0.44 ± 3.8		-0.19 ± 4.8		0.013†(4)
Number of eyes without conjunctival injection	P	1	3	27	73	32	86	34	100	33	100	
	K	3	7	33	84	35	89	34	97	36	97	
	F	0	0	28	73	36	94	32	94	34	97	
Number of eyes without corneal edema	P	29	78	30	81	33	89	32	94	32	97	
	K	31	77	35	89	36	92	33	94	36	97	
	F	25	64	35	92	37	97	32	94	35	100	
Number of eyes without superficial punctate keratitis	P	37	100	36	97	36	97	33	97	33	100	
	K	40	100	38	97	38	97	34	97	36	97	
	F	38	97	38	100	38	100	34	100	34	97	
Number of eyes with amount of cells in the anterior chamber ≤ 5 cells	P	0	0	20	54(5)	31	83(7)	30	88	31	93	0.008‡(5)
	K	0	0	11	28(5,6)	23	59(7)	29	82	34	91	0.011‡(6)
	F	2	5	21	55(6)	26	68	29	85	30	85	0.015‡(7)
Number of eyes without flare in the anterior chamber	P	1	2	34	91	37	100	34	100	33	100	
	K	1	2	36	92	38	97	35	100	37	100	
	F	0	0	35	92	38	100	34	100	35	100	
Number of eyes without irritation	P	12	32	13	35	15	40	18	52	18	54	0.015‡(8)
	K	10	25(8)	14	35	20	51	21	60	19	51	
	F	23	59(8)	18	47	20	52	20	58	24	68	
Number of eyes without pain	P	25	67	29	78	27	73	27	79	25	75	
	K	29	72	33	84	34	87	32	91	33	89	
	F	28	71	31	81	32	84	28	82	30	85	
Number of eyes without tearing	P	11	29	20	54	25	67	24	70	20	60	
	K	15	37	26	66	21	53	19	54	23	62	
	F	16	41	19	50	22	57	19	55	26	74	
Number of eyes without burning sensation	P	25	67	22	59	26	70(9)	24	70	26	78(11)	0.004‡(9)
	K	25	62	16	41	16	41(9,10)	17	48	18	48(11)	0.010‡(10)
	F	30	76	26	68	25	65(10)	25	73	26	74	0.007‡(11)
Number of eyes without photophobia	P	26	70	27	73	28	75	27	79	24	72	
	K	28	70	30	76	31	79	30	85	29	78	
	F	28	71	34	89	32	84	30	88	31	88	
Number of eyes without discomfort	P	37	100	35	95	37	100	34	100	33	100	
	K	38	95	35	92	39	100	34	97	37	100	
	F	38	97	38	100	38	100	34	100	35	100	

Note : Group P = prednisolone acetate, Group K = ketorolac tromethamine, Group F = fluorometholone acetate, BCVA = best-corrected visual acuity.

* P-values are shown only in the pairs with significant difference. Each number in paracenthesis identifies the pair and corresponding p-value. † ANOVA test, ‡ Mann-Whitney test

ing inflammation after cataract surgery[2-4]. In those studies, both drugs were prescribed 4 times a day in the first week, then the dosage was reduced in the following weeks. The current study showed different results. This might be due to difference in dosage prescribed and population studied. The patients enrolled in the current study were Asian with dark irides. This group of patients was predisposed to an exaggerated post-operative inflammatory response, requiring potent anti-inflammatory drugs[7].

The action of NSAIDs in reducing inflammation works through inactivation of cyclooxygenase. This enzyme converts arachidonic acid into cyclic endoperoxides, the precursors of prostaglandin. Arachidonic acid is liberated from phospholipids of the cell membrane by phospholipase A2. Corticosteroids counter inflammation by inhibiting phospholipase A2, therefore, they retard the release of arachidonic acid. The function of corticosteroids at the preceding step in inflammatory process may explain the higher potency upon NSAIDs in reducing post-operative inflammation[8].

Burning sensation after instillation of ketorolac was noted in the present study. This symptom could not be explained either by the osmolarity or acidity of the drug preparations. The osmolarity of ketorolac ophthalmic solution and fluorometholone acetate suspension is 287 and 290 mOsm/kg respectively. The pH of both drugs is 7.4, which was compatible with the pH of human tear.

Topical corticosteroids, especially prednisolone, have been known to increase intraocular pressure after prolonged use[1]. The authors found that increasing intraocular pressure from the pre-operative level in patients treated with prednisolone was statistically significantly different compared to the ketorolac group after two weeks of application. This finding supports substitution of ketorolac to prednisolone especially in steroid responders. Otherwise, monitoring of the intraocular pressure and adjusting prednisolone dosage according to the degree of remaining inflammation should be performed.

Fluorometholone in an alcohol base has been demonstrated among several corticosteroids to have a relatively low potential to elevate intraocular pressure[5]. Quantification of anti-inflammatory effect in rabbit cornea indicated fluorometholone as an effective but weak agent. Formulation of fluorometholone as acetate derivative enhances its effectiveness[6]. Fluorometholone acetate 0.1 per cent was shown to be significantly more effective than its alcohol base with non-significant difference compared to prednisolone acetate 1 per cent in a clinical trial of treatment of external ocular inflammation[9]. In addition, fluorometholone acetate sustained the relatively low potential to elevate intraocular pressure. There was no significant difference of developing ocular hypertension in patients treated with fluorometholone acetate 0.1 per cent compared to fluorometholone 0.2 per cent in a randomized comparative study after photorefractive keratectomy[10].

Competency and relatively low potential to elevate intraocular pressure of fluorometholone acetate has been confirmed in the current study. Post-operative anti-inflammatory effect was demonstrated to be comparable to prednisolone acetate and the effect on intraocular pressure was not significantly different from ketorolac.

In conclusion, topical prednisolone acetate, ketorolac tromethamine, and fluorometholone acetate are effective in reducing ocular inflammation following phacoemulsification and intraocular lens implantation. Ketorolac lowered the amount of cells in the anterior chamber slower than corticosteroids. However, the advantage of low potential to increase intraocular pressure encourages the prescription of ketorolac for patients vulnerable to ocular hypertension.

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การรักษาภาวะตาอักเสบหลังการสลายต้อกระจกด้วยยาหยอดตา: การศึกษาเปรียบเทียบระหว่างเพร็ดนิโซโลน อะซีเตท, คีโตโรแลค โทรเมทธามีนและฟลูออโร-เมทโธโลน อะซีเตท

อดิศักดิ์ ตรีนวรัตน์, พบ, ละอองศรี อัชชนียะสกุล, พบ*, ธรรมนูญ สุรชาติกำธรกุล, พบ*, พนิดา โกสียรักษ์วงศ์, พบ**

เพื่อเปรียบเทียบประสิทธิผลและผลแทรกซ้อนจากการใช้ยาหยอดตา prednisolone acetate, ketorolac trometha-mine, และ fluorometholone acetate ในการรักษาภาวะอักเสบหลังการสลายต้อกระจก โดยศึกษาในผู้ป่วยจำนวน 120 ตา แต่ละตาได้รับการสุ่มเลือกให้ใช้ยาชนิดใดชนิดหนึ่งวันละ 4 ครั้ง นาน 28 วัน ผู้ป่วยจะได้รับการตรวจทุกสัปดาห์รวม 4 ครั้ง โดยวัดระดับสายตา ความดันตา ระดับการอักเสบในช่องหน้าม่านตา และสอบถามอาการผิดปกติ พบว่ากลุ่ม prednisolone มีจำนวนตาที่การอักเสบลดลงมากกว่ากลุ่ม ketorolac ในสัปดาห์ที่ 1 และ 2 ขณะที่กลุ่ม fluorometholone มีจำนวนตาที่การอักเสบลดลงมากกว่ากลุ่ม ketorolac เฉพาะในสัปดาห์แรก ตาที่ได้รับ prednisolone มีความดันตาสูงกว่ากลุ่มที่ใช้ ketorolac ในสัปดาห์ที่ 3 ส่วนตาที่ได้รับ ketorolac จะมีอาการแสบตาบ่อยกว่า โดยสรุปยาทั้ง 3 ชนิดใช้รักษาภาวะอักเสบหลังการสลายต้อกระจกได้โดย prednisolone และ fluorometholone มีประสิทธิผลใกล้เคียงกัน แม้ว่า ketorolac จะออกฤทธิ์ช้ากว่า แต่ไม่ทำให้ความดันตาสูงขึ้นเมื่อเปรียบเทียบกับยากลุ่มสเตียรอยด์

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