Comparison of Loteprednol Etabonate 0.5% Tobramycin 0.3% Combination Eye Drop with Prednisolone acetate 1% for Treatment of Inflammation following Phacoemulsification.

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Abstract

Background: Inflammation is inevitable following cataract surgery. This study compared the efficacy and safety of topical loteprednol etabonate with prednisolone acetate in controlling ocular inflammation following cataract surgery.

Methods: All patients who underwent cataract surgery in Ramathibodi Hospital, receiving either loteprednol etabonate 0.5% plus tobramycin 0.3% ophthalmic suspension or prednisolone acetate 1%, four times daily, were included. Medical records of 299 eligible patients in one year were retrospectively reviewed. Demographic data, clinical findings, and subjective symptoms at days 8 and 28 postoperatively were recorded. The primary outcome was anterior chamber cell reaction grades.

Results: Anterior chamber cell at day 8 of 143, 12, and 14 patients in loteprednol etabonate group were graded as 0, 0.5+, and 1+ or more, while there were 56, 59, and 15 patients in prednisolone acetate group, respectively ($p < 0.001$). However, the proportion of patients in each group was not significantly different at day 28 ($p = 0.057$) by Pearson's chi-squared test. In these groups, changes in mean intraocular pressure were -1.66 mmHg and -1.56 mmHg, respectively, at day 8 ($p = 0.770$), while they were -2.18 mmHg and -1.25 mmHg, respectively, at day 28 ($p = 0.006$).

Conclusion: Loteprednol etabonate plus tobramycin ophthalmic suspension was not less effective than prednisolone acetate in controlling anterior chamber cell reaction during the postoperative period. Reductions in mean intraocular pressure were observed in both groups.

Keywords: phacoemulsification, postoperative, steroids, inflammation.

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Introduction

Cataract is the leading cause of blindness worldwide.[1-4] Thus far, removal of cataractous lenses remains the only curative treatment.[5,6] Cataract surgery is one of the most common ophthalmic procedures,[7,8] although its frequency varies considerably among countries.[9] Cataract extraction combined with intraocular lens implantation provides subjective improvement in visual acuity and quality of life.[9,10] Postoperative inflammation may result in discomfort, posterior synechiae, glaucoma, and pseudophakic cystoid macular edema, all of which lead to visual deterioration.[11] Topical anti-inflammatory drug treatment has been the primary method for alleviating ocular inflammation. Corticosteroids inhibit cyclooxygenase and lipoxygenase pathways of the inflammatory cascade, thereby reducing postoperative inflammation. However,

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the potential side effects of these drugs include elevated intraocular pressure (IOP), poor wound healing, and secondary infection.[12]

Loteprednol etabonate is an ester-based corticosteroid. It reportedly has a weaker effect on IOP elevation, compared with ketone-based corticosteroids such as prednisolone acetate (ie, an anti-inflammatory ophthalmic suspension commonly prescribed postoperatively).[13] Many studies have shown no significant differences in the resolution of postoperative inflammation between loteprednol etabonate 0.5% and either prednisolone acetate 1%, or fluorometholone acetate 0.1%.[14-16] Some studies have reported lower mean IOP in the loteprednol etabonate group, compared with other groups. However, the prior studies involved relatively small numbers of patients. Here, we performed a large retrospective chart review to compare efficacy and safety between loteprednol etabonate-tobramycin combination eye drop and prednisolone acetate eye drop with another antibiotics eye drop for controlling ocular inflammation following cataract surgery combined with intraocular lens implantation.

Materials and Methods

The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and Good Clinical Practices. Documentary Proof of Ethical Clearance was acquired from the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The requirement for informed consent was waived by the review board, due to the retrospective nature of the study.

This retrospective chart review was performed in Ramathibodi Hospital, Bangkok, Thailand. All patients, who underwent phacoemulsification with intraocular lens implantation from July 1, 2016 to June 30, 2017, and were prescribed either loteprednol etabonate 0.5% plus tobramycin 0.3% ophthalmic suspension, or prednisolone acetate 1% with topical antibiotics (either moxifloxacin 0.5% or levofloxacin 0.5% eye drops), four times daily each for postoperative inflammation control, were included. Those with < 18 years of age were excluded. Choices of postoperative steroids given totally depended on surgeons' preferences. Patients were also excluded if they had undergone combined operations with pterygium excision, keratoplasty, or vitrectomy. Patients were also excluded if they had received medications that might interfere with the assessments in this study (eg, antibiotic-steroid combination ointment), had received antiglaucoma medications prior to surgery but discontinued treatment during the data collection period, or had any intraoperative complications. Postoperative inflammatory status of the patients was not known prior to inclusion to reduce the selection bias.

A previous randomized noninferiority study initially intended to recruit 120 patients (60 per group) to yield 98% statistical power with a two-sided alpha of 0.05, a noninferiority margin of 0.35, an assumed standard deviation of 0.47, and an expected difference in anterior chamber (AC) cell reaction of 0 between groups. However, its power was lowered to 90% to reduce sample size to 40 in each group due to slow enrollment.[14] There would be enough patients following data collection period of one year in our institution.

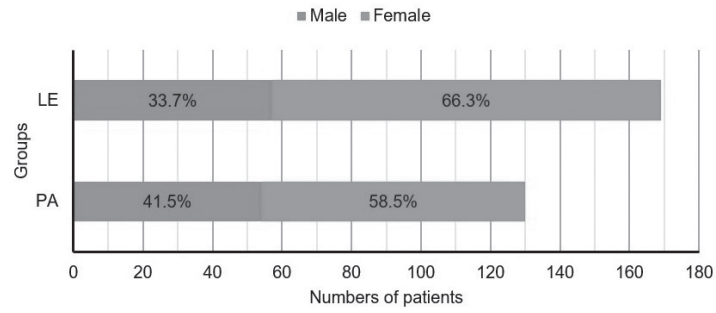
Data collected from the medical records review were patient demographic characteristics, preoperative visual acuity and IOP measurements, postoperative days 8 and 28 IOP measurements, postoperative days 8 and 28 AC cell reaction grades (ie, 0 = 0 cell, 0.5+ = 1-5 cells, 1+ = 6-15 cells, 2+ = 16-25 cells, 3+ = 26-50 cells, or 4+ > 50 cells, per 1 mm by 1 mm high power slit beam; in accordance with The SUN Working Group Grading Scheme for Anterior Chamber Cells)[17], postoperative day 28 visual acuity, and adverse events. Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity values, measured by experienced nurses who had no knowledge of which medication was given to the patients, were converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis with paired t-tests. Postoperative IOP values were recorded as changes from baseline, then compared using paired t-tests. AC cell grades, assessed by ophthalmology trainees or staffs in charge of the patients, were analyzed using Pearson's chi-squared test. Statistical analyses

were performed using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a p-value of < 0.05.

Results

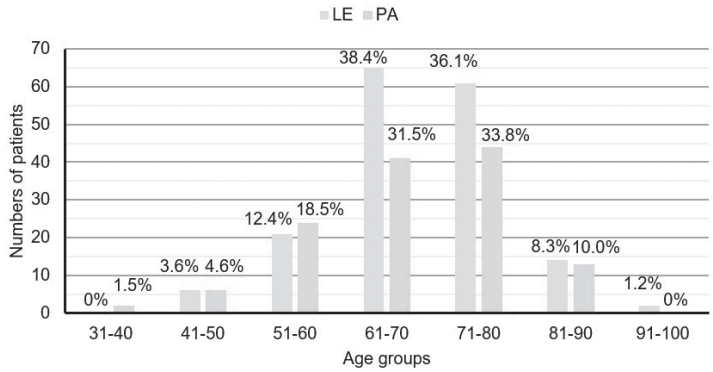
In total, 299 patients were included in this study: 169 (56.5%) received loteprednol etabonate 0.5% plus tobramycin 0.3% ophthalmic suspension four times daily (57 men and 112 women; LE group), while 130 (43.5%) received prednisolone acetate 1% with another antibiotic eye drop, four times daily (54 men and 76 women; PA group) as shown in Figure 1 (p = 0.166). Notably, most patients were women. In the LE group, an ophthalmology staff physician performed all 169 operations. Conversely, in the PA group, an ophthalmology staff physician performed 83 operations (63.8%), while ophthalmology trainees performed the remaining 47 operations (36.2%). Furthermore, age ranged from 47 to 96 years (mean, 69.1 years) in the LE group, while it ranged from 31 to 89 years (mean, 67.7 years) in the PA group (p = 0.233, 95% confidence interval (CI) -0.870 - 3.566; Figure 2). Baseline logMAR visual acuity were 0.487 (standard deviation [SD] = 0.437) and 0.595 (SD = 0.539), respectively, in the LE and PA groups (p = 0.056, 95% CI -0.219 - 0.003). Mean changes in logMAR visual acuity were -0.308 (SD = 0.251) and -0.340 (SD = 0.342), respectively; the difference between groups was not statistically significant (p = 0.347, 95% CI -1.000 - 0.035).

Figure 1: Patient sex distribution.



Abbreviations: LE, loteprednol etabonate group; PA, prednisolone acetate group.

Figure 2: Patient age distribution.



Abbreviations: LE, loteprednol etabonate group; PA, prednisolone acetate group.

Note: Percentages are calculated by groups.

The position of figure 1 and figure 2 is in the first paragraph of the results heading

Table 1 Postoperative days 8 and 28 anterior chamber cell reaction grades

AC cell grade	LE (n, %)	PA (n, %)	p-value
0	143, 84.6%	56, 43.1%	< 0.001 (D8)
0.5+	12, 7.1%	59, 45.4%	
1+ or more	14, 8.3%	15, 11.5%	
0	165, 97.6%	120, 92.3%	0.270 (D28)
0.5+	2, 1.2%	8, 6.2%	
1+ or more	2, 1.2%	2, 1.5%	

Abbreviations: AC, anterior chamber; D28, postoperative day 28; D8, postoperative day 8; LE, loteprednol etabonate group; PA, prednisolone acetate group

Table 1 shows the results of efficacy analysis (AC cell reaction grades). Due to inflammation in most patients were graded as 0 and 0.5+, other grades were needed to be grouped together for statistical analysis. On postoperative day 8, there were 143, 12, and 14 patients in LE group who had AC cell grade of 0, 0.5+, and 1+ or more, respectively; while there were 56, 59, and 15 patients in PA group who had AC cell grade of 0, 0.5+, and 1+ or more ($p < 0.001$). On postoperative day 28, there were 165, 2, and 2 patients in LE group, while there were 120, 8, and 2 patients in PA group, who had AC cell grade of 0, 0.5+, and 1+ or more, respectively ($p = 0.057$).

Table 2 Comparison of postoperative day 8 anterior chamber cell reaction grades according to surgical expertise in prednisolone acetate group

AC cell grade	PA-S (n, %)	PA-T (n, %)	p-value
0	42, 51.2%	14, 29.2%	0.043
0.5+	31, 37.8%	28, 58.3%	
1+ or more	9, 11.0%	6, 12.5%	

Abbreviations: AC, anterior chamber; PA-S, prednisolone acetate group with surgery performed by a staff physician; PA-T, prednisolone acetate group with surgery performed by a trainee

Table 2 shows subgroup analysis of postoperative day 8 AC cell grades in the PA group. Patients were stratified into those whose surgery was performed by an ophthalmology staff physician (PA-S) and those whose surgery was performed by an ophthalmology trainee (PA-T). There were 42, 31, and 9 patients in PA-S group, while there were 14, 28, and 6 patients in PA-T group, who had AC cell grade of 0, 0.5+, and 1+ or more, respectively; the difference between groups was statistically significant ($p = 0.043$). AC cell grades on postoperative day 8 were then compared between the LE and PA-S groups; the difference between groups was statistically significant ($p < 0.001$; Table 3).

Table 3 Comparison of postoperative day 8 anterior chamber cell reaction grades according to surgical expertise between groups

AC cell grade	PA-S (n, %)	LE (n, %)	p-value
0	42, 51.2%	143, 84.6%	
0.5+	31, 37.8%	12, 7.1%	< 0.001
1+ or more	9, 11.0%	14, 8.3%	

Abbreviations: AC, anterior chamber; LE, loteprednol etabonate group; PA-S, prednisolone acetate group with surgery performed by a staff physician

Table 4 Preoperative IOP, postoperative days 8 and 28 IOP, and IOP changes in each group

Group	IOP (mean ± SD, mmHg)	p-value (95% CI) for the difference between groups
Preoperative LE	13.98 ± 2.956	0.089 (-0.091, 1.290)
Preoperative PA	13.38 ± 3.070	
D8 LE	12.31 ± 3.217	< 0.001 (1.190, 2.136)*
D8 PA	11.82 ± 2.996	< 0.001 (1.082, 2.041)**
ΔD8 LE	-1.66 ± 3.115	0.770 (-0.782, 0.580)
ΔD8 PA	-1.56 ± 2.762	
D28 LE	11.79 ± 2.872	< 0.001 (1.747, 2.620)*
ΔD28 LE	-2.18 ± 2.876	0.006 (-1.600, -0.275)
ΔD28 PA	-1.25 ± 2.899	

Abbreviations: Abbreviations: CI, confidence interval; D28, postoperative day 28; D8, postoperative day 8; LE, loteprednol etabonate group; IOP, intraocular pressure; PA, prednisolone acetate group; SD, standard deviation; ΔD28, change from preoperative to postoperative day 28; ΔD8, change from preoperative to postoperative day 8

Note: Asterisks (*) indicate significant differences in IOP changes, compared with preoperative values, in LE group. Double asterisks (**) indicate significant differences in IOP changes, compared with preoperative values, in PA group.

The safety outcome was monitored by changes in IOP, as shown in Table 4. Mean preoperative IOP values were 13.98 (SD = 2.956) mmHg and 13.38 (SD = 3.073) mmHg in the LE and PA groups, respectively. The difference was not statistically significant (p = 0.090). Mean postoperative day 8 IOP and IOP change from baseline values were 12.31 (SD = 3.217) mmHg and -1.660 (p < 0.001) mmHg in the LE group. In the PA group, the corresponding values were 11.82 (SD = 2.996) mmHg and -1.56 (p < 0.001) mmHg. The difference between IOP changes in each group on postoperative day 8 was not statistically significant (p = 0.770). Mean postoperative day 28 IOP and IOP change from baseline values were 11.79 (SD = 2.872) mmHg and -2.18 (p < 0.001) mmHg in the LE group. The corresponding values were 12.13 (SD = 3.333) mmHg and -1.25 (p < 0.001) mmHg in the PA group. On postoperative day 28, the IOP change was significantly lower in the LE group than in the PA group (p = 0.006) mmHg.

Serious adverse events were not observed in this study. Nevertheless, mild adverse events were reported regarding prednisolone acetate 1% ophthalmic suspension; these

included a brief period of blurred vision after drop application, lower eyelid irritation, and whitish discharge. All symptoms resolved following cessation of eye drop application.

Discussion

Loteprednol etabonate 0.5% plus tobramycin 0.3% ophthalmic suspension appeared to have more effective control of postoperative inflammation with non-significant IOP rising, compared with prednisolone acetate 1% plus antibiotic eye drops. It may enhance patient compliance with postoperative medications due to fewer drops to be administered. And thus replace the use of prednisolone acetate 1% in conjunction with another antibiotics in patients who have difficulty applying eye drops. However, the cost of the combination eye drops was slightly more expensive than both separate eye drops at our hospital (325 baht versus 274.5 baht) and it might not be available at some centers.

This study compared loteprednol etabonate 0.5% plus tobramycin 0.3% ophthalmic suspension with prednisolone acetate 1% ophthalmic suspension for treatment of inflammation following cataract surgery combined with intraocular lens implantation. The results suggested that postoperative inflammation was effectively controlled by both loteprednol etabonate 0.5% and prednisolone acetate 1% regimens. The difference in postoperative day 8 AC cell grade was presumed to be related to surgical expertise. However, subgroup analysis showed significantly lower AC cell grade in the LE group than in the PA group. This suggested that loteprednol etabonate provided more effective control of postoperative inflammation, compared with prednisolone acetate, although the difference in control was not statistically significant at the final follow-up. Potential confounding factors included cataract hardness, surgical technique, ultrasonic phacoemulsification power, compliance, and an interval between PA and antibiotic drops.

Previous studies showed that cataract surgery had an IOP-lowering effect,[18-23] this study emphasized that postoperative IOP was lower than baseline IOP in both groups. The IOP change was significantly lower in the PA group than in the LE group at the final follow-up. The IOP-raising effect of topical corticosteroid treatment was therefore considered to be weaker than IOP-lowering effect of cataract surgery.

Our retrospective study had several limitations due to the nature of the study design. First, baseline patient characteristics of both groups were not the same. Nonetheless, differences in baseline characteristics between the two groups were not significant. To minimize selection bias, stringent inclusion and exclusion criteria were applied and the recruitment of the two groups was done without knowing the outcomes of interest. However, some charts were technically excluded due to missing of certain necessary information. Second, since the data was not primarily collected for research, even the included medical records might have bound to have some missing information. Besides surgeons' preference, postoperative regimens might have varied according to patients' risk profiles and the exact reasons were not mentioned in the charts. More importantly, intraocular inflammation after phacoemulsification depends considerably on many factors, including baseline patient characteristics, indications for surgery, type and grading of cataracts, phacoemulsification techniques and settings, surgical skill, judgment, and precise work of the surgeons. Therefore, further randomized controlled trials addressing the above and other unknown confounding factors that could have influenced the study results are needed to confirm the findings of this study.

Conclusion

Both loteprednol etabonate 0.5% plus tobramycin 0.3% ophthalmic suspension and prednisolone acetate 1% ophthalmic suspension reduced intraocular inflammation after uncomplicated phacoemulsification, without causing serious adverse events.

Abbreviations

AC, anterior chamber; CI, confidence interval; D28, postoperative day 28; D8, postoperative day 8; ETDRS, Early Treatment

Diabetic Retinopathy Study; IOP, intraocular pressure; LE, loteprednol etabonate; logMAR, logarithm of the minimum angle of resolution; PA, prednisolone acetate; PA-S, patients in prednisolone acetate group whose surgery was performed by an ophthalmology staff physician; PA-T, patients in prednisolone acetate group whose surgery was performed by an ophthalmology trainee; SD, standard deviation; SUN, Standardization of Uveitis Nomenclature; ΔD28, change from preoperative to postoperative day 28; ΔD8, change from preoperative to postoperative day 8

Data availability statement

Data are available upon reasonable request to the corresponding author.

Conflicts of Interest

An oral presentation of these data at the 31st Asia-Pacific Association of Cataract & Refractive Surgeons was partially funded by the Royal College of Ophthalmologists of Thailand.

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