

A Comparison of Diclofenac versus Dexamethasone for the Treatment of Postcataract Inflammation

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백내장 수술 후 염증치료를 위해 일반적으로 부작용이 많은 국소 점안 스테로이드를 사용해왔다. 최근 NSAID계열의 점안액이 항염증 치료약물로 개발되면서 선택적인 약물치료가 가능하게 되었으나 단일치료약물로 사용하는 경우는 드물다. 본 연구는 NSAID계 diclofenac 점안액의 백내장 수술 후 염증치료 효과를 스테로이드계 dexamethasone 점안액과 비교하여 단일 치료약물로서 사용할 수 있는 지 연구하고자 하였다. 백내장 수술을 받은 환자로써 안압이 22 mmHg 이상, 당뇨환자, 수술대상 눈에 이미 질환 및 수술 경력이 있는 자를 제외하였다. 백내장 수술 후 항염증 약물로서 diclofenac 또는 dexamethasone을 28일 동안 투여하고 항염증효과의 평가를 위하여 세극등 검사로서 전방내 염증세포와 결막, 각막등의 전안부 관찰을 수술 전, 수술 후 1, 3, 7, 14, 28일에 시행하였고, 시력검사는 수술 후 7, 28일에 시행하였다. 안전성의 평가는 안압검사와 세극등 검사상 관찰된 이상소견으로 평가하였다. 총 73 명의 연구대상 중 dexamethasone군은 41명, diclofenac군은 32명이며 두 군간에 나이, 백내장의 심한 정도, 안구질환 등에 있어 유의한 차이가 없었다. 전방내 항염증세포수의 감소에서 두 군간에 유의할 만한 차이가 없었고, 수술 후 최대 교정 시력에서도 동일한 효과를 보였다. 안전성에서 안압의 상승이 두 군간에 통계적인 유의한 차이를 보이지 않았으나 dexamethasone 군에서 1 명의 환자가 45 mmHg 이상 증가하여 약물치료가 필요하였으나 diclofenac군에서는 안압이 상승한 환자가 없었다. 결론적으로 효능 및 안전성에서 두 약물간에 통계적, 임상적으로 유의한 차이가 없었으며 diclofenac 점안액은 백내장 수술 후 항염증치료제로서 충분한 효과가 있으며 안압상승, 감염 등 부작용이 우려되는 dexamethasone 점안액의 대체약물로 사용될 수 있을 것으로 평가된다.

□ Key words: Diclofenac, Dexamethasone, Cataract Surgery, Inflammation

Cataract is one of the common eye diseases in which the lens is opacified by several factors such as aging, trauma and drug-induced reaction. Surgery is the treatment of choice and phacoemulsification is the most advanced technique for cataract surgery with advantages of less complication, rapid recovery of vision and resumption of normal activities.¹⁾ Anti-inflammatory eye drops are essential to control inflammation although it is partially self-limited after cataract extraction.²⁾ Topical corticosteroid eye drops have been used to achieve effective control of inflammation, but high potency steroids are subject to numerous adverse reactions including intraocular

hypertension and the increased risk of infections.^{3,4)} Diclofenac sodium is a potent non-steroidal anti-inflammatory drug (NSAID) approved by the Food and Drug Administration (USA) for clinical indication of inflammation after cataract surgery.⁵⁾ It has shown to be more effective than placebo^{6,7)} and as effective as prednisolone eye drops.^{8,9)} Also, the combination therapy with dexamethasone has shown to have better anti-inflammatory effect than dexamethasone alone.¹⁰⁾ The NSAIDs have many clinical advantages and have a potential for extensive use once its clinical efficacy becomes more clearly evident.^{11,12,13)} Dexamethasone, a highly potent steroid, has been widely prescribed for control of inflammation after cataract surgery in Korea, since the efficacy of diclofenac sodium as monotherapy has not been clearly established to substitute steroids. The objective of this study is to compare the efficacy and safety of diclofenac sodium with those of dexamethasone eye drops after cataract surgery.

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METHOD

Patients

Patients with age greater than 18-year-old who underwent cataract surgery of one eye without surgical complications at Kong Eye Center (Seoul, Korea) during the period from March, 1997 to April, 1997 were eligible. Preoperative evaluations including slit-lamp examination, fundus examination, visual acuity test and tonometry were carried out for appropriate selection of patients at least 14 days prior to surgery. Criteria for exclusion included intraocular pressure greater than 22 mmHg, history of ocular inflammation (iritis, uveitis), pseudoexfoliation, previous intra-ocular surgery in the operative eye, diabetes mellitus, arthritis, use of topical or systemic anti-inflammatory drugs within 2 weeks prior to surgery and hypersensitivity to NSAIDs or steroids.

Study Design and Treatment

Cataract Surgery Four ophthalmic surgeons with similar level of skills and experiences were involved to minimize the variation in the evaluation of the complications and the efficacy of medications after surgery. Phacoemulsification-silicon foldable lens implantation involved a process of fragmenting and aspirating the lens nucleus and cortical material with ultrasonic vibrations followed by implantation of a silicon foldable lens in the capsular bag through a 3.2 mm small incision.

Anti-inflammatory medications Patients were randomly assigned to receive diclofenac sodium 0.1% eye drops (Naclor[®], CIBA Vision, Switzerland) or dexamethasone 0.1% eye drops (Maxidex[®], Alcon, USA) after phacoemulsification-silicon foldable lens implantation in an open-labeled design. The study medications were instilled one drop 4 times daily for 7 days, then 3 times daily from day 8 to 28 postoperatively. No other anti-inflammatory medications were allowed to take systemically or topically.

Post-operative medications All patients received injections of cefazolin and tobramycin subconjunctivally once at the end of the operation followed by cefadroxyl 500 mg orally 2 times daily until day 6. Tobramycin 0.3% (Tobrex[®], Alcon, USA) eye drops were administered along with anti-inflam-

matory eye drops at least five minutes after the study drugs. Patients were instructed to observe any un-expected changes after surgery and consult with surgeons when they need to take other medications.

Efficacy Assessment

The grades of anterior chamber inflammatory cells Slit-lamp examination was performed for evaluation of anti-inflammatory effect of the study eye drops by counting inflammatory cells in anterior chamber of the eye. It is evaluated with grade 0 to +4 in which the lower grade has less inflammatory cells in anterior chamber (Table 1). The patients were examined at postoperative day 1 as baseline measurement. Inflammatory cells were assessed was assessed at postoperative day 3, 7, 14 and 28 for the evaluation of efficacy. All slit-lamp examinations were performed under standardized conditions by surgeons: dim room illumination, maximal lamp voltage, 3×1 mm aperture, illumination angle of 30 degrees, magnification of 16× and observation for five seconds.¹⁴⁾ Treatment was defined as therapeutic failure when any withdrawals from the study occurred due to adverse drug reactions or unsatisfactory response to the treatment. The patients who had the examination days with the grades of anterior chamber inflammatory cells greater than the baseline level were also considered as therapeutic failure.

The corrected visual acuity It was assessed with the Dr. Hahn's standard chart for 5 m distance preoperatively and at postoperative day 7 and 28 by a optometrist who was blind to the study.

Safety Assessment

Patients were assessed for any adverse events

Table 1. The grades of anterior chamber inflammatory cells

| Grade | Inflammatory Cells in the Anterior Chamber |
|-------|---|
| 0 | 0 |
| ± | 0-5 |
| +1 | 5-10 |
| +2 | 10-20 |
| +3 | 20-50 |
| +4 | over 50 |

postoperatively. The slit-lamp examination observed any changes in the conjunctiva, the cornea, and the eyelid for edema, injection, hemorrhage, keratitis punctate and corneal erosion, etc. The intraocular pressure was measured using tonometry by nurses who were blind to the study.

Statistical Analysis

Comparability of the treatment groups with respect to demographic characteristics was tested using Chi-square test, Fisher's exact test and student t-test. The grades of inflammation in anterior chamber were evaluated with Wilcoxon rank-sum test (Mann-Whitney U test). The corrected visual acuity was evaluated with student t-test. The proportions of the patients with therapeutic failures and adverse events in each group were compared with Fisher's exact test. All statistical tests performed in this study were two-sided with a probability level of 0.05 to declare statistical significance. The analyses were performed using SPSS PC+.

Results

Patient Characteristics

Seventy-three patients were enrolled in this prospective, open label study: 41 patients received dexamethasone 0.1% eye drop and 32 patients received diclofenac sodium 0.1% eye drop (Table 2). There were 43 males (59%) and 30 females (41%). The mean age was 60.7 years. Total 12 demographic variables were tested for comparability and there was no statistically significant difference between the groups.

All patients were assessed according to the assigned treatment regardless of violations because the study was evaluated based on an intent-to-treat analysis. Twenty-three patients (11 dexamethasone; 12 diclofenac sodium) were protocol violators with 37 visit violations (10.1%, 18 dexamethasone vs¹⁹ diclofenac sodium) out of a total of 365 planned postoperative visits. The protocol violations comprised of 1) intake of unacceptable concomitant medication, 2) failure to follow the scheduled appointment, 3) inappropriate care after surgery against the provided instruction, 4) non-compliance with the study medication, and 5) transfer to the other hospitals.

Three recipients of dexamethasone and 3 recipients of diclofenac sodium were prematurely withdrawn from the study. Reasons for withdrawal included adverse reactions (1 dexamethasone recipient), unsatisfactory therapeutic response (3 diclofenac sodium recipients) and violations of dosing schedule (2 dexamethasone recipients).

Efficacy Analysis

The grades of anterior chamber inflammatory cells

Diclofenac sodium diminished the grades of in-

Table 2. Patient characteristics

| Characteristics | Dexamethasone (n=41) | Diclofenac (n=32) | p-value |
|--------------------------------------|-------------------------|----------------------|---------|
| Age (years) | 59.7±14.2 | 61.68±13.1 | NS |
| Gender | | | NS |
| Male | 23 | 20 | |
| Female | 18 | 12 | |
| Type of cataract | | | NS |
| Congenital | 1 | 0 | |
| Juvenile | 2 | 2 | |
| Presenile | 5 | 3 | |
| Senile | 30 | 2 | |
| Traumatic | 3 | 0 | |
| Cataract maturity | | | NS |
| Immature | 37 | 26 | |
| Mature | 2 | 4 | |
| Hyper mature | 2 | 2 | |
| Eye in operation | | | NS |
| Right | 16 | 17 | |
| Left | 25 | 15 | |
| History of cataract operation | | | |
| Yes | 6 | 10 | |
| No | 35 | 22 | |

NS: not statistically significant, p>0.05

Table 3. Mean score of the anterior chamber inflammatory cells

| Postoperative day | Dexamethasone (n=41) | Diclofenac (n=32) | p-value |
|-------------------|-------------------------|----------------------|---------|
| 1 day | 4.60±0.74 | 4.50±0.80 | p-value |
| 3 days | 2.95±0.90 | 3.15±0.76 | NS |
| 7 days | 1.56±0.78 | 2.00±0.98 | NS |
| 14 days | 1.05±0.76 | 1.28±1.10 | p<0.05 |
| 28 days | 0.44±0.63 | 0.70±0.65 | NS |

Data are presented in mean±S.D., NS: not statistically significant, p>0.05

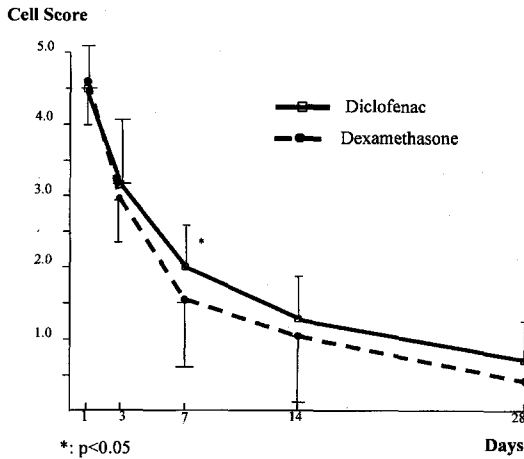


Fig. 1. Mean score of the anterior chamber inflammatory cells

Table 4. The corrected visual acuity after cataract surgery

| Postoperative day | Dexamethasone (n=41) | Diclofenac (n=32) | p-value |
|-------------------|----------------------|-------------------|---------|
| 7 days | 0.93 ± 0.13 | 0.95 ± 0.13 | NS |
| 28 days | 0.93 ± 0.13 | 0.95 ± 0.08 | NS |

Data are presented in mean±S.D., NS: not statistically significant, p>0.05

inflammatory cells in anterior chamber of the eye as rapidly and effectively as dexamethasone did for 28 days (0.70 versus 0.44 on 28 day, p=0.14). Statistically, there was no significant difference between the diclofenac sodium group and the dexamethasone group in the grades of anterior chamber inflammatory cells at postoperative day 3, 14 and 28 (p>0.05) except at day 7 (p=0.043) when sufficient anti-inflammatory effect was shown (Table 3, Fig. 1).

The corrected visual acuity

There were no statistically significant differences in the corrected visual acuity at any visits (p>0.05, Table 4, Fig. 2). One hundred percent of the dexamethasone group had the corrected visual acuity of 20/40 or better at postoperative day 7 and 28. In the diclofenac sodium group, 96% at postoperative day 7 and 100% at postoperative day 28 had the corrected visual acuity of 20/40 or better (Fig. 3). However, all patients gained the corrected visual acuity of 20/40 at the final assessment of study. The patients with any prior

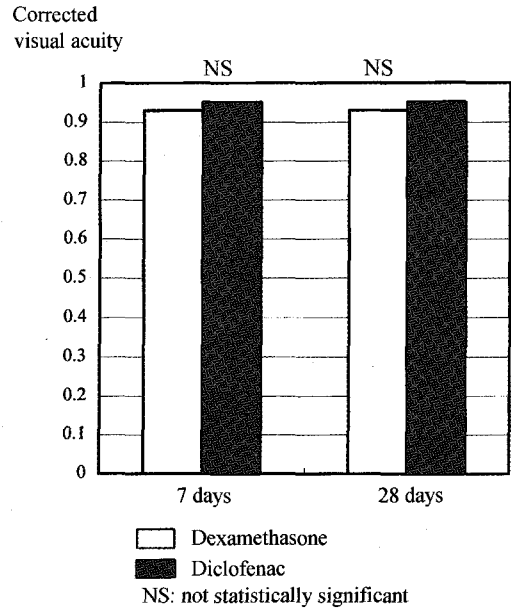


Fig. 2. The corrected visual acuity after cataract surgery

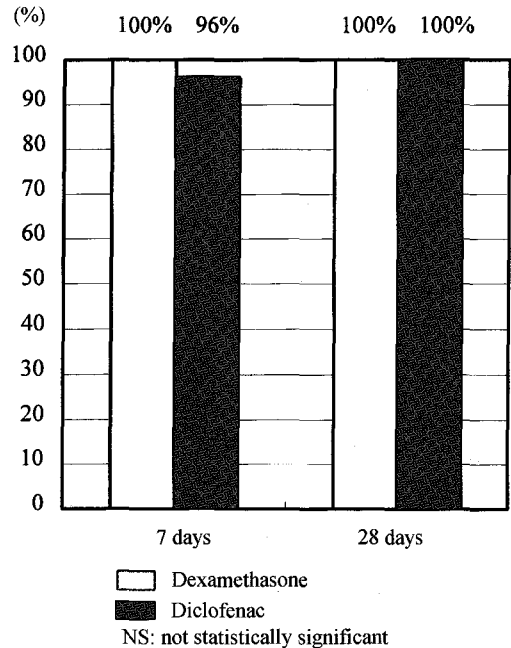


Fig. 3. Patients with corrected visual acuity over 20/40

diseases that might have hindered the improvement of the vision after cataract surgery were excluded during the visual acuity assessment because the major objective of this study was to assess the anti-inflammatory effect. In the dexamethasone group, 6

Table 5. Patients with elevated intraocular pressure

| Intraocular pressure | Dexamethasone (n=41) | Diclofenac (n=32) | p-value |
|----------------------|----------------------|-------------------|---------|
| ≥22 mmHg | 1 | 0 | NS |
| <22 mmHg | 40 | 32 | |
| Total | 41 | 32 | |

NS: not statistically significant, $p>0.05$

patients with corneal opacity, retinal degeneration, macular hole, retinal detachment, high myopia, macular edema or macular degeneration were excluded during the corrected visual acuity assessment; thus 32 patients have completed the study. In the diclofenac sodium group, 4 patients with branch retinal vein occlusion, retinal degeneration, macular degeneration or corneal opacity were excluded during the corrected visual acuity assessment; thus 24 patients completed the study. Therapeutic failure rates were similar between the groups (1 in the dexamethasone group and 3 in the diclofenac sodium group, $p=0.312$)

Safety Analysis

In the diclofenac sodium group, there was no patient with elevated intraocular pressure, a major adverse effect of steroid eye drops (Table 5). But in the dexamethasone group, one patient had an elevated intraocular pressure at day 22 and was replaced by fluorometholone 0.1% three times a day. Diclofenac sodium caused slightly more adverse effects at the cornea than dexamethasone throughout the observation by the slit-lamp examination. Three patients (1 keratitis punctate, 2 corneal erosion, 3/32, 9.3%) in the diclofenac sodium group and one patient (1 keratitis punctate, 1/41, 2.4%) in the dexamethasone group had probable treatment-related adverse events but neither were severe enough to discontinue the treatment.

Discussion

After cataract surgery, topical steroid eye drops have been administered to control inflammation in the anterior chamber that is normally clear by slit-lamp examination. Diclofenac sodium eye drop is one of recently approved NSAID to treat inflammation without risk of alteration in intraocular

pressure and is also valuable in treating and preventing cystoid macular edema (CME), a complication of cataract surgery.¹⁵⁾ We found diclofenac sodium to be as effective as dexamethasone in reducing anterior chamber inflammation, which is consistent with previous reports.^{11,12)} The variations in surgical skills and slit-lamp examination would have been insignificant because the participating four surgeons had very similar experiences and skills although they can not be totally excluded. The compliance was checked by assessing the frequency of prescription refill and confirming verbally and was excellent. The dosage schedule was chosen for convenience according to our routine administration schedule for topical steroids after cataract extraction. The differences in the corrected visual acuity were similar between the groups after surgery. One patient in the dexamethasone group has shown cystoid macular edema at postoperative day 6 and has taken diclofenac sodium eye drop before fluorescein angiography. Punctate keratitis or corneal erosion is a common toxic reaction of all eye drops, which are possibly induced by the preservatives of the study drugs or tobramycin 0.3%. The adverse reactions were not so severe enough to discontinue the study drugs.

Anti-inflammatory effect of diclofenac sodium is explained by reducing availability of free arachidonic acid to convert to leucotrienes in addition to inhibition of prostaglandin synthesis.¹⁶⁾ Roberts studied that the pretreatment with an NSAID before cataract surgery could reduce the amount of initial postoperative inflammation since prostaglandin release at the time of surgery is a major factor in the development of postoperative inflammation.¹⁷⁾ Diclofenac sodium has been safely administered concurrently with other ophthalmic medications such as antibiotics, β -blockers, carbonic anhydrase inhibitors, cycloplegics and mydriatics. Transient burning has been experienced in 15% of patients and hypersensitivity reactions and keratitis punctate have been reported rarely.^{5,18)} In cataract patients, the highest average concentration of diclofenac sodium has been 82 ng/ml at 2.4 hours after single drop instillation in aqueous humor, has remained above 20 ng/ml over 4 hrs and in the range of 3 and 16 ng/ml

through 24 hours.¹⁹⁾

The absorption variation of the study drugs was minimized with patient education for direction of proper instillation and having five-minute gap during any sequential administrations of the eye drops.

In our study, slit-lamp examination was used to evaluate efficacy. Slit-lamp evaluation is a valid and widely used method of assessing intraocular inflammation, although it is semi-quantitative unlike laser flare-cell metry, which provides quantitative results. El-Maghraby demonstrated that the measurements between laser flare cell meter and clinical slit-lamp assessments at postoperative time points had highly positive correlation.²⁰⁾

Conclusion

Diclofenac sodium 0.1% eye drop showed comparable anti-inflammatory effect to dexamethasone 0.1% eye drop which has been the standard therapy with higher risks of the increased infections and the intraocular pressure after cataract surgery. It can be concluded from our study that diclofenac sodium 0.1% eye drop can be an alternative to dexamethasone 0.1% eye drop in the treatment of inflammation after phacoemulsification-silicon foldable lens implant surgery in cataract patients. In the future, diclofenac sodium 0.1% can be studied with different dosage schedules or for the preoperative treatment to enhance the efficacy of anti-inflammation after cataract surgery.

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