Efficacy of Ketorolac 0.5% Ophthalmic Solution For Controlling the Postoperative Inflammation in Pediatric Cataract Surgery

Pediyatrik Katarakt Cerrahisinde Postoperatif İnflamasyonun Kontrolünde %0.5'lik Ketorolak Oftalmik Solüsyonun Etkinliği

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ABSTARCT

Purpose: To evaluate the efficacy and safety of ketorolac 0.5% ophthalmic solution to control postoperative inflammation in pediatric cataract surgery.

Materials and Methods: Forty one eyes of 41 children with congenital or developmental cataract were included in the study. The subjects were assigned to receive topical ketorolac 0.5% ophthalmic solution preoperatively and postoperatively (group 1) or without ketorolac 0.5% ophthalmic solution (group 2). Each patient had uneventful phacoemulsification with a placement of a foldable posterior chamber intraocular lens. Follow-up visits were performed 1, 3, 7 and 30 days postoperatively. The postoperative inflammation or associated complications such as cyclitic membrane, intraocular lens precipitates, anterior and posterior synechia and optic capture were evaluated for each group by slit-lamp examination and compared.

Results: There were significant differences in terms of inflammatory cells in the anterior chamber between group 1 and group 2 at follow-up visits that performed postoperatively 1st, 3rd and 7th day ($p<.05$).

Although significant differences were found between groups in aspect of the flare at postoperative 1st and 3rd day visits ($p<.05$), there was no significant difference at 7th day visit ($p>.05$).

In 6 patients from group 2 had inflammatory related complications including cyclitic membrane, posterior synechia, intraocular lens precipitates and optic capture. There was not statistically significant difference in terms of intraocular pressure between groups.

Conclusion: Ketorolac 0.5% solution seems effective and safe when started before surgery and continued 1 month postoperatively for the treatment of the postoperative inflammation in children.

Key Words: Cataract, ketorolac, pediatric, inflammation, surgery

ÖZ

Amaç: Pediyatrik katarakt cerrahisinde postoperatif inflamasyonun kontrolünde % 0.5'lik ketorolak oftalmik solüsyon kullanımının güvenlik ve etkinliğinin değerlendirilmesi.

Gereç ve Yöntem: Konjenital ve gelişimsel katarakt tanısı alan 41 hastanın 41 gözü çalışma kapsamına alındı. Hastalar preoperatif ve postoperatif topikal %0.5'lik ketorolak damla alanlar (grup 1) ve almayanlar (grup 2) olmak üzere 2 gruba ayrıldı. Tüm hastalara fakoemülsifikasyon ve katlanabilir arka kamara göz içi lens implantasyonu uygulandı. Kontrol muayeneleri ameliyattan 1, 3, 7 ve 30 gün sonra yapıldı. Postoperatif inflamasyon ya da ilişkili komplikasyonlar olan siklitik membran, göz içi lens lenste prespitatlar, anterior ve posterior sineşi ve optik tutsağı yönünden hastalar biyomikroskop ile değerlendirildi ve karşılaştırıldı.

Bulgular: İnflamasyon ön kamaradaki inflamatuar hücreler yönünden değerlendirildiğinde, postoperatif 1, 3 ve 7 gün sonra yapılan muayenelerde grup 1 ve grup 2 arasında belirgin fark vardı ($p<.05$). İnflamasyona ön kamaradaki flare açısından bakıldığında ise, postoperatif 1 ve 3 gün sonra yapılan muayenelerde grup 1 ve grup 2 arasında belirgin fark vardı ($p<.05$). Buna karşın postoperatif 7 gün sonra yapılan muayenede gruplar arasında fark gözlenmedi. Grup 2'deki 6 hastada siklitik membran, posterior sineşi, göz içi lenste prespitatlar ve optik tutsağını içeren inflamasyonla ilişkili komplikasyonlar gelişti. Göz içi basınçlar karşılaştırıldığında gruplar arasında fark gözlenmedi.

Sonuç: Çocuklarda postoperatif inflamasyonun kontrolünde cerrahiden önce başlanıp ardından postoperatif 1 ay süre boyunca %0.5'lik ketorolak oftalmik solüsyon kullanımı etkin ve güvenilir gözükmektedir.

Anahtar Kelimeler: Katarakt, ketorolak, pediyatrik, inflamasyon, cerrahi.

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INTRODUCTION

Cataract surgery has a higher incidence and more manifest postoperative inflammatory response in childhood compared with adults. These reactions are associated with younger age and may be affected by surgical technique, intraoperative manipulations to the iris and residual cortical material.[1]

Despite advances in technique many patients still show clinically significant inflammation after cataract surgery that needs treatment with anti-inflammatory medication.[2-4] Occasionally inflammation can cause many complications including posterior synechia, elevated intraocular pressure (IOP), pain, photophobia and cystoid macular edema.[5] Corticosteroids have been used to prevent and treat inflammation after cataract surgery for many years.[6,7]

The inflammation is due to the breakdown of the blood-aqueous barrier and release of inflammatory mediators, starting with arachidonic acid. Arachidonic acid is converted by cyclooxygenase (COX) and lipooxygenase enzymatic pathways to produce prostaglandins and leukotrienes respectively. Two types of the cyclooxygenase, named COX-1 and and COX-2, are defined. Nonsteroidal anti-inflammatory drugs (NSAIDs) are able to inhibit both COX-1 and COX-2 activity.[8] Also pretreatment with NSAIDs before cataract surgery has benefit of controlling postoperative inflammation by suppressing basal prostaglandin production and by reaching therapeutic concentrations during surgery, blocking COX-2 activity when it is produced.[9]

This study investigates the efficacy and safety of ketorolac 0.5% ophthalmic solution using preoperatively and postoperatively in the treatment of inflammation after pediatric cataract surgery.

MATERIALS AND METHODS

A retrospective chart review was performed for 41 children with pediatric cataract operated at a tertiary referral center between March 1, 2008 and December 31, 2012. This study evaluated the efficacy and safety of preoperative and postoperative use of ketorolac 0.5% ophthalmic solution to treat ocular inflammation after pediatric cataract surgery. Informed consent was obtained from parents of the patients. A comprehensive medical history was obtained from parents and an ophthalmological examination was performed on each patient prior to cataract surgery. Exclusion criteria included use of systemic or topical corticosteroids and NSAIDs, allergy to NSAIDs, microphthalmos, corneal diseases and glaucoma or serious systemic disease that could interfere with the study.

Preoperatively, patients had an ophthalmologic examination consisting of a slit-lamp examination, IOP measurement by I care PRO tonometer (Icare Finland, Helsinki, Finland) and dilated fundus examination. Patients were assigned to group 1 or group 2. Mydriatic eye drops (tropicamide 0.5%, phenylephrine hydrochloride 2.5%) were given every 15 minutes for 3 times beginning 2 hours before surgery. Cataract surgeries were performed by an experienced surgeon under general anesthesia and the same surgical approach was used in each case. Surgeries were performed using phacoemulsification through a 2.75 mm clear corneal incision. Sodium hyaluronate with the percentages 3% and 1.8% was used in each case. All children had posterior capsulotomy and anterior vitrectomy. A foldable, acrylic, posterior chamber intraocular lens (IOL) was inserted through the incision, which was closed with 10-0 nylon suture. Sodium hyaluronate was removed by bimanual technique and stromal hydration was performed with balanced salt solution.

The treatment protocol is same in both group 1 and group 2, except ketorolac 0.5% solution that was only used in group 1. Preoperative ketorolac treatment protocol was 1 drop 4 times daily beginning three days before surgery and postoperative ketorolac treatment protocol was 1 drop 8 times first two weeks followed by 1 drop 4 times daily at 3th and 4th week.

Other postoperative treatments for both groups consisted of cyclopentolate 1% solution 3 times daily 1 drop for two weeks, ofloxacin 0.3% solution 1 drop 8 times daily first week followed 4 times daily for 1st month and dexamethasone 0.1% solution 1 drop 12 times daily first week followed 8 times daily ^{2nd} week and tapered over 6 weeks.

Anterior chamber inflammation was evaluated at each follow-up visit by slit-lamp examination. Follow-up visits were performed 1, 3, 7 and 30 days postoperatively. Anterior chamber cells and flare were graded subjectively as following: for anterior chamber cells 0=none, 1=1-15 cells, 2=16-30 cells, 3=greater than 30 cells and for anterior chamber flare, 0=none, 1=trace, 2=mild, 3=moderate and 4=excessive intensity.

At each follow-up visit, postoperative complications, including fibrin formation, anterior and posterior synechia, cyclitic and pupillary membrane formation, were documented and compared.

All systemic and local complaints of patients were reported to the investigators at each follow-up visit during the study. Moreover, if a seriously discomforting symptom occurs at any time, parents or patients were told to call investigators or return to examination before the planned follow-up visit.

Table 1: *Comparison of groups in terms of inflammatory reaction and complications after cataract surgery.*

	Group 1 (21 eyes)	Group 2 (20 eyes)	Statistical Difference	Statistical Test
Sex (Male/Female)	11/10	8/12	0.427	Chi-square
Mean age. ±SD. Min-Max	4.8±1.7 (2-8)	4.4±2.0 (2-7)	0.564	Mann Whitney U
Anterior chamber cell				Mann Whitney U
Post-op 1st day	1.7±0.6	2.1±0.4	0.033	
Post-op 3rd day	0.9±0.5	1.4±0.6	0.008	
Post-op 7th day	0.2±0.4	0.7±0.7	0.012	
Anterior chamber flare				Mann Whitney U
Post-op 1st day	0.9±0.4	1.3±0.5	0.018	
Post-op 3rd day	0.4±0.4	0.9±0.5	0.001	
Post-op 7th day	0.0±0.3	0.2±0.4	0.194	
Intraocular pressure (IOP)				Mann Whitney U
Preop IOP	13.4±2.1	13.0±1.4	0.728	
Post-op 1st day IOP	14.0±2.0	13.5±1.3	0.448	
İnflammatory related complications				Chi-square
Cyclitic membrane. IOL precipitates. anterior or posterior synechia. sineşi. optic capture	1	6	0.032	

SD; Standart Deviation. post-op; postoperative. pre-op; preoperative. IOP; Intraocular Pressure.

All data were entered in the SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA), which was then utilized for data analyses. A P value less than 0.05 was considered significant. Chi-square and Mann Whitney U tests were used.

RESULTS

Forty one eyes of forty one patients were enrolled the study (19 boys and 22 girls). Twenty one patients were assigned to the group 1 (21 eyes) and the remaining 20 patients (20 eyes) were assigned to the group 2. The mean patient age±SD was 4.6±1.8 years (range 2 to 8 years) and the median age was 5 years. Both group 1 and group 2 had comparable baseline features. Anterior chamber cells and flare increased in both group1 and group 2 after the surgery and returned to normal 30 days postoperatively. There were significant differences in terms of inflammatory cells in the anterior chamber between group 1 and group 2 at follow-up visits that performed postoperatively 1st, 3rd and 7th day ($p<.05$), (Table 1). Although significant differences were found between group 1 and 2 in aspect of flare at postoperative 1st and 3rd day visits ($p<.05$), there was no significant difference at 7th day visit ($p>.05$). In 6 patients from group 2 had inflammatory related complications including cyclitic membrane, posterior synechia, IOL precipitates and optic capture in spite of appropriate treatment on the postoperative period (Table 2). There was no statistically significant difference in IOP between group 1 and group 2. None of the eyes had an IOP elevation that exceeded 20 mmHg.

Table 2: *Inflammation related complications after cataract surgery.*

İnflammation related complications	Group1 (21eyes)	Group 2 (20 eyes)
Cyclitic membrane	1	3
Anterior or posterior synechia	0	1
İOL precipitates	0	1
İOL capture	0	1

DISCUSSION

Many aspects of cataract surgery have developed extremely in recent years. Although innovations such as foldable IOLs, new phaco machines and smaller corneal incisions have reduced the severity of postoperative inflammation, especially it is still present and can lead complications in children.[2-4]

Severe postoperative inflammation or fibrinoid reaction is a trouble predominantly in infants and younger children. The postoperative inflammations after the cataract surgery exhibits the findings including increased cells and flare, precipitates on the endothelium and the IOL, anterior and posterior synechias, and inflammatory cyclitic membranes.[1,10]

Breakdown of the immature blood-aqueous barrier and inadequate fibrinolytic activity of the trabecular meshwork in children may result fibrinoid reaction after cataract surgery. Additionally, the formation of pupillary membran and opacification of the anterior hyaloid face are due to severe fibrinoid response.[11] Consequently, procedures that may prevent or decrease inflammation in children is thought quite significant.[12] Thermal, chemical and mechanic stimulation may induce to produce the prostaglandins derived from arachidonic acid, and the inflammatory process was mediated by these mediators. In most cases, topical corticosteroids have been used for controlling the inflammation after cataract surgery, over the decades.[13,14]Another treatment option in children is heparin sodium. Addition of heparin to the irrigating solution has been recommended to reduce postoperative inflammatory response and associated complications including synechia, pupil irregularity and IOL decentration.[11]

A different choice in terms of the postoperative inflammation is NSAIDs which have been available in ophthalmic preparations for more than 30 years. Moreover NSAIDs are used for a wide clinical spectrum including cystoid macular edema, refractive surgery and allergic conjunctivitis.[15-18] Flach et al.,[3] demonstrated the efficacy of ketorolac in treatment of postoperative inflammation. The patients taking ketorolac exhibited a significant decrease in symptoms and signs of inflammation and a more stable blood-aqueous barrier than patients taking vehicle. In addition, NSAIDs could be more efficient when treatment begins before surgery because pretreatment with NSAIDs would result in reduction of basal prostaglandins and increase the inhibitory effect on COX-2 activity in producing inflammatory-induced prostaglandins.[9] Moreover in a study using diclofenac sodium showed that preoperative use of NSAIDs 3 days before surgery decreased the postoperative inflammation compared to patients who did not obtain diclofenac sodium prior to the surgery.

Although the study found statistically significant difference, there were no systemic circumstances predisposing to these patients to a significant postoperative inflammatory reaction. The postoperative inflammatory reaction exhibited in these patients is not frequently significant.[19]

In patients with possibility of severe inflammatory reaction, the anti-inflammatory effect of preoperative and postoperative use of ketorolac may be quite valuable.[9] In addition to treatment of postoperative inflammation, NSAIDs is used to as an analgesic for treating postoperative pain and discomfort including excimer laser keratectomy and radial keratotomy.[20,21] Nonsteroidal anti-inflammatory drugs are also useful for keeping mydriasis throughout cataract surgery.[22,23] This effect is due to suppressing biosynthesis of prostaglandins in the intraocular tissues which was affected by surgery and trauma in the anterior segment.[24] Another clinical use of NSAIDs is to prevent and treatment of cystoid macular edema.[16]

Although NSAIDs have many clinical uses, they may lead corneal complications including ulceration and perforation and significantly decrease corneal sensation in normal eyes.[25,26] The use of low-dose generic diclofenac after cataract surgery may cause corneal adverse effects.[27] Nevertheless, Guidera et al.[25] reported that these severe adverse effects have not been related to use of ketorolac as well as corneal complications associated with NSAIDs. These corneal complications were not observed in our study.

This study evaluated the efficacy and the safety of administering ketrolac 3 days preoperatively and 30 days postoperatively for controlling inflammation after cataract surgery in children. The inflammation parameters returned to normal at the end of 1st month in group 1 taking ketorolac preoperatively and postoperatively, and group 2 without taking ketorolac throughout the study. There were significant differences in inflammation parameters between group 1 and group 2. Although inflammation-related complications including cyclitic membrane, posterior synechia, IOL precipitates and optic capture were observed in only one patient of group 1, they were observed in 6 patients of group 2. In fact in the current study, lower complication rate in group 1 can be attributed to milder inflammatory reaction than group 2.

The main limitation of the present study is the lack of a laser flare-cell meter system. Other limitation of the study is the relatively few patients included both groups. Further studies are required to demonstrate that use of ketorolac for the treatment of postoperative inflammation in children. It may likely stabilize blood-aqueous barrier and prevent inflammation-related complications, in the early postoperative period.

In conclusion, this study demonstrates that ketorolac seems effective and safe when started before surgery and continued 1 month postoperatively for the treatment of the postoperative inflammation in children. Ketorolac treatment that starting a few days prior to the surgery may provide increased stabilization of the blood-aqueous barrier and lead a more prominent anti-inflammatory effect after the surgery. Therefore, preoperative and postoperative administration of ketorolac is suggested strongly for the patients expecting a serious postoperative inflammation after cataract surgery or other intraocular surgeries.

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