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Review Article

Extended Postoperative Ciprofloxacin Prophylaxis for Post-Phacoemulsification Endophthalmitis

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Abstract

Purpose: This study investigated the efficacy of extended oral ciprofloxacin prophylaxis in reducing the incidence of endophthalmitis after cataract surgery.

Setting: Single-center study conducted at a tertiary health facility.

Design: This was a retrospective observational study.

Methods: This study was conducted on patients who underwent uncomplicated phacoemulsification surgery. Two cohorts were analyzed: one receiving oral ciprofloxacin twice daily for one-week post-surgery and another not receiving ciprofloxacin. The patients who did not receive ciprofloxacin were operated on between June 2013 and October 2019, while the others underwent surgery between June 2011 and April 2021. Endophthalmitis incidence, patient demographics, and surgical variables were assessed between the two groups. Statistical analyses included chi-square tests, Fisher's exact tests, logistic regression, and Kaplan–Meier estimates.

Results: Of 1172 eyes (1015 patients), 548 received ciprofloxacin, and 624 did not. The ciprofloxacin group reported a 0% incidence of endophthalmitis compared to 0.8% in the non-ciprofloxacin group. While the chi-square test revealed significant differences (p=0.036), Fisher's exact test did not reach significance at values less than <0.05. The efficacy of oral ciprofloxacin in preventing endophthalmitis was 100%. The odds ratios for sex, age, and unilateral/bilateral surgery were not significant. Challenges in achieving statistical significance, attributable to zero events in the ciprofloxacin group, were acknowledged.

Conclusion: As an additional treatment, oral administration of two 750 mg tablets of ciprofloxacin daily for one week after phacoemulsification surgery is superior to a single intracameral antibiotic injection.

Keywords: Endophthalmitis, Extended Prophylaxis, Oral Ciprofloxacin, Phacoemulsification

Introduction

Postoperative endophthalmitis is a serious complication linked to intraocular surgery, with the highest published incidence rate standing at 0.35% [1]. The results from the Endophthalmitis Study Group revealed that prophylactic use of intracameral cefuroxime can reduce this rate to less than 0.08%, a significantly lower level [2]. Despite this considerable decrease, the risk of endophthalmitis persists, potentially leading to blindness. Its occurrence is both drastic and disastrous for patients and an immense source of stress for surgeons. Therefore, preventing postoperative endophthalmitis is of great clinical importance. This aspect prompts ophthalmic surgeons to pursue additional measures to improve postoperative safety. The risk of post-cataract endophthalmitis extends beyond the operation duration; it persists for a certain period until the incisions are completely healed. To the best of the author's knowledge, all preventive measures implemented thus far, restricted to the perioperative duration, have not adequately covered the vulnerable period of wound healing. The author believes that additional efforts are needed to identify the optimal antibiotic regimen and delivery route for postoperative prophylaxis.

In this study, two cohorts were examined: one group received oral ciprofloxacin postoperatively, while the other did not. The primary aim was to compare the occurrence of endophthalmitis between patients who received oral ciprofloxacin twice daily for one week and those who did not. The primary objective of this study was to determine the value of extended postoperative oral ciprofloxacin for prophylaxis and assess its effectiveness.

Materials and Methods

This was a retrospective observational study based on data from patients who had previously undergone cataract surgery. This was a single-center study conducted at a tertiary health facility. The patients were selected based on those who had undergone uncomplicated phacoemulsification surgery. The surgeries were routinely performed under sub tenon anesthesia as outpatient procedures. All the implanted intraocular lenses are monofocal hydrophobic lenses. Patients aged 18 years or older who had undergone uncomplicated cataract surgery were included in the study. Patients with intraoperative complications, such as posterior capsule rent and vitreous loss, were excluded from the study. All patients received routine prophylactic measures. Before surgery, patients received 5% povidone iodine for 3 minutes. Post surgery, patients were given an intracameral injection of 1mg/0.1cc cefuroxime and a sub tenon injection of 0.3cc cefuroxime, both with the same dilution.

This study received ethical approval from the institutional review board of Diyarbakir Gazi Yasargil Training and Research Hospital, and it adhered to the principles outlined in the Declaration of Helsinki. The study included two cohorts: all patients who underwent surgery performed by two different surgeons. The groups were classified based on the surgeons' approach to postoperative patient care, specifically whether they prescribed oral ciprofloxacin, in the form of two 750 mg tablets per day, for one week following the surgery. The patients who did not receive ciprofloxacin were operated on between June 2013 and October 2019, while the others underwent surgery between June 2011 and April 2021. All the patients who underwent surgery were scheduled for follow-up visits on the first operative day, first week, first month, second month, third month, and sixth month. Assuming a 0.06% prevalence of endophthalmitis based on previously published papers prompted the researcher to consider a minimum effect size [2]. The Cohen d test requires a sample size of 1168 with a significance level of 0.01, an effect size of 0.1, and a power of 80%. Additionally, Green's rule of thumb suggested 500 cases per group for logistic regression analysis. Considering both results, this study boasts a sufficient sample size, with the first cohort comprising 548 eyes and the second including 624 eyes. If any, the surgeons managed the endophthalmitis cases by pursuing various treatment options, including intravitreal antibiotic injections (such as ceftazidime 2.25/0.1mg/cc and vancomycin 1mg/0.1cc), systemic steroids, or referrals for vitrectomy surgery. The surgeon-reported endophthalmitis cases were considered more reliable than the hospital's data analysis, as ICD codes assigned by staff occasionally fail to accurately represent the true situation. Therefore, surgeons reported the cases directly instead of relying solely on collected raw data.

Statistical Analysis

The data were collected and analyzed to assess statistically significant differences between the two groups in terms of age, sex, and whether one or both eyes underwent surgery.

a) The Shapiro–Wilk test was used to test the assumption of a normal distribution.

b) The Levene test was used for assessing the homogeneity of variance.

c) Two sample z tests assumed that the difference between the two groups was within the equivalence bound of 5%.

d) Categorical variables and prevalence rates were examined using both the chi-square test and Fisher's exact test.

e) A logistic regression test was conducted to determine the impact of cipro usage on the prevention rate.

f) The timing of endophthalmitis occurrence was estimated using the Kaplan–Meier method and compared by the log-rank test.

The statistical online calculator "datatab.net" was used for logistic regression analysis, the chi-square test, and the log-rank test. The statistical online calculator "statskingdom.com" was used for the Shapiro–Wilk test, Levene test, two sample z test, and logistic regression analysis. The statistical online calculator "clincalc.com" was used for the Fisher exact test and the fragility index test.

Results

In this study, the distributions of age, sex, and unilateral/bilateral surgery were analyzed among 1172 eyes from 1015 patients divided into two groups: 548 eyes received ciprofloxacin, while 624 eyes did not receive ciprofloxacin. Variances were normally distributed or had substantial sample sizes (α=0.05). Gender variance was equal (p=0.275), while age and unilateral/bilateral surgery were unequal (age p=0.017, unilateral/bilateral p=0.001). Both groups' averages were presumed to be equal (gender p=0.999, age p=0.980, unilateral/bilateral p=0.998).

The incidence rate of endophthalmitis in the group not receiving ciprofloxacin was 0.8% (95% CI: 0.00053 to 0.015). However, in the ciprofloxacin group, the incidence rate was 0.0%. The chi-square test revealed a significant difference (p=0.036), but the Fisher exact test yielded 0.0646, which was significant at <0.10 and not at <0.05. At <0.05, the fragility index was zero. In the group that received ciprofloxacin, the odds of endophthalmitis were 0, which was distinct from the 0.008 odds in the group that did not receive ciprofloxacin. With an odds ratio of 0, the odds ratio was 0 (-29.98 to 15.31, p = 0.05), indicating a significant difference in postoperative endophthalmitis odds. The efficacy of oral ciprofloxacin in conjunction with all other postoperative measures for preventing endophthalmitis was 100%. In the group not receiving ciprofloxacin, the percentage increase in endophthalmitis was indeterminable due to the zero odds observed in the first group. The odds ratios for sex, age, and unilateral/bilateral surgery were not significant (0.94,

1.0, and 1.52, respectively). The highest odds ratio, following the use of ciprofloxacin, was for unilateral/bilateral surgery. However, Chi-Square Automatic Interaction Detector (CHAID) decision tree analysis revealed no impact of other variables on endophthalmitis (Figure 1).

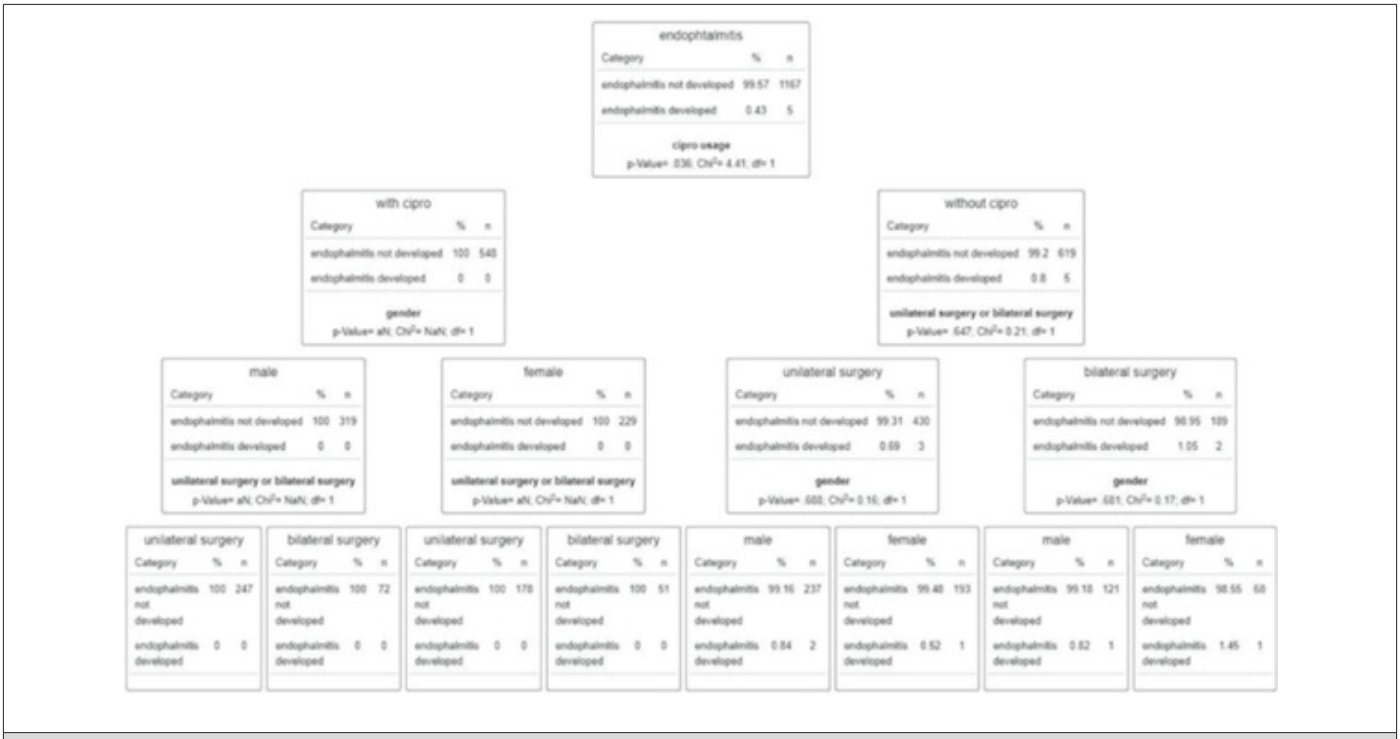

Figure 1: The Chi-Square Automatic Interaction Detector (CHAID) decision tree represents a machine learning algorithm that employs the chi-square test to evaluate the significance of independent categorical variables (cipro usage, sex, unilateral or bilateral surgery) in the study. In each column, the algorithm utilized the chi-squared test to identify the most substantial difference in the distribution of the target variable across categories. Notably, cipro usage emerged as the most substantial difference. In the 'Cipro not received' group, the second most substantial difference was unilateral or bilateral surgery. Conversely, within the 'cipro received' group, where the rate of endophthalmitis was zero, all other variables exhibited identical differences.

In the group not receiving ciprofloxacin, the median time to endophthalmitis post-surgery was 0.5 months (95% CI: 0.25 to 4 months). The absence of endophthalmitis cases in the group that received ciprofloxacin notably affected the timing of endophthalmitis occurrence between the two groups (log-rank test p=0.036).

Discussion

The patients in this study adhered to all standard postoperative measures. These included strict aseptic preparation procedures such as prepping and draping the patient, using appropriate personal protective equipment, establishing a new sterile field, and obtaining fresh instruments before the procedure. Additionally, they underwent the application of 5% povidone-iodine and received an intracameral injection of cefuroxime at the time of surgery. Notably, although the ESCRS study did not employ this preventive measure, subconjunctival cefuroxime injection was administered at the end of surgery. Nevertheless, despite implementing these preventive measures, the group not receiving ciprofloxacin experienced five cases of endophthalmitis, resulting in an incidence rate of 0.8%. This rate is notably higher than what is typically reported in the literature. One potential contributing factor could be that the rate is derived directly from the surgeon's report rather than from data analysis. Certainly, the surgeon's knowledge of all patients with endophthalmitis ensures the absence of missing data. On the other hand, the subjective nature of relying solely on the surgeon's report would introduce bias and may pose a potential weakness, despite being initially considered a strength. Another potential reason could be the surgeon effect; however, this study did not analyze its potential impact on the results. It is worth noting that both surgeons perform non cataract operations and possess similar surgical experience, practice, and surgical volume. Therefore, any difference based on the surgeon's diversification or experience was not thought to be significant, aligning with what is reported in the literature [2-4]. This study analyzed stand-alone uncomplicated phacoemulsification cases. Surgeon experience and postoperative patient care attitudes were consistent across the cases, with the only difference being the use of ciprofloxacin.

The 95% confidence interval of the odds ratio in this series, which includes 1, implies that the difference between the groups is not statistically significant. The absence of any endophthalmitis cases in the ciprofloxacin-treated group obscures the statistical analysis. For a clearer understanding of the effect of ciprofloxacin, assuming that only one case of endophthalmitis occurred in the

group that received ciprofloxacin, the statistical analysis suggested an impressive 336.5% preventive effect of ciprofloxacin intake, with an odds ratio of 4.3 (95% Confidence Interval [CI]: -0.68 to 3.63; p=0.05). Moreover, at a significance level of <0.05, the fragility index is zero. However, if additional endophthalmitis cases were assumed to develop in the group that did not receive ciprofloxacin, raising the fragility index to 1, the study would potentially achieve statistical significance at the 0.05 significance level. Surely, obtaining a valid statistical result regarding the efficacy of any prophylactic measure to effectively reduce the actual risk of endophthalmitis would necessitate a significantly larger number of patients and a longer observation period to detect any potential endophthalmitis cases developing in the ciprofloxacin-treated group and to address potential confounding factors. However, this approach is beyond the scope of this study. A prospective, randomized controlled trial could offer more robust evidence and statistical results. Considering a potential endophthalmitis complication for any patient is out of the question, and its execution is challenging. The author considered this a weakness of the study when comparing the two cohorts.

According to the literature, a postoperative endophthalmitis rate of 0.06% is considered a solid result [2,5]. Some studies have indicated the potential to reduce this rate by using intracameral moxifloxacin instead of cefuroxime [6]. Despite several studies reporting that intracameral moxifloxacin is safer and more effective than cefuroxime, the overall success rate has not reached statistical significance [7-10]. Although moxifloxacin has a broader spectrum and is stronger than ciprofloxacin, its permanence in the eye after surgery is very limited, and it may not be effective in preventing endophthalmitis [11]. Dhaliwal et al. emphasized that the permanence of any preventive agents in the eye is more effective than any other measures. That is actually the main emphasis of this study too, that ciprofloxacin's extended presence in the eye after phacoemulsification is more preventive than intracameral usage alone [11]. However, there is an overall declining trend in postoperative endophthalmitis rates. Ciprofloxacin is a broad-spectrum quinolone antibiotic known for its ability to effectively penetrate tissues throughout the body, making it effective against various infections [12]. Pseudomonas aeruginosa or Staphylococcus aureus is under coverage, too [12]. Ophthalmic solutions of ciprofloxacin are already FDA-approved for treating corneal ulcers and conjunctivitis caused by susceptible strains [12]. Oral administration of 750 mg ciprofloxacin was considered for prophylaxis in intraocular surgery before the 1990s [13]. However, the results were contradictory; some studies showed promising results while others did not [13,14]. Generally, these studies analyzed aqueous and vitreous concentrations after short-term topical or oral administration. In the present study, all patients in the second group received 750mg of oral ciprofloxacin twice daily for 7 days. To the best of the author's knowledge, this study is the first to observe the long-term preventive effect of systemic ciprofloxacin. This prolonged oral administration explains the favorable clinical results, ensuring sustained coverage against microorganisms in the vitreous body over an extended period. The author of this study believes that following the ESCRS's very low endophthalmitis report, surgeons worldwide felt reassured for themselves and their patients, leading to the abandonment of systemic prophylaxis globally. The incidence rate has decreased to approximately 0.06%. Surgeons worldwide feel reassured for themselves and their patients, as the threat of endophthalmitis has almost been halted. Contrary to this assurance, along with the anticipated increase in cataract surgery cases accompanying the growth of the older population contributes to an increase in endophthalmitis cases. Despite the incidence rate not increasing, the rise of occurrence is concerning in respect to its future burden. The main concern with systemic ciprofloxacin is tendon issues [15]. In this study, the patients were not sorted into risk groups based on their kidney disease. However, no one reported any Achilles tendon complaints. The patients usually reported gastrointestinal problems, but they did not indicate any issues during follow-up. Nonetheless, ciprofloxacin should not be given to high-risk patients.

Any general ophthalmologist in an emerging country performing common and basic surgeries typical in a state-funded hospital must ensure both self-reliance and patient well-being. All precautions should be taken by any surgeon. Additionally, blepharitis is common among these patients, and they often experience a gritty feeling a few days after surgery. Moreover, the use of well-used wipes is also prevalent. Considering that post cataract surgery wounds are vulnerable to external influences during the healing process, this vulnerability may explain the greater rate of endophthalmitis in this patient population. Despite implementing all perioperative preventive measures, patients in the group not receiving ciprofloxacin may not have been adequately protected in the postoperative phase. This rationale supports the claim that ciprofloxacin intake can significantly reduce the incidence of endophthalmitis, potentially even to 0%. Consequently, the author suggests that prophylaxis should extend beyond the immediate postoperative period. The author claims that systemic prophylaxis with ciprofloxacin 750 mg twice daily for one week immediately after cataract surgery raises the barrier against possible culprits and helps maintain eye safety during the susceptible period.

Conclusion

The findings suggest that oral ciprofloxacin, when administered for an extended period postoperatively, may play a significant role in preventing postoperative endophthalmitis. The author recommends taking two 750mg tablets per day postoperatively, as they penetrate intraocular content more effectively and provide extended coverage against microorganisms during the critical first postoperative week. Oral administration for one week after surgery is superior to a single intracameral antibiotic injection as an additional measure. However, ophthalmic surgeons should consider the benefits and limitations of oral ciprofloxacin prophylaxis in their postoperative care strategies, weighing the potential preventive effects against the challenges associated with prolonged administration.

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While preparing this work, the author used ChatGPT 3.5 to check punctuation, syntax errors, and the flow of the phrases. The

author edited the content as needed. After using this tool, the author reviewed and edited the content as needed and took full responsibility for the publication's content.

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Conflict of Interest

None.

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