# Alternative Pharmacotherapy Paradigm to Cataract Surgery

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## Abstract

Cataracts are the leading cause of reversible blindness worldwide and cataract extraction is the treatment of choice and leads to an improvement in the quality of life. Surgical techniques are refined and complex and yield an extremely high rate of success with a short recovery period. To further maximize surgical outcomes, post-operative treatments of uncomplicated cataract extraction include three topical pharmaceutical agents: an antimicrobial, a potent corticosteroid, and a non-steroidal anti-inflammatory drug (NSAID). Studies have shown the importance of antimicrobial prophylaxis in reducing ocular infection and endophthalmitis with the use of the newer generation of fluoroquinolones. Furthermore, the usages of topical corticosteroids and NSAIDs have reduced and prevented anterior chamber inflammation and macular edema, respectively. The regimen, however, varies among ophthalmologists because of a lack of published data that establishes the optimal regimen. Although the technological advances in cataract extraction and intraocular lens (IOL) development are well documented, the pre-, peri-, and post-operative treatment paradigm since the 1970s and 1980s has not deviated much until recently, with the European Society of Cataract and Refractive Surgery endophthalmitis study and other studies addressing the necessity of topical steroid. Also rising costs, better surgical technologies, and advancements in IOL development, should ophthalmologists maintain a three-drug regimen post-surgery or tailor the post-operative management to the individual patient?

## Keywords

Cataract surgery, phacoemulsification, endophthalmitis, cystoid macular edema, bromfenac, ketorolac, nepafenac, topical steroids

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The 'standard of care' is an interesting concept and one that is, to varying degrees, dictated not by scientific data but by the potentials for legal ramifications. The 'standard of care' can be equated to the column on the pantheon: once built, it is very difficult to tear down or modify. Ophthalmology as a surgical specialty does not escape this trap.

## History of Cataract Surgery

Sushruta first described cataract surgery, in what was termed 'couching' in India, around the sixth century BCE in which the native cataractous lens is "pushed out of the field of vision."[1] In 1748, Jacques Daviel, a French surgeon, made an incision in the cornea along the inferior limbus, incised the lens capsule, and expressed the lens material.[1] In 1940, Harold Ridley, a Royal Air Force ophthalmologist, introduced the concept of implanting an artificial lens into the eye and in 1949 successfully implanted the first polymethyl methacrylate intraocular lens (IOL).[1] In 1967, Charles Kelman introduced phacoemulsification, a technique that utilizes ultrasonic waves to emulsify the cataractous lens without having to make such large incisions during cataract extraction.[1,2] The development of less-invasive surgical techniques, including lens extraction by ultrasound phacoemulsification, and improved instrumentation in the late 1970s and 1980s ushered in a new era for cataract surgery and IOL development. Phacoemulsification could be conducted through incisions of 3 mm or less, greatly reducing peri-operative morbidity and hastening the time to visual recovery. Concomitant advances in instrumentation allowed for a more complete removal of pro-inflammatory lens cortical material and for IOLs (toric, multifocal, and accommodating) to be placed more safely. Refinements in surgical technology yielded additional reductions in incision size, and sutureless wounds, while development of viscoelastic and IOLs yielded unprecedented levels of success in visual recovery and function. More recently, an emerging technology, ultra short-pulse lasers (femtoseconds), is gaining wide acceptance and appears to, once again, shift the paradigm in cataract and refractive surgery. Yet the management of post-cataract surgery has not changed significantly. Patients are given a topical antimicrobial pre- and post-surgery for endophthalmitis prophylaxis, and a topical steroid along with a non-steroidal anti-inflammatory drug (NSAID) to decrease inflammation and the incident of cystoid macular edema.[3]

With better technology, surgical training, and surgical techniques, we ask: "Is pre-operative topical antimicrobial and topical steroid necessary in post-uncomplicated cataract extraction?" Based on recently published data, the paradigm in pharmacological approach is shifting slowing.

## Alternative Pharmacological Approaches to Cataract Surgery

The standard of care as indicated by the American Academy of Ophthalmology (AAO) post-cataract surgery includes an antimicrobial, a topical steroid, and topical NSAIDs.[3] The regimen, however, varies among ophthalmologists because of a lack of published data that establishes the optimal regimen – therefore, it is the decision of individual ophthalmologists to employ a regimen best suited to their cataract patients. Studies have shown the importance of antimicrobial prophylaxis in reducing ocular infection and endophthalmitis with the use of the newer generation of fluoroquinolones[5,6] along with the usage of topical corticosteroids and NSAIDs to reduce and prevent anterior chamber inflammation and macular edema, respectively.[4,7] More recently, collaboration among ophthalmologists raised the issue relating to pre-operative antimicrobial therapy.[8]

Sterilizing and suppression of the microbial flora pre-operatively have been shown to decrease the risk of post-operative infection. Many methodologies are used to sterilize the surgical site, which include iodine tincture and/or pre-operative topical antimicrobial administration. Studies have shown the validity of pre-treatment in reducing endophthalmitis. More recently, the European Society of Cataract and Refractive Surgery (ESCRS) conducted a long-term, prospective, and retrospective study to evaluate the validity of administering an antimicrobial prior to surgery in reducing the incidence of endophthalmitis.[9] This study and others demonstrated the incidence of endophthalmitis was not statistically different between those receiving pre-treatment and those not receiving pre-treatment. This is a landmark finding since the current ophthalmic teaching indicates the need for pre-operative treatment.[10] Post-operative antimicrobial therapy is still indicated; however, the question is "Should we pre-treat all cataracts with an antimicrobial and start topical steroids post-surgery?" This debate will persist among ophthalmologists for some time.

## European Society of Cataract and Refractive Surgery Endophthalmitis Study

The ESCRS endophthalmitis study was a multicenter, double-blind, placebo-controlled, partially masked randomized study to assess the clinical effectiveness of using intracameral cefuroxime with or without perioperative topical levofloxacin for the prevention of endophthalmitis after routine phacoemulsification (see *Table 1*).[9,11] Since the ESCRS study, intracameral antibiotics have become the standard in Europe. However, while this has not been widely adapted in North America their use is increasing. The ESCRS study compared the outcomes among four treatment groups, including a control group and patients receiving frequently applied topical fluoroquinolone drops (levofloxacin 0.5 %) – as well as patients receiving an intracameral injection of cefuroxime 1 mg.[9]

An independent study, that is, not directly related or associated with the ESCRS study, reproduced the identical fluoroquinolone dosing regimen used in the ESCRS study. Investigators measured aqueous humor antibiotic levels over a 90 minute post-dose period. The regimen of two pre-operative drops (one each at 30 and 60 minutes pre-operatively) plus three pulsed drops (one every five minutes at the end of surgery) produced the highest reported levels of fluoroquinolone in aqueous humor (4.4 µg/ml).[12] This independent study was able to demonstrate that, in contrast to topical drops, the intracameral injection (1 mg or 1,000 µg cefuroxime in this case) was capable of delivering a much higher dose instantaneously to the aqueous humor, since topical agents must first diffuse through the cornea.[12]

**Table 1: Results of European Society of Cataract and Refractive Surgeons Study[9,20,38]**

| Group A | Group B |
|---|---|
| Intervention | Intervention |
| Placebo vehicle drops × 5*<br>No intracameral injection | Placebo vehicle drops × 5*<br>Intracameral cefuroxime 1 mg |
| Endophthalmitis incidence rates | Endophthalmitis incidence rates |
| Intent-to-treat (n=4,054) | Intent-to-treat (n=4,056) |
| Total: 14 (0.345 %; 95 % CI 0.119 to 0.579 %) | Total: 3 (0.074 %; 95 % CI 0.015 to 0.216 %) |
| Proven: 10 (0.247 %; 95 % CI 0.118 to 0.453 %) | Proven: 2 (0.049 %; 95 % CI 0.006 to 0.178 %) |
| Per protocol (n=3,990) | Per protocol (n=3,997) |
| Total: 13 (0.326 %; 95 % CI 0.174 to 0.557 %) | Total: 3 (0.075 %; 95 % CI 0.016 to 0.219 %) |
| Proven: 9 (0.226 %; 95 % CI 0.103 to 0.428 %) | Proven: 2 (0.050 %; 95 % CI 0.006 to 0.181 %) |
| Group C | Group D |
| Intervention | Intervention |
| Levofloxacin drops 0.5 % × 5*<br>No intracameral injection | Levofloxacin drops 0.5 % × 5*<br>Intracameral cefuroxime 1 mg |
| Endophthalmitis incidence rates | Endophthalmitis incidence rates |
| Intent-to-treat (n=4,049) | Intent-to-treat (n=4,052) |
| Total: 10 (0.247 %; 95 % CI 0.119 to 0.454 %) | Total: 2 (0.049 %; 95 % CI 0.006 to 0.178 %) |
| Proven: 7 (0.173 %; 95 % CI 0.070 to 0.356 %) | Proven: 1 (0.025 %; 95 % CI 0.001 to 0.137 %) |
| Per protocol (n=3,984) | Per protocol (n=4,000) |
| Total: 10 (0.251 %; 95 % CI 0.120 to 0.461 %) | Total: 2 (0.050 %; 95 % CI 0.006 to 0.181 %) |
| Proven: 7 (0.176 %; 95 % CI 0.071 to 0.362 %) | Proven: 1 (0.025 %; 95 % CI 0.001 to 0.139 %) |

** Two drops given pre-operatively and three drops given post-operatively. All groups also received povidone–iodine 5 % pre-operatively and topical levofloxacin 0.5 % four times daily post-operatively for six days. CI = confidence interval.*

### Intracameral Cefuroxime

Patients were randomized into four groups. Two of the four groups were treated with intracameral cefuroxime (1 mg in 0.1 ml normal saline solution) at the end of surgery. Two groups (one treated with intracameral cefuroxime, one untreated) received peri-operative topical levofloxacin 0.5 % in a standard regimen. The study was masked for levofloxacin, but not for intracameral cefuroxime. All groups also received povidone–iodine 5 % pre-operatively and topical levofloxacin 0.5 % four times daily post-operatively for six days.[9,13]

The incidence of endophthalmitis in the groups not receiving intracameral cefuroxime was statistically significantly higher than that in the groups receiving intracameral cefuroxime. Twenty-nine cases were diagnosed with post-operative endophthalmitis, of which 20 were infectious in nature. Five of the 29 reported cases occurred in groups receiving intracameral cefuroxime. Of these five cases, three had a

**Table 2: Results of Cost-effectiveness Analysis of Antibiotic Prophylaxis[20,38]**

| Antibiotic Prophylaxis | Cost Per Person ($) | Cohort Net Cost* ($ millions) | Cost-effectiveness Ratio† | Threshold Effectiveness Ratio Compared with Intracameral Cefuroxime (Number of Prevented Cases) |
|---|---|---|---|---|
| Intracameral | | | | |
| Cefuroxime | 2.83 | -0.48 | Cost saving | NA |
| Moxifloxacin | 13.81 | 0.44 | 1,800 | 4.87 (984) |
| Subconjunctival | | | | |
| Gentamicin | 2.95 | -0.64 | Cost saving | 1.04 (210) |
| Cefazolin | 3.57 | -0.58 | Cost saving | 1.26 (254) |
| Topical | | | | |
| Sulfacetamide | 2.30 | -0.71 | Cost saving | 0.81 (164) |
| Polymyxin/trimethoprim | 12.36 | 0.30 | 1,211 | 4.36 (881) |
| Ciprofloxacin | 24.90 | 1.55 | 6,288 | 8.79 (1,775) |
| Ofloxacin | 33.74 | 2.44 | 9,867 | 11.90 (2,405) |
| Moxifloxacin | 55.00 | 4.56 | 18,474 | 19.40 (3,920) |
| Gatifloxacin | 57.60 | 4.82 | 19,527 | 20.32 (4,105) |
| Four antibiotic combination‡ | 11.65 | 0.40 | 1,976 | 4.11 (831) |

** Net cost in a cohort of 100,000 eyes includes cost savings of prevented infections. † Includes cost saving from averted endophthalmitis. ‡ Intracameral cefuroxime, subconjunctival gentamicin, subconjunctival cefazolin, and topical sulfacetamide. NA = not applicable.*

proven infectious cause (two cases of *Staphylococcus. epidermis* in the group receiving intracameral cefuroxime and one case of *S. warneri* in the group receiving intracameral cefuroxime and topical levofloxacin). The incidence of post-operative endophthalmitis was lower in patients receiving intracameral cefuroxime and peri-operative topical levofloxacin than in those receiving intracameral cefuroxime alone. The absence of prophylactic intracameral cefuroxime was associated with a statistically significant increase in the risk of presumed infectious post-operative endophthalmitis. The absence of topical levofloxacin was not associated with a statistically significant increase in risk of presumed infectious post-operative endophthalmitis. Data indicated intracameral injections of cefuroxime reduced the risk of infectious endophthalmitis after phacoemulsification cataract surgery.

Gupta et al.[14] investigated whether intracameral cefuroxime increases the risk of macular edema. Patients were randomized to intracameral cefuroxime (1 mg of cefuroxime in 0.1 ml normal saline solution) or an equal volume of intracameral balanced salt solution. Macular edema was measured using ocular coherence tomography (OCT).[14] The results showed no statistically significant differences in macular edema between in the groups four to six weeks after surgery. The use of intracameral cefuroxime did not affect post-operative visual acuity. The data supports the safety of using intracameral cefuroxime in routine cataract surgery.[14]

### Intracameral Moxifloxacin

Lane and colleagues[15] evaluated the safety of intracameral moxifloxacin. Participants were randomized to receive intracameral moxifloxacin 0.5 % (250 µg/0.050 ml) or balanced salt solution. The parameters assessed included macular edema, visual acuity, intraocular pressure (IOP), effects on the cornea (endothelial cell density and thickness, corneal clarity, and edema), inflammation in the anterior chamber (aqueous cell count), and effects on the blood-–aqueous barrier (aqueous flare). The results showed that there were no statistically significant differences between the two groups in safety parameters pre-operatively or at follow- up visits at one day, two to four weeks, and three months post-operatively. The data demonstrated that intracameral injection of moxifloxacin ophthalmic solution appears to be safe for the prophylaxis of endophthalmitis after cataract surgery.[15]

### Intracameral Vancomycin and Gentamicin

Ball and Barrett investigated whether the use of vancomycin and gentamicin increases the risk of macular edema after phacoemulsification cataract surgery.[16] Patients were randomized to receive no antibiotics or vancomycin (20 µg/ml) and gentamicin (8 µg/ml) in the infusion fluid at the time of cataract surgery. The results did not yield statistically significant differences in macular edema or visual acuity between the groups. Data indicated the use of intracameral vancomycin and gentamicin did not increase visual rehabilitation or the risk of macular edema. One observational study showed a statistically significant reduction in the incidence of post-operative endophthalmitis when intracameral vancomycin plus topical fusidic acid was compared with topical fusidic acid alone.[16,17]

### Intracameral Cefazolin

Two observational studies showed a statistically significant reduction in the rate of post-operative endophthalmitis with the use of intracameral cefazolin plus topical antibiotics compared with topical antibiotics alone. No toxic effects or anaphylactic reactions were reported in either study.[18,19]

## Economic Considerations

Sharifi et al. determined the cost-effectiveness from a societal perspective in the US of different antibiotic regimens for the prevention of endophthalmitis after cataract surgery (see *Table 2*).[20] The modes of administration for the antibiotics were intracameral (cefuroxime or moxifloxacin), topical (sulfacetamide, polymyxin/trimethoprim, ciprofloxacin, ofloxacin, moxifloxacin, or gatifloxacin), and subconjunctival (gentamicin or cefazolin). A combination regimen of intracameral cefuroxime, subconjunctival gentamicin, subconjunctival cefazolin, and topical sulfacetamide was also assessed. The risk of endophthalmitis in the absence of any intervention was estimated to be 0.247 %.[20] The risk of endophthalmitis when intracameral cefuroxime or the four antibiotic combination regimen was used was estimated to be 0.045 %. Assuming a 100 % prevention of endophthalmitis, the cost per case of endophthalmitis was estimated to be $3,793. The productivity losses caused by endophthalmitis were excluded from the cost analysis.[20]

Four treatment modalities (intracameral cefuroxime, subconjunctival gentamicin, subconjunctival cefazolin, and topical sulfacetamide) were associated with savings in net costs. Intracameral cefuroxime yielded a net cost savings of approximately $480,000 because of the endophthalmitis cases that were averted. When the treatment costs saved from prevented cases of endophthalmitis were excluded, the cost-effectiveness ratio of intracameral cefuroxime over no intervention was $1,403 per case of post-operative endophthalmitis prevented.[20] All the fluoroquinolones tested (ciprofloxacin, ofloxacin, moxifloxacin, or gatifloxacin) were not cost saving, even after assuming that all potential cases of endophthalmitis were averted after their use. Approximately a five-fold increase of intracameral moxifloxacin and an eight-fold increase of the least expensive topical fluoroquinolone, e.g., ciprofloxacin, were needed over intracameral cefuroxime to achieve the same cost-effectiveness ratio as it directly related to clinical effectiveness (the number of endophthalmitis cases prevented).[20] The most expensive topical fluoroquinolones, e.g., gatifloxacin and moxifloxacin, needed to be at least 19 times more effective than intracameral cefuroxime to achieve a cost-effective equivalence. For all regimens, except topical sulfacetamide and subconjunctival gentamicin, the number of cases that would need to be prevented exceeded the number of cases expected without treatment (247 per 100,000 patients). Sensitivity analyses varying the cost of antibiotics, cost of endophthalmitis treatment, risk of infection, and degree of complications from intracameral injections (anaphylaxis or toxic anterior segment syndrome) confirmed the robustness of these findings. The data indicated that the use of intracameral cefuroxime was more cost-effective than that of commonly used topical antibiotics for the prevention of endophthalmitis after cataract surgery.

## Topical Steroid—Indicated or Not Indicated

The use of a topical steroid in the post-operative period is also under discussion. At the start of the twenty-first century, the idea that topical steroids would no longer be needed in uncomplicated cataract surgery would have been a very radical concept, if not downright inconceivable. Today, with the advancements in surgical techniques, e.g., small incision, surgical technologies (torsional phacoemulsification and femtosecond), and the more efficacious NSAIDs, the concept of 'no steroids' is not as radical. The complications[21–26] and benefits,[4,26–30] e.g., controlling and preventing macular edema, associated with topical steroids are well documented. The initial indication for steroid usage post cataract surgery was secondary to the inflammation. This inflammation was caused by the type of lens implanted, the quality of the lenses in the earlier years, and the methodology of extracting a cataractous lens. IOLs today are of higher quality, have better quality control during production, better surgical techniques, better surgical equipment, and require a shorter surgical time. Collectively, these factors minimize the degree of inflammation. Yet, ophthalmologists, on the whole, persist in prescribing topical steroids.

The reasons for the persistence of steroid usage are multifactorial, but two key factors appear to be consistent over the years: unpredictability and expectation. The unpredictability of how one patient will respond to surgery compared to the next, even when the surgeon performs the same procedure on similar patients with no significant comorbidities, is a factor. Another factor is patient's expectations—realistic or unrealistic. Patients today are better informed than patients 20 years ago and this is a direct result of technology, e.g., the computer and the Internet.

One option is to use what are termed 'safe steroids.' These steroids, e.g., loteprednol etabonate ophthalmic suspension, are potent, efficacious, and have fewer side effects when compared to prednisolone acetate and other potent steroids.[30]

Difluprednate ophthalmic emulsification 0.05 % was approved by the US Food and Drug Administration (FDA) and indicated for the treatment of inflammation and pain associated with ocular surgery. The major benefit associated with difluprednate is its twice-a-day dosing frequency. The twice-daily doses enhance therapeutic compliance. Another benefit is dose uniformity, i.e. dosing concentration, which was predictable compared to that of other topical steroids for which the drop concentrations were highly variable.[32] However, reports have indicated that the use of difluprednate is associated with significant IOP elevation and the drug is expensive.[26,32,33]

## Topical Non-Steroidal Anti-Inflammatory Drugs

Despite the advancements in technology associated with cataract surgery, inflammation will occur, e.g., iridocyclitis, and patients will complained of discomfort and photophobia. The goal of any anti-inflammatory agent is to suppress the inflammation quickly and thereby enhance recovery. Since the late 1990s, topical NSAIDs have been a mainstay of the post-operative regimen. Although the pharmacokinetic and pharmacodynamics of the various topical NSAIDs differ, it is well documented that topical NSAIDs possess both analgesic and anti-inflammatory properties[35–37] without the side effects commonly associated with topical steroids.

Current topical NSAIDs include ketorolac, nepafenac, and bromfenac. Studies have shown, as a class, that topical NSAIDs are efficacious in controlling post-operative inflammation in the anterior segment, give good pain control and good visual recovery (rehabilitation), and, equally important, in minimizing the incidence of cystoid macular edema in both diabetics and non-diabetics.[4,36] A recent study by Duong et al. demonstrated that NSAIDs alone were efficacious in controlling anterior segment inflammation.[36] The study also demonstrated that topical NSAIDs were equally efficacious as topical steroids in preventing the development of cystoid macular edema both, clinically and by OCT.[36] One real drawback to NSAIDs is that, although all the NSAIDs are covered by insurance companies, the co-pay tier for the respective NSAIDs is dependent on the state and county the patients reside in, which can translate into a costly endeavor for patients on fixed incomes.

## The Future

The future of pharmacotherapy after cataract surgery is a work-in process and open for discussion and further research. Antimicrobial prophylaxis use pre-operatively to decrease or prevent endophthalmitis is an ongoing debate, with European ophthalmologists favoring intracameral and US ophthalmologists favoring pre-operative dosing of fourth-generation fluoroquinolones. Topical steroids may be 'standard' in the post-operative period, but their side effects require vigilance in preventing or minimizing complications. Conversely, a 'safer' steroid or lower dosage may be on the horizon. Sustained-release devices, e.g., pellets, injected or impregnated into the IOL may be a methodology to deliver the medication in low doses, but more efficacious since it does not have to cross the tear film and cornea. Another methodology is a combination drug similar to those used to treat glaucoma, e.g., dorzolamide hydrochloride–timolol maleate (Cosopt). Although topical NSAIDs are indicated post-surgery, three different medications with varying dosing frequency will only increase patient confusion and potentially can lead to non-compliance. Bromfenac is dosed once-daily, which significantly increases the compliance rate; however, more potent NSAIDs may negate the need for topical steroids.

## Conclusion

The paradigm in pharmacotherapy post-uncomplicated cataract surgery has deviated from the 'norm' as indicated by the AAO Preferred Practice Pattern. Intra-operative intracameral injection of cefuroxime and cefazolin has been widely employed in Europe since the ESCRS study and has begun to gain a foot hold in the US. Intracameral antibiotics have been shown to decrease the incidence of endophthalmitis and macular edema, and to be cost-effective.

Topical steroids, e.g., prednisolone acetate 1 %, are commonly prescribed after cataract surgery. Studies have shown the risks associated with topical steroids and a recent study demonstrated that topical steroid use is not necessary in controlling inflammation after cataract surgery.

Topical NSAIDs in uncomplicated cataract surgery are indicated and should be a mainstay because they provide an anti-inflammatory property that contributes to both decreasing and preventing cystoid macular edema. Non-steroidals also function in pain control without the side effects associated with narcotics or opioids, e.g., dependency.

The author believes that the pharmacological approach based on the patient's ocular and medical history should be tailored to each patient who undergoes cataract surgery, as opposed to a general 'standardized' treatment for all patients. Tailoring the treatment will increase compliance and decrease the cost to the patients. ■


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