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Subconjunctival antibiotics: an alternative to intracameral antibiotics for endophthalmitis prophylaxis in cataract surgery

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Abstract

Background: *There has been an increase in the use of routine intracameral antibiotics for endophthalmitis prophylaxis in cataract surgery. However, this can be associated with serious adverse events. Previously, subconjunctival antibiotics were the preferred route but there is minimal literature directly comparing the two. Hence, the safest and most efficacious route of prophylactic antibiotic administration remains controversial.*

Purpose: *To evaluate the efficacy and safety of subconjunctival with intracameral antibiotics for postoperative endophthalmitis (POE) prophylaxis in patients undergoing uncomplicated cataract surgery*

Methods: *A literature review was conducted in Cochrane and PubMed for studies that compared the efficacy of prophylactic subconjunctival and intracameral antibiotics for post-cataract endophthalmitis. Searches were not limited to English or study design.*

Results: *Three observational studies showed that subconjunctival and intracameral antibiotics both reduced POE rates. Intracameral antibiotics demonstrated a high efficacy (OR = 0.25, 95% CI 0.13-0.46, p < 0.0001) but was also associated with increased potential complications. All studies were conducted in a sequential nature during which cataract surgery techniques and instrumentation have improved in recent years.*

Conclusion: *In institutions with a high incidence of endophthalmitis, routine intracameral antibiotic use would be more appropriate. However, in facilities with lower rates of POE, the subconjunctival route of delivery can be an alternative due to its better safety profile.*

Keywords: *cataract surgery, endophthalmitis prophylaxis, intracameral antibiotics, subconjunctival antibiotics*

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Introduction

Strategies to reduce rates of postoperative endophthalmitis (POE) after cataract surgery have evolved significantly over time.[1] Preoperative and intraoperative measures such as eyelid hygiene, operating room preparation, sterile technique, and surgical advancements have all reduced the incidence of POE.[2-4] The introduction of prophylactic antibiotics, traditionally using topical and subconjunctival route, has further reduced POE rates. In the last few decades, there has been an increase in the use of routine intracameral antibiotics in cataract surgery for endophthalmitis prophylaxis.

In reality, cataract surgeons base their practice on their individual experience, influence from mentors and colleagues, and their own interpretation of available literature.[5] Intracameral injections are often associated with potential adverse effects, leading many cataract surgeons to prefer the subconjunctival route.[6]

The underlying principles of selecting the ideal agent and route for routine prophylactic antibiotics use should include an appropriate indication and reproducible dosage that offers adequate coverage against common pathogens. Additionally, there should be minimal potential to promote resistance and an excellent safety profile; its benefits must outweigh the risks.

POE can be caused by bacterial entry into the eye intraoperatively or postoperatively. Intraoperative inoculation can occur from bacteria present in the ocular surface or adnexa or from suboptimal operating environment, surgical technique, or instrumentation. These can be mitigated by lid hygiene, meticulous surgical preparation, and draping with topical povidone-iodine.

Postoperatively, bacteria present in the tear film or ocular adnexa can enter the eye via suboptimal wound closure.[7-9] The presence of antibiotics on the ocular surface is therefore required to eradicate the bacteria and commonly used prophylaxis includes postoperative subconjunctival and postoperative topical antibiotics.[10]

In the context of a decreasing incidence of POE due to advancements in surgical techniques and instrumentation for cataract surgery, surgeons should re-evaluate the routine use of intracameral antibiotics prophylaxis, which can have potentially devastating adverse effects. Subconjunctival antibiotics could be a safer alternative.

Methods

Search strategy

Literature search was performed in Cochrane and PubMed using a predefined search strategy. A review of articles that compared subconjunctival and intracameral antibiotics for POE prophylaxis in cataract surgery was conducted. Titles

and abstracts were screened according to the inclusion and exclusion criteria. The search was not limited to English or study design. Search terms included differing combinations of 'subconjunctival antibiotics', 'intracameral antibiotics', 'endophthalmitis' 'prophylactic antibiotics', 'perioperative antibiotic' and 'cataract surgery'.

Inclusion and exclusion criteria

Articles were included if they compared the prophylactic use of subconjunctival with intracameral antibiotics in adult cataract surgery with the primary outcome being POE rates. Excluded articles were those where the primary outcome was not endophthalmitis rates, the operation was not cataract surgery, involved treatment of endophthalmitis rather than prophylaxis, pediatric cataract surgery, surveys of practice, retractions, case reports, and animal studies.

Data extraction

The data collected from included studies were first author, publication date, number of eyes, duration of study, study design, prophylactic antibiotic regimen, and incidence of POE.

Statistical analysis

In this meta-analysis, the authors used odds ratio due to the low rate of POE reported in the observational studies. The I^2 statistic was used to assess heterogeneity among studies. I^2 values from 0% to 24%, 25% to 50%, and greater than 50% were considered to indicate low, moderate, and high heterogeneity, respectively. The forest plot was analyzed using RevMan version 5.4. In this review, with only three included studies, funnel plots were not appropriate. For the same reason, no subgroup or sensitivity analyses were performed. Due to the small number and the heterogeneity of the included studies, we described data for each study narratively.

Results

The electronic search identified three observational studies that directly compared prophylactic subconjunctival intracameral antibiotics in cataract surgery for the prevention of POE. The screening process is described in Figure 1 and the specific searching strategy is described in Appendix A. The characteristics of the included studies are shown in Table 1.

Three studies reported the use of subconjunctival *versus* intracameral antibiotic injections.[11-13] A significant reduction in POE rates was demonstrated in patients who received intracameral antibiotic injections compared to those who received subconjunctival antibiotics (OR = 0.25, 95% CI (0.13, 0.46), $p < 0.0001$, $I^2 = 4\%$) (Fig. 2.). There was low heterogeneity demonstrated amongst the studies; however, this was not statistically significant.

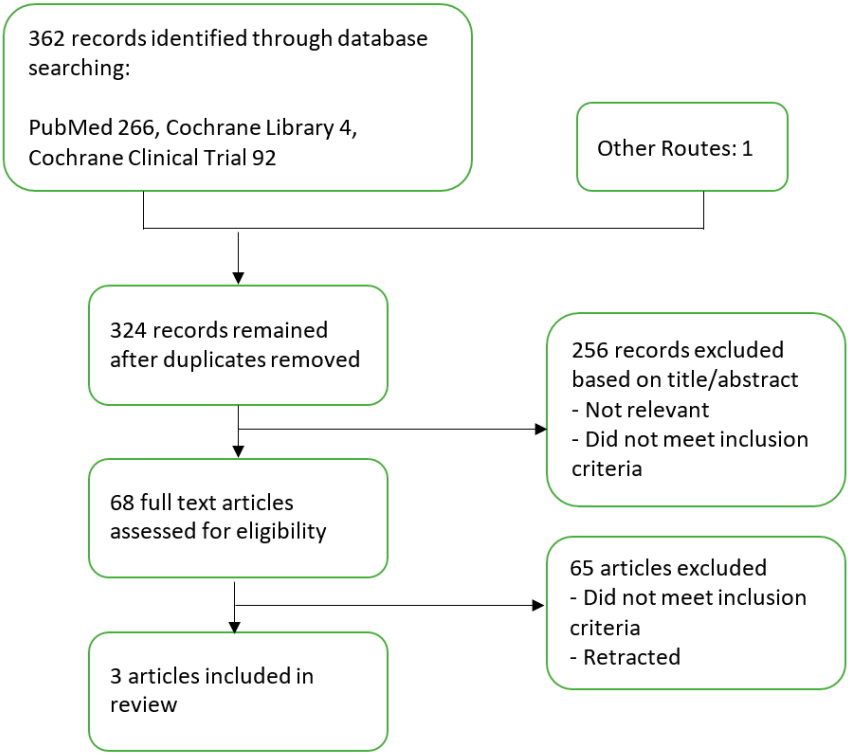

Fig. 1. Flow diagram showing the selection process used to include studies in the review.

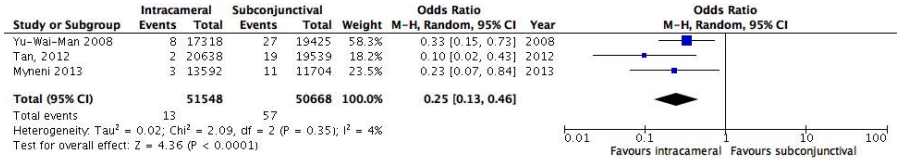

Fig. 2. Forest plot of the rate of postoperative endophthalmitis comparing prophylactic intracameral and subconjunctival antibiotics. The vertical line indicates no difference between the groups. Risk ratios are represented by diamond shapes, and 95% confidence intervals are depicted by horizontal lines. Squares indicate point estimates, and the size of each square indicates the weight of the given study in the meta-analysis. M-H, Mantel-Haenszel, random-effects model.

Table 1. Main characteristics of the studies included in the review

First author, date	Prophylactic antibiotic regimen	Duration of regimen (months)	Period of regimen	No. of eyes	Incidence of POE (%)
Yu-Wai-Man, 2007	Subconjunctival cefuroxime	47	Jan 2000 – Nov 2003	19,425	27 (0.139)
	Intracameral cefuroxime	37	Nov 2003 – Dec 2006	17,318	8 (0.046)
Tan, 2012	Subconjunctival cefazolin and gentamicin	83	July 1999 – June 2006	29,539	19 (0.064)
	Intracameral cefazolin and subconjunctival gentamicin	59	July 2006 – June 2010	20,638	2 (0.010)
Myneni, 2013	Subconjunctival cefuroxime	59	Mar 2004 – Feb 2008	11,704	11 (0.09)
	Intracameral cefuroxime	59	Mar 2009 – Feb 2012	13,592	3 (0.02)

POE: postoperative endophthalmitis

Discussion

During the 1990s, the subconjunctival route of antibiotic administration was the traditional approach for prophylactic antibiotic in cataract surgery. Since the publication of the prospective, randomized controlled study by the European Society of Cataract and Refractive Surgery (ESCRS) in 2007, there has been an increase in the use of routine intracameral antibiotics in several European countries.[14]

However, prior to the ESCRS study, Jonathon *et al.* demonstrated that preoperative antisepsis (OR, 0.19; 95% CI, 0.05–0.69) and subconjunctival antibiotics (OR, 0.46%; 95% CI, 0.29–0.70) were the only types of POE prophylaxis that were independently associated with reduced rates of endophthalmitis.[15]

Yu-Wai-Man *et al.* demonstrated that the rate of endophthalmitis reduced with the sequential changeover from subconjunctival cefuroxime to intracameral cefuroxime over a period of 6 years.[13] Interestingly, there was also a drop in endophthalmitis rates in each respective group, over 3 years (2000–2003 subconjunctival and 2004–2006 intracameral), suggesting that an improvement in surgical techniques and instrumentation could be a contributing factor. A subgroup of the study further demonstrated that an infective breakout of endophthalmitis, confirmed by Bayesian statistics, was linked to the discontinuation of subconjunctival cefuroxime. Similarly, Lehmann *et al.* found that the non-administration of subconjunctival cefuroxime was associated with subsequent endophthalmitis.[16]

Tan *et al.* compared the efficacy of intracameral and subconjunctival delivery of antibiotics over a period of 11 years (1999–2010).[11] Again, the intracameral cefazolin was shown to reduce the incidence of endophthalmitis by six-fold. However, 12–15% of the earlier cataract surgeries were being performed as extracapsular cataract extraction by trainee surgeons. This may have contributed to an exaggerated effect of the intracameral antibiotic changeover given the surgical advancements that occurred during the same period. By comparison, the rates of endophthalmitis in the group receiving subconjunctival cefazolin (0.064%) were still lower than the reported POE rates (0.07%) of those who received intracameral cefuroxime in the ESCRS study.[14]

In a similarly sequential fashion to the two aforementioned studies included in the review, Myneni *et al.* reported a four-fold reduction in POE rates with prophylactic intracameral cefuroxime.[12] Interestingly, there was an outbreak in 2007 that resulted in eight of the 11 endophthalmitis cases that occurred in the pre-intracameral phase. However, prior to this outbreak, the incidence of POE in patients who received subconjunctival cefuroxime was comparable (3/11704) to those who received intracameral delivery (3/13592).

In 2006, a survey conducted amongst ophthalmologists showed tha the following countries preferred subconjunctival delivery: United Kingdom (66.5–77%), Australia (75%), and New Zealand (63%).(17) This may be attributed to a large number of studies in which intracameral antibiotics were not used and have reported similar[18] or even lower (0.014–0.04%)[6,11,19,20] endophthalmitis rates than those observed in the ESCRS intracameral antibiotic group (0.07%).[14] The unusually high rates in the ESCRS control group compared to the literature, despite the use of iodine, has been another matter of heated discussion. This may have particularly exaggerated the effect of intracameral antibiotics in prophylaxis for POE, given the existing high rates of POE in the control group.

Several subsequent studies have also reported lower endophthalmitis rates associated with intracameral antibiotics use.[21,22] However, the majority of these studies did not compare the use of intracameral directly with subconjunctival delivery. A further limitation is the sequential nature, pre- and post-adoption of intracameral antibiotic use, in which improvements in endophthalmitis rates may be attributed to advances in surgical technique and awareness of operating field cleanliness.

Multiple systematic reviews have been conducted to compare the efficacy of perioperative antibiotic for the prevention of endophthalmitis after cataract surgery. Most notably, Gower *et al.* found that intracameral cefuroxime was associated with lower POE rates. However, the heterogeneity of the study designs prevented the review from performing meta-analysis.[23] Other meta-analyses have cited similar challenges, including high levels of bias.[24] In the context of

'big data' reports and mostly retrospective studies, careful consideration of routine intracameral use is encouraged, especially with limitations in study design.[25]

There have been reports of serious complications associated with intracameral antibiotics, including retinal detachment,[26,27] retinal infarct,[28] vancomycin-related hemorrhage occlusive vasculitis,[29,30] cefazolin-associated retinal toxicity,[31] and toxic anterior segment syndrome.[32] Administration of intracameral antibiotics can also increase the intraocular pressure (IOP), thereby compromising ocular circulation. In situations where an elevated IOP is detected after intracameral injection, subsequent withdrawal or release of aqueous humor may result in an antibiotic dosage that is below the minimal inhibitory concentration (MIC). If fluid is not released when there is elevated IOP, then ocular circulation may be compromised.

Practical limitations related to dose preparation also carry risks for dilution and dosage errors, increasing the potential for causing toxic anterior segment syndrome.[32] While there are studies advocating for routine intracameral antibiotics in all cataract surgeries,[33,34] there are logistical challenges against such indiscriminate use. Other considerations such as individual patient concerns —including anaphylaxis— and public health considerations —including a high number needed to treat and increasing bacterial resistance— must be accounted for in the decision making.[35]

Gram-positive, coagulase negative *Staphylococci* is the most common pathogen that contaminates the anterior chamber, suggesting that patient's own surface bacterial flora is often the primary source of infection.(3) However, in recent years, an increasing bacterial resistance to cefuroxime has seen *Enterococci* emerge as the leading cause.[36] A Swedish retrospective study of intracameral cefuroxime highlighted the important gaps in antimicrobial coverage that include gram-negative organisms, *Enterococci*, and methicillin-resistant *Staphylococci aureus*. The final pathogen is particularly concerning due to an increasing community incidence.[37] Shornstein *et al.* highlighted this issue in a study where all the culture positive cefuroxime-injected endophthalmitis patients demonstrated systemic-level resistance to cefuroxime with half of the cases caused by *Enterococcus*.[38] Furthermore, all cultured POE eyes that received intracameral moxifloxacin were associated with bacteria that were sensitive to this drug, suggesting that submaximal dosing compromised bactericidal activity. It is important to note that the intracameral route of delivery is associated with a narrow therapeutic efficacy;[39] therefore, levels that do not achieve MIC will be ineffective, but higher concentrations can lead to toxicity.

Since 2011, the regulator of national guidelines in France has recommended routine intracameral prophylaxis, which has prevented further studies from

being conducted. Similarly, it is considered unethical to omit intracameral antibiotics in Sweden.[40,41] Brezin expressed his concerns, in the *Eurotimes* (May 2020), regarding the inclusion of routine intracameral antibiotics in the French national health guidelines and the medicolegal issues involved. There are many other expert ophthalmologists that share this opinion, questioning the benefit of intracameral antibiotics and emphasizing the underlying principle of medical practice, *Primum non nocere*.[42,43,44]

On the other hand, a low rate of POE has been demonstrated without the use of intracameral antibiotics. Ness *et al.* and Sharma *et al.* did not find compelling reasons to recommend routine use of intracameral cefuroxime during cataract surgery, especially in centers with low infection rates.[45,46] In Netherlands, the low POE rate of 0.03% has seen the Dutch Ophthalmological Society recommend intracameral cefuroxime only in patients who are at high risk of developing endophthalmitis (capsule breaks, clear corneal incisions), while questioning its systematic use.[40] The same principle is also recommended in Japan.[47]

Some studies suggest a reduction in the rates of endophthalmitis following the injection of subconjunctival antibiotics given at the end of cataract surgery.[16,48] Colleaux *et al.* concluded that immediate postoperative subconjunctival antibiotics achieved a low rate of endophthalmitis compared to no injections (0.011% *versus* 0.179%, $p = 0.009$).[49] Mahamoudreza *et al.* showed that patients who received subconjunctival cephazolin at the end of cataract surgery had a 99.7% reduction in their mean eyelid colony counts.[50] Although not statistically significant, the results were comparable to the 99.9% reduction rate achieved by povidone-iodine, the only prophylaxis supported by level I evidence and now considered standard of care.[51]

In a Sydney metropolitan hospital, Walsh *et al.* reported an overall incidence of POE of 0.04% from 2012 to 2014.[52] The breakdown of prophylactic antibiotic use showed an inclination for subconjunctival (44%) compared to intracameral (42%) administration. However, statistical analysis demonstrated no significant difference in the rates of POE between the subgroups of antibiotic administration. The authors also noted the surprising outcome whereby intracameral antibiotics were not the preferred choice given the results of the widely referenced ESCRS trial.

More recently, Lim *et al.* performed a retrospective audit of cataract cases performed in another Sydney metropolitan hospital that revealed a zero incidence of endophthalmitis.[53] Although an exact breakdown of the antibiotic delivery route is not mentioned, the inference that can be made that subconjunctival and intracameral both help reduce POE rates. Conversely, there are studies that showed neither subconjunctival nor intracameral antibiotics had a protective effect against endophthalmitis.[54]

Subconjunctival cefuroxime has been demonstrated to achieve rapid and adequate aqueous concentrations, suggesting that intraoperative subconjunctival antibiotics followed by intensive topical treatment would help maintain high aqueous levels of antibiotics during the riskiest period of contamination.[55] The protective effect of intracameral antibiotics is also relatively brief. A study of gentamicin levels in the aqueous of the anterior chamber, after gentamicin was added to the infusion bottle (0.1 mL of 40 mg/mL gentamicin added to 500 mL of irrigating fluid), showed levels reduced to half within 51 minutes.[56] Another study on cefuroxime levels after intracameral injection, showed that there was a four-fold reduction in concentration of cefuroxime within an hour.[57] By contrast, subconjunctival antibiotics were found to maintain bactericidal levels in the anterior chamber for up to 12 hours.[30]

It is noted that there are also potential side effects associated with the use of subconjunctival gentamicin. These include chemosis,[58] toxic muscle myopathy,[59] and macular toxicity.[60] However, it has also been shown to be well tolerated locally with minimal conjunctival irritation. As a result, subconjunctival gentamicin is rarely used now, and has been replaced by cephalosporins, either cefazolin or cefuroxime. Although, there are no significant adverse effects associated with subconjunctival cephalosporins, the only theoretical risk could be inadvertent penetration of the eye by the hypodermic needle during injection.

Conclusion

This literature review found that subconjunctival antibiotics reduced rates of POE in cataract surgery. In comparison to intracameral antibiotics, subconjunctival antibiotics exhibited a preferable safety profile. In institutions with a low incidence of endophthalmitis, subconjunctival or topical antibiotics may be preferred. In facilities with higher rates of POE, intracameral antibiotics may be considered. It should not be required in a routine, uncomplicated cataract surgery performed by an experienced surgeon in a surgical facility with good hygiene practices. Ultimately, surgeons must choose the route of prophylactic antibiotic administration after consideration of the risks and benefits for each individual patient.

Declarations

Ethics approval and consent to participate

Not required.

Consent for publication

Not required.

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Appendix A. Search strategy

PubMed: 266 records (up to May 2021) #1 (Subconjunctival antibiotics) AND (intracameral antibiotics) #2 (Subconjunctival antibiotics) AND (endophthalmitis) #3 (Subconjunctival antibiotics) AND (endophthalmitis) AND (cataract surgery) #4 (Perioperative antibiotics) AND (endophthalmitis)
Cochrane Library: 96 records (up to May 2021) #1 MeSH descriptor: [endophthalmitis] explode all trees #2 MeSH descriptor: [subconjunctival antibiotics] explode all trees #3 MeSH descriptor: [intracameral antibiotics] explode all trees #4 MeSH descriptor: [prophylactic antibiotics] explode all trees #5 MeSH descriptor: [caratact surgery] explode all trees #6 MeSH descriptor: [perioperative antibiotic] explode all trees #7 #1 and #2 #8 #2 and #3 #9 #4 and #5 #10 #2 and #5 #11 #6 and #1