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Comparative analysis of the safety and efficacy of intracameral cefuroxime, moxifloxacin and vancomycin at the end of cataract surgery: a meta-analysis

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Abstract

Background—Current practice methods are unclear as to the most safe and effective prophylactic pharmacotherapy and method of delivery to reduce postoperative endophthalmitis occurrence.

Methods—A systematic review and meta-analysis using Meta-analysis of Observational Studies in Epidemiology guidelines was performed to compare the efficacy of intracameral cefuroxime, moxifloxacin and vancomycin in preventing postphacoemulsification cataract surgery endophthalmitis. A safety analysis of intracameral antibiotics was concurrently performed.

Data sources—BIOSIS Previews, CINAHL, ClinicalTrials.gov, Cochrane Library, Dissertations & Theses, EMBASE, PubMed, ScienceDirect and Scopus were searched from inception to January 2017. Data were pooled using a random effects model. All articles were individually reviewed and data were extracted by two independent reviewers. Funnel plot, risk of bias and quality of evidence analyses were performed.

Results—Seventeen studies with over 900 000 eyes were included, which favoured the use of intracameral antibiotics at the end of cataract surgery (OR 0.20; 95% CI 0.13 to 0.32; P<0.00001). The average weighted postoperative endophthalmitis incidence rates with intracameral cefuroxime, moxifloxacin and vancomycin were 0.0332%, 0.0153% and 0.0106%, respectively.

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Secondary analyses showed no difference in efficacy between intracameral plus topical antibiotics versus intracameral alone (P>0.3). Most studies had low to moderate risk of bias. The safety analysis showed minimal toxicity for moxifloxacin. Dosing errors led to the majority of toxicities with cefuroxime. Although rare, vancomycin was associated with toxic retinal events.

Conclusion—Intracameral cefuroxime and moxifloxacin reduced endophthalmitis rates compared with controls with minimal or no toxicity events at standard doses. Additionally, intracameral antibiotics alone may be as effective as intracameral plus topical antibiotics.

Introduction

Endophthalmitis is a sight-threatening inflammation of the eye. For patients and surgeons alike, one of the most feared complications of cataract surgery is acute postoperative endophthalmitis (POE).[1] With over 10 million cataract surgeries performed worldwide every year,[12] effective POE prophylaxis is necessary. Povidone-iodine solution has historically been the standard for POE prophylaxis, [3] but other modalities include intracameral (IC), topical, subconjunctival and oral antibiotics. Of the identified risk factors for POE, many authors state that both the route of administration and the type of antibiotic are important factors for risk mitigation, [4–6] which has led to an increased number of IC antibiotic studies. Currently, although IC administration is widely accepted, there is no consensus on the best prophylactic therapy or route of administration for POE prevention.[67] However, antibiotics including cephalosporins, fluoroquinolones and vancomycin have been tested for effective POE prevention.

The aim of this study was to evaluate the safety and efficacy of intracameral cefuroxime (ICC) intracameral moxifloxacin (ICM) and intracameral vancomycin (ICV) as prophylactic pharmaco-therapy for prevention of POE.

Methods

Eligibility criteria for considering studies for this review

We conducted a systematic review and meta-analysis of relevant literature using the Meta-analysis of Observational Studies in Epidemiology guidelines.[8] The methods are described in detail in online supplementary eMethods. We considered randomised controlled trials (RCT) and observational studies that evaluated patients undergoing phacoemulsification cataract surgery with a minimum sample size of 500 eyes. Interventions included IC antibiotics (ie, cefuroxime, moxifloxacin or vancomycin) at the end of cataract surgery. Comparisons included non-IC antibiotics (topical, subconjunctival or non-specified) at the end of cataract surgery. The primary outcome was the incidence of postcataract surgery endophthalmitis. Secondary analyses examined the effects of geographic location, and the addition of topical antibiotics on POE incidence. Studies were excluded if they included extracapsular cataract extraction (ECCE) surgeries that could not be separated from phacoemulsification surgery data. Culture results from POE cases were reviewed to determine the spectrum of microorganisms causing endophthalmitis in this population.

We also reviewed studies within our literature search that reported safety or toxicity data with ICC, ICM and ICV. Eligible studies included animal models or postoperative humans

who underwent phacoemulsification cataract surgery. Toxicity to the cornea, anterior chamber (AC), or retina, or a change in intraocular pressure (IOP) or visual acuity (VA) were analysed.

search methods for identifying studies

We identified published studies from BIOSIS Previews (ISI Web of Knowledge), CINAHL (EBSCOhost), ClinicalTrials. gov, Cochrane Library (Wiley Interscience), Dissertations & Theses Global (ProQuest), EMBASE (Embase. com), PubMed (National Library of Medicine), ScienceDirect (Elsevier) and Scopus (Elsevier) from inception to January 2017. There were no language restrictions. To optimise search criteria, we developed a detailed and comprehensive search strategy with an information specialist (MM) for each electronic database (online supplementary eMethods). EndNote V.X7 was used for deduplication (EndNote, Thomson Reuters).

study selection

Each article was independently reviewed by two reviewers. The titles and abstracts (if available) were screened. Full-text copies were obtained for all potentially relevant articles and reviewed for inclusion and data collection. Disagreements in selection were reconciled by a separate reviewer. Language interpreters assisted in reviewing non-English articles, resulting in a single person reviewing these articles. References in full-text articles were screened for relevance and added if they met inclusion criteria. We contacted authors as needed for additional study details to assist in the data analysis.

Data collection and risk of bias assessment

We extracted the following: type of study, IC antibiotic used, country of origin, incidence of POE with and without IC antibiotics, dose of antibiotic, use of topical antibiotics, location of toxicity and microorganisms isolated in POE. Two risk of bias tools were used. For the efficacy analysis, we used a Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions. For the safety analysis, we used the Office of Health Assessment and Translation Risk of Bias Rating Tool for Human and Animal Studies. Funnel plots were evaluated using Review Manager V.5.3 (RevMan V.5.3).[9] Additionally, we used the GRADEprofiler (V.3.6.1) to assess the quality of evidence.

Data synthesis and analysis

We used RevMan V.5.3[9] for the statistical analysis. Studies were stratified by the antibiotic used post surgery. As the primary outcome was dichotomous, OR estimates and corresponding 95% CIs were calculated for each study. OR estimates were combined using the random effects Mantel-Haenszel method. Summary of OR estimates was given for each stratum and collection of studies. ORs compared IC versus non-IC antibiotics. Heterogeneity was assessed by the Q and I^2 statistics, calculated for each stratum and for the full collection of studies. Results were displayed using forest plots. Funnel plots enabled evaluation of publication bias.[9] Secondary analyses examined the effect of geographic location (Europe vs non-Europe) on the risk of POE while stratifying by antibiotic type. Similarly, the effect on POE of topical antibiotics in conjunction with the primary IC antibiotic was examined and

stratified by antibiotic type. The number and percent of microorganisms identified in POE cases as well as the safety analysis were tabulated as descriptive statistics.

Results

Results for the efficacy of IC antibiotics

We reviewed 4849 titles and abstracts; for 70 of these, the full text was evaluated (figure 1). Seventeen articles met the inclusion criteria.[4710–25] The European Society of Cataract & Refractive Surgeons (ESCRS) study was the only RCT[4]; 16 were observational studies (15 retrospective cohort studies[10–1315–2325] and 1 case–control study[7]). Within the 16 observational studies, 9 compared ICC 1 mg/0.1 mL (4 ICC only and 5 ICC with topical antibiotics),[10–1315–1824] 6 compared ICM 100–500 mcg/0.1 mL (with 1 study ranging from 5 to 50 mcg/0.1 mL)[19] (2 ICM only and 4 ICM with topical antibiotics),[71119202425] and 5 compared ICV 1 mg/0.1 mL (1 ICV only and 4 ICV with topical antibiotics)[71121–23] against their corresponding controls (ie, postoperative topical, subconjunctival or oral antibiotics). One study did not define the antibiotic doses administered.[7] The 16 observational studies enrolled 909 582 eyes and the 1 RCT enrolled 16 211 eyes (online supplementary eTable 1).

Common reasons for excluding studies included the lack of a control or comparison group, and the inability to separate ECCE from phacoemulsification data. Of the 17 studies, 8 were based in Europe (including the RCT),[410121315–1721] 2 were based in Canada,[711] 2 in the USA,[2224] 2 in India,[1825] and 1 each was based in Japan,[19] Australia[23] and Colombia.[20] The Matsuura *et al*'s study used a bag and chamber flushing technique.[19] All other studies used a small volume injection at the end of surgery. Rudnisky *et al* were contacted and calculation of values from their published study was performed for the groups who received ICM and ICV.[7]

The 17 included studies had mild to moderate risk of bias (online supplementary eFigures 1 and 2). Confounding variables were most common as some observational studies did not control for preoperative antibiotic regimen, use of steroid drops, surgical incision site, phacoemulsification method, surgical complications or patient comorbidities. However, studies that recognised these variables controlled their risk of bias through matching and analytical tests. The remaining sources of bias were determined to be low risk for most studies, which included selection of participants, departure from intended interventions, missing data, measurement of outcomes and reporting. Random effect analysis funnel plots of the 17 included studies reflected only minimal bias (online supplementary eFigure 3).

Using GRADEprofiler, the overall quality of evidence for the included observational studies was moderate (online supplementary eTable 2). Quality was downgraded by one level to account for the risk of bias due to confounding in multiple studies. Quality was upgraded due to the large effect found in the pooled data for observational studies. The overall quality of the RCT was graded as high due to the study design, low risk of bias, large measure of effect and direct comparisons.

The overall pooled data favoured the use of IC antibiotics at the end of phacoemulsification cataract surgery (OR, 0.20; 95% CI 0.13 to 0.32; P<0.00001). Within ICC groups, a lower

incidence of endophthalmitis in the treatment group was observed (OR, 0.26; 95% CI 0.15 to 0.45; P<0.00001). These data are similar to the RCT (OR, 0.21; 95% CI 0.08 to 0.54; P=0.001).[4] A lower incidence of endophthalmitis in treatment groups was also observed for ICM (OR, 0.30; 95% CI 0.13 to 0.67; P=0.004) and ICV (OR, 0.09; 95% CI 0.02 to 0.42; P=0.002) (figure 2).

In secondary analyses, there was no statistically significant difference in POE rates between patients treated with IC antibiotics plus topical antibiotics and patients treated with IC antibiotics alone within the cefuroxime (χ^2=0.04; df=1; P=0.85), vancomycin (χ^2=0.31; df=1; P=0.58) and moxifloxacin groups (χ^2=0.78; df=1; P=0.38) (online supplementary eFigure 4).

Geographic forest plot analysis showed statistical significance in favour of IC antibiotics regardless of location. The average weighted POE incidence of ICC in Europe was 0.0366% compared with 0.0303% in non-European countries. For ICV, the incidence was 0.0079% compared with 0.0113%, respectively. There were no moxifloxacin studies performed in Europe for comparison (online supplementary eFigure 5).

The average weighted incidence rates of POE with ICC,[4,10–18,24] ICM[7,11,19,20,24,25] and ICV[7,11,21–23] from the 16 observational studies and 1 RCT were 0.0332%, 0.0153% and 0.0106%, respectively.

Results for the safety analysis of IC antibiotics

Thirty-three studies met the inclusion criteria for the safety and toxicity analysis. Of these studies, there were 7 animal studies, 7 case series, 15 cohort studies, 2 cohort and animal studies, and 2 RCTs. Animal studies included rabbit and rat eyes. Eleven studies discussed the safety of ICC,[26–36] 3 discussed ICV safety[37–39] and 15 discussed ICM safety.[19,40–52] Three studies compared ICC versus ICV[53–55] and one study compared ICV versus ICM.[56] Cefuroxime doses ranged from 1 to 10 mg/0.1 mL, vancomycin doses ranged from 0.0375 to 1 mg/0.1 mL, and moxifloxacin doses ranged from 15 to 500 mcg/0.1 mL. Postoperative follow-up ranged from 1 day to 12 months.

Of the 33 studies analysed for risk of bias, the principal causes of moderate to high bias were confounding variables and protocol deviations. Selection, attrition and reporting bias were determined to be low to moderate risk of bias (online supplementary eFigures 6–8). Lack of homogeneity between studies (eg, differences in study methods, species and antibiotic concentrations) was the greatest challenge in comparing studies.

In the cefuroxime group, a total of 503 eyes were analysed for safety and toxicity of ICC (table 1). Of these, 69 (14%) eyes were reported to have toxic effects from the antibiotic; 23 had corneal oedema (CE),[29,32,53] 6 had endothelial cell death,[57] 17 developed toxic anterior segment syndrome (TASS),[33] 13 had cell or fibrin formation in the AC,[32,34] 14 had elevated IOP,[29,32] 18 had macular oedema[31,32,36] and 15 had poor VA.[29,32,36]

In the vancomycin group, 171 eyes were analysed for safety and toxicity of ICV (table 2). None of the studies comparing vancomycin with control groups found any significant changes in IOP, endothelial cell density, AC inflammation, CE or macular oedema.[37,38,53–56]

However, a case series showed 36 eyes with vancomycin-associated haemorrhagic occlusive retinal vasculitis (HORV) resulting in VA worse than 20/200 in 22 of the eyes.[39]

In the moxifloxacin group, 1243 eyes were analysed for safety and toxicity of ICM (table 3). Fifty-five eyes treated previously with penetrating keratoplasty had increased central corneal thickness ($P<0.05$) and decreased endothelial cell density ($P<0.05$).[43] At 500 mcg/0.1 mL, Akal *et al*[50] found 8 of 10 rat eyes with elevated caspase-3 and 9 of 10 eyes with elevated caspase-8 indicating increased apoptotic activity ($P>0.05$). Matsuura *et al* reported that 15 mcg/0.1 mL was safe and provided concentrations above MIC90 (minimum inhibitory concentration to inhibit 90% of organisms) for 2 hours for most of the resistant pathogens.[45]

Analysis of microorganisms identified in Poe cases

The data for causative infectious agents of POE were extracted from the 17 included studies. Ten studies provided data,[4121316–25] which included 145 endophthalmitis cases. The predominant microorganisms causing POE in postphacoemulsification cataract surgeries were coagulase-negative *Staphylococcus* (*S. epidermatis*, *S. hominis*, *S. saprophyticus*, *S. warneri*) (33 of 145; 22.8%). The second most common group was unspecified gram-negative rods (15 of 145; 10.3%). Other common organisms were *Staphylococcus aureus* (7 of 145; 4.8%), gram-positive organisms (unspecified) (7 of 145; 4.8%) and *Streptococcus pneumoniae* (8 of 145; 5.5%). In addition, one case of *Aspergillus fumagatus* (0.7%), four cases of *Pseudomonas aeruginosa* (2.8%) and three cases of methicillin-resistant *Staphylococcus aureus* (MRSA) (2.1%) were also reported. A large fraction of cases yielded no growth (56 of 145; 38.6%) (online supplementary eFigure 9).

Discussion

An effective and safe prophylactic treatment at the end of cataract surgery is needed to prevent serious sight-threatening endophthalmitis. In this meta-analysis, we identified nearly two decades of POE data from 909 582 eyes (observational studies) and 16 211 eyes (RCT), giving this analysis sufficient power to detect very small differences in rare outcomes such as endophthalmitis. Overall pooled data favoured the use of IC antibiotics to reduce POE rates when compared with controls (figure 2). ICC findings were consistent with the ESCRS findings.[4] Additionally, χ^2 analysis showed no difference between IC plus topical antibiotics compared with IC antibiotics alone, which suggests that postoperative topical antibiotics may provide no additional benefit.[142458] Pooled weighted averages for POE incidence favour ICM or ICV with incidences of 0.0153% and 0.0106%, respectively, compared with ICC (0.0332%). Quality of studies was graded at moderate to high with predominately low to moderate risk of bias.

Our systematic review of IC antibiotic safety suggests that ICC is relatively safe, but has had more complications with contamination, dilution errors and TASS along with macular toxicity compared with vancomycin and moxifloxacin (tables 1–3). ICV at 1 mg/0.1 mL showed no significant corneal or AC toxicities.[373853–55] However, ICV has more recently been associated with rare cases of HORV.[39] Two studies with ICM 500 mcg/0.1 mL suggest decreased corneal cell density and increased apoptotic markers of the cornea. However, the

majority of studies suggest no significant toxicities to the cornea, AC, retina or VA.
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IC antibiotic selection

ICC is the only IC antibiotic that has been analysed for efficacy by an RCT and has the most observational studies of the three antibiotics. From a phone survey of 250 ESCRS members, over 90% of surgeons would use cefuroxime if an approved product were commercially available.[59] Although Aprokam is approved in Europe, a product which likely overcomes the risks associated with dilution error preparations, it remains unavailable in some nations and has not been approved by the Food and Drug Administration. Challenges to cefuroxime use include the potential for allergic reactions in patients with beta-lactam allergies,[6061] overdosing risks associated with preparation in areas where Aprokam is not available, and poor coverage of methicillin-resistant, penicillin-resistant gram-positive bacteria or multiresistant enterococci and some gram-negative species such as *Pseudomonas*.[62]

In our study, the incidence and OR of POE for ICV were the lowest; however the total population size was the smallest of the three groups. Vancomycin has superior MRSA coverage but does not cover gram-negative bacteria. This may be meaningful as only 2% of POE cases in this study were caused by MRSA versus 10% caused by gram-negative bacteria. The risk of vancomycin-resistant bacteria is also an important consideration.[63]

There are currently no RCTs that have evaluated the efficacy of ICM for POE prevention. In our study, the average weighted incidence of POE with ICM was lower than ICC but higher than ICV. The predominant dose concentration used in included studies was 100 mcg/0.1 mL vs undiluted 500 mcg/0.1 mL.[7202564] Analysis suggests 500 mcg/0.1 mL may be more effective than 100 mcg/0.1 mL; however, this is based on only four studies.[7202564] Literature review showed a low postoperative toxicity profile for ICM, possibly due to its self-sterilising properties which negates addition of potentially harmful preservatives in solution.[6566] Moxifloxacin also provides broader antimicrobial coverage of bacteria that have been isolated in POE compared with cefuroxime and vancomycin.[6768]

study strengths and limitations

Other reviews and meta-analyses on this topic leave the question as to the added value of this study.[6970] Given that ECCE is known to have increased POE rates,[71] this study aims to represent the most current practice methods with only phacoemulsification cases. Additionally, this study compared IC alone to IC plus topical postoperative antibiotics to assess the impact on POE incidence. Most importantly, this study provides a novel systematic review comparing the safety and toxicity of ICC, ICM and ICV. Limitations of this analysis include the lack of RCTs for ICM and ICV. Only one RCT has been performed analysing IC antibiotics.[4] All other studies included were observational studies, which have a higher risk of bias. As study cohorts were not evaluated concurrently, this can lead to bias as surgical techniques improve over time. Furthermore, variability in techniques such as lens type,[4] incision type and location,[72] complications,[73] and experience and age of the surgeon[473] could not be adjusted in this analysis. However, we attempted to reduce risk of bias by only including phacoemulsification cataract surgeries, which we believe makes the

data more robust as evidence suggests ECCE has a higher rate of endophthalmitis.[71] Consequently, many large studies that could not separate ECCE or meet other inclusion criteria were excluded from this study, specifically, several studies from France, Sweden, Israel and Iran.[7274–79] These studies reported an ICC POE incidence range from 0.05% to 0.023%, which approximates our study finding of 0.0332%. Lastly, this study targeted IC antibiotics and therefore leaves the question of whether IC antibiotics are superior to postoperative, topical antibiotics alone. It has been suggested that the primary POE reducing element is the antibiotic type (eg, fourth-generation fluoroquinolones), despite the route of administration.[7] Conversely, the ESCRS study strongly favoured IC use of cefuroxime over topical third-generation fluoroquinolones.[4] A future analysis with focused search criteria for this question is needed.

Conclusion

Our study assessed two decades of POE incidence from over 900 000 eyes reported in 17 studies. The average weighted incidence rates of POE were 0.0332% (ICC), 0.0153% (ICM) and 0.0106% (ICV). Additionally, IC antibiotics alone may be as effective as IC plus postoperative topical antibiotics; however, the lack of direct comparison and the variety of topical antibiotics could suggest an alternative interpretation. These data showed that although very rare, ICV has been associated with HORV. ICC had minimal toxicity events at standard doses. ICM was the most studied antibiotic for safety and found to have a low toxicity profile at all studied concentrations. Future direct comparison studies of IC antibiotics as well as an RCT for ICM efficacy and tolerance would add to the current literature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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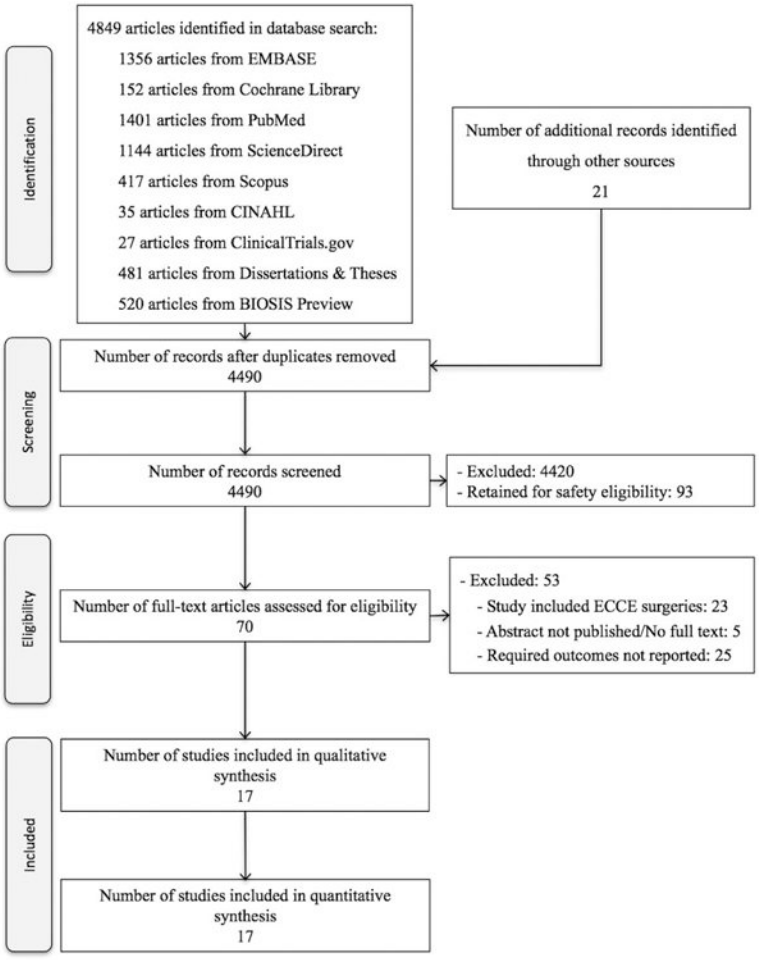

Figure 1.

Flow chart of study selection. Flow diagram of study selection for the efficacy of intracameral antibiotics at the end of cataract surgery in reducing postoperative endophthalmitis incidence. ECCE, extracapsular cataract extraction.

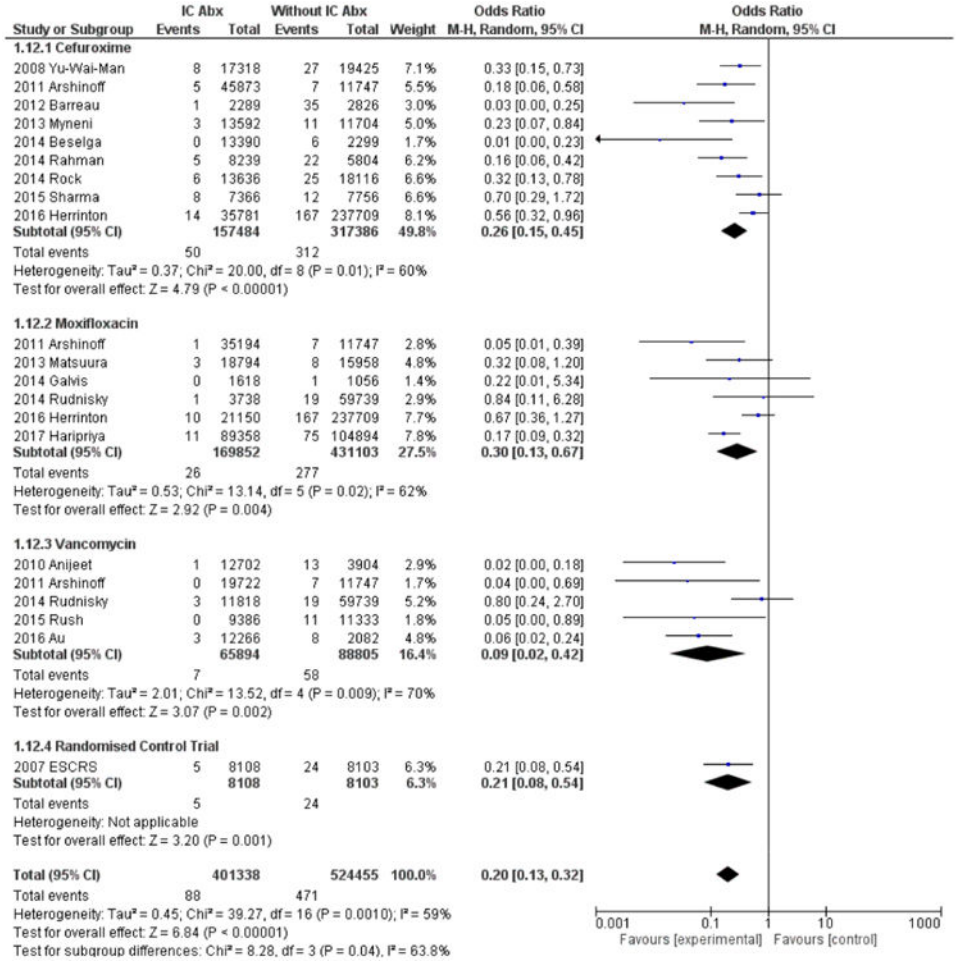

Figure 2.

Forest plot of postoperative endophthalmitis incidence with and without intracameral antibiotics. Pooled data comparing incidence of postphacoemulsification cataract surgery endophthalmitis rates with and without IC antibiotics (ie, cefuroxime, moxifloxacin and vancomycin). Abx, antibiotic; ESCRS, European Society of Cataract & Refractive Surgeons; IC, intracameral.

Table 1

Postoperative safety profile of intracameral cefuroxime

structure	study	Dose of IC cefuroxime	(−) no toxicity, (+) toxicity		Additional details
			Eyes (−)	Eyes (+)	
Cornea	Çakır *et al*[33]	1 mg/0.1 mL	7*	10*	Cohort. Toxic anterior segment syndrome after cataract surgery.
	Lam *et al* [28]	1 mg/0.1 mL	34*	0*	Cohort. No significant effect on ECD (P=0.74) compared with normal saline.
	Montan *et al*[5]	1 mg/0.1 mL	45*	0*	Cohort. No significant ECL with ICC (P>0.05).
	Ozlem *et al*[53]	1 mg/0.1 mL	8†	2†	Animal study. ICC versus ICV versus BSS. No corneal thickening at 3 and 6 hours. The levels of oxidative stress products were higher in the ICC group (P<0.001).
	Pérez-Canales *et al*[54]	1 mg/0.1 mL	30*	0*	Case series. ICC versus ICV groups. CCT thickening resolved by 1-month follow-up. ECD reduced in both groups at 1 week after phacoemulsification. No significant reduction in the percentage of hexagonal cells at 1 or 3 months postoperatively compared with preoperatively.
	Sakarya and Sakarya [30]	3 mg/0.1 mL	6*	0*	Case series. Accidental dilution error. No significant change in ocular findings was noted at 6 months, including macular oedema, VA loss or IOP elevation.
	Olavi[29]	5 mg/0.1 mL	1*	15*	Case series. Accidental dilution error. Fifteen eyes were noted to have CE.
	Delyfer *et al*[32]	10 mg/0.1 mL	4*	2*	Case series. Accidental dilution error. Two eyes had CE.
AC	Çakır *et al*[33]	1 mg/0.1 mL	0*	17*	Cohort. Toxic anterior segment syndrome after cataract surgery.
	Montan *et al*[5]	1 mg/0.1 mL	45*	0*	Cohort. No significant induced laser fare intensity (P>0.05).
	Pérez-Canales *et al*[54]	1 mg/0.1 mL	30*	0*	Case series. ICC versus ICV groups. AC cell was higher on day 1 with ICV, but resolved by day 7.
	Gradin and Mundia[34]	1 mg/0.1 mL	28*	7*	Cohort. No significant AC inflammation between control and ICC (P=0.857).
	Delyfer *et al*[32]	10 mg/0.1 mL	0*	6*	Case series. Accidental dilution error. All six cases with significant AC inflammation.
IOP	Pérez-Canales *et al*[54]	1 mg/0.1 mL	30*	0*	Case series. ICC versus ICV groups. No significant effect on IOP.
	Olavi[29]	5 mg/0.1 mL	8*	8*	Case series. Accidental dilution error. Eight eyes had elevated IOP.
	Delyfer *et al*[32]	10 mg/0.1 mL	4*	2*	Case series. Accidental dilution error. Two eyes had elevated IOP.
Retina	Gupta *et al*[27]	1 mg/0.1 mL	34*	0*	RCT. No macular thickening (P=0.34) at 5 weeks postoperatively.
	Lam *et al*[28]	1 mg/0.1 mL	34*	0*	Cohort. No difference in central macular thickness (P=0.32) postoperatively.
	Le Dû and Pierre-Kahn[31]	1 mg/0.1 mL	0*	6*	Case series. Macular oedema reported per OCT. Possible dilution error.

structure	study	Dose of IC cefuroxime	(−) no toxicity, (+) toxicity		Additional details
			Eyes (−)	Eyes (+)	
	Pérez-Canales *et al*[55]	1 mg/0.1 mL	0 *	30 *	Case series. ICC versus ICV. Macular thickness increased from baseline (P=0.501 at 1 week and P=0.005 at 3 months). Macular thickness was comparable in both groups, suggesting postoperative inflammation rather than antibiotic choice.
	Giménez-de-la-Linde *et al*[35]	1 mg/0.1 mL	221 *	0 *	Cohort. No evidence of cystoid macular oedema in 221 cases.
	Wong *et al*[36]	9 mg/0.1 mL	7 *	6 *	Cohort. Macular oedema developed, however, by 1 week symptoms had resolved.
	Delyfer *et al*[32]	10 mg/0.1 mL	0 *	6 *	Case series. Accidental dilution error. All developed macular oedema.
VA	Lam *et al*[28]	1 mg/0.1 mL	34 *	0 *	Cohort. No significant effect on VA compared with those treated with normal saline.
	Pérez-Canales *et al*[55]	1 mg/0.1 mL	30 *	0 *	Case series. No difference in VA between ICC and ICV at 1, 4 and 12 week(s) (P=>0.5).
	Olavi[29]	5 mg/0.1 mL	8 *	8 *	Case series. Accidental dilution error; eight eyes had reduced VA.
	Wong *et al*[36]	9 mg/0.1 mL	7 *	6 *	Cohort. Accidental dilution error. Six patients had visual acuity of 20/70 or worse.
	Delyfer *et al*[32]	10 mg/0.1 mL[8]	5 *	1 *	Case series. Dilution error. One patient had a persistent halo with reduced VA.

The commercially available product Aprokam (cefuroxime) has a concentration of 1 mg/0.1 mL.

*Human eyes.

†Rabbit eyes.

AC, anterior chamber; BSS, balanced salt solution; CCT, central corneal thickness; CE, corneal oedema; ECD, endothelial cell density; ECL, endothelial cell loss; IC, intracameral; ICC, intracameral cefuroxime; ICV, intracameral vancomycin; IOP, intraocular pressure; OCT, optical coherence tomography; RCT, randomised controlled trial; VA, visual acuity.

Table 2

Postoperative safety profile of intracameral vancomycin

			(−) no to toxicity, (+) toxicity		
structure	**study**	**Dose of IC vancomycin**	**Eyes(−)**	**Eyes (+)**	**Additional details**
Cornea	Lindquist and Robinson [37]	0.0375 mg/0.1 mL	3†	0†	Animal study. No significant difference in ECD between experimental (right eye ICV) and control (left eye BSS) groups (P=0.13)
		0.075 mg/0.1 mL	3†	0†	
		0.1875 mg/0.1 mL	3†	0†	
		0.750 mg/0.1 mL	3†	0†	
	Kowalski *et al*[56]	0.100 mg/0.1 mL	3†	0†	Animal study. ICM compared with ICV. The corneal thickness increased on day 1; however, thickness returned to normal on day 7. No difference in CCT was found between groups.
	Gimbel *et al*[38]	1 mg/0.1 mL	50*	0*	Cohort study. No adverse effects on the corneal endothelium were demonstrated with the use of ICV with gentamicin. No P value reported.
	Ozlem *et al*[53]	1 mg/0.1 mL	10†	0†	Animal study. ICC versus ICV versus BSS. Neither caused corneal thickening or oedema at 3 and 6 hours. The levels of oxidative stress products were significantly higher in the ICC group (P<0.001) but not significantly changed in the ICV group (P>0.05).
	Pérez-Canales *et al* [54]	1 mg / 0.1 mL	30*	0*	Case series. ICC versus ICV groups. CCT elevated at 1 week, but resolved by 1 month follow up. ECD reduced in bothgroups at 1 week post phacoemulsifcation, but no changes at 1-month and 3-month follow up. No significant reduction in percentage of hexagonal cells at 1 or 3-month postoperative compared to preoperative.
AC	Pérez-Canales *et al*[54]	1 mg/0.1 mL	30*	0*	Case series. ICC versus ICV groups. AC cell was higher on day 1 with ICV, but resolved by day 7 for both groups.
IOP	Pérez-Canales *et al* [54]	1 mg/0.1 mL	30*	0*	Case series. ICC versus ICV groups. No significant difference in IOP between two groups.
Retina	Pérez-Canales *et al*[55]	1 mg/0.1 mL	0*	30*	Case series. ICC versus ICV groups. Average macular thickness increased compared with baseline (P=0.017 at 1 week; P=0.000 at 1 month; P=0.000 at 3 months). Macular thickness changes were comparable in both groups, suggesting that retinal thickening could be a consequence of postoperative inflammation rather than antibiotic choice.
	Witkin *et al* [39]	1 mg / 0.1 mL	0*	36*	Case series. Authors characterised presenting signs of haemorrhagic occlusive retinal vasculitis associated with ICV.
VA	Witkin *et al*[39]	1 mg/0.1 mL	6*	22*	Case series. Only 6 eyes had 20/40 or better VA; 22 of 36 eyes (61%) had 20/200 or worse and 8 of 36 eyes (22%) had no light perception.

*Human eyes.

†Rabbit eyes.

AC, anterior chamber; BSS, balanced salt solution; CCT, central corneal thickness; ECD, endothelial cell density; IC, intracameral; ICC, intracameral cefuroxime; ICM, intracameral moxifoxacin; ICV, intracameral vancomycin; IOP, intraocular pressure; VA, visual acuity.

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Table 3

Postoperative safety profile of intracameral moxifloxacin

			(−) no toxicity, (+) toxicity		
structure	**study**	**Dose of IC moxifoxacin**	**Eyes (−)**	**Eyes (+)**	**study details**
Cornea	Matsuura *et al*[40]	15 mcg/0.1 mL	36†	0†	Cohort. There was no difference in ECC and CCT in 15 mcg/0.1 mL and control as well as in comparison of 50 mcg/0.1 mL. Matsuura *et al* used the bag and chamber flushing method for ICM administration in their studies. This method irrigates the anterior chamber and the area behind the intraocular lens.
		15 mcg/0.1 mL versus 50 mcg/0.1 mL	66†	0†	
	Matsuura *et al*[19]	20 mcg/0.1 mL	555*	0*	Cohort. No difference was observed in ECL between treatment (ICM) and control.
	Kowalski *et al*[56]	25 mcg/0.1 mL	3†	0†	Animal study. ICM compared with ICV. The corneal thickness increased on day 1; however, thickness returned to normal on day 7. No difference in CCT was found between groups.
		50 mcg/0.1 mL	3†	0†	
	Matsuura *et al*[45]	50 mcg/0.1 mL	6*	0*	Cohort. No toxic finding reported.
	Arbisser[41]	100 mcg/0.1 mL	200*	0*	Cohort. No stromal oedema was observed.
	Akal *et al*[50]	500 mcg/0.1 mL	2‡	8‡	Animal study. Staining for apoptotic activity with caspase-3 and caspase-8 was higher in the moxifloxacin group versus control and sham injection (P>0.05).
	Arslan *et al*[43]	500 mcg/0.1 mL	0*	55*	Cohort. All patients had a history of PK. ECC was reduced (P<0.001) and CCT increased (P<0.001). However, results are similar to other reported phacoemulsification cases.
	Asena *et al*[49]	500 mcg/0.1 mL	48†	0†	Animal study. No differences in the corneal findings.
	Espiritu *et al*[42]	500 mcg/0.1 mL	65*	0*	Cohort. No difference in ECC (P=0.737) and pachymetry (P=0.65).
	Kim *et al*[46]	500 mcg/0.1 mL	9†	0†	Animal study. No statistical difference in CCT (P=0.06).
	Kobayakawa *et al*[4]	[7] 500 mcg/0.1 mL	6†	0†	Animal study. Corneal damage rate was found to be 0% with moxifloxacin.
	Ekinci Koktekir and Aslan[44]	500 mcg/0.1 mL	30*	0*	Cohort. Postoperative pachymetry in ICM versus control was not significantly different (P=0.345).
	Lane *et al*[48]	500 mcg/0.1 mL	26*	0*	RCT. ICM versus BSS. No difference in ECC or CCT at 3 months (P>0.05).
	Zhou *et al*[51]	500 mcg/0.1 mL	91*	0*	Cohort. No difference between patients receiving ICM and topical moxifloxacin drops.
	Cetinkaya *et al*[52]	500 mcg/0.1 mL	33*	0*	Cohort. No difference in corneal oedema compared with control.
AC	Arbisser[41]	100 mcg/0.1 mL	200*	0*	Cohort. Postoperative day 1 AC cell was lower in the ICM group (P=0.0007).
	Espiritu *et al*[42]	500 mcg/0.1 mL	65*	0*	Cohort. AC cell noted on postoperative day 1 which resolved on next exam.
	Lane *et al*[48]	500 mcg/0.1 mL	17*	9*	RCT. Not significantly different from controls (P>0.05).
	Zhou *et al*[51]	500 mcg/0.1 mL	91*	0*	Cohort. No difference between patients receiving ICM and topical moxifloxacin drops.

structure	study	Dose of IC moxifoxacin	(−) no toxicity, (+) toxicity		study details
			Eyes (−)	Eyes (+)	
	Cetinkaya *et al*[52]	500 mcg/0.1 mL[16]	33*	0*	Cohort. No difference between patients receiving ICM and topical moxifloxacin drops.
IOP	Matsuura *et al*[40]	15 mcg/0.1 mL	36†	0†	Cohort. No difference in IOP (P>0.5) at 3 months for both comparisons.
		15 mcg/0.1 mL versus	33†	0†	
		50 mcg/0.1 mL			
	Ekinci Koktekir and Aslan[44]	500 mcg/0.1 mL	30*	0*	Cohort. No difference in IOP versus control (P=0.15).
	Lane *et al*[48]	500 mcg/0.1 mL	26*	0*	RCT. No difference in IOP versus control (P>0.05).
	Cetinkaya *et al*[52]	500 mcg/0.1 mL[16]	33*	0*	Cohort. No difference in IOP versus control (P>0.05).
Retina	Matsuura *et al*[40]	15 mcg/0.1 mL	36†	0†	Cohort. No difference in FT at 1 and 3 months for both comparisons (P>0.05).
		15 mcg/0.1 mL versus	33†	0†	
		50 mcg/0.1 mL			
	Arbisser[41]	100 mcg/0.1 mL	31*	0*	Cohort. Macular thickness and volume showed mean increases of less than 3% and 4% in all sectors, respectively, compared with preoperative readings.
	Ekinci Koktekir and Aslan[44]	500 mcg/0.1 mL	30*	0*	Cohort. No difference in macular thickness versus control groups (P=0.107).
VA	Espiritu *et al*[42]	500 mcg/0.1 mL	65*	0*	Cohort. All eyes had VA 20/30 or better.
	Lane *et al*[48]	500 mcg/0.1 mL	26*	0*	RCT. All eyes had VA 20/30 or better.
	Zhou *et al*[51]	500 mcg/0.1 mL	91*	0*	Cohort. No difference between patients receiving ICM and topical moxifloxacin drops.
	Cetinkaya *et al*[52]	500 mcg/0.1 mL	33*	0*	Cohort. No significant difference in VA compared with control.

*Human eyes.

†Rabbit eyes.

‡Rat eyes.

AC, anterior chamber; BSS, balanced salt solution; CCT, central corneal thickness; ECC, endothelial cell count; ECL, endothelial cell loss; F T, foveal thickness; IC, intracameral; ICM, intracameral moxifloxacin; ICV, intracameral vancomycin; IOP, intraocular pressure; PK, penetrating keratoplasty; RCT, randomised controlled trial; VA, visual acuity.